
Hematology
Cancer
Consortium

ASH 2020 Update

Acute Lymphoblastic Leukemia

Lead:

Jeyachandran / Smita

Dr Jayachandran P K
Associate Professor, Medical Oncology.
Cancer Institute (Adyar), Chennai

ASH 2020 Abstract No: 464

Hyper-CVAD and Sequential Blinatumomab in Adults with Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia: Results from a Phase II Study

Early incorporation of Blinatumomab in Ph-negative B-cell ALL would decrease the need for intensive chemotherapy, lead to deeper and more durable responses, and improve survival.

Methods:
14-59 years Ph negative B-ALL

Intervention:
Hyper-CVAD alternating with high-dose methotrexate and cytarabine for up to 4 cycles, followed by 4 cycles of Blinatumomab with IT 8 doses, POMP with Blina maintenance

Primary end point: CR rates and MRD at end of induction

Characteristic	N (%) / median [range]
Age (years)	36 [17-59]
ECOG performance status ≥2	6 (18)
WBC (x10^9/L)	3.1 [0.5-360.9]
Karyotype	
Diploid	10 (29)
High hyperdiploidy	3 (9)
Low hypodiploidy / near triploidy	5 (15)
KMT2A rearranged	3 (9)
Complex	2 (6)
Others	11 (32)
CD19 expression	99.6 [30-100]
CD20 expression ≥20%	13/29 (45)
CRLF2+	6/30 (20)
TP53 mutation	9/33 (27)

Median Follow up : 22 months

Conclusion: CR rates – 100%, MRD negativity – 97%; 2 year Durable remission rates – 79%; 2yr OS – 86%. Hyper CVAD with Blina is highly effective and well tolerated as front line therapy.

ASH 2020 Abstract No: 586

Reduced-Intensity Induction with Dasatinib Vs. Hypercvad + 2nd Generation TKIs with MRD-Guided Follow-up Therapy Leads to Comparable Rates of MRD-Negative Remission While Reducing Transfusions and Neutropenia in Ph+ ALL

Reduced-intensity induction (RII) with imatinib yields comparable outcomes to HyperCVAD with imatinib with fewer induction deaths and an improved CR rate in Ph+ ALL. AlloBMT remains the goal of therapy in Ph+ ALL. RII with dasatinib for the treatment of Ph+ ALL and compared to patients who received HyperCVAD with a 2nd generation TKI

Methods:

Retrospective Study

Adults - Ph positive ALL

Intervention:

Weekly VCR, Weekly D1 and D2 Dexa, Dasatinib 100mg OD daily, IT prophylaxis – compared with Hyper CVAD with Dasatinib or Nilotinib. Rtx was given based on CD20 status

Primary end point: MRD at end of induction

Results:

RII – N = 21 (Sep 2017 to Jun 2020)

Hyper CVAD – N = 24 (July 2011 – Jun 2020)

Comparable for sex, median age, old age >60, WBC at presentation

	HyperCVAD with 2nd Gen	RII with Dasatinib	p
Median Days Hospitalized for Induction (Range)	18 (7-52)	15 (5-40)	0.34
Median Days to ANC Recovery >500 (Range)	17 (1-37)	14 (0-23)	0.001
Median Units pRBCS within 30 days of Induction Start (Range)	7 (2-24)	3 (0-10)	0.001
Median Units Platelets within 30 days of Induction Start (Range)	10 (0-63)	5 (0-15)	0.02

Conclusion: RII with dasatinib followed by MRD-guided follow-up therapy facilitates MRD negative remissions with less toxicity than HyperCVAD

ASH 2020 Abstract No: 467

NOR-GRASPALL2016 (NCT03267030): Asparaginase Encapsulated in Erythrocytes (eryaspase) – a Promising Alternative to Peg-Asparaginase in Case of Hypersensitivity

Hypersensitivity is the most common cause of truncated asparaginase therapy, and truncated treatment has been associated with decreased event-free survival. Asparaginase encapsulated in erythrocytes (eryaspase) is an formulation of asparaginase to prolong the half-life of asparaginase and to reduce toxicity e.g. hypersensitivity, since the erythrocyte membrane prevents activation of the immune system and protects asparaginase against elimination.

Methods:

Phase II single arm Study multicentre – Nordic/Baltic
Non high risk ALL with hypersensitivity to Peg Asp

Intervention:

Eryaspase 150 U/ kg (1-7 doses) to complete the planned course of asparaginase

Primary end point: Asparaginase enzyme activity (AEA) was measured for treatment efficacy.

Results:

N = 38 (36 children and 2 adult) - 171 doses
97.4% - allergy; 59.5% - severe allergy
Median AEA-level - 798 U/L [IQR: 387;864]. 90.7% of all
(D14)AEA >100U/L – 90.7%; AEA> 400U/L – 69.3%
AE: 8 of 36 patients (22%).
Possible allergy – 6; severe allergy – 1.
Rash – 3; Fever – 2
Low AEA levels after allergy – 3 out of 6
Hepatotoxicity – 2
Mild Hyperlipidemia - 2

Conclusion: Eryaspase consistently demonstrated prolonged AEA in patients who developed hypersensitivity reactions to PEG-asp. Treatment with eryaspase was well tolerated. We conclude that eryaspase is a promising alternative to PEG-asp in case of hypersensitivity.

ASH 2020 Abstract No: 1024

Bortezomib and Rituximab in Newly Diagnosed Adolescent and Adult CD20-Positive Philadelphia (Ph) Negative Precursor B-Cell Acute Lymphoblastic Leukemia: A Phase II Study

Expression of CD20 in precursor B-cell ALL - associated with poor outcomes. Addition of rituximab with intensive chemotherapy in this subset of ALL has led to improvement in EFS. Bortezomib is an active drug in relapsed ALL as well as has synergistic activity with rituximab in B-cell lymphomas

Methods:

Phase II Study

ND adolescents (> 14 years) & adults
CD20 positive/ Ph negative pre B-ALL

Intervention:

Pediatric inspired regimen
+ Rituximab + Bortezomib

Primary end point: MRD at end of induction

Results:

N = 35 (Dec 2017 to Aug 2019)
End of Induction MRD negativity = 70.9%
End of consoliadation MRD negativity = 88%

Median FU: 18 months
EFS 81.8%
OS 84.7%

Toxicities:

No significant increase
< Grade 3 neuropathy 26%

Conclusion: The combination of bortezomib, rituximab and paediatric-inspired ALL regimen is active and well tolerated in in de-novo CD20 positive Ph-negative precursor B-ALL.

Dr Jaikumar G.R.,
Assistant Professor, Paediatric Oncology
JIPMER (Jawaharlal Institute of Postgraduate Medical Education & Research) , Puducherry

ASH 2020 Abstract No:2793
Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia Harboring Heterogenous Genomic Profiles Respond to Venetoclax in Combination with Chemotherapy

Venetoclax (Ven), selective BCL-2 inhibitor in combination with chemotherapy (Ctx) was studied for safety, efficacy and genomics in patients (<25 Yrs) with Relapsed/Refractory (R/R) Acute Lymphoblastic Leukemia

Methods: Phase 1, 2 parts

Study
- Part 1: Ven 800 mg + Ctx after 21 days of Ven (n=5)
- Part 2: Ven 800 mg + Ctx from day 4 of Ven (n=20)

End points: Primary – Safety of Ven,
Secondary- efficacy of Ven ± Ctx
Ctx regimen: Dexa/VCR/peg-Asp (DVP) (n=16)
Ara-C/Eto/Peg-Asp (C) (n=9)

Results: Median of 3.5 (1-9) prior therapy
Median duration: Ven therapy 2.1mo (0.4-4.6)
Ven Discontinuation- Prog. Disease 28%

Toxicity
Grade ¾ adverse events FN- 52%, Anemia- 44%,
Fatal- 32% (Unrelated to Ven)

Objective response rate (ORR)
Ven+ DVP- 56%, Ven + C- 11%

MRD negativity in pts with CR/CRi/CRp
Ven+ DVP- 38%, Ven + C- 11%

Genetic analysis was performed for 18 patients
Ven + DVP (n=12), Ven + C (n=6)], CREBBP- 66% CR(n=3)
RB1, PTPN11, PDGFRB- 100% CR (n=2 each)
KMT2A (n=2) KMT2D (n=4) 50% CR

Gene expression profiling revealed BCL-xL and MCL1 levels higher than BCL-2 expression
No correlation between gene expression levels and response

Conclusion:
Ven+ Ctx well tolerated with ORR 56%.
Ven+ Ctx achieved response in wide variety of mutations including KMT2A rearrangement.

ASH 2020 Abstract No:586 :

In Vitro Drug Response Profiling in BCP and T-ALL Primary Samples Adds a Robust Functional Layer Enabling Optimized Guidance of Individualised Therapy in Relapsed and Refractory Pediatric Acute Leukemia Patients

Targeted therapy on actionable genomic lesions had limited survival impact so far
Drug response profiling (DRP) provides functional information layer and DRP was correlated with outcome

Methods: DRP Retrospective analysis 23 T & 50 BCP ALL
Sensitivity & resistance defined by IC50 outlier analysis
Outcome data was available for 36 BCP and 15 T-ALL

Results: First line BCP-ALL Dexa DRP predicted D8 PD Response and D15 MRD- AIEOP BFM 09
87.5% R/R ALL had assc. between response & DRP

R/R BCP ALL: Sensitivity and resistance to calicheamicin correlated with response to Inotuzumab.
No correlation between sensitivity to MEK inhibitors and RAS pathway alterations.

R/R T- ALL: Bortezomib sens. corr. with outcome (N=5)
T ALL had high sensitivity to Dasatinib IC50 1.9nM
Pts with high IC50 to Dasatinib were refractory/ shorter response duration to TKI + Ctx combination

Table 1:

Targeted Therapy in BCP-ALL

	N patients	DRP	Outcome
Dasatinib	2	2 res.	2 non-responder
Trametinib	1	1 intermediate	Short term response
Palbociclib	1	1 Ribocilib sens.	PD
Calicheamicin	2	1 sens. / 1 res.	1 CR / 1 SD

Targeted Therapy in T-ALL

	N patients	DRP	Outcome
Dasatinib	2	2 sens.	1 CR; 1 PD
Imatinib	1	1 res.	SD 3 weeks
Ruxolitinib	1	1 sens.	Short term response
Selinexor	1	1 sens	SD 3 months
Bortezomib/ Ventoclax	5	2 sens. / 1 med. / 2 res.	2 mol. CR / 1 CMR / 2 SD

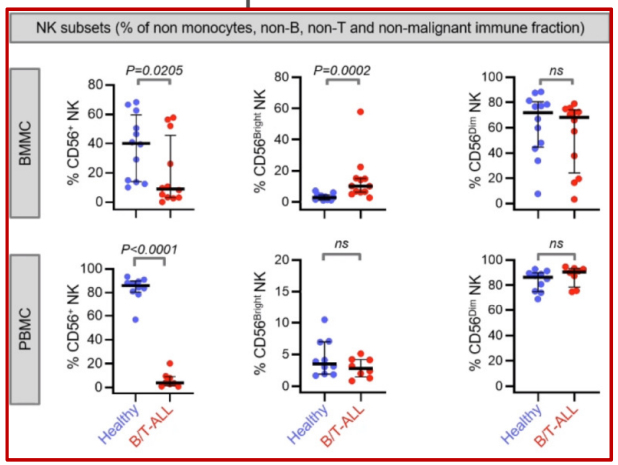
T- ALL sensitive to Selinexor achieved significant decrease in PB blast count and improved quality of life as 4th line monotherapy
Stable disease was achieved for 3 months

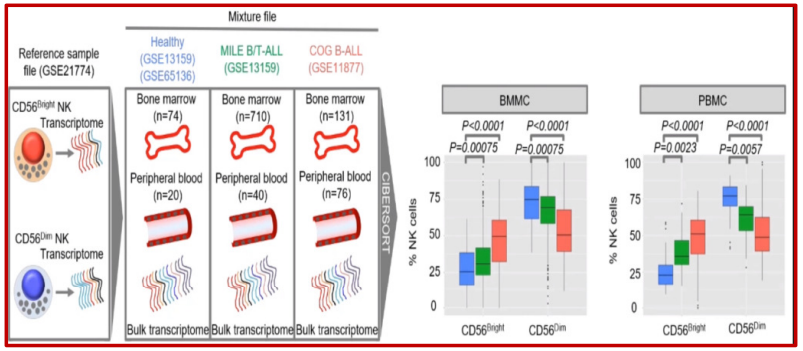
Conclusion: Association between DRP and response is established- needs evaluation in prospective trials.
Integration of molecular and functional information may help us select specific agents in resistant disease.
BFM & ITCC planning an international multi-arm study utilising DRP to select appropriate therapy for R/R ALL

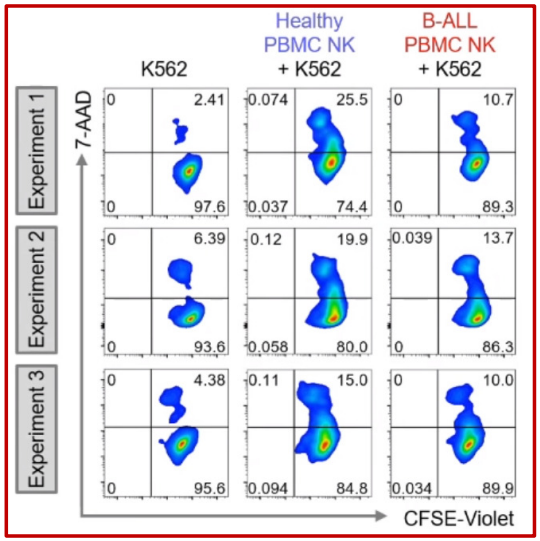
Dr Poonkuzhali Balasubramanian
Professor, Haematology
CMC Vellore

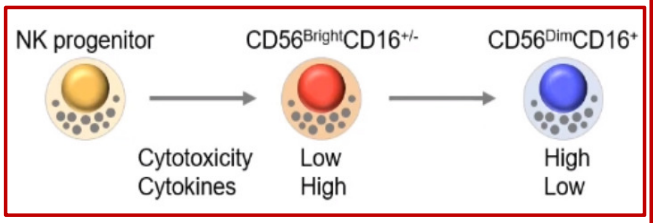
ASH 2020 Abstract No: 397
Activated Natural Killer Cells Are Associated with Poor Clinical Prognosis in High-Risk B- and T- Cell Acute Lymphoblastic Leukemia

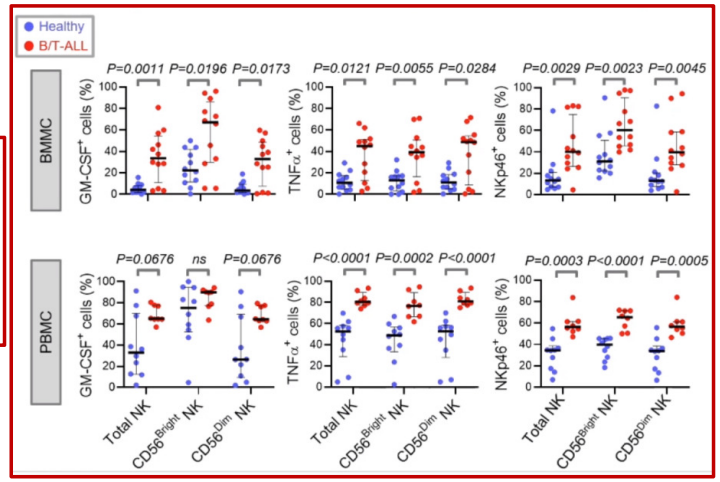
To develop NK therapies against B/T-ALL, it is important to identify the phenotypic and functional deficiencies in NK cells of ALL patients

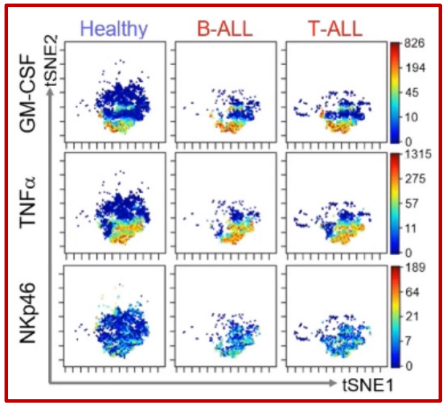


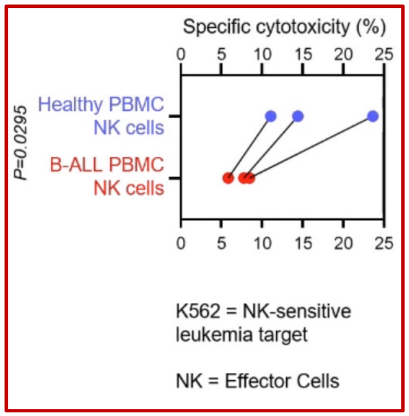












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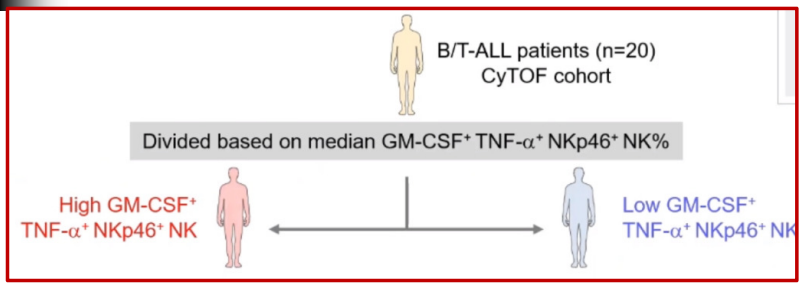
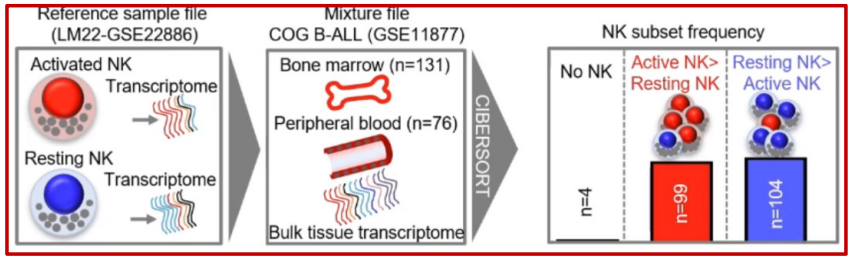
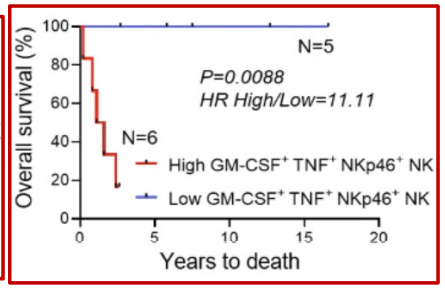
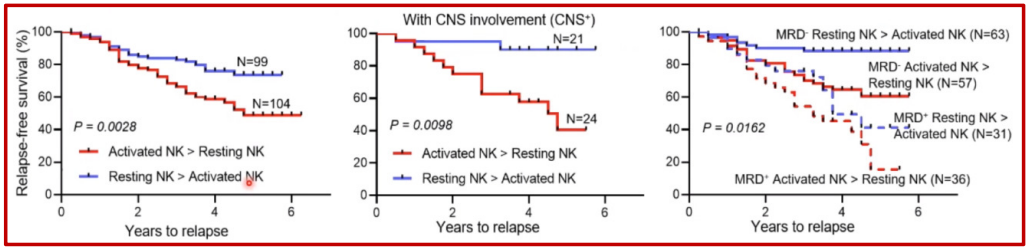
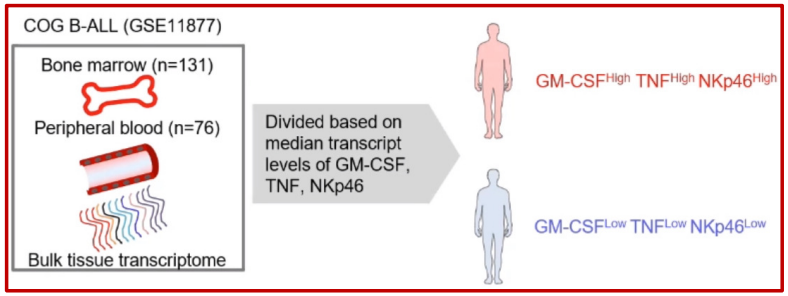
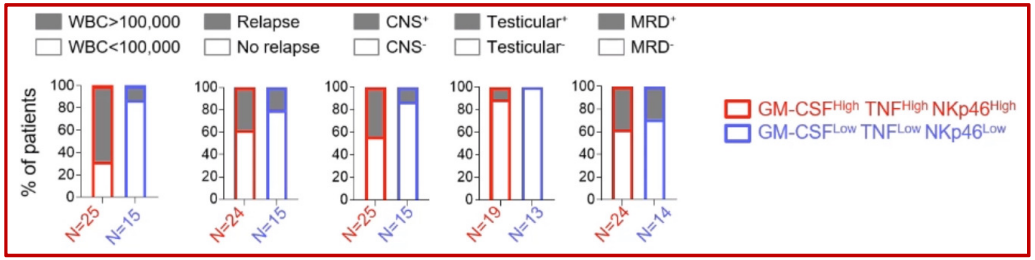


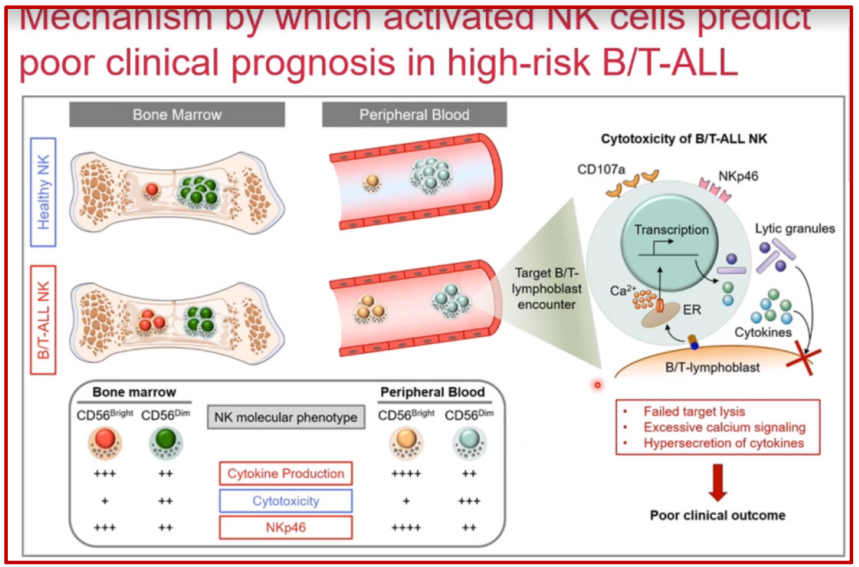












ASH 2020 Abstract No: 2910
Molecular Subtypes with Distinct Clinical Phenotypes and Actionable Targets in Adult B Cell Precursor ALL Treatment According to GMALL Protocols

- **BCP-ALL molecular driver subtypes (n=14-23) have been identified by transcriptome sequencing**

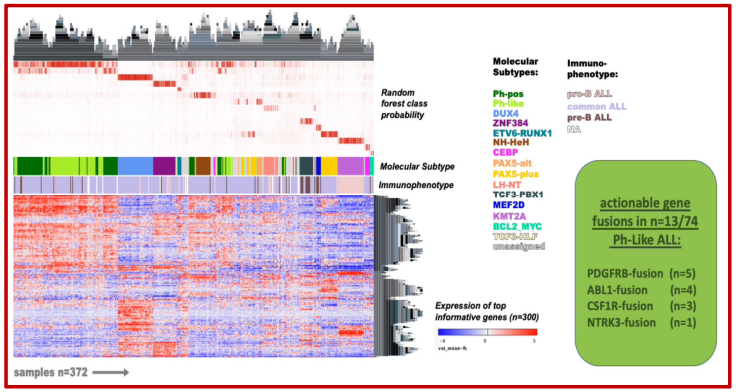
*(Liu YF et al., **EBioMedicine**, 2016; Li JF et al. **Proc Natl Acad Sci**, 2018; Gu Z et al. **Nat Genet**, 2019; Bastian L et al. **Leukemia** 2019)*

- **Clinical phenotypes are insufficiently characterized, especially in adult BCP-ALL**
- **Gene fusions involving *ZNF384* define a molecular BCP-ALL subtype with:**
  - → peak incidence in AYA
  - → ‚immature' features (gene expression, lineage determination)
  - → intermediate prognosis (small pediatric cohorts)

to characterize:

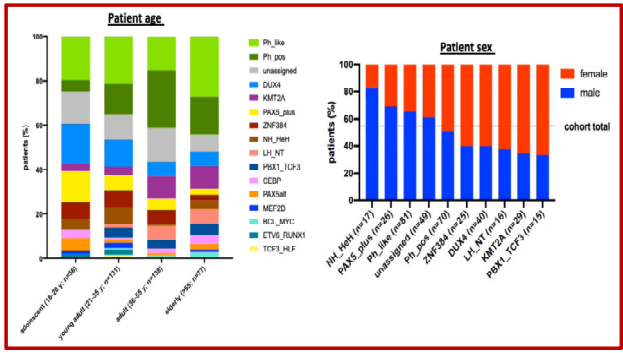
1.) the molecular subtype distribution and
2.) clinical phenotypes

of adult BCP-ALL patients homogeneously treated according to GMALL protocols



actionable gene fusions in n=13/74 Ph-Like ALL:

PDGFRB-fusion	(n=5)
ABL1-fusion	(n=4)
CSF1R-fusion	(n=3)
NTRK3-fusion	(n=1)



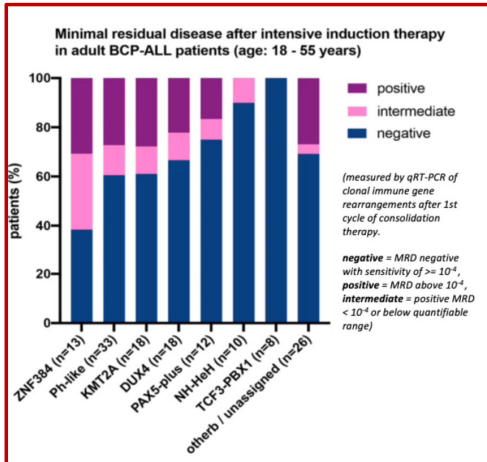
Reference cohort (n=275):
- adult and pediatric BCP-ALL
- integrative analysis: *RNA-Seq, WES, gene-panel sequencing, SNP-Arrays, DNA-Methylation Chips*

(Bastian L et. al **Leukemia** 2019)

Prospective cohort (n=189):
- adult BCP-ALL
- RNA-Seq: 2x100 bp, 30 Mio reads / sample Nova-Seq

Subgroup definition
Random forest training (300 gene set)

adult BCP-ALL frist diagnosis samples from GMALL study cohorts for analysis (n = 372)

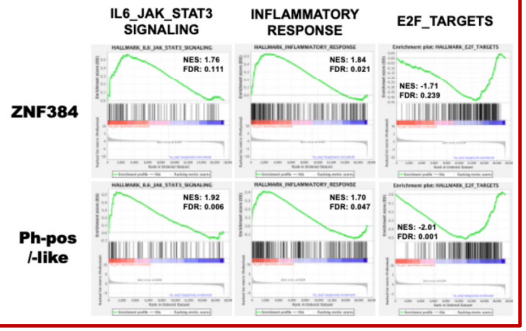


(measured by qRT-PCR of clonal immune gene rearrangements after 1st cycle of consolidation therapy.

***negative** = MRD negative with sensitivity of >= 10^{-4}, **positive** = MRD above 10^{-4}, **intermediate** = positive MRD < 10^{-4} or below quantifiable range)*

ZNF384 fusion partners:

EP300-ZNF384:	*n=16*
TCF3-ZNF384:	*n=2*
TAF1-ZNF384:	*n=2*
EWSR1-ZNF384:	*n=1*



- **BCP-ALL subtypes show an age-dependent distribution across adult patients**
- **Sex-specific host factors favor the selection of leukemogenic drivers**
  (male predominance: Ph-like, Near haploid – High hyperdiploid,
  female predominance: DUX4, KMT2A)
- **ZNF384r ALL seems to be associated with unfavorable therapy response in adults and shares JAK/STAT activation patterns with Ph-pos / Ph-like ALL**

Dr Ranjit Sahoo
Addl Professor, Medical Oncology
All India Institute of Medical Sciences (AIIMS),
New Delhi

ASH 2020 Abstract No: 694

Tumor Associated Macrophages Express High-Levels of FLT3 Ligand, Which Induces Activation of FLT3 Signaling That Promotes Survival of Neoplastic Cells in B-Cell Acute Lymphoblastic Leukemia

- Almost all B-ALL blasts aberrantly express FLT3 and its high expression of FLT3 increases the odds of relapse/death in patients, however gain-of-function mutations of FLT3 are relatively rare (<5%).
- Hypothesis: TAMs of M2-phenotype (CD68/163+) express FLT3L and is related to its impact on outcome.

Outcomes:

1. High levels of FLT3L (234.7 ± 47.6 pg/ml) in plasma from 28 patients with B-ALL at diagnosis and at MRD-ve CR (286.9 ± 71.2 pg/ml) , as c/w age-matched healthy donors (41.2 ± 15.5 pg/ml) by using ELISA.
2. FLT3-transcripts were high in TAMs vs. Blasts in the RNA (n=5) and Culture-Media (n=18)
3. Co-Culture experiments of blasts with TAMs (to assess the involvement of FL/FLT3 signaling): Less apoptosis (Annexin-V and PI) and Immunoblotting revealed high levels of phosphorylated FLT3 and ERK, indicating the activated FLT3 signaling cascade in these cells.

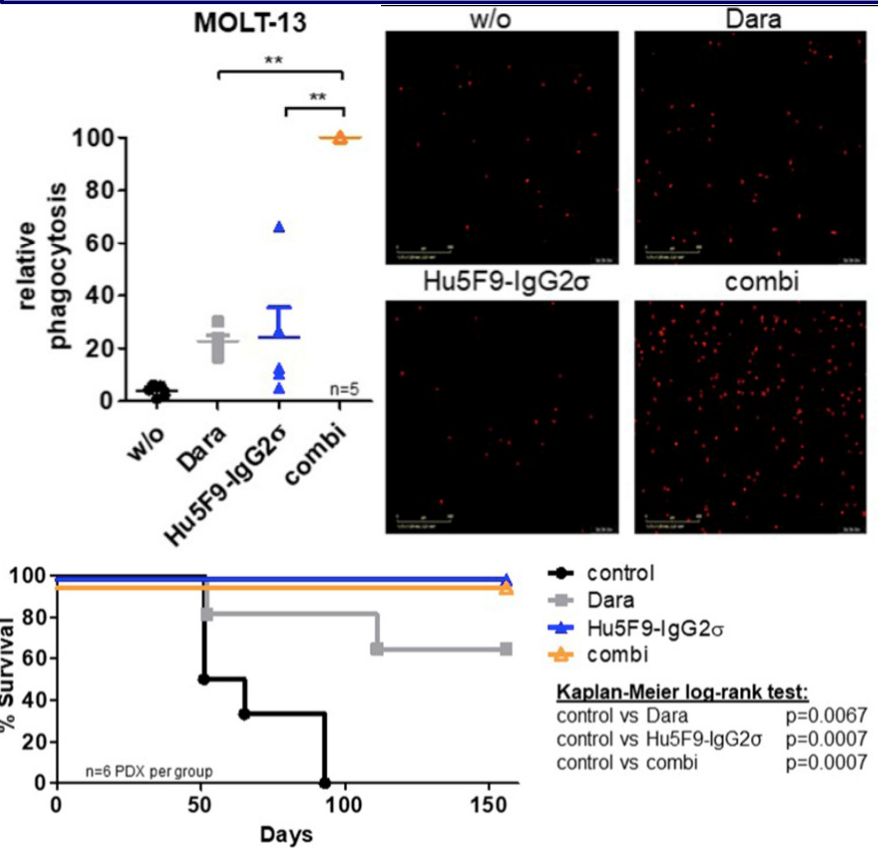
Investigator Conclusions:

Elevated level of FLT3L noted in the plasma of patients with B-ALL is produced primarily by TAMs, which reside in the microenvironment of neoplastic cells and could be responsible for the poor outcome.

Dr TVSVGK Tilak
Professor, Medical Oncology
AFMC, Pune

ASH 2020 Abstract No:2384 :
Co-Targeting of CD38 and CD47 in T Cell Acute Lymphoblastic Leukemia

Immunotherapeutic interventions in T-cell ALL [T-ALL] are practically non-existent. In addition to Most T-ALL surface expression of CD38 and T-ALL cells also express CD47 ["Don't eat me" against macrophage – dependent phagocytosis.



In this study, the efficacy of Dara and a CD47 blocking antibody (Fc-modified version of Hu5F9-G4, termed Hu5F9-IgG2σ) alone or in combination in T-ALL in cell lines & Patient Derived Xenograft [PDX] samples.

In vitro cell lines- MOLT-13; HSB-2 & P-12
In vivo (Phase II) Samples- NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ (NSG) mice

Median Phagocytosis

	MOLT-13	Random PDX (n=12)	Rel/Ref PDX (n=16)
Control	5%	6%	2%
Dara Alone	23%.	46%	14%
Hu5F9-IgG2σ	27%	9%	37%
Combination	~ 99%	Maximal	Maximal

Conclusion: Dara with CD47 blockade increases phagocytosis in vitro and PDX. This combination is a highly promising therapeutic strategy in T-ALL, especially in the relapsed/refractory setting.

Acute Myeloid Leukemia

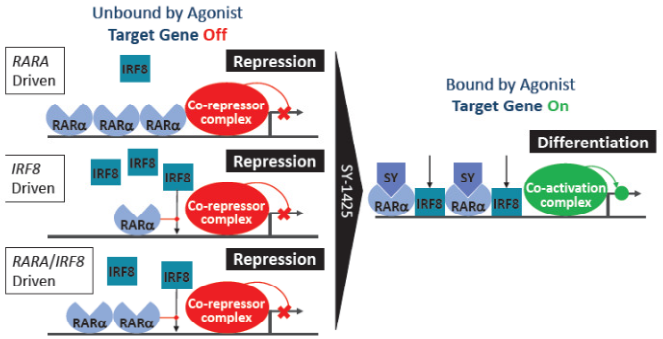
Lead:

Rajan / Vikram

ASH 2020 Abstract No:112 :

SY-1425, a Potent and Selective RARα Agonist, in Combination with Azacitidine Demonstrates a High Complete Response Rate and a Rapid Onset of Response in RARA-Positive Newly Diagnosed Unfit Acute Myeloid Leukemia

Increased recognition of a subset of AML (~30%) who are defined as RARA positive AML based increased RARα and/or IRF8 pathway activation (Real time data and epigenetically driven)



Subset potentially resistant to Venetoclax. Fiore et al ASH 2020 abs
Potential novel prognostic marker for this therapy

In this study – Phase II study RARA + (22) and –ve (29) cases enrolled.
ND and unfit cases. Total of 51 cases enrolled
Aza at 75 mg/m2 IV/SC daily on days 1-7
SY-1425 at 6 mg/m2/day PO in divided doses twice daily on d: 8-28

- **Use of RARA agonists can bring about differentiation as seen in APL. However, ATRA not effective**
- **SY-1425 same as Tamibarotene, selective and potent RARα**
- **Preliminary data that is synergizes with Azacitidine**

Ref: 1. Cancer Discovery 2017
2. Haematologica 2018 (3) ESH 2017

	RARA + (18)	RAR- (28)
ORR	67%	39%
CR	61%	29
C –M/CT (CR)	89%	NA
Median time to IR	1.2 mths	2.9 mths

- **Well tolerated – mostly low grade non-hem toxicities**

Association with (RARA+ve AML)	- monocytic expression signature (MES) - AML M4/M5

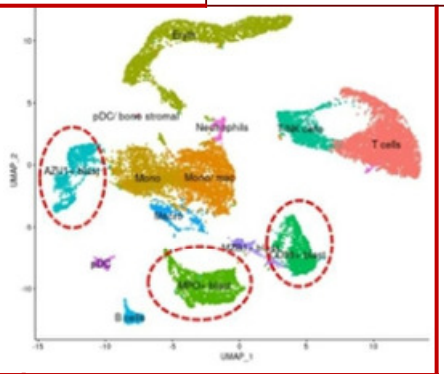
Dr Poonkuzhali Balasubramanian
CMC, Vellore

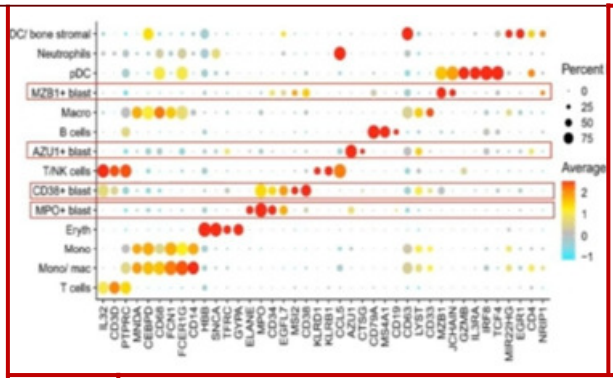
ASH 2020 Abstract No: 30

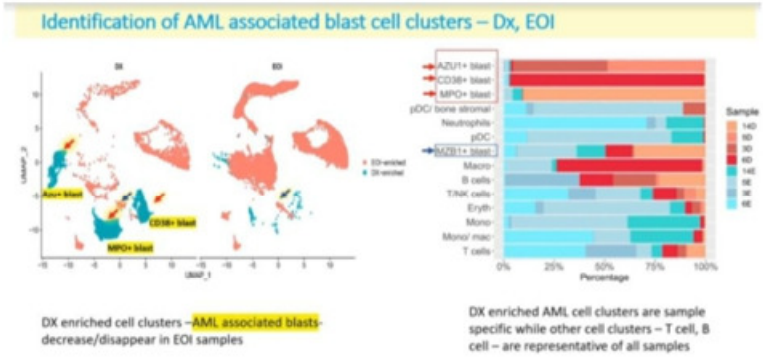
Single Cell Transcriptomics Revealed AML and Non-AML Cell Clusters Relevant to Relapse and Remission in Pediatric AML

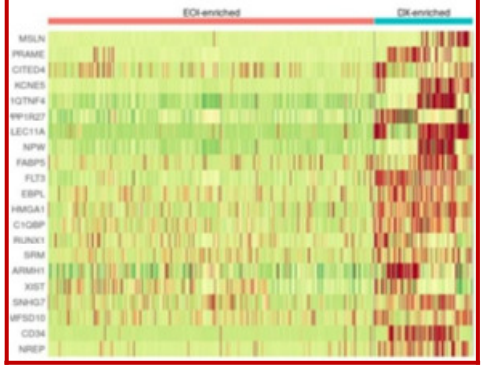
scRNA-Seq allows in-depth analysis of the heterogeneous AML landscape to provide a detailed view of the tumor microenvironment, revealing populations of blasts and immune cells which may be relevant to relapse or CR

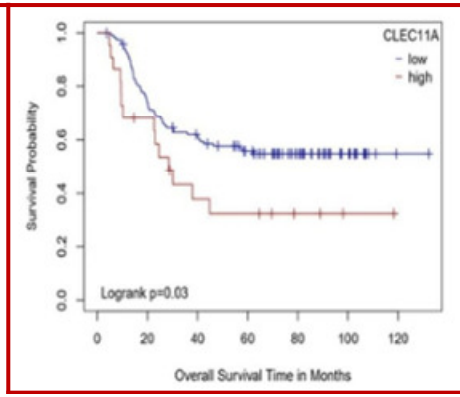
- To develop a gene signature to identify AML associated blasts
- To identify cell types associated with relapse/remission
- Identify novel gene markers/pathways associated with relapse/remission

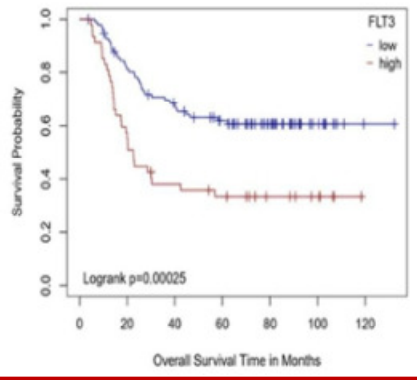


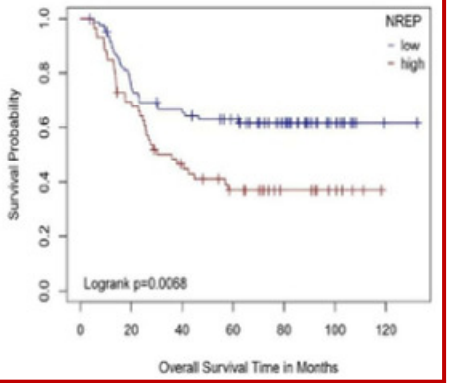


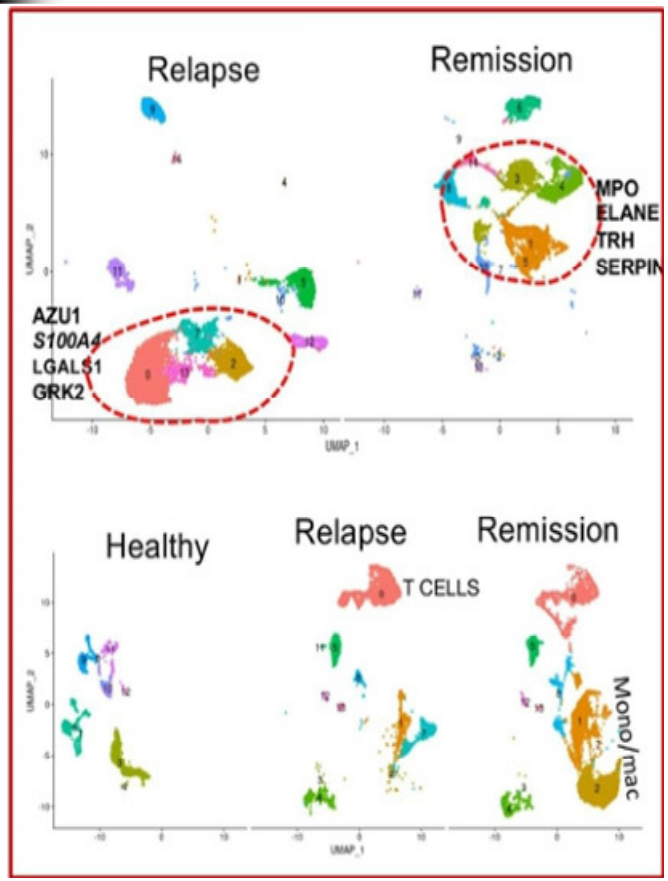


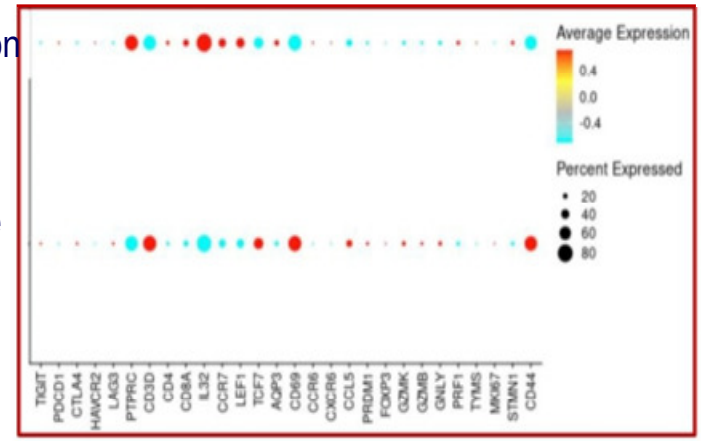


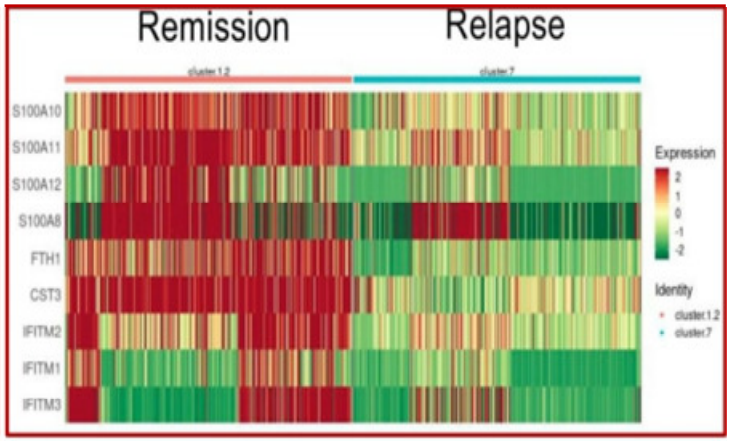












Conclusions

- Developed a novel gene signature to identify AML blast cells with high sensitivity – single cell and bulk transcriptome data.
- Gene signature was used to identify sample specific AML blasts relevant to relapse/remission
- Unique molecular signature of relapse/remission non-AML cell clusters in both Dx and EOI:
  - More effector T cells in relapse samples with enhancement of specific exhaustion markers
  - More CD8+ T cells in remission samples
  - more differentiated macrophages/monocytes in remission samples
- Identified genes and the pathways they regulate have diagnostic and therapeutic potential in AML relapse/remission

Col (Dr) Rajiv Kumar
Command Hospital (Air Force), Bengaluru

ASH 2020 Abstract No:591 :

Results of a Phase 2, Randomized, Double blind study of Sorafenib vs Placebo in combination with intensive chemotherapy in previously untreated patients with FLT3-ITD Acute Myeloid Leukemia

The ALLG conducted a randomized phase 2 study in 99 adults aged 18-65 years with newly diagnosed *FLT3*-ITD positive (allelic ratio (AR) ≥0.05) AML to determine whether addition of SOR to IC would improve event-free survival (EFS).

Midostaurin is the only approved FLT3 inhibitor in AML

Sorafenib was investigated in the SORAML trial in combination with IC in newly diagnosed AML <60y age.

A subgroup analysis of 46 patients with FLT3-ITD showed a trend towards increased OS.

Ref: SORAML trial (Röllig, Lancet Onc 2015)

- Patients 18-55 yrs received induction with IDAC-3 (idarubicin [IDA] 12 mg/m^2 D1-3and ara-C 1.5 g/m^2 BD D1,3,5,7); patients 56-65 received 7+3 (IDA 12 mg/m^2 D1-3 and ara-C 100 mg/m^2 D1-7 IVI).
- Patients were randomized 2:1 to SOR or PBO400 mg BD on days 4-10 of induction and each consolidation cycle.
- For consolidation,patients 18-55 yrs received 2 cycles of IcE (IDA 9 mg/m^2 D1-2, ara-C 100 mg/m^2 D1-5 IVI and etoposide 75 mg/m^2 D1-5), those 56-65 yrs received 2 cycles of IDAC-2(IDA 12 mg/m^2 D1-2 and ara-C 1g/m^2 BD D1,3,5).
- Maintenance was with SOR/PBO 400 mg bd days 1-28 for 12 cycles. Allogeneic HCT (allo-HCT) was at investigator discretion.

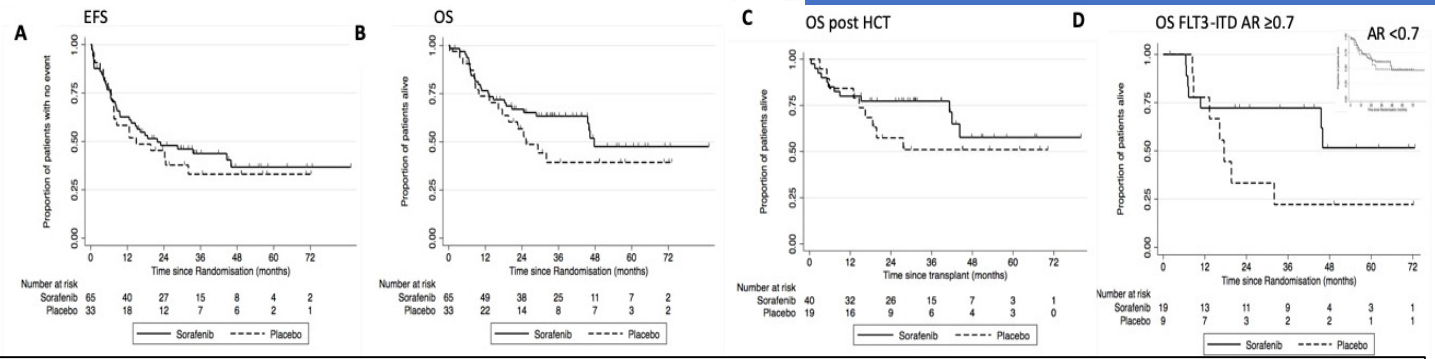


Table 2 Treatment outcomes

	Median (mo)		At 2 years (%)		HR (95% CI)
	SOR	PBO	SOR	PBO	
EFS	21.8	14.9	47.9	45.4	0.87 (0.50-1.49)
OS	47.7	25.3	66.8	56.4	0.70 (0.38-1.29)
OS 18-55 yrs	NR	29.3	71.9	63.2	0.66 (0.30-1.45)
OS 56-65 yrs	28.7	22.6	55.9	37.0	0.63 (0.23-1.74)
OS FLT3-ITD AR 0.05 to <0.7	47.7	29.3	64.7	67.9	0.89 (0.42-1.90)
OS FLT3-ITD AR ≥0.7	NR	17.6	73.0	33.3	0.45 (0.16-1.30)

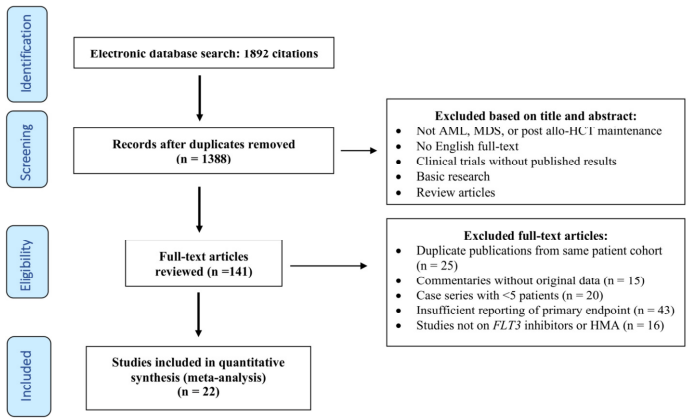
NR : not reached

SOR did not improve EFS when combined with intensive chemotherapy in adults with newly diagnosed FLT3-ITD AML. Although not powered for significance, SOR showed a trend for improved OS among patients with higher FLT3-ITD AR or receiving HCT in CR1

ASH 2020 Abstract No:1528 :
Safety and Efficacy of Maintenance Treatment Following Allogenic Hematopoietic Cell Transplant in Acute Myeloid Leukemia and Myelodysplastic Syndrome – a Systematic Review and Meta-Analysis

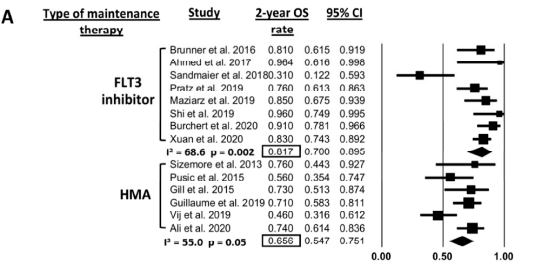
Prognosis of patients (pts) with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who relapse after allogeneic hematopoietic cell transplant (allo-HCT) is extremely poor.

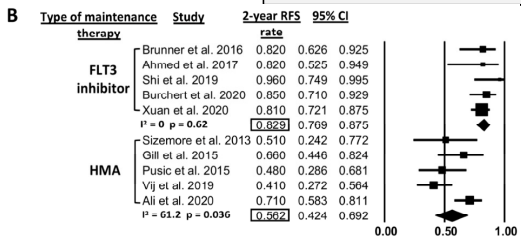
PRISM diagram of systematic review and meta-analysis

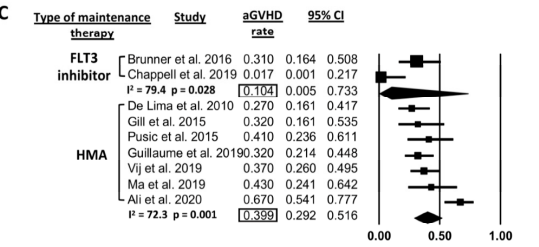


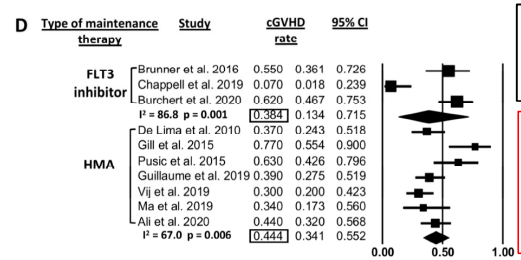
Hypomethylating agents (HMA) or FLT3 inhibitors have been used in several studies for relapse prevention following allo-HCT with mixed results leaving the question regarding the safety and efficacy unanswered.

A total of 829 pts was included with 462 and 367 receiving post-allo-HCT treatment with FLT3 inhibitors or HMA, respectively.
All pts treated with FLT3 inhibitors had AML, while 231 AML and 112 MDS pts were treated with HMA, respectively.
Among studies on FLT3 inhibitors, sorafenib was used in 10 studies with midostaurin and quizartinib being used in 1 study each. Azacitidine was used in 8 studies, decitabine in 3 studies and 1 study used both azacitidine and decitabine









Patients treated with FLT3 inhibitors:
2-year OS and RFS rates: 81.7% (70.0 – 89.5%), and 82.9% (76.9 – 87.5%).
Acute and chronic GVHD: 10.4% (0.5 - 73.3%) and 38.4% (13.4 – 71.5%)
HMA-treated pts:
2-year OS and RFS rates: 65.6%(54.7 – 75.1%) and 56.2% (42.4 – 69.2%)
Acute and chronic GVHD :39.9% (29.2 – 51.6%) and 44.4% (34.1 – 55.2%)

Limitations: Retrospective design in 10 studies, Small sample sizes, Heterogenous patient populations/reporting of outcomes/transplant outcomes

Maintenance therapy with FLT3 inhibitors or HMA following allo-HCT in AML and MDS pts appears to be safe and can potentially be associated with prolonged RFS and OS although its efficacy needs to be verified in randomized trials.

Col (Dr) Sanjeev Khera
Army Hospital R&R, New Delhi

593: Newly Diagnosed Childhood AML Patients Treated with Bortezomib Show Superior Survival If CD74 Is Expressed: A Report of 991 Patients from the Children's Oncology Group AAML1031 Protocol

Prospective, multicenter, randomized clinical trial conducted in USA .

Objective: Whether addition of Bortezomib on COG AAML 1031 protocol, would have a more favorable outcome in patients <30 yrs with de novo AML with CD74 expression.

- CD74 associated with response to bortezomib in multiple myeloma
- To see this association in CD74 expression by difference from normal (ΔN) FCM in AML

- n =1139, Arm A (n=561, no Bortezomib), Arm B (n=578 Bortezomib)
- End points : CR, OS, EFS & adverse events.
- Overall, Bortezomib had high toxicity/no survival benefit

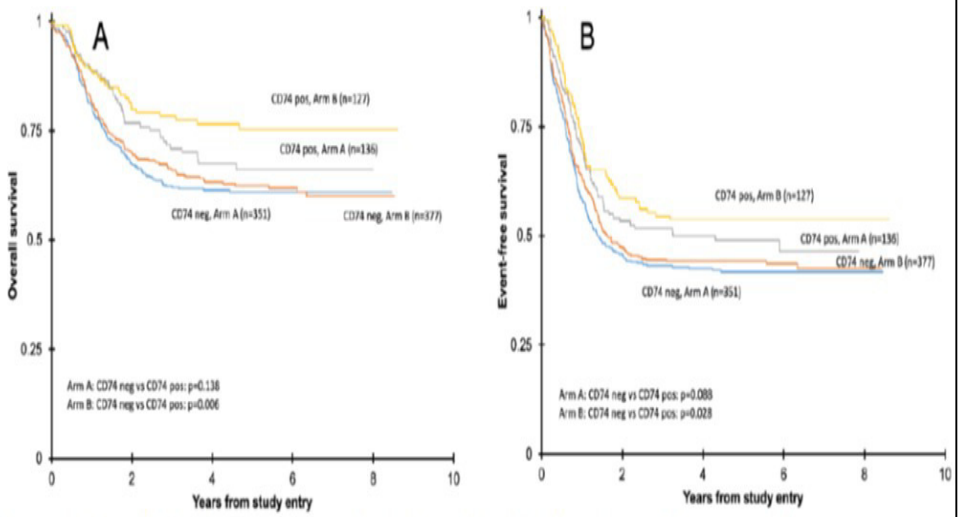


Figure 1. OS and EFS of patients treated with (Arm B) and without (Arm A) bortezomib.

- Total **CD74+ (n=263)** had higher age, low TLC, high prevalence of low risk protocol, t(8:21) enriched, low CEBPA, inv 16 and KMT2A and high CR (morphology NOT MRD), significant superior OS/EFS
- **In Arm B OS (75.3% vs 62.5%, p=0.006) and EFS (53.6% vs 44.3%, p=0.028)**
- Arm A-Not Significant
- Arm A vs. Arm B outcomes for CD74-positive patients with and without bortezomib exposure were NS
- Hazard ratio of 0.67 (95% CI: 0.44 - 1.02) and p=0.061

Patients receiving Bortezomib that were CD74-positive showed a superior response to therapy compared to patients who did not express CD74, by both OS and EFS

Col (Dr) Ashok Mesram
INHS Avini, Mumbai

ASH 2020 Abstract No: 459

Comparison of Subcutaneous Injection Versus Intravenous Infusion of Cytarabine for Induction Therapy in Young Adult Acute Myeloid Leukemia: Results of a Prospective, Multicenter, Noninferiority, Randomized Trial

Open-label, prospective, multicenter, noninferior, randomized clinical trial conducted in 10 hematological centers in China.
Objective: whether sc injection of cytarabine (CA) is noninferior to CI of cytarabine in "3+7" induction regimen for young adult patients with de novo AML.

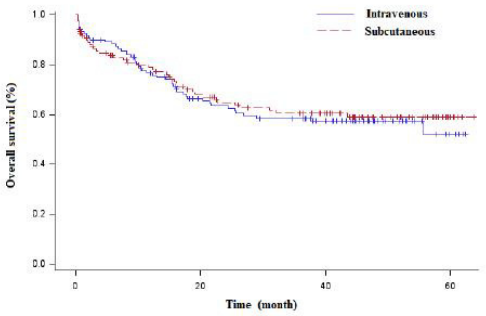
- Usually, CA is given as CI
- concentration of Ara-CTP was higher after sc injection than during CI for about 5 hours*
- SC CA is much convenient & inexpensive

Ref: Liliemark JO, Semin Oncol]

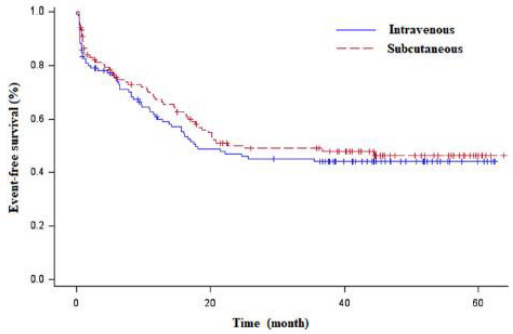
- n =240, between March 2015 and August 2017, with final follow-up in June 2020.
- Patients were randomized to receive idarubicin 10 mg/m^2 for 3 days and CA 100 mg/m^2/d by CI infusion daily for 7 days (n=120) or idarubicin 10 mg/m^2 for 3 days and CA 100mg/m^2/d sc injection every 12 hours for 7 days (n=120).
- End points : Primary was CR, secondary were OS, EFS & adverse events

CR was achieved by 71.7% patients in sc group vs 70.8% in CI group, (difference, 0.9%[1-sided 95% CI, -8.8% to ∞]); p for noninferiority=0.003) after first cycle of induction therapy.

A



B



The efficacy of sc injection of CA was non inferior to CI infusion of cytarabine for the standard induction therapy in young adult de novo AML, with equivalent toxicity

SC injection of cytarabine offers a convenient and inexpensive alternative therapy to young adult de novo AML.

Col (Dr) Rajan Kapoor
Command Hospital, Kolkata

ASH 2020 Abstract No:25

Study of Venetoclax Added to Cladribine + Low Dose AraC (LDAC) Alternating with 5-Azacytidine in Older Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

Phase2 ,prospective single centre study at M D Anderson cancer centre

Objective- whether venetoclax to the low intensity CLAD/LDAC alternating with 5-AZA improve response rates and outcomes .

Introduction-

(CLAD/LDAC)alternating with dec itabine for older patients with AML, yielding higher rates of CR and improved outcomes compar ed to (HMAs) i.

(Lancet Haematology 2018)

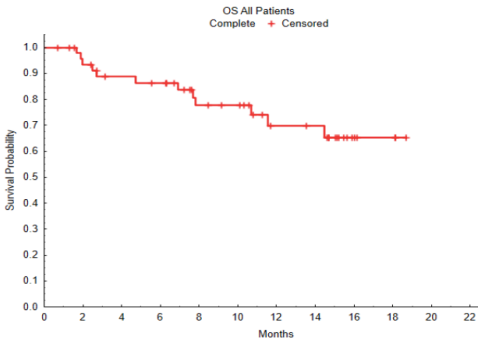
Addition of venetoclax to HMAand CLAD/LDAC can improve outcome

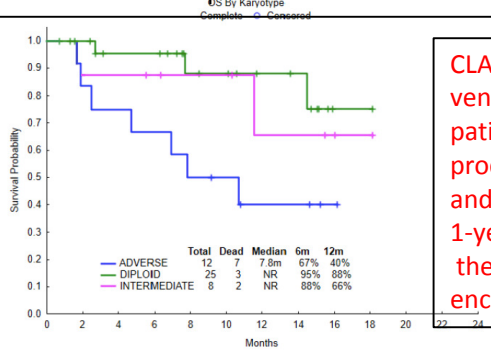
Methods –

Induction with cladribine 5 mg/m2 IV over 30 minutes on D1-5 followed by araC 20mg SQ BID on D1-10.

Consolidation/maintenance with 2 cycles of cladribine on D1-3 + araC 20 mg SQ BID on D1-10 alternating with 2 cycles of AZA 75 mg/m2 on D1-7, for up to 18 cycles. Venetoclax 400 mg was added on days 1-21 of each cycle.

- N=48,median age68(57 -84) , 37(77%) achieved CR, 8 (17% had CR with (CRi). for Cr/Cri rate of 94%. 36 (80%) pts were negative for MRD by flow cytometry at the time of CR/CRi.
- With a median follow-up of 11+ months, the median overall survival (OS) has not been reached (NR), with 6- and 12-month OS rates of 86% and 70%, respectively .
- The median OS of pts with or without MRD at CR were 10.7m and NR, respectively (P=0.056)





CLAD/LDAC plus venetoclax alternating with AZA plus venetoclax is an effective and well tolerated among older patients with newly diagnosed AML,
producing high rates of durable MRD negative remission and meaningful blood count recovery. With approximately 1-year follow-up,
the rates of overall and relapse-free survival are encouraging in this cohort of older AML patients.

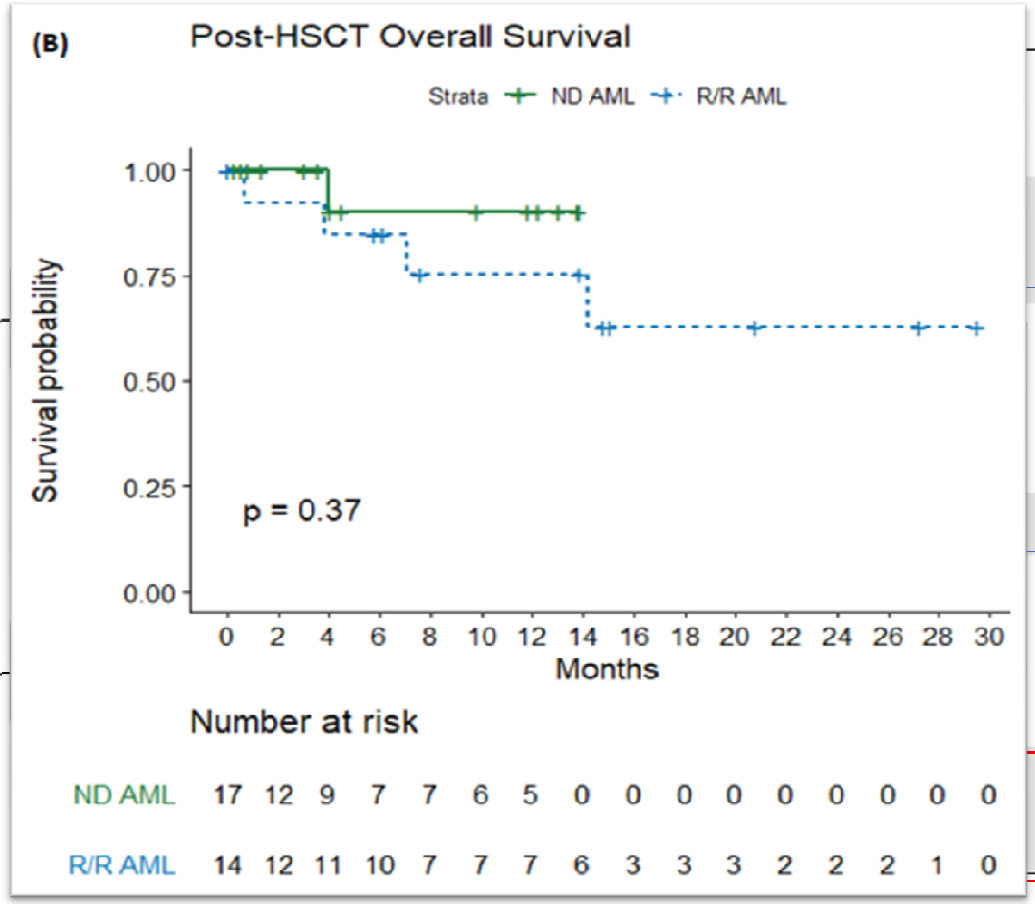
Dr Sushil S
CMC, Vellore

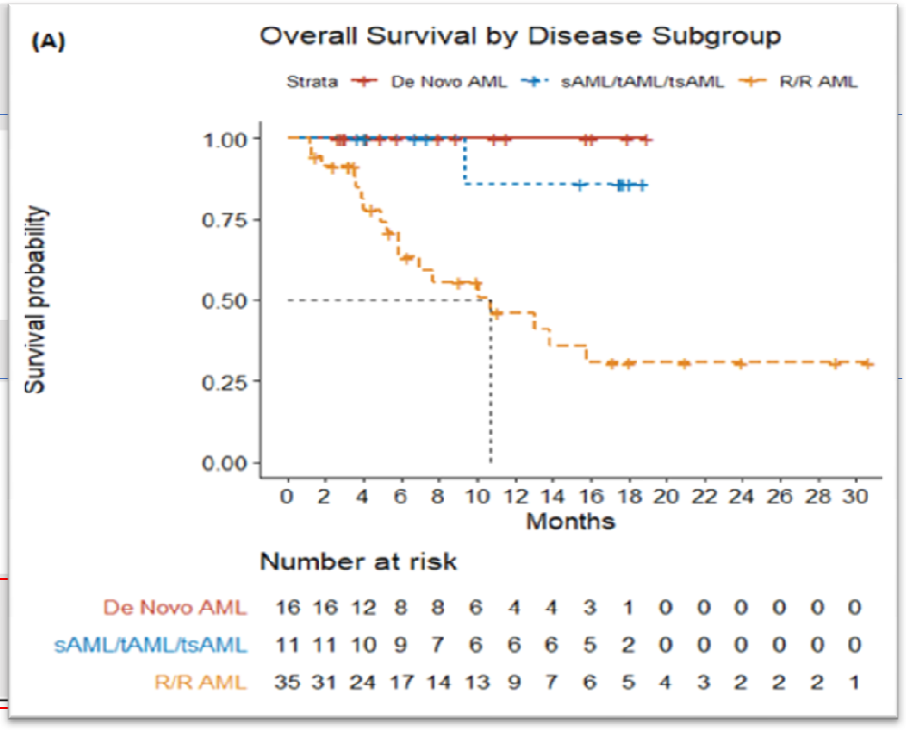
A Phase Ib/II Study of the BCL-2 Inhibitor Venetoclax in Combination with Standard Intensive AML Induction/Consolidation Therapy with FLAG-IDA in Patients with Newly Diagnosed or Relapsed/Refractory AML

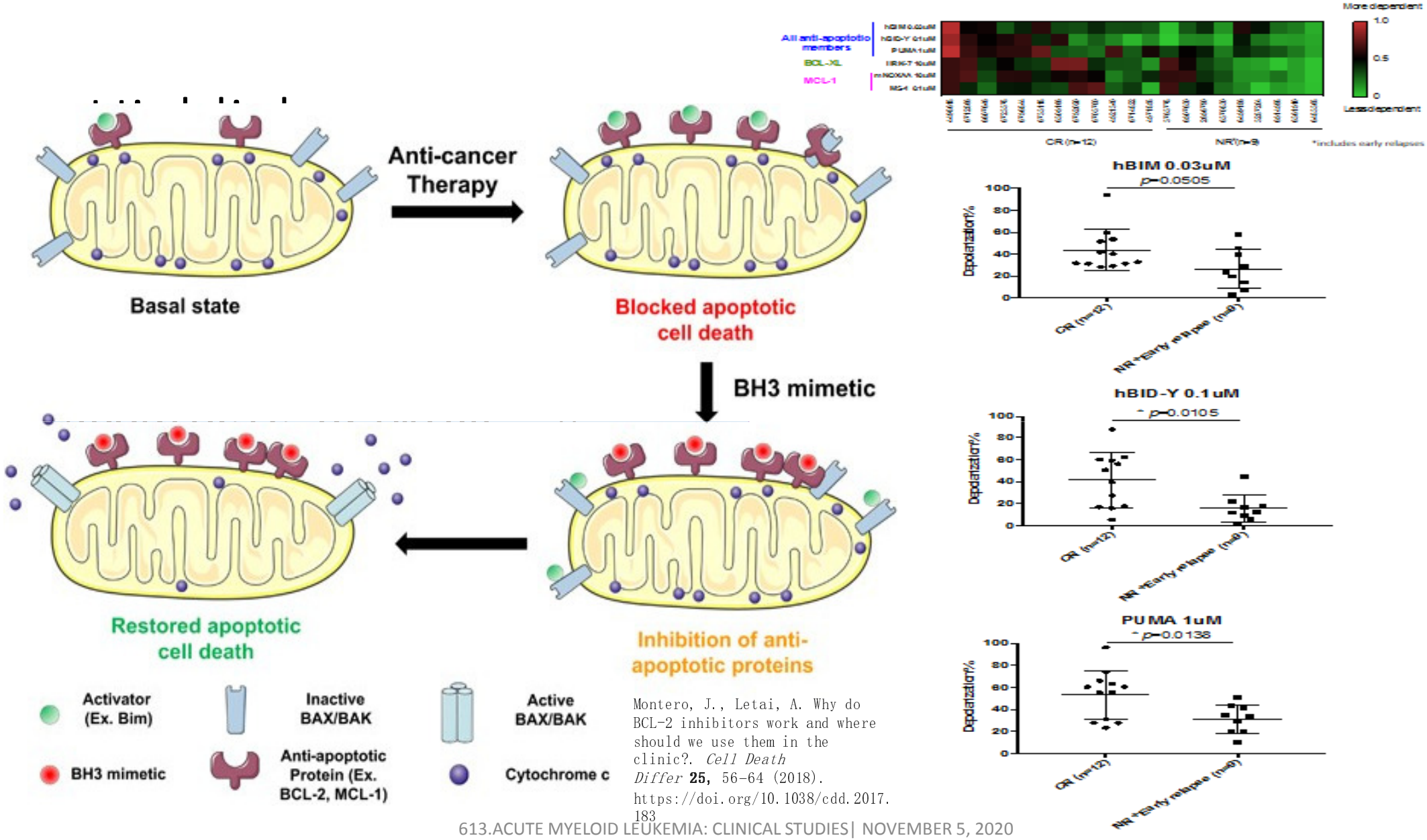
Iman Aboudalle, MD, Marina Y Konopleva, MD PhD, Tapan M. Kadia, MD, Kiran Naqvi, MDMPH, Kenneth Vaughan, RN, Mehmet Kurt, RN, Antonio Cavazos, Sherry A. Pierce, BSN, BA, Koichi Takahashi, MD, Lucia Masarova, MD, Musa E. Yilmaz, MD, Elias Jabbour, MD, Guillermo Garcia-Manero, MD, Steven M. Kornblau, MD, Farhad Ravandi, MD, Jorge Cortes, MD, Hagop M. Kantarjian, MD, Courtney D. DiNardo, MD MSc

40 patients screened
6 patients not treated

Phase Ib (R/R AML; N=16) | **Phase 2A (ND AML; N=27)** | **Phase 2B (R/R AML; N=19)**



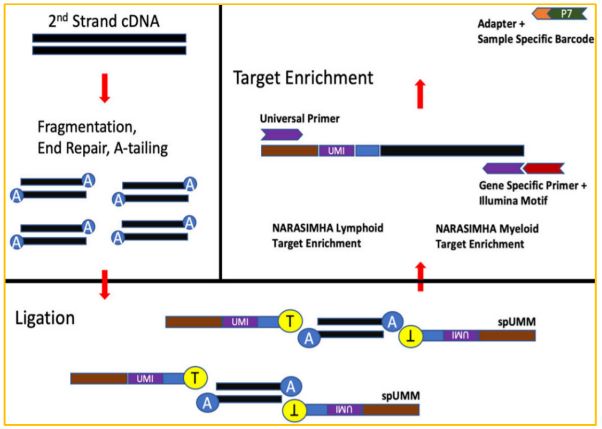




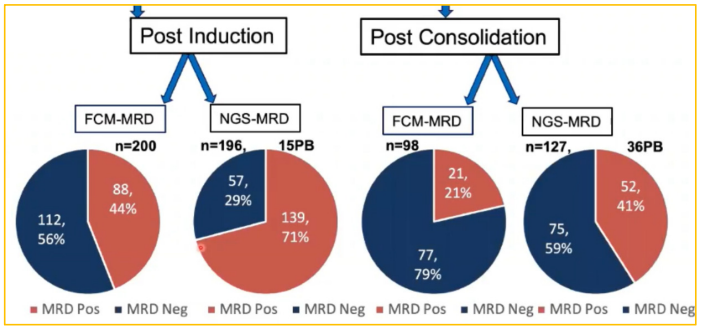
Montero, J., Letai, A. Why do BCL-2 inhibitors work and where should we use them in the clinic?. *Cell Death Differ* **25,** 56-64 (2018). https://doi.org/10.1038/cdd.2017.183

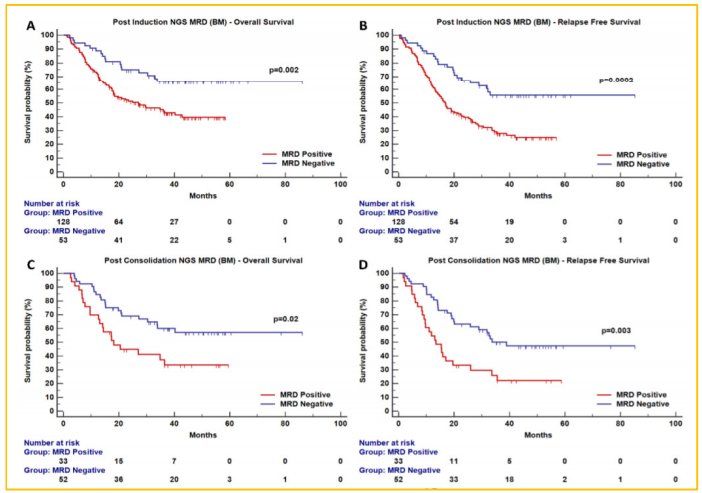
ASH 2020: Abstract 361: Molecular Measurable Residual Disease Detection in Acute Myeloid Leukemia Using Error Corrected Next Generation Sequencing

- FCM-MRD for AML suffers from low sensitivity as compared to B-ALL.
- Clinical utility of error corrected NGS-MRD in AML using single molecule molecular inversion probes (smMIPS).

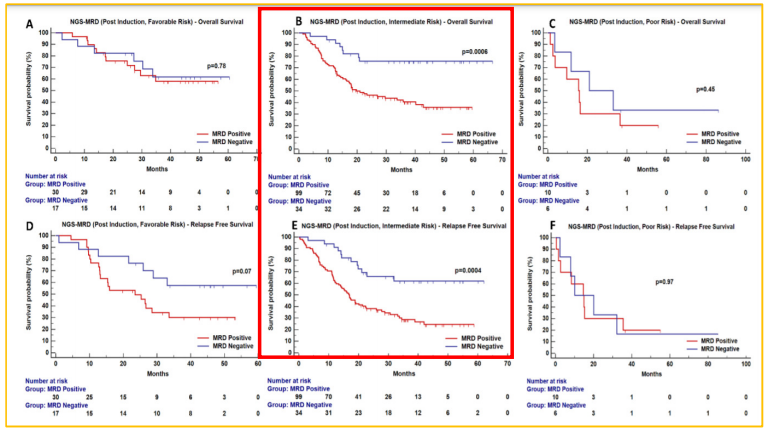


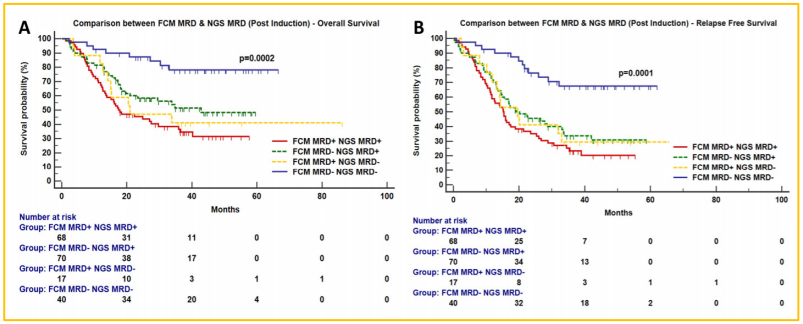
LOD: 0.05% (SNV); 0.03%(INDELS); 0.002% (ITDs)





Genes most informative:
NPM1, FLT3, NRAS, KIT, IDH1, IDH2, WT1, RUNX1, GATA2, KRAS, U2AF1, PHF6, JAK2, PTPN11, RAD21, TET2





- Advantages v/s Disadvantages of smMIPS
  - Sensitivity in the clinic for most mutations is close to 0.1% VAF.
  - Higher sensitivity →complex indels such as *NPM1* and *FLT3*-ITD
- Comparability to FCM-MRD, advantage in certain situations
- Lack of comparison with real time PCR for *RUNX1-RUNX1T1*.
  - Increases the applicability of approach to >90% of AML patients
- Demonstrate that panel-based error corrected NGS-MRD is clinically relevant and synergistic in application to FCM based AML MRD monitoring.

ASH 2020 Abstract No. 1911

Distinct Clinical and Genetic Factors Predict Early Versus Late Mortality in AML Patients Undergoing Induction Chemotherapy

Long-term survival after intensive induction chemotherapy in acute myeloid leukemia (AML) is limited by both early mortality and disease resistance. A central clinical challenge is predicting which patients will experience early toxicity during induction or resistant disease.

Methods:

Retrospective cohort of ND AML (2014-2019)
N=290

Inclusion: consecutive adult patients treated with standard induction chemotherapy ("7+3" or CPX-351)

Clinical / pathology/ laboratory / Clinical data
Gene mutations by targeted NGS

Statistics:
For early mortality: multivariable logistic regression model
For OS: multivariable model with allogeneic SCT as a time-varying covariate

Median age = 61 years (range 19-76)
De novo – 71% (Sy AML – 15%; therapy related – 14%)

Results:

Survival landmarked at 60 days (median FU 26m)
Median OS – 33.9 m
Median EFS – 28 .0 months

Death within 60 days – 8%
Common cause of death: shock , respiratory failure

Factor a/w 60 day mortality:

- pretreatment albumin < 3 mg/dL,
- pretreatment LDH >= 600 U/L, and
- mutations in TET2 or RUNX1

Factors a/w inferior OS

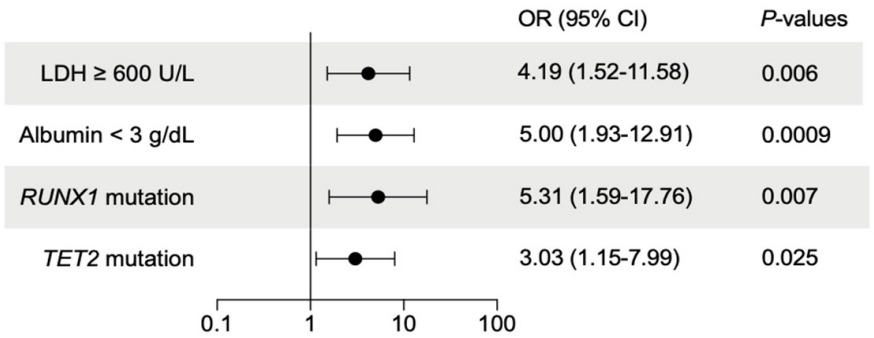
- age >= 60, secondary AML,
- pretreatment LDH >= 600 U/L, *TP53* mutation, *U2AF1* mutation, or 11q23 rearrangement

multivariable models for failure to achieve remission by day 60 & for RFS landmarked at day 60 – were applied to the OS model, All variables remained significant, indicating that disease resistance is a main driver of OS after 60 days.

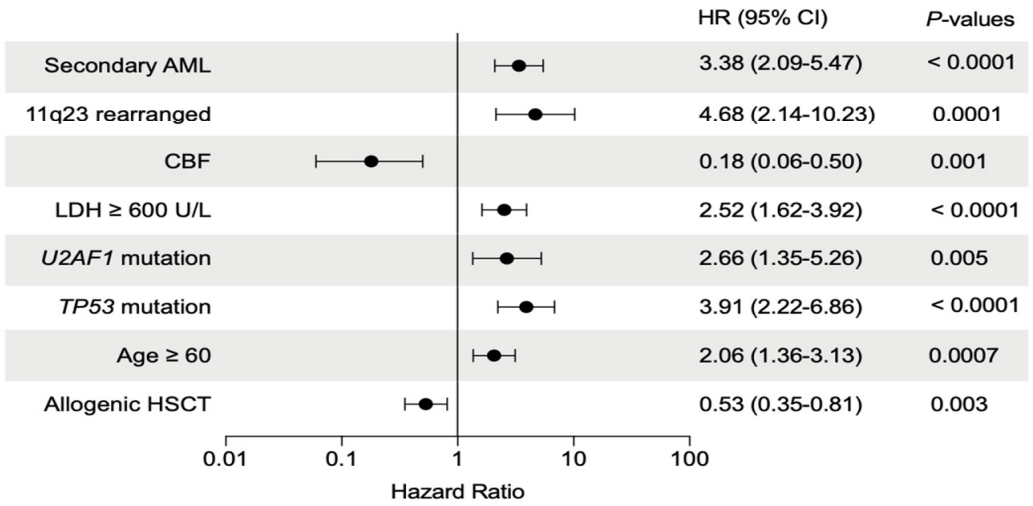
A **Table.** Characteristics of Early Mortality Patients (n = 24).

Age, years	
Median (range)	62 (27-76)
≥ 60	58.3%
Sex	
Female	58.3%
Male	41.7%
Cause of death	
Shock	41.7%
Respiratory failure	20.8%
Stroke	16.7%
Renal failure	12.5%
Unknown	8.3%
Baseline laboratories	
LDH ≥ 600 U/L	50.0%
Albumin < 3 g/dL	45.8%
Creatinine ≥ 1.5 mg/dL	20.8%
Total bilirubin ≥ 1.3 mg/dL	16.7%
Clinical course	
ICU admission	75.0%
Hypoxia	66.7%
Renal replacement therapy	33.3%
Stroke	25.0%
Cardiac event	8.3%
Clinical ontogeny	
Therapy-related	12.5%
Secondary	20.8%
De novo	66.7%
Karyotype	
Complex	20.8%
11q23 rearranged	8.3%
CBF	8.3%
Gene mutations	
TET2	37.5%
FLT3	25.0%
RUNX1	25.0%
NPM1	16.7%
TP53	8.3%

B Multivariate Analysis of Early Mortality



C Multivariate Analysis of Overall Survival



Conclsuion: Overall, we show that early and late outcomes in AML are associated with distinct sets of pretreatment clinical, genetic, and laboratory characteristics and for the first time show that disease-specific mutations are associated specifically with induction toxicity.

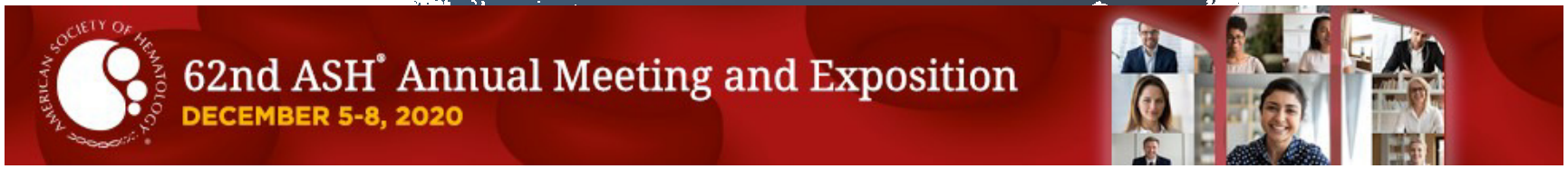
Myelodysplatic Syndromes

Lead:

Biju / Sharat

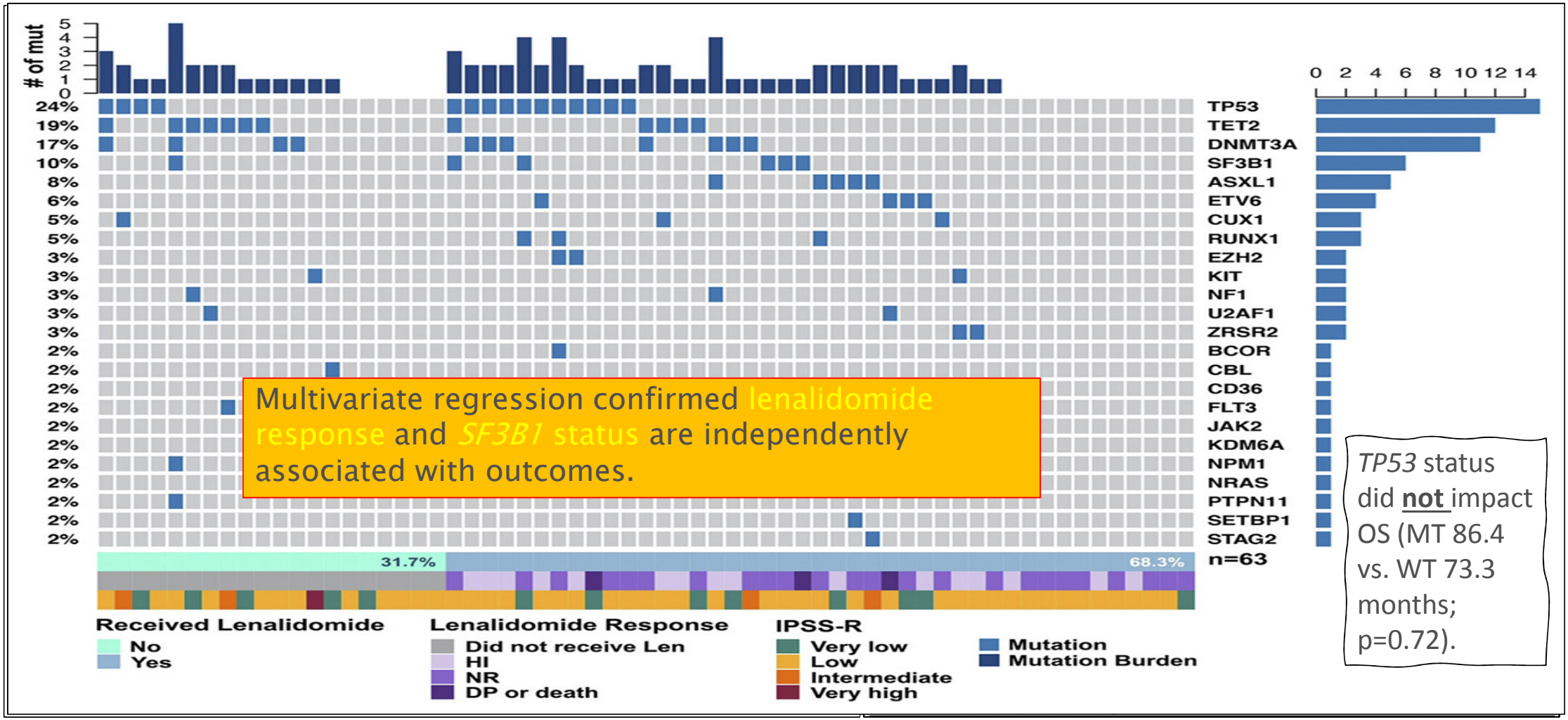
MDS ABSTRACTS ASH 2020

HCC webinar



SF3B1 Mutations and Not *TP53* Are Associated with Poor Outcomes in Patients with Del(5q) Myelodysplastic Syndromes (MDS)

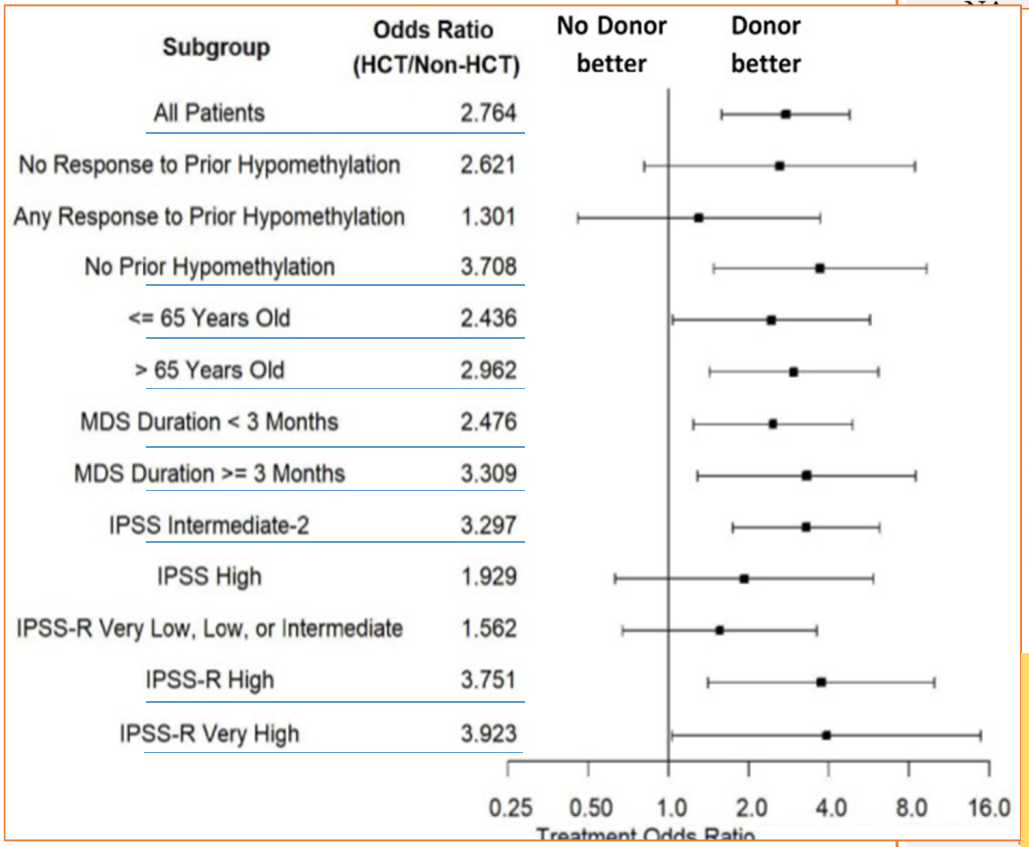
Onyee Chan, MD, Najla Al Ali, MD, David A. Sallman, MD, Eric Padron, MD, Jeffrey E. Lancet, MD, Rami Komrokji, MD

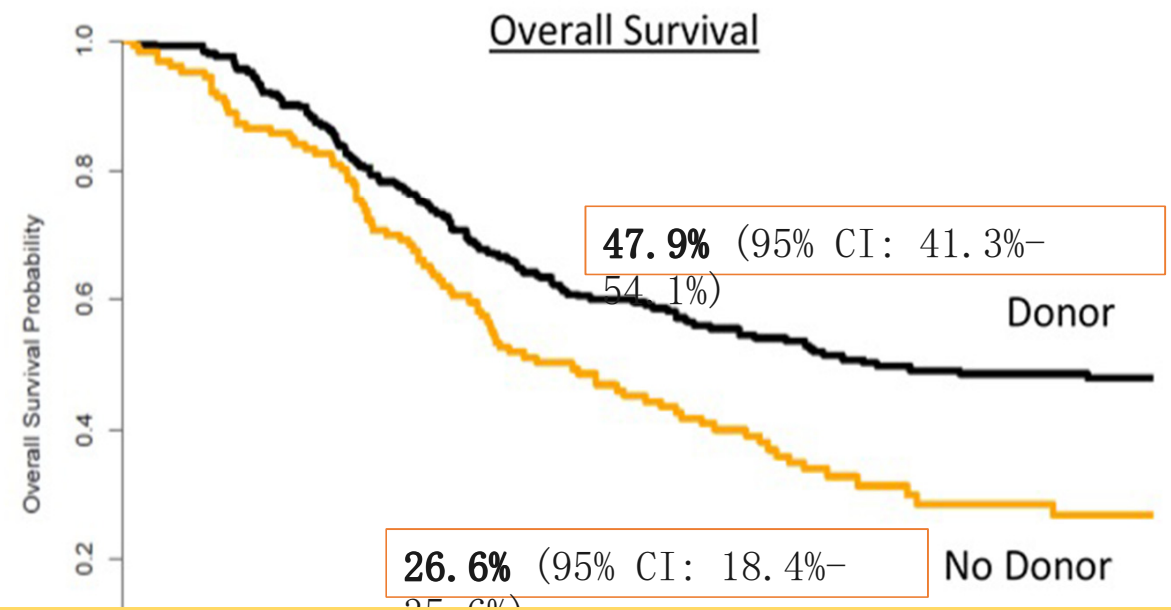


A Multi-Center Biologic Assignment Trial Comparing Hematopoietic Cell Transplantation to Hypomethylati Care in Patients Aged 50-75 with Advanced Myelody Marrow Transplant Clinical Trials Netv

Ryotaro Nakamura, MD, Wael Saber, MD MS, Michael J Martens, PhD, Alyssa Ramirez, Ba
Roni Tamari, MD, Asmita Mishra, MD, Richard T. Maziarz, MD, Joseph P. McGuirk, DO, Pet
Mrinal M. Patnaik, MDMBBS, Rammurti Kamble, MD, Stephen J. Forman, MD, Mikk
Adam M. Mendizabal, MS, Brent Logan, PhD, Mary M. Horowitz, MD MS

	Donor Arm (N=260) N (%)	No Donor Arm (N=124) N (%)	Total (N=384) N (%)
Age (years)			
Mean (SD)	65.6 (5.6)	66.0 (5.9)	65.7 (5.7)
Median (Range)	66.3 (50.1, 75.3)	67.3 (50.7, 75.1)	66.7 (50.1, 75.3)
65 or Older	155 (59.6%)	80 (64.5%)	235 (61.2%)
Gender			
Female	95 (36.5%)	48 (38.7%)	143 (37.2%)
Male	165 (63.5%)	76 (61.3%)	241 (62.8%)
Ethnicity			
Hispanic or Latino	11 (4.2%)	9 (7.3%)	20 (5.2%)
Not Hispanic or Latino	233 (89.6%)	108 (87.1%)	341 (88.8%)
Unknown	9 (3.5%)	7 (5.6%)	16 (4.2%)





Also in the as-treated analysis, comparison of the HCT and No HCT arms demonstrated a *significant advantage in 3-year OS (47.4% vs. 16.0%, p<0.0001) and LFS (39.3% vs. 10.9%, p<0.0001)* for subjects who underwent HCT.

1289 Initial Results of a Phase I/II Study of Venetoclax in Combination with Azacitidine in Treatment-Naive and Relapsed/Refractory High-Risk Myelodysplastic Syndrome (MDS) or Chronic Myelomonocytic Leukemia (CMML)

Kiyomi Morita, MD, PhD, Kiran Naqvi, MD, MPH, Guillermo Montalban Bravo, MD, Philip A. Thompson, MB, MS, Koichi Takahashi, MD, PhD, Yesid Alvarado, MD, Elias Jabbour, MD, Hagop M. Kantarjian, MD and Guillermo Garcia-Manero, MD

Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

n=9 AZA 75 mg/m^2 x 5 Ven 100 mg/200mg/400 mg from D 1-7	ORR	Marrow CR	Early death
TN (no TP53 mutation)	100%	100%	0
R R (TP 53 mutation =2)	75%	75%	0

Primary end point- maximum tolerated dose and dose limited toxicity of Ven +Aza ;
ORR as assesssed by IWG 2006 criteria

Table 1

Characteristics	Patients (all, N=9) N (%) / median (range)	treatment-naive (N=5) N (%) / median (range)	R/R (N=4) N (%) / median (range)
Age, years	66 (59-83)	66 (60-83)	67 (59-73)
Gender (Male)	8 (89)	5 (100)	3 (75)
ECOG performance status			
≥2	2 (22)	1 (20)	1 (25)
Prior Treatment			
untreated	5 (56)	5 (100)	0
relapsed/refractory	4 (44)	0	4 (100)
Diagnosis			
MDS	6 (67)	4 (80)	2 (50)
CMML	3 (33)	1 (20)	2 (50)
IPSS			
INT-2	7 (78)	4 (80)	3 (75)
High	2 (22)	1 (20)	1 (25)
BM blast (%)	12 (7-19)	12 (8-19)	14 (7-19)
Karyotype			
normal			
complex			
TP53			
mutated			
Venetoclax			
100mg			
200mg			
400mg			
Best respo			
Overall re			
marrow C			
Stable Di			
Eearly dea			

Figure 2

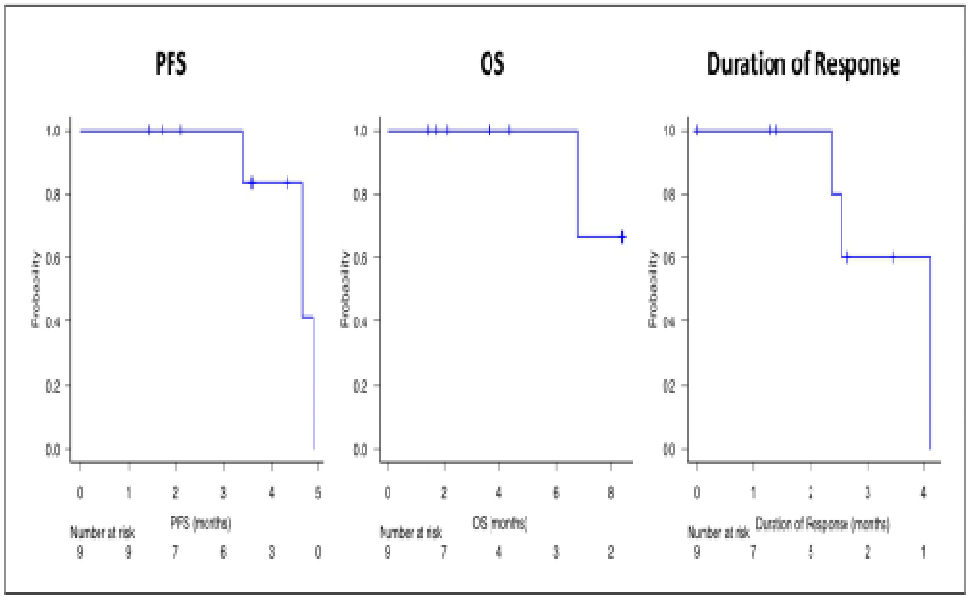


Figure 1

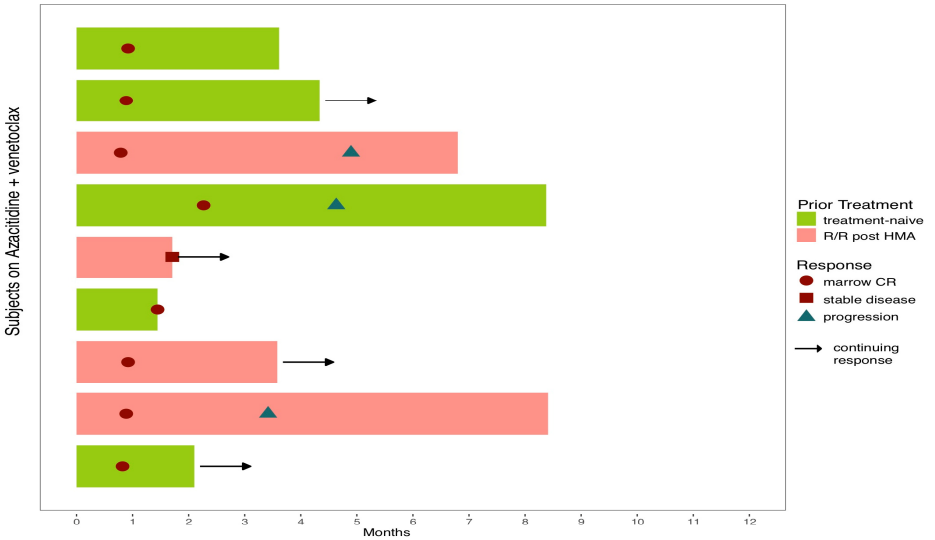
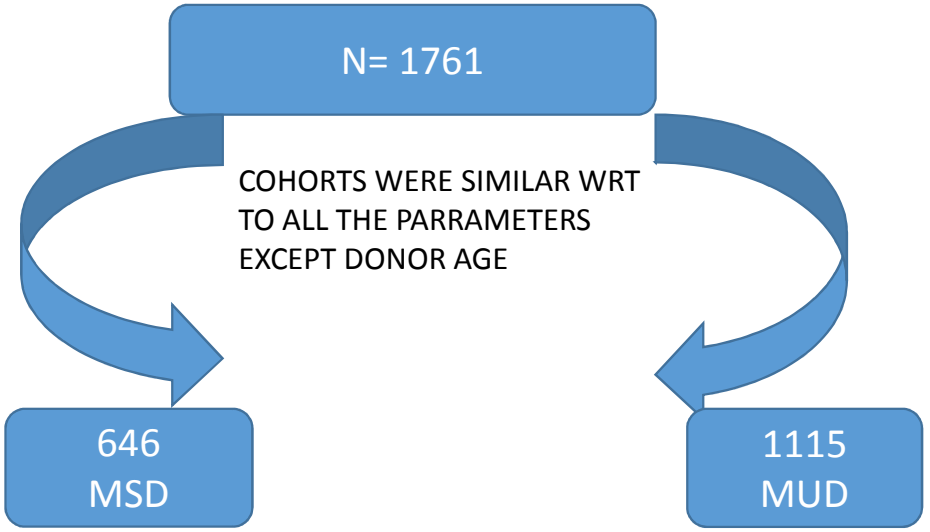


Table 2

Adverse Events	Grade 1-2	Grade 3	Grade 4	Grade 5	Overall
Anemia	0	1 (11%)	0	0	1 (11%)
Neutropenia	0	1 (11%)	3 (33%)	0	4 (44%)
Thrombocytopenia	0	0	3 (33%)	0	3 (33%)
Arthralgia	2 (22%)	0	0	0	2 (22%)
Bone pain	2 (22%)	0	0	0	2 (22%)
Constipation	2 (22%)	0	0	0	2 (22%)
Headache	1 (11%)	0	0	0	1 (11%)
Insomnia	1 (11%)	0	0	0	1 (11%)
Nausea/vomiting	1 (11%)	0		0	1 (11%)

3345 Younger HLA-Matched Unrelated Donor Allogeneic Hematopoietic Cell Transplantation (allo-HCT) for Myelodysplastic Syndromes (MDS) Is Associated with Superior Disease-Free Survival Compared to Older HLA-Identical Sibling Donors: CIBMTR Analysis

Guru Subramanian Guru Murthy, MD1*, Soyoung Kim2,3*, Zhen-Huan Hu, MPH4*, Noel Estrada-Merly, MS5*, Ryotaro Nakamura, M.D.6, Betul Oran, MD, MS7, Bart L. Scott, MD8, Ronald Sobecks, MD9 and Wael Saber, MD, MS10



There was a significant difference in DFS (p=0.01) but not OS (p=0.14) among donor groups.
Compared to MUD ≤35 years, DFS was inferior in HLA identical sibling donor age ≥60 but not in HLA-identical sibling donor age 50-59
risk of relapse was significantly higher in patients receiving allo-HCT from HLA-identical sibling donor compared to MUD≤35
HLA-identical sibling donor cohort was associated with lower risk of acute GVHD (p<0.001) and chronic GVHD (overall p=0.007) as compared to MUD ≤35 cohort

Table 1: Multivariate analysis of outcomes

Variable			95% CI	95% CI	
1. Overall survival	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**
Main group					
MUD (donor age 18-35)	1111	1.000			0.1471
HLA-identical sibling (donor age 50-59)	268	1.077	0.897	1.294	0.4277
HLA-identical sibling (donor age >=60)	375	1.169	0.997	1.371	0.0539
2. Disease Free Survival					
Main group					
MUD (donor age 18-35)	1110	1.000			0.0119
HLA-identical sibling (donor age 50-59)	268	1.097	0.888	1.356	0.3913
HLA-identical sibling (donor age >=60)	375	1.231	1.074	1.411	0.0029
3. Non-Relapse Mortality (Fine-Gray)					
Main group					
MUD (donor age 18-35)	1110	1.000			0.0760
HLA-identical sibling (donor age 50-59)	268	0.711	0.511	0.989	0.0428
HLA-identical sibling (donor age >=60)	375	0.795	0.604	1.046	0.1017
4. Relapse (Fine-Gray)					
Main group					
MUD (donor age 18-35)	1109	1.000			<.0001
HLA-identical sibling (donor age 50-59)	268	1.536	1.163	2.028	0.0025
HLA-identical sibling (donor age >=60)	375	1.680	1.377	2.050	<.0001
5. Chronic GVHD					
Main group					
MUD (donor age 18-35)	1104	1.000			0.0070
HLA-identical sibling (donor age 50-59)	266	0.860	0.698	1.059	0.1544
HLA-identical sibling (donor age >=60)	372	0.721	0.589	0.884	0.0017
6. Acute GVHD (grade 2-4)					
Main group (<= 2 mon)					
MUD (donor age 18-35)	1102	1.000			<.0001
HLA-identical sibling (donor age 50-59)	265	0.540	0.402	0.724	<.0001
HLA-identical sibling (donor age >=60)	369	0.507	0.405	0.635	<.0001
Main group (> 2 mon)					
MUD (donor age 18-35)	649	1.000			0.5274
HLA-identical sibling (donor age 50-59)	194	1.189	0.864	1.636	0.2873
HLA-identical sibling (donor age >=60)	276	1.114	0.809	1.533	0.5080

Figure 1A: Disease free survival by donor type and age

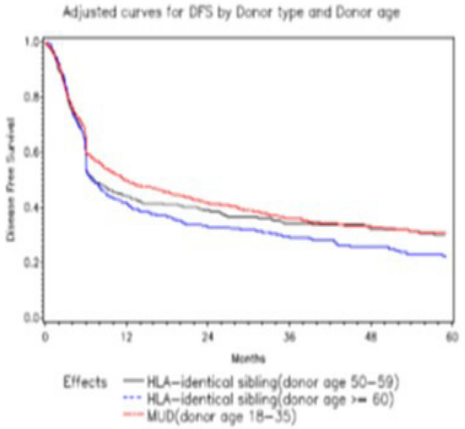
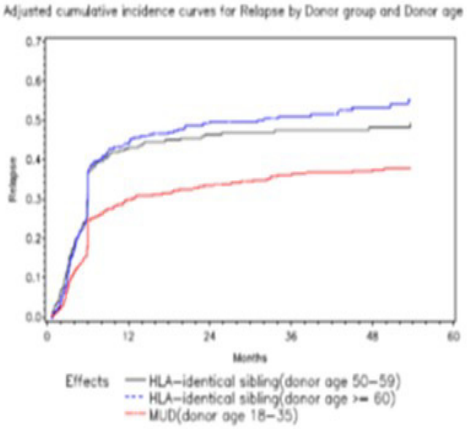
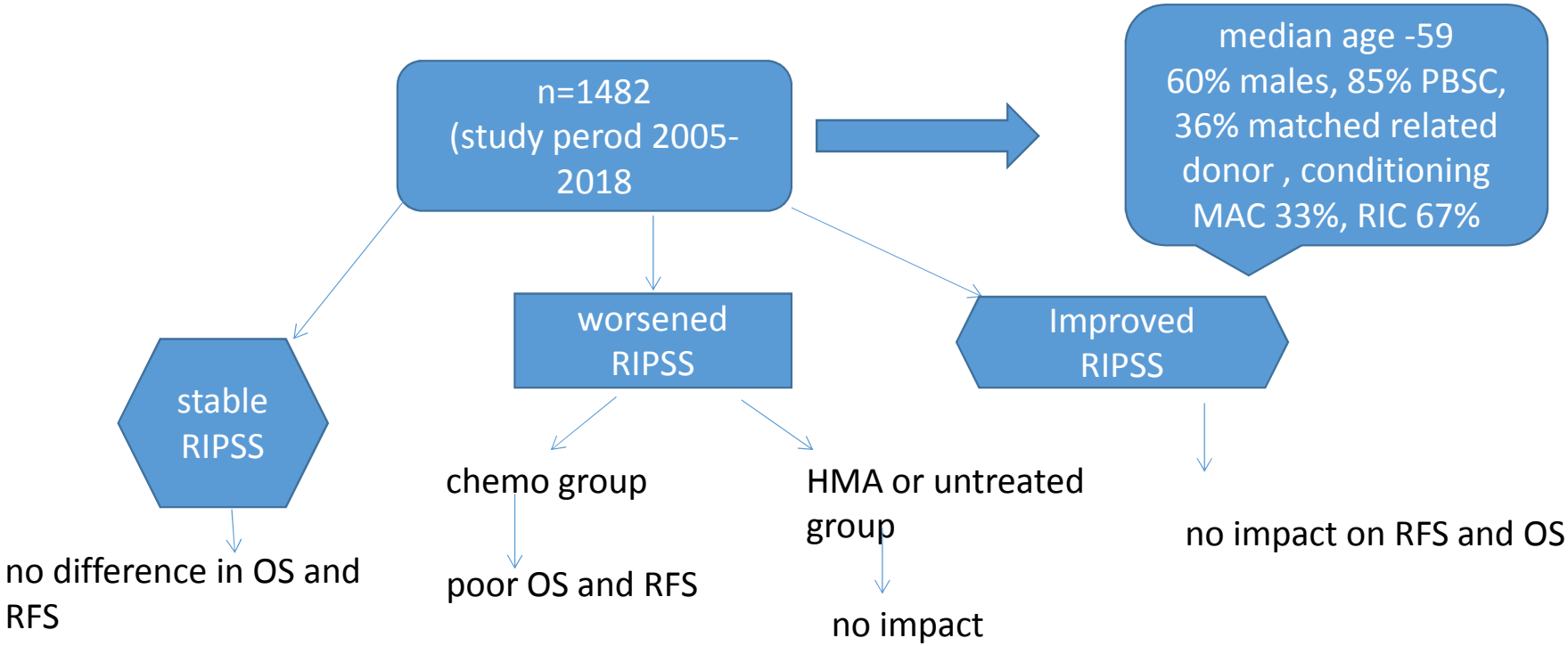


Figure 1B: Cumulative incidence of relapse by donor type and age



2438 Does a Change in IPSS-R between Diagnosis and Transplant Have an Impact on Transplant Outcome in Patients with MDS? a Retrospective Analysis from the EBMT Chronic Malignancies Working Party

Christof Scheid, MD1, Dirk-Jan Eikema2*, Riitta Niittyvuopio3*, Johan Maertens4*, Jakob Passweg5*, Didier Blaise, MD6, Jennifer Byrne, FRCP, FRCPath, PhD7*, Nicolaus Kröger8*, Martin Bornhäuser, MD9*, Patrice Chevallier, MD, PhD10, Jean-Henri Bourhis11*, Jan J. Cornelissen, MD, PhD12, Henrik Sengeloev13*, J ürgen Finke Sr., MD, PhD14, John A Snowden, Urs Schanz, MD18, Amit Patel, PhD19*, Linda Koster2*, Liesbeth C. de Wreede, PhD20*, Patrick J Hayden, MD21,Francesco Onida, MD22, Marie Robin23* and Ibrahim Yakoub-Agha24



- **A change in IPSS-R was noted in 77.5% of patients with prior chemotherapy, 72% with prior HMA and 59.8% of untreated patients.**

- **Negative prognostic impact in chemotherapy-treated patients-**
  - **a) worsening of IPSS-R,**
  - **b) blast count**
  - **c) cytogenetic score**

- **Significant negative factors in HMA-treated or untreated patients -**
  - **a)worsened blast count**
  - **b) cytogenetics**
- **No positive effect of improved IPSS-R, decreased blasts or improved cytogenetics in any of the subgroups of treated or untreated patients**

1462 Reduced Intensity Conditioning for Allogeneic Hematopoietic Stem Cell Transplantation of AML in CR and MDS—a Systematic Review and Meta-Analysis of Randomized Controlled Trials

Yanzhi Song, MD[1], Zhichao Yin[2*], Erhui Yuan[1*], Yajing Wang[1*] and Tong Wu, MD[1]*
[1]*Department of Bone Marrow Transplantation, Beijing Boren Hospital, Beijing, China*
[2]*Department of Hematology, Beijing Boren Hospital, Beijing, China*

- Reduced intensity conditioning (RIC) regimens can reduce NRM but increase relapse incidence (RI) and as a result of it, has the similar overall survival (OS) to the MAC regimen according to the results of published clinical trials.
- To clarify whether RIC is as effective as MAC but safer than it for AML in CR and MDS, a systematic review was done.

- Two reviewers independently comprehensively searched the related databases and websites and hand searched the reference lists. They also independently screened and evaluated the retrieved studies and then extracted data of included studies with the Cochrane Collaboration recommended tools.
- Only randomized controlled trials (RCTs) were included.

Figure 1. Flow diagram of screening studies for inclusion in systematic review

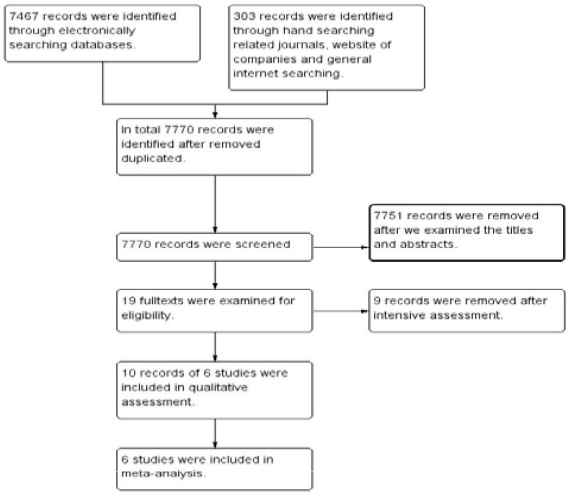


Figure 2. Overall survival (OS) outcome

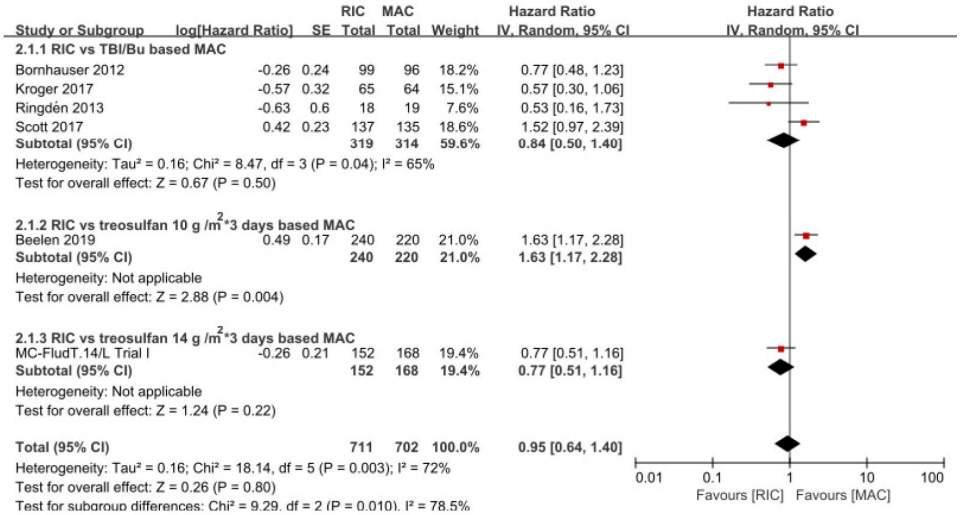


Figure 3. relapse incidence (RI) outcome

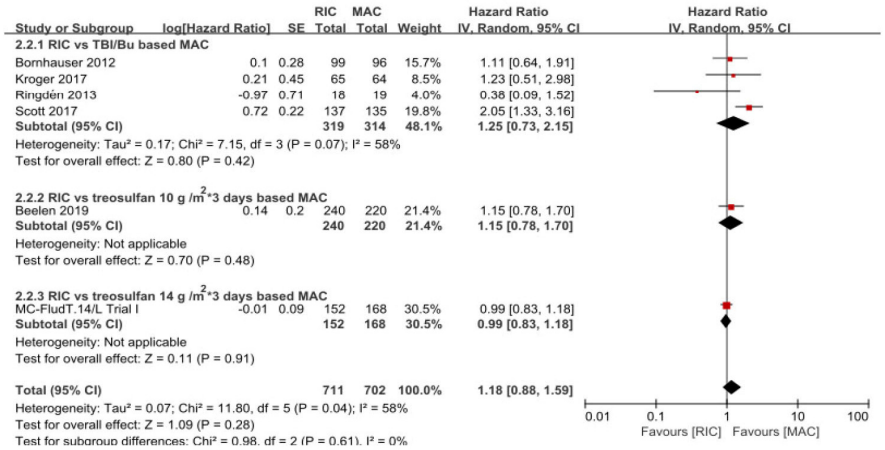
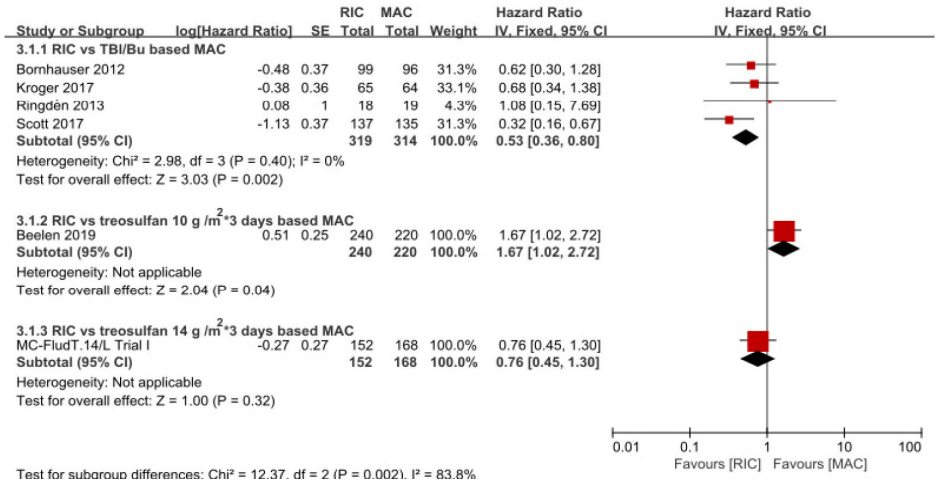


Figure 4. non-relapse mortality (NRM) outcome



- RIC had a trend to reduce the incidence of aGVHD compared to TBI/Bu based MAC (HR=0·79, P=0·08) and III–IV aGVHD (HR=0·61, P=0·07).
- RIC didn't show significant difference to treosulfan based MAC regimen on the two outcomes.
- The cGVHD was similar between RIC and MAC (P=0·96), results of included results had significant heterogeneity and random effects model was used.
- Graft failure was rare in both RIC (2·6%) and MAC (1·1%) arms.

Conclusions

- For AML in CR and MDS patients, RIC has similar OS, LFS and RI compared to MAC regimens.
- RIC regimens has less NRM compared to TBI/Bu based MAC but not treosulfan based regimens.
- Treosulfan based MAC has a promising result in one RCT with less NRM than even RIC.
- RIC had trend to reduce the incidence of aGVHD and grade III-IV a GVHD compared to TBI/Bu based MAC but not treosulfan regimens with cGVHD rates being similar.

2198 The COMMANDS Trial: A Phase 3 Study of the Efficacy and Safety of Luspatercept Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low-, Low-, or Intermediate-Risk MDS in Erythropoiesis Stimulating Agent-Naive Patients Who Require RBC Transfusions

Matteo Della Porta[1,2*], *Uwe Platzbecker, MD*[3], *Valeria Santini*[4], *Guillermo Garcia-Manero, MD*[5], *Rami S. Komrokji, MD*[6], *Rodrigo Ito*[7*] *and Pierre Fenaux, MD, PhD*[8]

[1]*Cancer Center IRCCS Humanitas Research Hospital, Milan, Italy*
[2]*Department of Biomedical Sciences, Humanitas University, Milan, Italy*
[3]*Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany*
[4]*Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy*
[5]*Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX*
[6]*Moffitt Cancer Center, Tampa, FL*
[7]*Bristol Myers Squibb, Princeton, NJ*
[8]*Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France*

- Erythropoiesis-stimulating agents (ESAs) remain a standard of care among patients with lower-risk MDS (LR-MDS) defined by International Prognostic Scoring System-Revised (IPSS-R) as Very Low-, Low-, or Intermediate-risk MDS, and endogenous serum erythropoietin (sEPO) levels ≤ 500 U/L.
- Recent studies of epoetin alfa and darbepoetin alfa have demonstrated efficacy among patients with LR-MDS, but the patient population in whom a clinically significant effect is seen may be limited (Fenaux P, et al. *Leukemia* 2018;32:2648-2658; Platzbecker U, et al. *Leukemia*2017;31:1944-1950).
- Luspatercept is a first-in-class erythroid maturation agent with a mechanism of action distinct from ESAs (Suragani RNVS, et al. *Nat Med* 2014;20:408-414).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

ABSTRACT

BACKGROUND

Patients with anemia and lower-risk myelodysplastic syndromes in whom erythropoiesis-stimulating agent therapy is not effective generally become dependent on red-cell transfusions. Luspatercept, a recombinant fusion protein that binds transforming growth factor β superfamily ligands to reduce SMAD2 and SMAD3 signaling, showed promising results in a phase 2 study.

METHODS

In a double-blind, placebo-controlled, phase 3 trial, we randomly assigned patients with very-low-risk, low-risk, or intermediate-risk myelodysplastic syndromes (defined according to the Revised International Prognostic Scoring System) with ring sideroblasts who had been receiving regular red-cell transfusions to receive either luspatercept (at a dose of 1.0 up to 1.75 mg per kilogram of body weight) or placebo, administered subcutaneously every 3 weeks. The primary end point was transfusion independence for 8 weeks or longer during weeks 1 through 24, and the key secondary end point was transfusion independence for 12 weeks or longer, assessed during both weeks 1 through 24 and weeks 1 through 48.

RESULTS

Of the 229 patients enrolled, 153 were randomly assigned to receive luspatercept and 76 to receive placebo; the baseline characteristics of the patients were balanced. Transfusion independence for 8 weeks or longer was observed in 38% of the patients in the luspatercept group, as compared with 13% of those in the placebo group (P<0.001). A higher percentage of patients in the luspatercept group than in the placebo group met the key secondary end point (28% vs. 8% for weeks 1 through 24, and 33% vs. 12% for weeks 1 through 48; P<0.001 for both comparisons). The most common luspatercept-associated adverse events (of any grade) included fatigue, diarrhea, asthenia, nausea, and dizziness. The incidence of adverse events decreased over time.

CONCLUSIONS

Luspatercept reduced the severity of anemia in patients with lower-risk myelodysplastic syndromes with ring sideroblasts who had been receiving regular red-cell transfusions and who had disease that was refractory to or unlikely to respond to erythropoiesis-stimulating agents or who had discontinued such agents owing to an adverse event. (Funded by Celgene and Acceleron Pharma; MEDALIST ClinicalTrials.gov number, NCT02631070; EudraCT number, 2015-003454-41.)

Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

Uwe Platzbecker, Ulrich Germing*, Katharina S Götze*, Philipp Kiewe*, Karin Mayer*, Jörg Chromik*, Markus Radsak*, Thomas Wolff*, Xiaosha Zhang, Abderrahmane Laadem, Matthew L Sherman, Kenneth M Attie, Aristoteles Giagounidis**

Summary

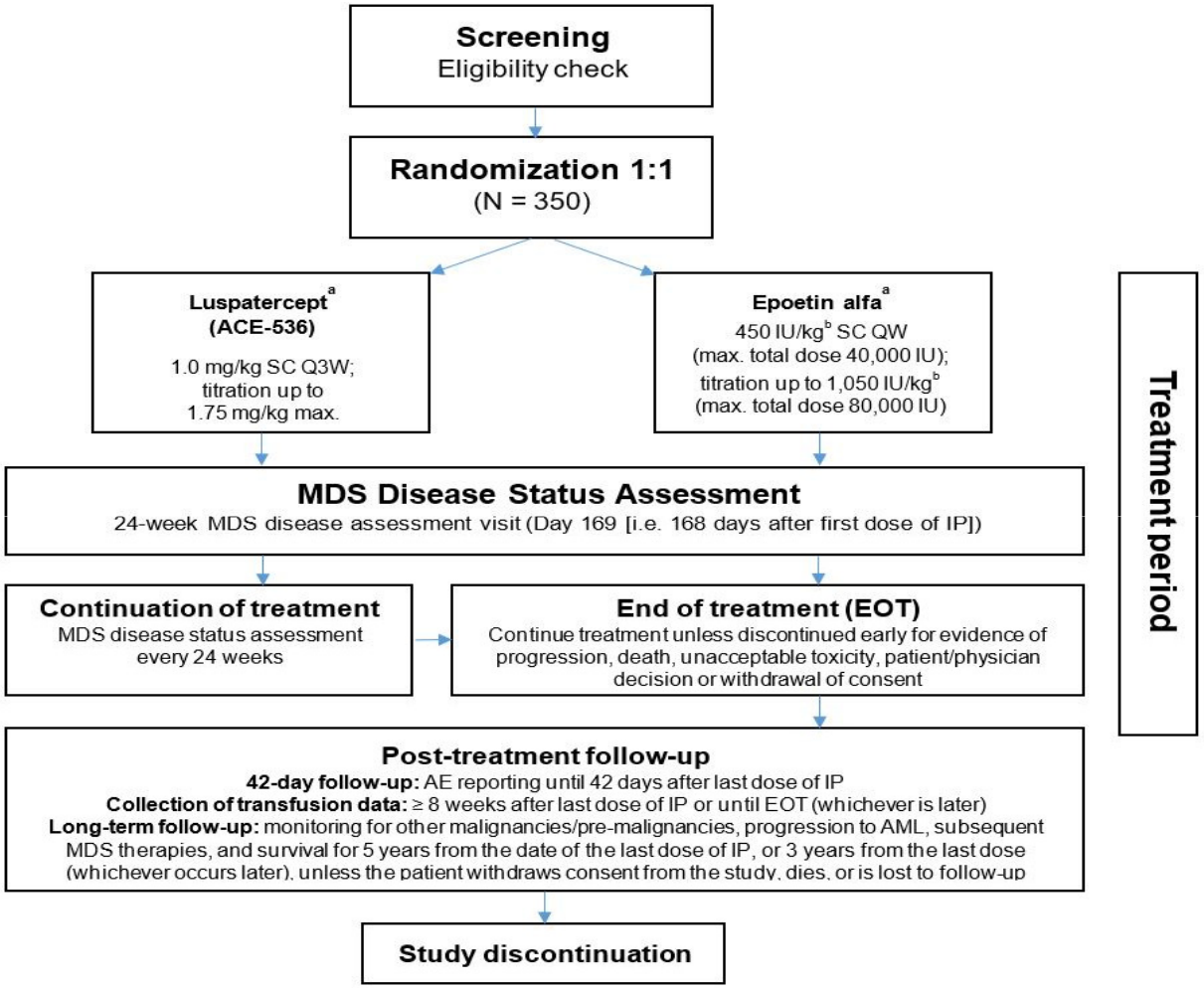
Background Myelodysplastic syndromes are characterised by ineffective erythropoiesis. Luspatercept (ACE-536) is a novel fusion protein that blocks transforming growth factor beta (TGF β) superfamily inhibitors of erythropoiesis, giving rise to a promising new investigative therapy. We aimed to assess the safety and efficacy of luspatercept in patients with anaemia due to lower-risk myelodysplastic syndromes.

Methods In this phase 2, multicentre, open-label, dose-finding study (PACE-MDS), with long-term extension, eligible patients were aged 18 years or older, had International Prognostic Scoring System-defined low or intermediate 1 risk myelodysplastic syndromes or non-proliferative chronic myelomonocytic leukaemia (white blood cell count <13 000/μL), and had anaemia with or without red blood cell transfusion support. Enrolled patients were classified as having low transfusion burden, defined as requiring less than 4 red blood cell units in the 8 weeks before treatment (and baseline haemoglobin <10 g/dL), or high transfusion burden, defined as requiring 4 or more red blood cell units in the 8 weeks before treatment. Patients received luspatercept subcutaneously once every 21 days at dose concentrations ranging from 0·125 mg/kg to 1·75 mg/kg bodyweight for five doses (over a maximum of 12 weeks). Patients in the expansion cohort were treated with 1·0 mg/kg luspatercept; dose titration up to 1·75 mg/kg was allowed, and patients could be treated with luspatercept for a maximum of 5 years. Patients in the base study were assessed for response and safety after 12 weeks in order to be considered for enrolment into the extension study. The primary endpoint was the proportion of patients achieving modified International Working Group-defined haematological improvement–erythroid (HI-E), defined as a haemoglobin concentration increase of 1·5 g/dL or higher from baseline for 14 days or longer in low transfusion burden patients, and a reduction in red blood cell transfusion of 4 or more red blood cell units or a 50% or higher reduction in red blood cell units over 8 weeks versus pre-treatment transfusion burden in high transfusion burden patients. Patient data were subcategorised by: luspatercept dose concentrations (0·125–0·5 mg/kg *vs* 0·75–1·75 mg/kg); pre-study transfusion burden (high transfusion burden *vs* low transfusion burden, defined as ≥4 *vs* <4 red blood cell units per 8 weeks); pre-study serum erythropoietin concentration (<200 IU/L, 200–500 IU/L, and >500 IU/L); presence of 15% or more ring sideroblasts; and presence of *SF3B1* mutations. Efficacy analyses were carried out on the efficacy evaluable and intention-to-treat populations. This trial is currently ongoing. This study is registered with ClinicalTrials.gov, numbers NCT01749514 and NCT02268383.

Findings Between Jan 21, 2013, and Feb 12, 2015, 58 patients with myelodysplastic syndromes were enrolled in the 12 week base study at nine treatment centres in Germany; 27 patients were enrolled in the dose-escalation cohorts (0·125–1·75 mg/kg) and 31 patients in the expansion cohort (1·0–1·75 mg/kg). 32 (63% [95% CI 48–76]) of 51 patients receiving higher dose luspatercept concentrations (0·75–1·75 mg/kg) achieved HI-E versus two (22% [95% CI 3–60]) of nine receiving lower dose concentrations (0·125–0·5 mg/kg). Three treatment-related grade 3 adverse events occurred in one patient each: myalgia (one [2%]), increased blast cell count (one [2%]), and general physical health deterioration (one [2%]). Two of these treatment-related grade 3 adverse events were reversible serious grade 3 adverse events: one patient (2%) had myalgia and one patient (2%) had general physical health deterioration.

Interpretation Luspatercept was well tolerated and effective for the treatment of anaemia in lower-risk myelodysplastic syndromes and so could therefore provide a novel therapeutic approach for the treatment of anaemia associated with lower-risk myelodysplastic syndromes; further studies are ongoing.

Figure. COMMANDS study design.



The COMMANDS trial is registered at ClinicalTrials.gov (NCT03682536) and EudraCT (number 2017-003190-34).

1472 Treosulfan- Versus Melphalan-Based Reduced Intensity Conditioning in Sequential HLA—Haploidentical Transplantation Using Ptcy As GvHD Prophylaxis in High-Risk MDS /AML of the Elderly: A Matched-Pair Analysis

Alessia Fraccaroli, MD[1*], *Sarah Haebe, MD*[2*], *Heidrun Drolle*[1*], *Elena Stauffer, Elena.Stauffer@med.uni-muenchen.de*[3*], *Veit Buecklein, MD*[4*], *Dusan Prevalsek*[5*], *Michael von Bergwelt, MD, PhD*[1*] *and Johanna Tischer*[6*]

[1]*Department of Medicine III, University Hospital of Munich-Grosshadern, Ludwig-Maximilians University, Munich, Germany, Munich, Germany*
[2]*Department of Medicne III, University Hospital Munich, Muenchen, Germany*
[3]*Department of Medicine III, University Hospital of Munich-Grosshadern, LMU, Munich, Germany*
[4]*Department of Medicine III, University Hospital, LMU Munich, Munich, Germany*
[5]*Department of Medicine III, University Hospital of Munich-Grosshadern, Ludwig-Maximilians University, Munich, Germany, Munich, DEU*
[6]*Department of Internal Medicine III, University Hospital of Munich-Grosshadern, Ludwig-Maximilians University, Munich, Germany, Munich, Germany*

- Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) using T-cell-replete grafts and post-transplantation cyclophosphamide (PTCY) provides a popular curative approach for older patients (pts) with high-risk (HR) MDS/AML.
- Sequential therapeutic concept is used to optimize disease control and gain time, especially in patients with active disease.
- However, data for treosulfan- based conditioning in unmanipulated HLA-haplo-HSCT for HR AML/MDS pts in context of sequential conditioning is rare.

- Matched-pair analysis of 26 patients treated with either a treosulfan- or melphalan-based sequential conditioning for haplo-HSCT using PTCY as GvHD prophylaxis in HR MDS/AML was done.
- Retrospective analysis of the outcome and toxicity profile of 26 patients undergoing sequential haplo-HSCT at our center between January 2009 and June 2019 was undertaken.

	Treosulfan-Haplo-HSCT group	Melphalan – Haplo-HSCT group	P-value
Number of patients	13	13	
Median age	63 years	63 years	
Diagnosis	MDS -2, AML - 11	MDS – 2, AML - 11	
Engraftment day	20 days (100%)	19 days (69%)	
Acute GVHD (II-IV)	23%	44%	
Severe Non-hematologic toxicities (III-IV)	2/13	7/13	
NRM (Day +100)	0%	31%	(p=0.06)
CI of relapse (at 1 year)	23%	0%	(p=0.004)
Overall survival	69%	62%	(p=0.72)
Progression-free survival	69%	62%	(p=0.72)

- Thirteen patients with HR AML/MDS and >54 years who underwent sequential haplo-HSCT with treosulfan RIC (3 x 10g/m^2) were considered for matching with melphalan based RIC regimen.

Sequential haplo-HSCT using treosulfan is safe in older patients with lower NRM at expense of higher relapse incidence.

Myeloproliferative Neoplasm

Lead:

Ranjit Sahoo / Uday Kulkarmi

Correlation of Survival and Other Clinical Benefits With Imetelstat Therapy in High-Risk, JAK Inhibitor–Refractory Myelofibrosis [IMBark] Mascrennhas et al

- MF-Patients R/R to JAKi have poor survival outcomes. Imetelstat: 13-mer oligonucleotide competitively inhibits telomerase enzyme activity by targeting the human telomerase RNA template, thus targeting MF malignant stem and progenitor cell proliferation
- Randomized, single-blind phase II study comparing 2 doses of imetelstat (9.4 vs 4.7 mg/kg IV Q3W) in R/R int.-2/HR MF patients
- **Current analysis evaluated association between OS and spleen response (SVR35), symptom response (TSS50), and fibrosis improvement**

Survival*	**4.7 mg/kg (n = 48)**	**9.4 mg/kg (n = 59)**
Median OS, mos	19.9 (17.1-33.9)	28.1 (22.8-31.6)
12-mo OS, %	78.6 (63.9-87.9)	84.0 (71.6-91.4)
24-mo OS, %	42.0 (27.4-56.0)	57.9 (43.6-69.7)
Fibrosis improvement	4/20 (20.0)	16/37 (43.2)
	HR 0.37 (CI: 0.14-0.98) P = .0443	
TSS50 @ Wk24, %	6.3	32.2
	HR 0.78 (CI: 0.40-1.49) P = .4491	
SVR35 at any time	1/48 (2.1)	7/59 (11.9)
	HR 0.44 (CI: 0.11-1.85) P = .2647)	

Investigator Conclusions:

- Imetelstat continued to show dose-related OS improvement in Int.-2/HR MF-patients refractory to JAKi
- Improvements in bone marrow fibrosis significantly correlated with lower risk of death, while others did not (SVR35, TSS50)
- Phase-3 will initiate in 2021

MANIFEST: Novel BET Inhibitor, CPI-0610, Plus Ruxolitinib in JAK Inhibitor–Naive Patients With Myelofibrosis

- BET proteins regulate BET and NF-kB target genes which promote MF via[1]:
  - Increased cytokine production resulting in inflammation, extramedullary hematopoiesis, BM fibrosis, & causing atypical erythroid and megakaryocytic differentiation
- CPI-0610, novel, first-in-class, oral, small-molecule BET inhibitor
- Current analysis presents findings from MANIFEST Arm 3, in enrolled JAK inhibitor–naive patients who received CPI-0610 + ruxolitinib
- Endpoints, Primary: SVR35, Key Secondary TSS50

Outcomes:

- SVR35 at Wk 24 achieved in 42 of 63 patients (67%,CI: 54-78)
- TSS50 achieved in in 34/60 (57%, CI: 43-69)
- Hemoglobin increased in patients with BL levels < 10 g/dL
- BM fibrosis improved ≥ 1 grade in 16/48 (33%)
- Anemia 33% (g3/4, 29%), Thrombocytopenia 32% (g3/4, 8%)
- Discontinuation 3%

Investigator Conclusions:

- Encouraging responses
  - SVR35, TSS50
  - Hb, BM improvements
- Phase-3 study planned.

Phazar: A Phase Ib Study to Assess the Safety and Tolerability of **Ruxolitinib** in Combination with **Azacitidine** in **Advanced Phase Myeloproliferative Neoplasms (MPN)**, Including Myelodysplastic Syndromes (MDS) or Acute Myeloid Leukaemia (AML) Arising from MPN [ISRCTN16783472

- After fixing MTD of Rux, cohorts of 3-5 pts with MPN-AP/MP-BP were included
- Aza fixed at 75 mg/m2 for seven days in a 28 day cycle
- Rux at allocated dose levels 0, 1, 2 and 3 = 10, 15, 20 and 25 mg BD resp
- BM response after 3 and 6 cycles
- OS and PFS as end points

Table 1 – Baseline characteristics

Baseline Characteristics			N = 34
Age (years)		Median (Range)	73 (56-86)
Gender (Male)		N (%)	20 (58.8)
Diagnosis:	MPN-BP	N (%)	15 (44.1)
	MPN-AP		19 (55.9)
ECOG Status:	0	N (%)	10 (29.4)
	1		14 (41.2)
	2		6 (17.6)
	3		2 (5.9)
	N/A		2 (5.9)
Transfusion Dependent:	Red Blood Cell	N (%)	14 (45.2)
	Platelet		7 (22.6)
Haemoglobin (g/dL)		Median (Range)	91.0 (51.0 – 143.0)
Platelet Count ($10^9/L$)		Median (Range)	65.0 (4.0 – 984.0)
White Blood Cell Count ($10^9/L$)		Median (Range)	18.4 (0.7 – 178.7)

Mutations: JAK2 in 68%, CALR in 16% Triple Neg in 16%

Doses Received

Dose	N
10 mg BD	3
15 mg BD	3
20 mg BD	4
25 mg BD	21
Nil	3

Response: AP

Response	N
CR	1
Marrow CR	4
PR	1
SD	4
PD	3

Response: BP

Response	N
PR	4
SD	3

In total, **20** of **34** patients were evaluable for disease response
Median Duration of response: MPN:AP 322 days, MPN:BP 199 days

ADR	%
Febrile Neutropenia	29%
Sepsis	14%
Infections	14%

At 12 months, median
PFS: 42.1% (95% CI: 17.9, 64.7)
LFS: 26.4% (95% CI: 6.5, 52.2)
OS: 42.4% (95% CI: 23.8, 59.8)

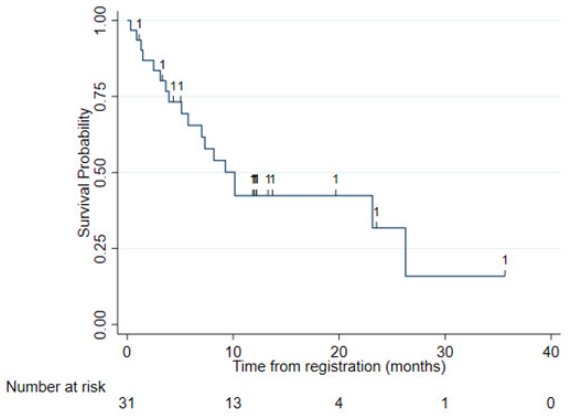


Figure 1 - Kaplan-Meier graph showing overall survival for patients in the interventional arm

Molecular Characterization of Participants in the Phazar Trial Reveals Prognostic Impact of Mutations in Advanced-Phase-MPN

- NGS sequencing data were available for 24 interventional trial and 13 observational cohort participants
- 11/13 observational pts received best supportive care, while 2/13 were treated with high-dose chemotherapy
- Other mutations: median 2 (range 0-4) per sample

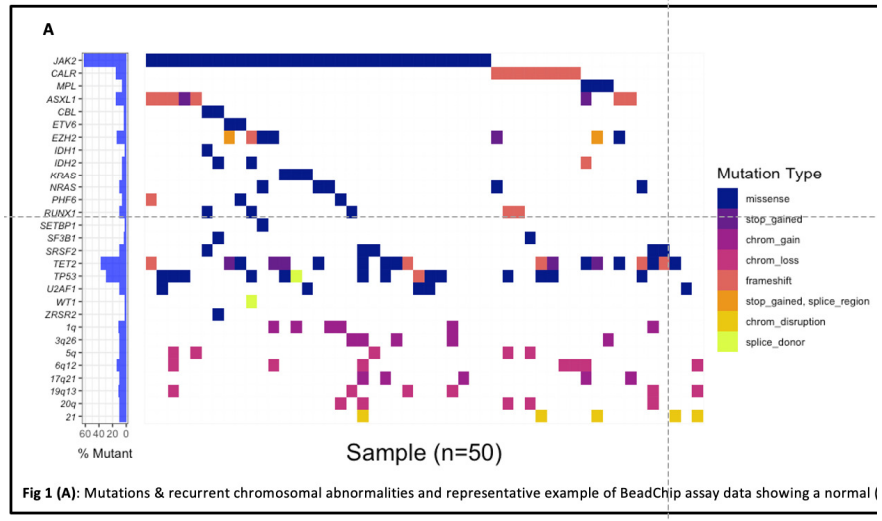


Fig 1 (A): Mutations & recurrent chromosomal abnormalities and representative example of BeadChip assay data showing a normal (

Driver	%
JAK2	59%
CALR	16%
MPL	8%

Mutation	%
Epigenetic Regulators	57% *(TET2, 38%; EZH2, 19%; ASXL1, 14%; PHF6, 5%; SETBP1, 3%)*
Spliceosome Mutations	22% (*SRSF2, 8%; U2AF1, 8%; SF3B1, 5%*
High Molecular Risk	65% *ASXL1, EZH2, IDH1/2, SRSF2, TP53, U2AF1 Q157)*
TP53	27%

- **Clinical Correlation**
- No impact of baseline driver mutation on OS or response
- >3 mutations impaired OS (1 yr OS 12% vs 55%, *p=0.02*))
- High Risk Mutations impaired response rates
- Loss of >1 chromosome except 5q del (1yr OS 27% vs 58%, *p=0.05)*
- Chromothripsis (1yr OS 0% vs 53%, *p=0.002*)

ASH 2020 Abstract no 481

Long-Term Use of Ropeginterferon Alpha-2b in Polycythemia Vera: 5-Year Results from a Randomized Controlled Study and Its Extension

- Adults, WHO diagnosed PV, cytoreduction-naïve or hydroxyurea (HU)-pre-treated for < 3 years
- Randomized 1:1 (stratified by age > 60 years, prior thromboembolic events, and HU pre-treatment) to receive ropeg or Hydroxyurea PROUD-PV and CONTINUATION-PV
- Hematologic parameters, phlebotomy need, *JAK2*V617F allele burden, and molecular response
- 5-year analysis – 70 patients in ropeg arm and 57 in control arm remained on study; discontinuation rates balanced (ropeg: 26.3%; control: 25.0%).

Parameter	Ropeginterferon alpha-2b (N=70)	Control (N=57)	P value
Hematocrit <45% without phlebotomy	81.8%	63.2%	0.01
Major thromboembolic adverse event	1.2% patient-years	1.2% patient-years	
Median allele burden	37.3% to 7.3%	38.1% to 42.6%	P < 0.0001
Molecular response	69.1%	21.6%	RR 3.2 (95% CI: 2.1 to 4.9, p < 0.0001)
Progression	1 to secondary MF	2 to secondary MF and 2 to Acute leukemia	
Controlled hematocrit and molecular response	58.5%	17.3%	RR 3.52 (2.13 to 5.81, p < 0.0001)
Treatment related adverse events any grade ≥grade 3	25.6% 16.5%	24.2% 16.5%	

ASH 2020 Abstract no 483

Interferon-Alpha (IFN) Therapy Discontinuation Is Feasible in Myeloproliferative Neoplasm (MPN) Patients with Complete Hematological Remission

- 381 patients treated with IFN
- Median age 44 years [IQR: 33-54]
- 171- PV, 169 - ET and 34 - PMF
- Drivers - JAK2V617F 78.8%, *CALR* - 15.5%, *MPL* - 2.9% of patients respectively.
- Median driver variant allele frequency (VAF) at time of IFN therapy initiation - 34% [12; 51].

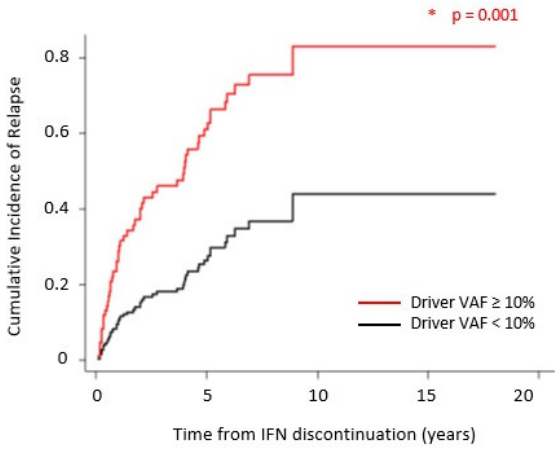


Figure A: Cumulative Incidence of relapse after IFN discontinuation, for patients with driver VAF ≥ 10% at time of IFN discontinuation compared to MPN patients with VAF < 10%.
VAF: Variant Allele Frequency. COX regression analysis was used for groups comparison.

- Reasons to start IFN - age younger than 50 years (44.9%), intolerance/resistance to previous therapies (17.8%), pregnancy (1.8%) CHR achieved with IFN in 77.2% of patients.

- Median follow-up of 72.4 months [28.4; 119.7] from IFN initiation
- 131 patients still on IFN treatment, 250 patients discontinued therapy.

- Reasons for discontinuation - toxicity in 128 (50.4%), prolonged hematological CHR in 76 (29.9%), failure in 16 (6.3%) and other in 30 (11.8%) patients.

- At time of IFN discontinuation, 170 (66.9%) patients were in CHR and the median driver mutation VAF was 12% [3; 35]. Of note, IFN was re-introduced in 61 patients who lost CHR with a second CHR rate of 83.6%, arguing for the absence of development of IFN resistance in post-discontinuation relapses.

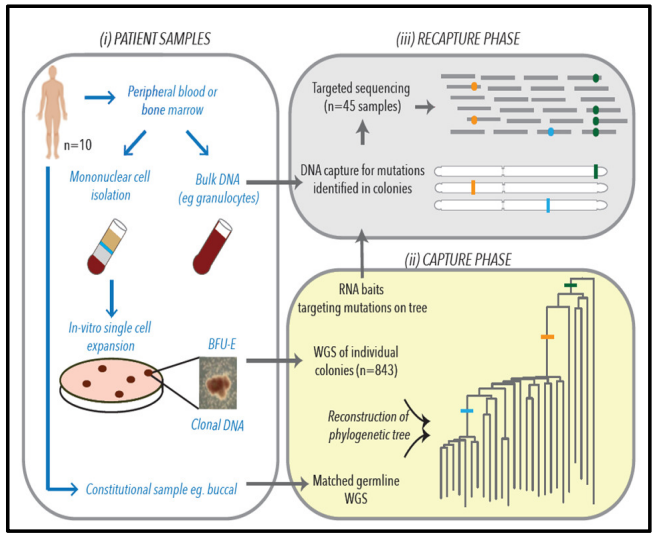
- OS (HR 0.23, 95%CI [0.5; 1.14], p=0.07) and EFS (HR 0.53, 95%CI [0.19; 1.45], p=0.217) were not significantly different between patients who discontinued and those who continued IFN.

LBA-1: Driver Mutation Acquisition in Utero and Childhood Followed By Lifelong Clonal Evolution Underlie Myeloproliferative Neoplasms

Objective:

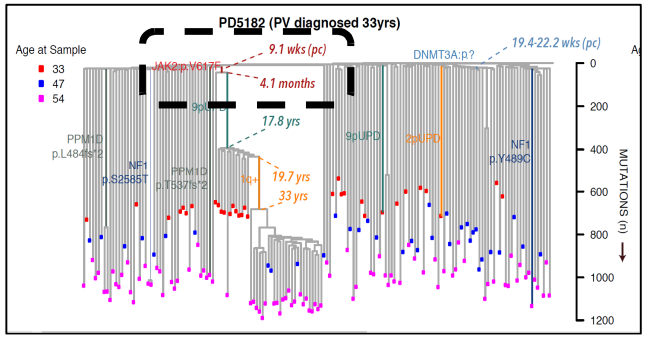
- MPNs are unique cancers capturing the earliest stages of tumorigenesis through to disease evolution.
- Timing of driver mutations and clonal dynamics in adult Ph- MPN.

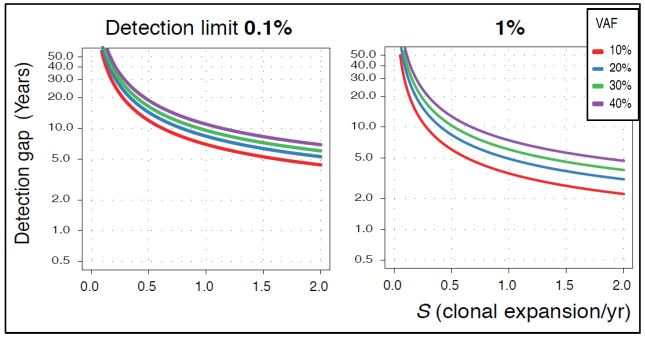
Methods:



Results:

- In utero and childhood acquisition of *JAK2* mutations & *DNMT3A* mutations.
- Ageing per se didn't drive such clonal haematopoiesis – it simply took an age for the clones to grow.
- Cancer driver mutations could occur sequentially – decades apart. Different orders including *JAK2* mutations coming second.
- Clone growth rates varied: <10%/yr to >200%/yr for multiply mutated clones
- *JAK2*V617F clones grew at different rates in different individuals – ie patient-specific factors (germline, environment) influence its consequences.
- Rate of expansion of mutant-JAK2 predicted the time to MPN diagnosis





Conclusion:

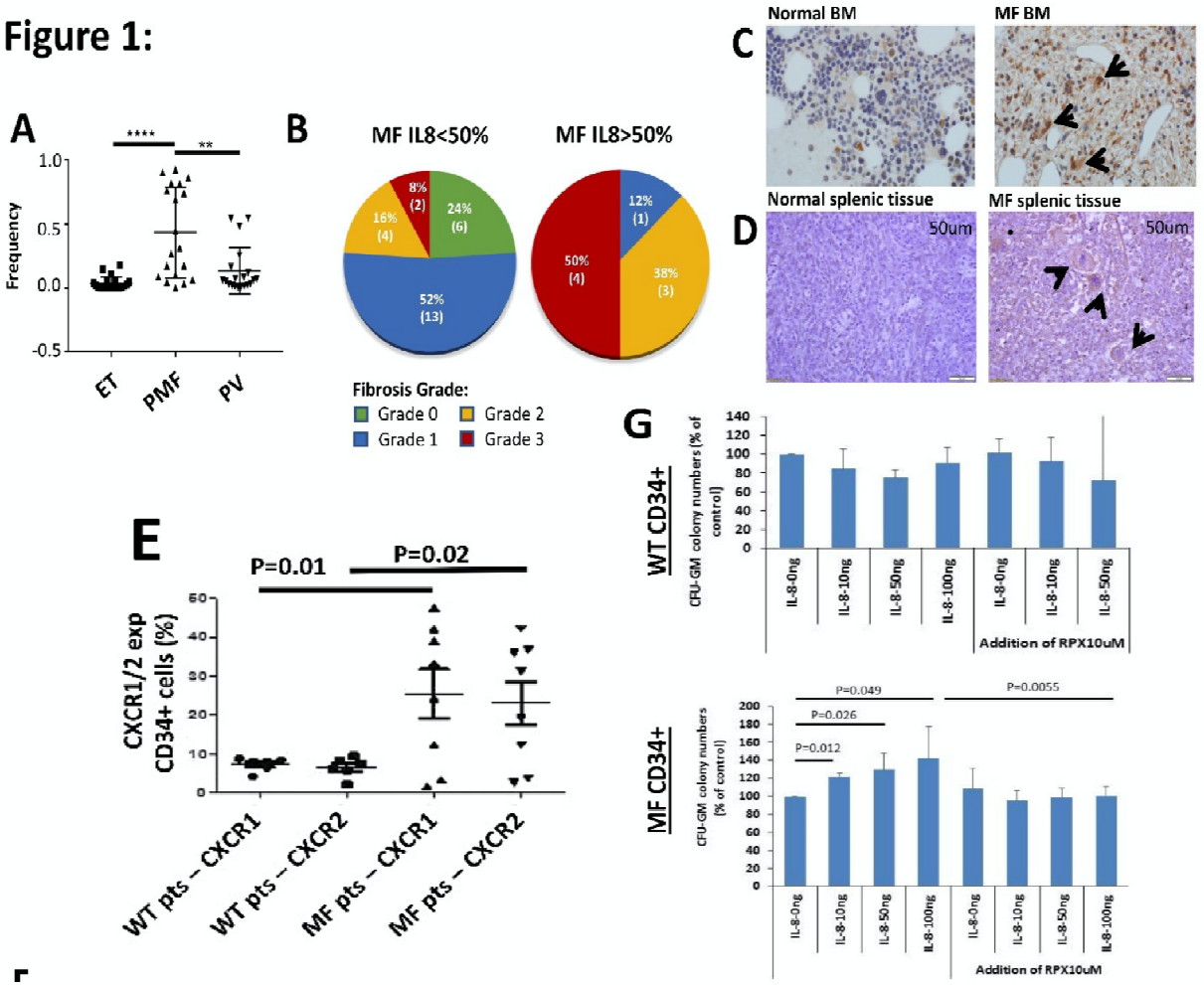
MPN originate from driver mutation acquisition very early in life, even before birth, with life-long clonal expansion & evolution, establishing a new paradigm for blood cancer development

ASH 2020 Abstract 713
Increased Interleukin-8 (IL8)-CXCR2 Signaling Promotes Progression of Bone Marrow Fibrosis in Myeloproliferative Neoplasms

: Andrew Dunbar et al.

- Elevated proinflammatory cytokines (IL8) is a hallmark of MPN and associated with adverse outcome.
- Delineate the role of IL8 and its cognate receptors *CXCR1/2* in MF pathogenesis
- Single cell cytokine assay (microchip) for IL8- CD34+ cells: 60 MPN, 10 controls (A,B)
- Flow cytometry: increased *CXCR2* and *CXCR1* expression (high IL8 clone) (E)
- Integrated RNA-Seq/ATAC-Seq analysis (high IL-8 pt):
  - up-regulation of IL8-CXCR2 signaling, pro-inflammatory pathways (i.e TNFa, NFkB, etc)
  - increased expression/accessibility of *S100A8/A9* (involved in fibrosis)
- CFU assay: CD34 + cells of MF high IL-8 pt vs normal (G) and with the *CXCR*1/2 antagonist Reparixin

Figure 1:



ASH 2020 abstract 713
Increased Interleukin-8 (IL8)-CXCR2 Signaling Promotes Progression of Bone Marrow Fibrosis in Myeloproliferative Neoplasms :

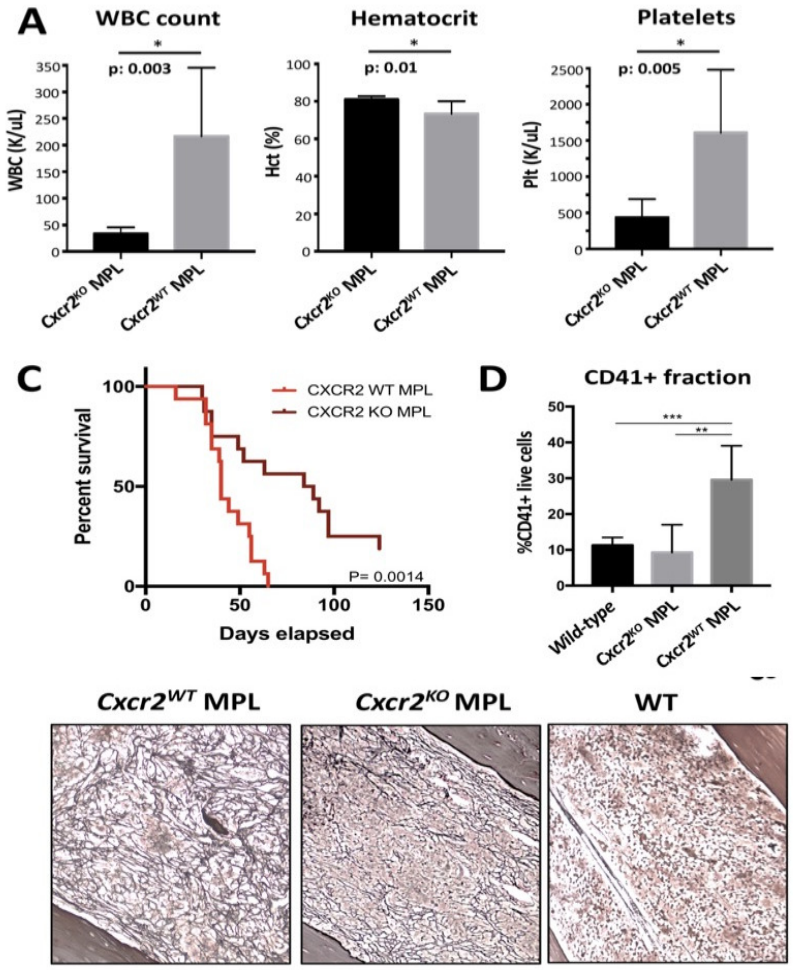
Andrew Dunbar et al.

- In vivo studies
  - Models with knocked out Cxcr2 and wild type Cxcr2 (Vax-Cre-Cxcr2f/f)
  - human MPL^{W515L} transplant model ($hMPL^{W515L}$) of MF

- Comparison of Cxcr KO Vs Cxcr WT
  - improved leukocytosis, thrombocytosis and splenomegaly
  - Reduced bone marrow fibrosis
  - Reduction in dysplastic megakaryocytes
  - Improvement of overall survival

Conclusions

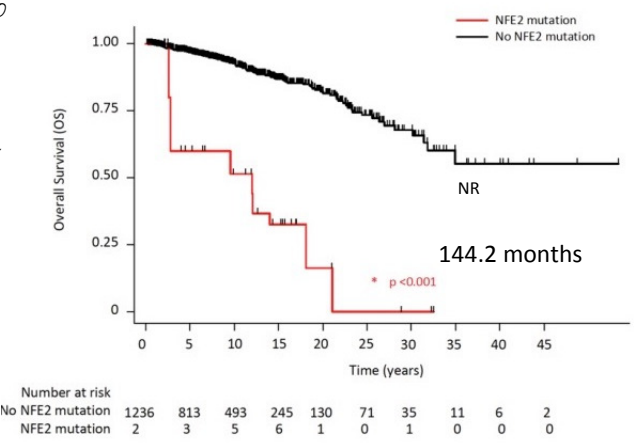
1. IL8 secreting clones are associated with increased symptom severity, fibrosis, up-regulation of inflammatory genes *S100A8/A9*,
2. *Cxcr2* KO abrogates fibrosis formation and prolongs survival
3. CXCR1/2 inhibition impairs colony forming capacity of MF CD34+ cells
4. pharmacologic inhibition of this pathway should be investigated as potential therapy in MF and in PV/ET patients at high risk of fibrotic transformation

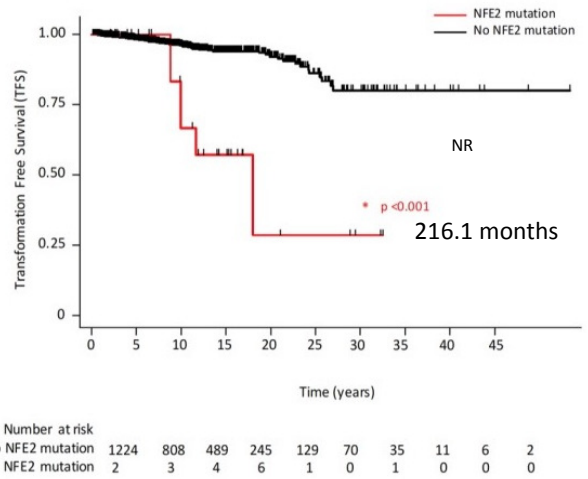


ASH 2020 Abstract no 343

NFE2 Mutations Impact AML Transformation and Overall Survival in Patients with Myeloproliferative Neoplasms (MPN): Lin-Pierre Zhao et al.

- *NFE2* (nuclear factor erythroid 2): overexpression or enhanced truncated mutation in of patients of MPN .
- **Aim**: to evaluate the phenotypic characteristics and prognostic impact of *NFE2* somatic mutations
- Cohort: 707 patients with NGS panel targeting 36 myeloid genes
- Phenotype: PV, PMF, ET, unclassified MPN
- Mutation profile: *JAK2*V617F (73.1%), *CALR* (14.1%), *MPL* (3.3%)
- 64 (9.05%) patients harbored a *NFE2* mutation with a variant allelic frequency (VAF) ≥ 0.5% and 36 had a VAF ≥ 5% (clinically significant)
- *NFE2* mutations were present in **7.3%, 5.3% and 3.6% of PV, PMF and ET patients,** respectively
- No significant association with clinical/molecular MPN characteristics
- CR rates: 52.8% vs 61.7% (p=0.026)
- Independently associated with AML/MDS transformation free survival (TFS) *NFE2* mutation (HR 9.92, 95%CI[3.21; 30.64], p< 0.001) and overall survival (HR 9.37, 95%CI [4.18; 21.03], p<0.001) (other age, PMF subtype, HR mutations)
- No difference was observed in terms of thrombo-hemorrhagic events or secondary myelofibrosis free survivals





Non Hodgkin Lymphoma
High grade

Lead:

Manju / Anu

Rituximab with R-DA-EPOCH with or without Autologous Stem Cell Transplantation (ASCT) As First Line Treatment in Patients with Aggressive B-Cell Lymphoma with *MYC* and *BCL-2* and/or *BCL-6* Gene Rearrangements or Increase Copy Number

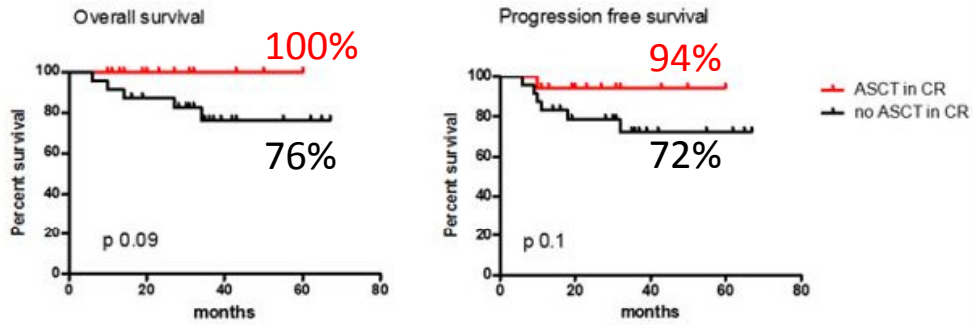
Previously reported short-term efficacy of R-DA-EPOCH in aggressive B-NHL with *MYC* +*BCL-2* +/-*BCL6* (DHL/THL)

Long-term results in an unselected series of DHL/THL

(1) to confirm preliminary results (2) to define role of ASCT

63 (51 DLBCL, 5 BCLU, 7 HGBCL)
Median age 63 yrs
54 (86%) Stage III/IV, 41 (65%) High IPI, EN disease (79%)
FISH: 34 - DHL, 10 THL,19 c-*MYC*-ICN. **IHC:** 81% - GCB, 73% DE

Figure 1



Survival of patients in CR after induction therapy who received or not ASCT consolidation

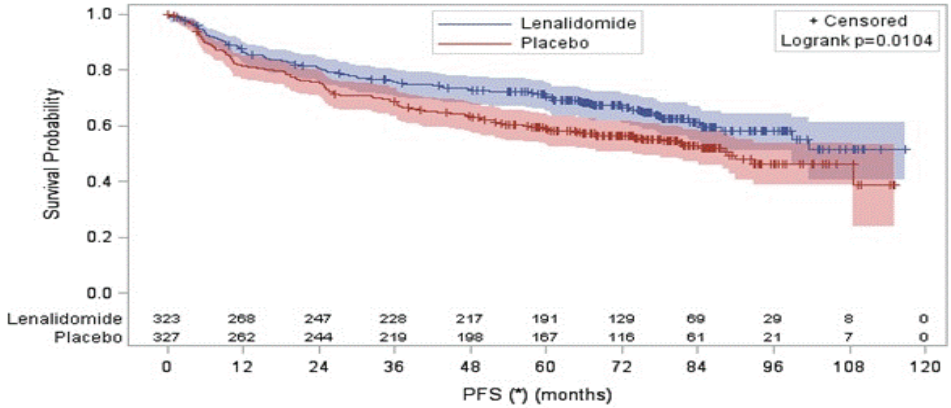
Median 6 cycles R-DA-EPOCH (Range 1-6).
[12 pre-treated with one R-CHOP]
24pts – AutoSCT (17 in CR, 6 in PR, 1 with PD)

CONCLUSION: Role of consolidative ASCT seems encouraging, but remains to be proven by prospective randomized studies.

ORR 81% - **CR 68%**
3y- PFS & OS - 67% and 69% respectively. Median F/U 32 mths.
Multivariate analysis - only ASCT - favorable OS (p 0.013).
3y-OS/PFS patients in CR after chemo +/- ASCT : 100% vs 76% and 94% vs 72% respectively

Final Analysis of the International Double-Blind Randomized Phase III Study Lenalidomide Maintenance in Elderly DLBCL in Response after R-CHOP (REMARC study)

(LEN) maintenance after R-CHOP (60-80yrs)
Randomized 1:1
2009 -14, 794 pts; After R-CHOP, LEN (n=323) or PBO (n=327)
2 years of LEN (25 mg/day -21/28) or placebo (PBO).
Primary endpoint - PFS.
Secondary endpoints - safety, PR to CR conversion, OS.



Median PFS - Not reached (LEN) vs 89mths in PBO group (p=0.01)
LEN- 24 pts (35%) converted from PR to CR compared to 22 pts (27%) in PBO (p=0.29)
Grade 3 or 4 AEs - **Neutropenia** (57% vs. 22%) in LEN and PBO arms, respectively.
59% of pts D/C LEN and 39% D/C PBO for toxicity.
Median number of cycles was 15 in LEN and 26 in PBO arms.

ABC profile PFS and OS similar in LEN group (n=78) compared to the PBO group (n=66), p=0.15 and p=0.59
Multivariate analysis: **PBO**, age≥ 70, IPI 3-5, **ABC, PR after R-CHOP** as independent factors for an inferior PFS

***Conclusion*. 2 years of LEN maintenance in pts responding to R-CHOP signif improved PFS regardless of COO**

CNS prophylaxis in high-risk DLBCL - Background

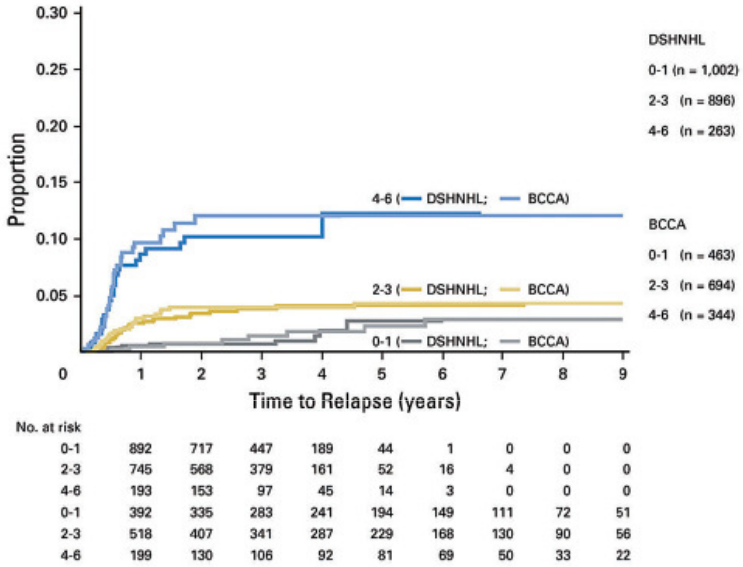
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2511–2516, 2017
doi:10.1093/annonc/mdx353
Published online 16 July 2017

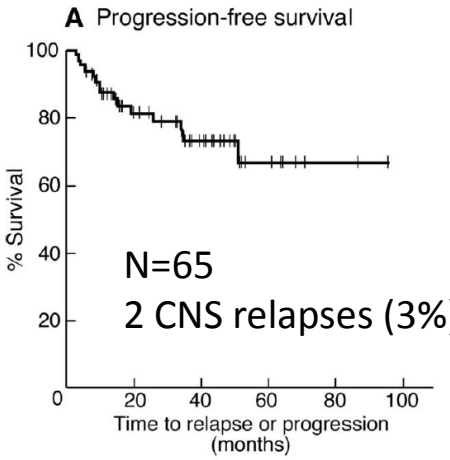
ORIGINAL ARTICLE

Central nervous system relapse of diffuse large B-cell lymphoma in the rituximab era: results of the UK NCRI R-CHOP-14 versus 21 trial

Case report forms outlining CNS prophylaxis details administered on study were returned in 984/1080 (91.1%) cases, with data missing for 96 cases. A total of 177/984 patients (18.0%) received CNS prophylaxis within the trial. The type of prophylaxis administered was IT MTX (163/177), IV MTX (2/177), IT MTX and IT cytarabine (1/177) and prophylaxis-type unknown (11/177). Table 2 shows the proportion of patients receiving CNS prophylaxis by EN sites of involvement at baseline.



IV MTX as CNS Prophylaxis Is Associated With a Low Risk of CNS Recurrence in High Risk DLBCL (Abramson et al. Cancer 2010) n=65



Lack of Effectiveness of IV High-Dose Methotrexate for Prevention of CNS Relapse in Patients with High-Risk DLBCL: A Retrospective Analysis from Alberta, Canada

Retrospective 2012-2019.
3.5g/m3 – 3 doses after cycle 2,4,6 RCHOP
906 patients (Median F/U 35.3 months)

CNS relapse rates by CNS IPI (p<0.0001).
0-1 : 1.9% (95% C.I. 0.0-30.7%)
2-3: 4.9% (95% C.I. 0.5-18.0%)
4-6: 12.2% (95% C.I. 4.0-25.2%)
Prophylactic HD-MTX - 115 (35.3%) HR

CONCLUSION
This analysis could not demonstrate benefit of current practice using prophylactic HD-MTX.
ASCT may be a more effective strategy

Figure 1: Risk of CNS relapse by CNS-IPI score

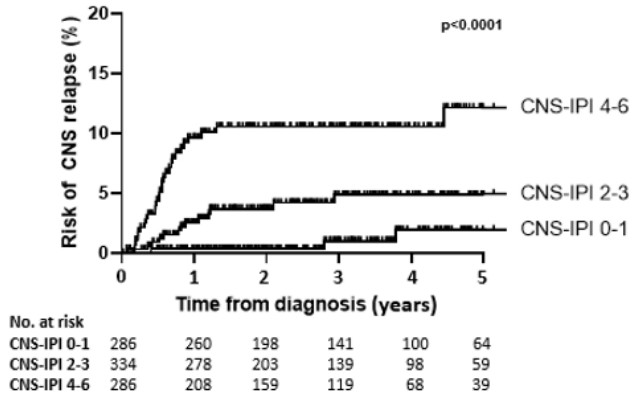


Table 1: Risk of CNS relapse by treatment arm in APLCPG high-risk patients (n=326)

Treatment	No. of patients	Risk of CNS relapse with vs. without treatment	Hazard ratio	95% C.I.	P value
HD-MTX prophylaxis	115	11.2% vs. 12.2%	0.92	0.44-1.91	0.82
Higher intensity chemoimmunotherapy	35	5.7% vs. 12.6%	0.64	0.20-1.98	0.43
Consolidative autotransplant	68	6.0% vs. 13.7%	0.55	0.24-1.25	0.15

Table 2: Multivariate analysis of CNS relapse, progression-free survival, and overall survival by treatment arm in APLCPG high-risk patients, controlling for CNS-IPI score, double hit lymphoma, and testicular involvement (n=326)

Treatment	CNS relapse			Progression-free survival			Overall survival		
	Hazard Ratio	95% C.I.	P value	Hazard Ratio	95% C.I.	P value	Hazard Ratio	95% C.I.	P value
HD-MTX prophylaxis	1.61	0.72-3.59	0.25	1.06	0.71-1.58	0.78	1.12	0.72-1.75	0.61
Higher intensity chemoimmunotherapy	0.38	0.08-1.95	0.25	0.59	0.30-1.18	0.14	0.63	0.29-1.37	0.25
Consolidative autotransplant	0.30	0.09-1.01	0.051	0.41	0.24-0.71	0.001	0.56	0.32-0.98	0.043

Prognostic Value of Circulating Tumor DNA (ctDNA) in Autologous Stem Cell Graft and Post-Transplant Plasma Samples Among Patients with Diffuse Large B-Cell Lymphoma

Reid W Merryman, MD, Robert A. Redd, MS, Eleanor Taranto, MD, Gulrayz Ahmed, MD, Erin Jeter, Kristin M McHugh, Jennifer R. Brown, MD PhD, Jennifer Crombie, MD, Matthew S. Davids, MD, David C. Fisher, MD, Arnold S. Freedman, MD, Eric Jacobsen, MD, Caron Jacobson, MD MMSc, Austin I. Kim, MD, Ann S. LaCasce, MD MSc, Benjamin L. Lampson, MD PhD, Samuel Ng, MD PhD, Oreofe O. Odejide, MDMPH, Parastoo B. Dahi, MD, Yago Nieto, MD, Robin M. Joyce, MD, Yi-Bin Chen, MD, Alex F. Herrera, MD, Philippe Armand, MD PhD

- CtDNA levels track with treatment response in DLBCL, and the persistence or recurrence of ctDNA during and after upfront therapy is associated with subsequent DLBCL relapse (***Kurtz et al, 2015; Roschewski et al, 2015***).
- Following HSCT for ALL & CLL, ctDNA is associated with subsequent relapse and poorer progression-free survival (PFS) (***Logan et al, 2013, 2014***).
- A pilot study by ***Herrera et al, BJH 2016***, showed that detectable ctDNA(via NGS) post allo-SCT was associated with increased risk of progression/death (Hazard ratio 3·9, *P* = 0·003) and increased risk of relapse/progression (Hazard ratio 10·8, *P* = 0·0006).

Samples from patients in 3 cohorts:

C1 – underwent ASCT at Dana-Farber Cancer Institute (DFCI) from 2003-2013

C2 – prospectively enrolled on a banking protocol at DFCI and underwent ASCT from 2014-2016

C3 – underwent ASCT from 2015-2016 and participated in a multicenter phase II trial of post-ASCT pembrolizumab maintenance

Material collected –

- apheresis stem cell (ASC) samples or
- serially collected post-ASCT peripheral blood mononuclear cell (PBMC) and plasma samples

– C1 – Archival tumor tissue and ASC samples were retrospectively collected for analysis.

– C2/C3 – tumor tissue and serially collected post-ASCT PBMC and plasma samples as mandated by protocol, and a subset had available pre-ASCT PB or ASC samples.

❖ **Hypothesis** – hypothesized that circulating tumor DNA (ctDNA) identified using immunoglobulin-based next generation sequencing (IgNGS) in ASC or PB samples could predict relapse.

SS1

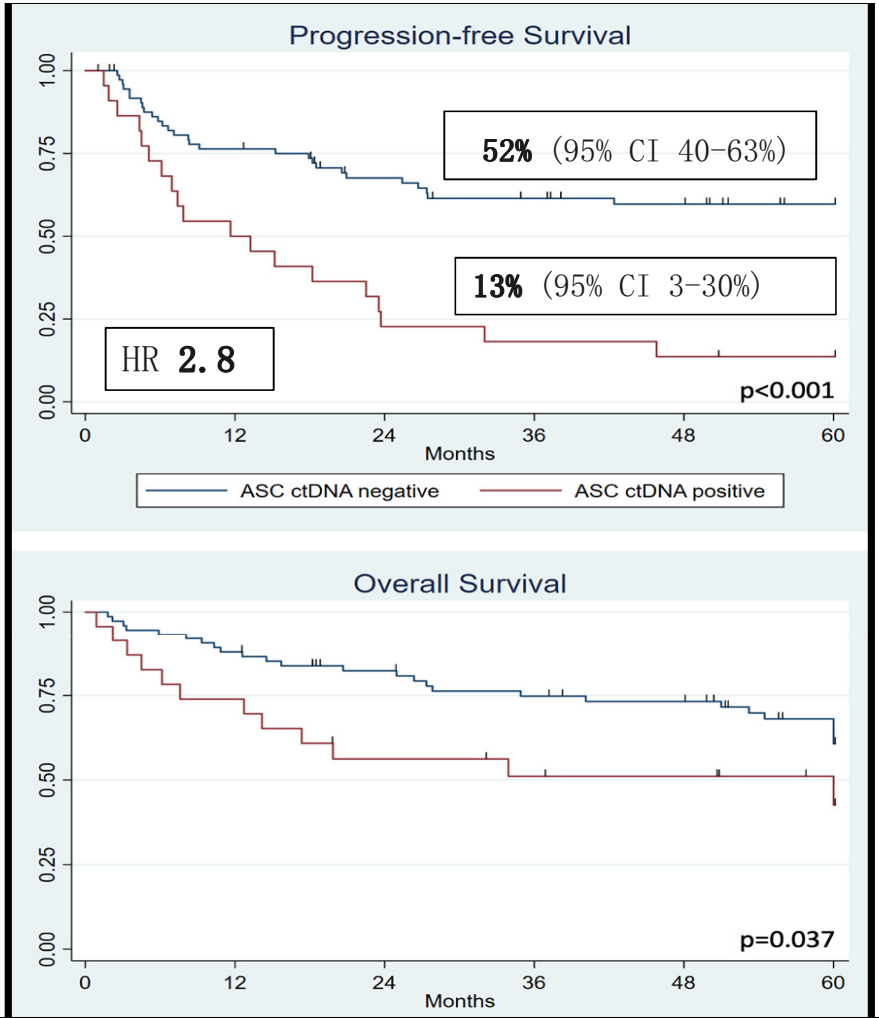
Slide 78

SS1 Sushil Selvarajan, 10-12-2020

Results

152 pts enrolled

Among 141 pts with sufficient DNA for testing, a clonotype was identified in 112 (78%) with a higher detection rate in more recent cohorts – C2 (93%) and C3 (90%) vs C1 (67%).



- The sensitivity and specificity of ASC ctDNA for progression or death were **36%** and **95%**, respectively.
- ASC ctDNA (HR 2.5, p=0.002) was the *only significant predictor of PFS in a multivariable model* that included pre-ASCT positron emission tomography (PET), lines of therapy, age, and primary refractory status!!!

Post-ASCT peripheral blood Analysis	Outcome of pts with ≥1 ctDNA-positive sample	Median lead-time (range)	Relapse detection rate (among pts with ≥1 sample within 100 days of relapse)
Plasma	18/21 (86%) relapsed	52 days (range 0-518)	90% (18/20)
PBMC	20/35 (57%) relapsed	114 days (range 0-1330)	87% (20/23)

Background

NATIONAL CANCER INSTITUTE

The Molecular Diagnosis of Diffuse Large B Cell Lymphoma v.2.0

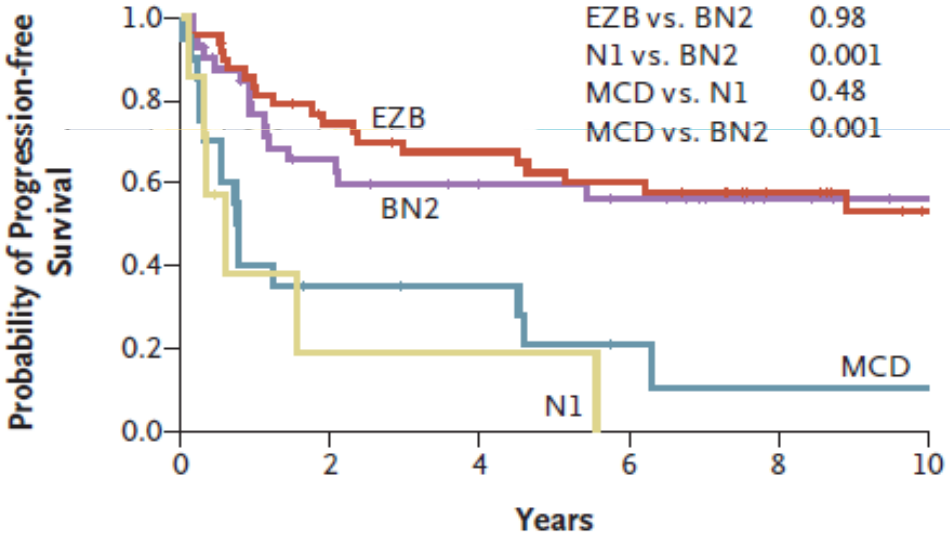
N Engl J Med 2018;378:1396-407.
DOI: 10.1056/NEJMoa1801445

GENE EXPRESSION SUBGROUPS

GENETIC SUBTYPES

A Progression-free Survival among Patients Whose Tumors Were Genetically Classified

Comparison	P Value
4-Way	8.88×10^{-6}
EZB vs. MCD	6.07×10^{-5}
EZB vs. N1	5.62×10^{-5}
EZB vs. BN2	0.98
N1 vs. BN2	0.001
MCD vs. N1	0.48
MCD vs. BN2	0.001

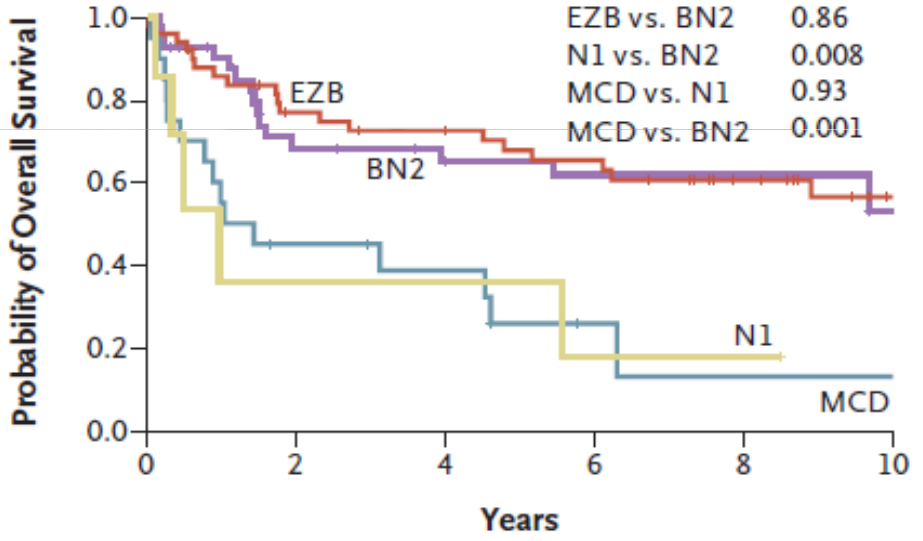


No. at Risk

MCD	20	6	5	2	1	1
BN2	41	22	17	15	8	5
N1	7	1	1	0	0	0
EZB	49	32	27	24	17	11

B Overall Survival among Patients Whose Tumors Were Genetically Classified

Comparison	P Value
4-Way	1.70×10^{-4}
EZB vs. MCD	2.13×10^{-4}
EZB vs. N1	0.005
EZB vs. BN2	0.86
N1 vs. BN2	0.008
MCD vs. N1	0.93
MCD vs. BN2	0.001



No. at Risk

MCD	20	8	6	2	1	1
BN2	42	24	20	18	11	5
N1	7	2	2	1	1	0
EZB	50	34	30	27	19	11

Double-Hit Signature with *TP53* Abnormalities Predicts Poor Survival in Patients with Germinal Center Type Diffuse Large B-Cell Lymphoma Treated with R-CHOP

Joo Y Song, MD, Anamarija M. Perry, MD, Alex F. Herrera, MD, Lu Chen, PhD, Pam Skrabek, MD, Michel Nasr, MD, Rebecca Ottesen, Janet Nikowitz, Victoria Bedell, Joyce Murata-Collins, PhD, Yuping Li, PhD, Christine McCarthy, Raju Pillai, MD, Jinhui Wang, PhD, Xiwei Wu, PhD, Jasmine M. Zain, MD, Leslie L. Popplewell, MD FACP, Larry W Kwak, MD PhD, Auayporn P. Nademanee, MDBS, Joyce Niland, PhD, David W. Scott, MBChB, PhD, Qiang Gong, PhD, Wing (John) C. Chan, MD, Dennis D. Weisenburger, MD

•**Study outline & Methods**: 87 cases of *de novo* GCB DLBCL - extensively characterized by combining the results of IHC, cell-of-origin GEP (Nanostring), DH GEP (DLBCL90), FISH cytogenetic analysis for DH lymphoma, copy number analysis (CNA), and targeted deep sequencing using a custom mutation panel of 334 genes.

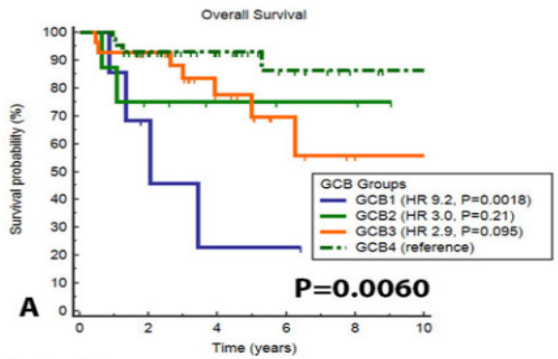
•**Four distinct molecular groups in terms of outcomes.** These groups were then validated in an independent cohort of 188 cases

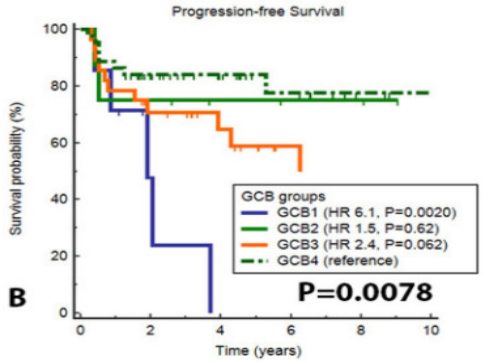
GCB1: DHITsig-positive with TP53 inactivation(DHIT+TP53): **Worst overall survival** (OS; Hazard Ratio (HR)=9.2, P=0.0018) and shortest progression-free survival (PFS; HR=6.1, P=0.002) compared to other groups).

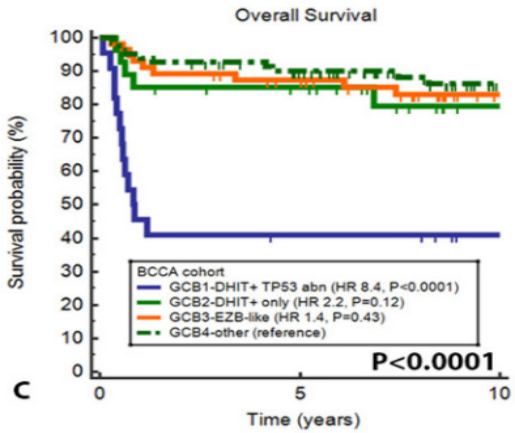
GCB2: DHITsig-positive (DHIT-TP53): Most(88%) had an *EZH2* mutation and/or *BCL2* translocation (EZB of Schmitz et al). Also had a high *MYC* mutations (63%). Typically DHITsig-pos cases have a poor OS when compared to DHITsig-neg cases, however **this group demonstrated good survival**, after removing the cases with *TP53* abnormalities.

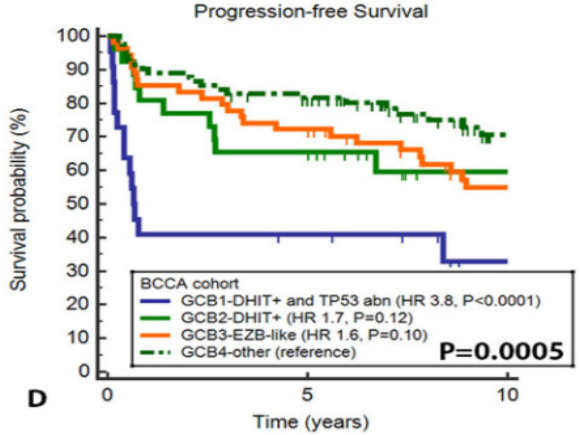
GCB3: DHITsig-negative and EZH2 mutation and/or BCL2 translocation (EZB-like): 28 cases (32%) that were DHITsig-neg and had an *EZH2* mutation and/or *BCL2* translocation. **The survival of this group was intermediate** compared to the other groups.

GCB4: DHITsig-negative and not EZB-like (GCB Other): The largest group of cases (51%) were DHITsig-neg and lacked *EZH2* mutations and *BCL2* translocations. These cases had frequent mutations in *SGK1* (16%) and histone modifying genes (50%), as well as *TET2* mutations. **The survival of this group was excellent.**









Non Hodgkin Lymphoma
Low grade / CLL

Lead:

Anu Korula

ASH 2020 Abstract no: 123

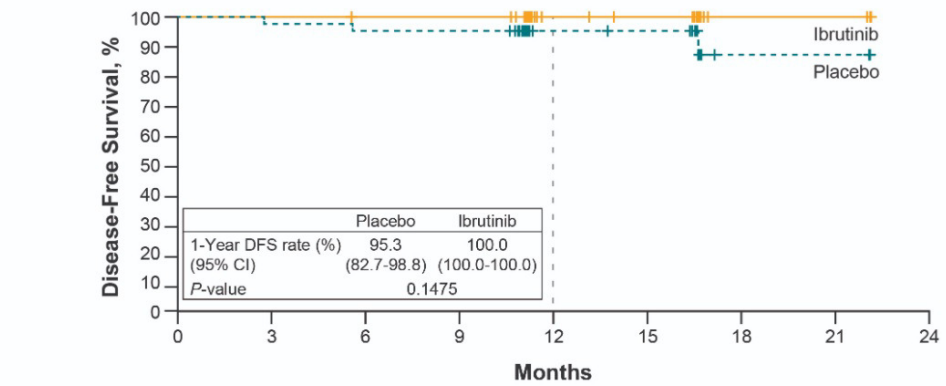
Ibrutinib (Ibr) Plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results From the MRD Cohort of the Phase 2 CAPTIVATE Study

CAPTIVATE is a multicenter phase 2 study of first-line Ibr + Ven with 2 cohorts: Minimal Residual Disease (MRD) and Fixed-Duration
For both cohorts, patients received 3 cycles of Ibr lead-in followed by 12 cycles of combined Ibr + Ven

Confirmed uMRD (58%, n=86)- Randomized to placebo vs Ibr
Not confirmed uMRD (42%, n=63)- Randomized to Ibr vs Ibr + Ven

Median duration of Rx- Ibr-28.6 months, Ven- 12.0 months

Figure. DFS by Randomized Treatment Arm in Confirmed uMRD Group[a]



[a]The 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.

Table. PFS Rates by Randomized Treatment Arms

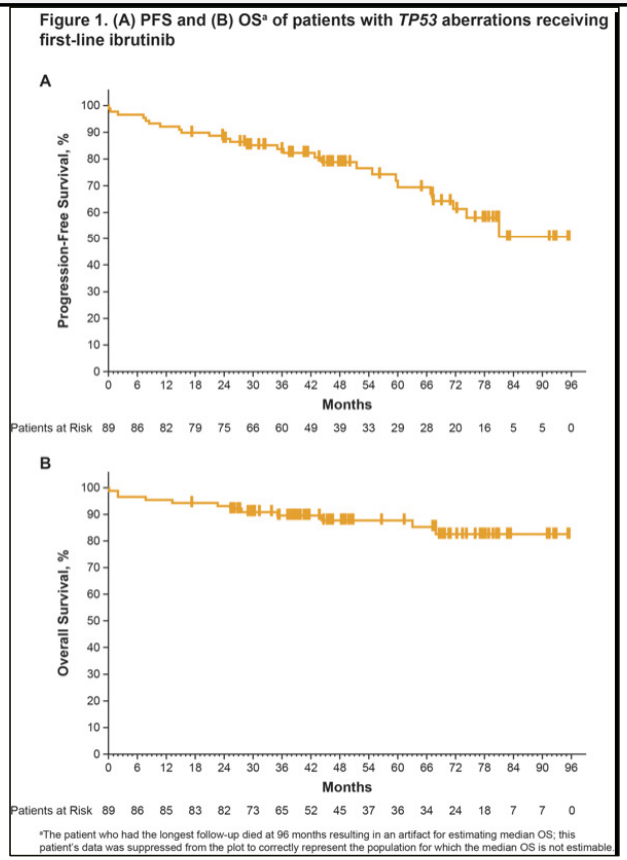
	30-Month PFS Rate % (95% CI)
Pts with Confirmed uMRD	
Placebo (n=43)	95.3 (82.7–98.8)
Ibr (n=43)	100.0 (100.0–100.0)
Pts without Confirmed uMRD	
Ibr (n=31)	95.2 (70.7–99.3)
Ibr + Ven (n=32)	96.7 (78.6–99.5)

Adverse events- Grade3/4- Neutropenia 36%, Hypertension 10%, Thrombocytopenia 10%, Diarrhea 5%

ASH 2020 Abstract No: 642

Long-Term Efficacy of First-Line Ibrutinib Treatment for Chronic Lymphocytic Leukemia (CLL) With 4 Years of Follow-Up in Patients With TP53 Aberrations (del(17p) or TP53 Mutation): A Pooled Analysis From 4 Clinical Trials

The outcomes of CLL with p53 aberration on chemo-immunotherapy is dismal. Ibrutinib has improved the outcomes. Long-term results from 4 trials were pooled.



89 Patients from PCYC-1122e and 1130, ECOG1912 and RESONATE-2 were analysed. 45 received Ibr alone, 44 received Ibr plus anti-CD20.

Long term data of PFS and OS was analysed.
53% stage III/IV, 38% Bulky disease, 69% IgVH unmutated
Median Follow-up- 50 months

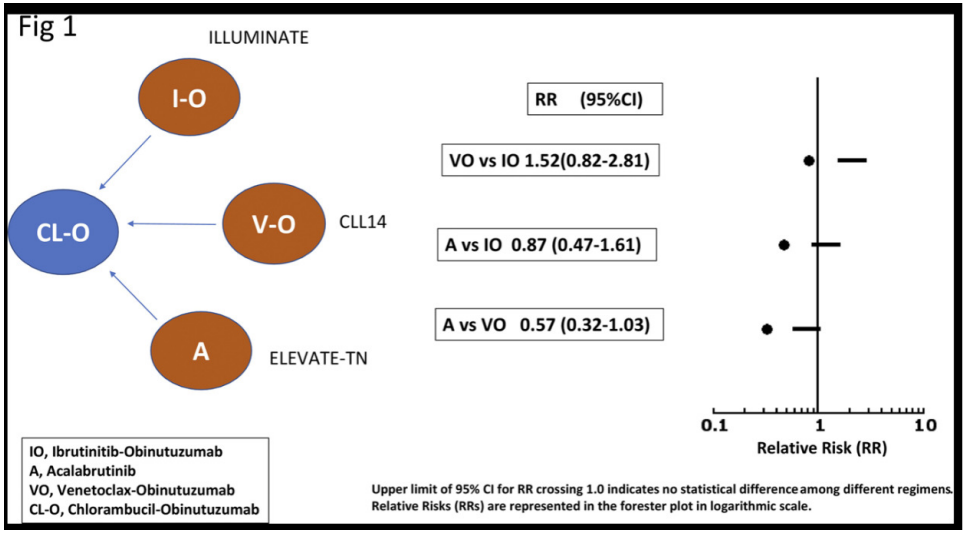
Median PFS- Not reached
Median duration of treatment- 46 months
Reason for discontinuation- 20% PD, 12% study closure, 10% AE
Grade ¾ AE- Infection-22%, HTN 13%, AF 12%, Bleed 7%

Ibrutinib associated with significant improvement in survival outcomes in this high-risk subset of CLL

ASH 2020 Abstract No: 642

Comparison between Time-Limited,Venetoclax-Based and Continuous Bruton Tyrosine Kinase Inhibitors-Based Therapy in the Upfront Treatment of Chronic Lymphocytic Leukemia (CLL):a Systematic Review and Network Meta-Analysis

Fig 1



TAs have not been tested in head-to-head trials. Systematic review and network meta-analysis was performed.

RCT testing TA in upfront CLL were included. HR for PFS, OR for response and adverse event rates were considered.

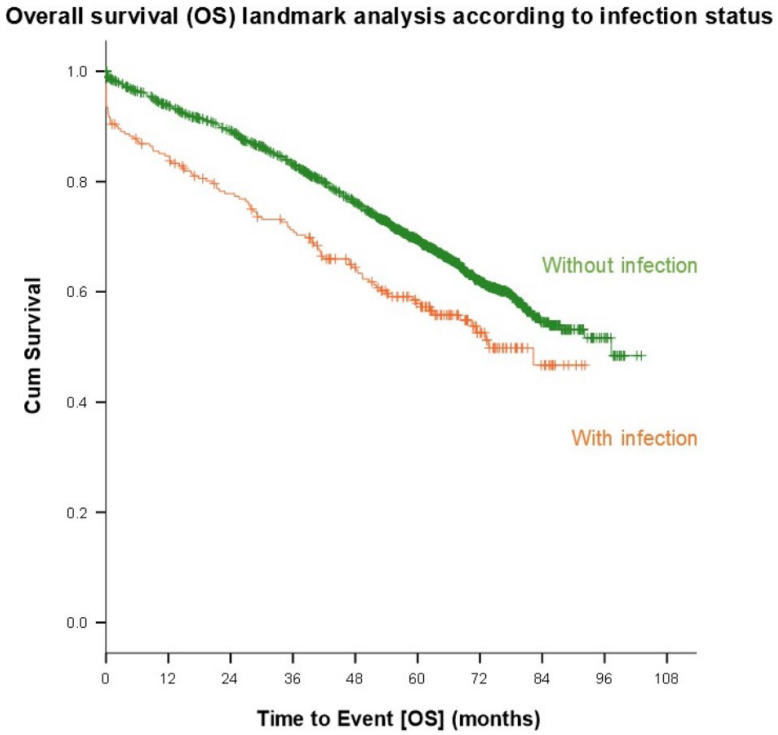
6 studies identified, 3 were included in the NMA. 1336 patients treated on these trials- 113 IO, 216 VO and 179 A.

No diference in PFS, ORR or AE between the Targeted agents

ASH 2020 Abstract no: 1313

Severe Infections in Patients with Chronic Lymphocytic Leukemia Treated with (Immuno-)Chemotherapy: A Pooled Analysis of Gcllsg Trials

Data of first line pts from 5 clinical trials (CLL7- FCR regimen, CLL8-FC vs FCR, CLL 10- FCR vs BR, CLL-11- CLB,CLB-R,CLB-Ob and CLL2M-BR) were analysed.
Clinical, laboratory, genetic and event-related data were pooled.



Total population- 2,291 patients (Median age 64 yrs)

Median observation time- 71.7 months (R- 43.7-81.0 months)

Infections

≥ Grade 3- 229 (10%)

82.5% G3 9.6% G4 7.9% G5	FCR – 12.1% BR- 11.4% CLB- 10.3%	FC 35- 8.8% CLB-Ob- 7.6% CLB-R- 7.4%

Bacterial- 13.5%, Viral- 15.3%, Fungal- 2.2%, **75.1% unspecified**

Patients equally matched in clinical, cytogenetic, molecular characteristics – with or without infections

No difference in CR/PR rates (79.9% vs 83.2%) with/without infections

Overall survival significantly shorter in pts with severe infections compared to patients without severe infections (median 73.7 months vs 97.3 months, HR 1.503, 95% CI 1.217-1.856, $p < 0.001$).

2941 Initial Treatment vs Watch and wait in Advanced-stage Follicular Lymphoma in the Rituximab Era – an Analysis of the National Cancer Database (NCDB)

Rituximab era [existing studies limited by sample sizes]

- RCT - Rituximab at Dx vs WW – longer TTNT, no diff in OS *(Ardeshna et al, 2014)*
- No impact of WW vs IT on TTNT *(Solal-Celigny et al., 2012)*

2011-2016, Stage III-IV FL.

- **14417 patients [10755 - IT (74.6%), 3662 (25.4%) – WW]**
- **13050 - Grade 1-2 FL, 4286 - Grade 3 FL.**

Gr 1-2 FL were more likely than Gr 3 - WW (29.8% vs 12.5%; p<0.01).

WW - older, more likely female, higher education, more likely insurance.

Gr 1-2 FL -5yr OS [WW vs IT (76.3% vs 76.2%)

Gr 3 FL – 5yr OS [WW vs IT (65.3% vs 73.5%).

In multivariate analysis

Gr 1-2 FL – similar OS [WW vs IT] p=0.25)

Gr 3 FL – worse OS [WW vs IT p=0.002)

Table 2. Factors associated with overall survival in multivariate analysis

	HR (95% CI)	P-value
Age increase by 10 years	1.95 (1.86, 2.04)	<.001
Male vs female	1.22 (1.12, 1.34)	<.001
Charlson / Deyo comorbidity score, 0 vs > 0	0.63 (0.58, 0.70)	<.001
Stage 3 vs stage 4	0.78 (0.71, 0.86)	<.001
Education: not-high school graduate in patient's zip code, < 10.9% vs >10.9%	0.77 (0.69, 0.85)	<.001
No insurance/Medicaid vs Private insurance/Medicare	1.64 (1.37, 1.98)	<.001
Previous malignancies (Yes vs No)	1.31 (1.15, 1.50)	<.001
Interaction term between grade and initial management		0.005

Conclusion:

Confirms lack of OS benefit -advanced stage, grade 1-2 FL [WW vs IT]

In contrast, advanced stage, grade 3 FL – worse OS with WW approach

Figure 1. Overall survival for patients with grade 1-2 FL by management at diagnosis

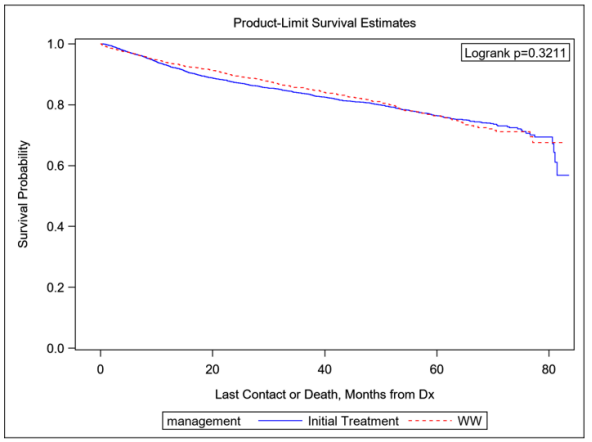
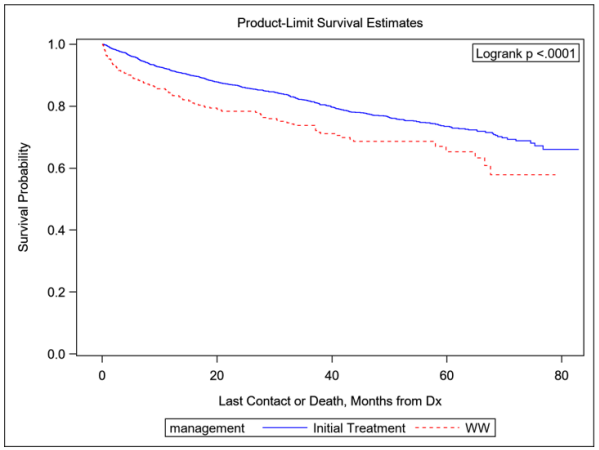


Figure 2. Overall survival for patients with grade 3 FL by management at diagnosis



Note: Under the assumption that grade 3b FL almost always received initial treatment, the red curve (WW) included only grade 3a patients. The plot showed that grade 3a patients on WW had worse OS compared to grade 3 patients who received initial treatment.

1192 Lenalidomide/RCHOP (R2CHOP) Produces High Response Rates and Overall Survival in New, Untreated Diffuse Large B Cell Lymphoma Transformed from Follicular Lymphoma-

Transformation of LG FL to DLBCL - poor prognosis. 5yr OS after RCHOP without ASCT 40%, ORR to lenalidomide as single agent - 45% (21% CR (*Witzig, Ann Onc 2011*).

Phase II trial R2CHOP untreated de novo/transformed DLBCL (NCT00670358)
- subset of transformed DLBCL.

RCHOP, pegfilgrastim Day 2, Lenalidomide 25 mg D 1-10/21.
Primary outcome - EFS Secondary outcomes ORR, CR, OS, PFS.
iPET2 and EoT PET

Results:
39 pts - 2013 to 2020; Median age 64
70% - prior FL, 30% - concurrent FL.
79% stage II-IV disease ; 39% - high IPI 4-5.
ORR 97% (32/33), 29 (88%) – CR, 3 - PR.
12mth EFS 87.9% , 2yr PFS/OS 84.5% vs 96.9%.
30 (91%) - hematologic AE ≥3

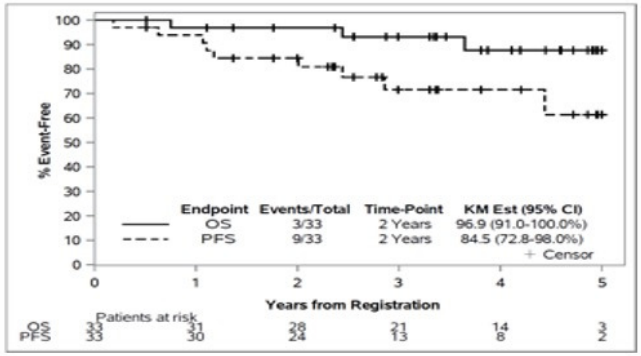
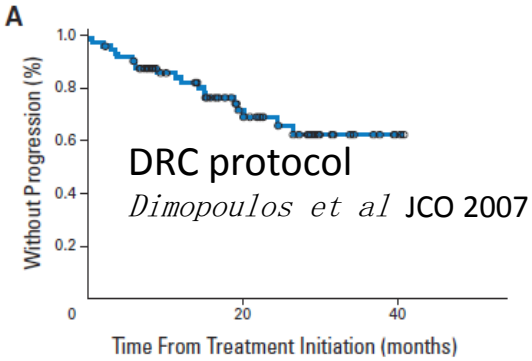
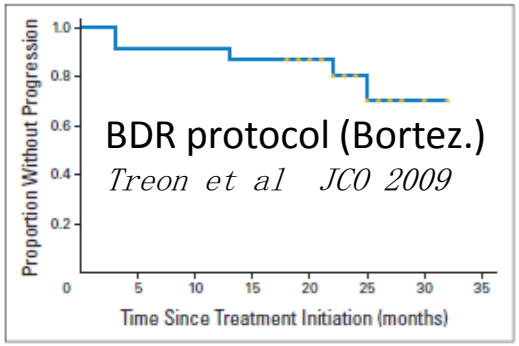


Figure 1: Kaplan-Meier (KM) estimates of progression free survival (PFS) and overall survival (OS).

Conclusion:
R2CHOP - effective in transformed DLBCL - high response rates, PFS seen in current study

337 Bortezomib in Combination with Dexamethasone, Rituximab and Cyclophosphamide (B-DRC) As First – Line Treatment of Waldenstrom's Macroglobulinemia: Results of a Prospectively Randomized Multi-center European Phase II Trial





Randomized 1:1 to DRC (Dexa 20mg D1, Ritux 375mg/m^2 IV D1 & 1400 mg SC d1 cycle 2-6, Cyclo 100 mg/m^2 D1-5 or to B-DRC (DRC + Bortez. SC 1.6mg/m^2 day 1, 8, 15) - 6 cycles
Primary endpoint PFS. Secondary endpoints – CR/ORR, OS, toxicity.

Results: 202 Randomized. Median F/U 27.5mths. Median age 68 yrs.
Mutational status: MYD88^{MT} and CXCR4^{WT} – no diff between 2 groups. Outcome not stratified by mutation.
Median PFS - not reached vs 50mths [B-DRC vs DRC]
2yrs PFS 80.6 % vs 72.8 % (p=0.32). Median OS not reached in either treatment arm.
ORR 91.2% vs 86.7 %
B-DRC and DRC were well tolerated

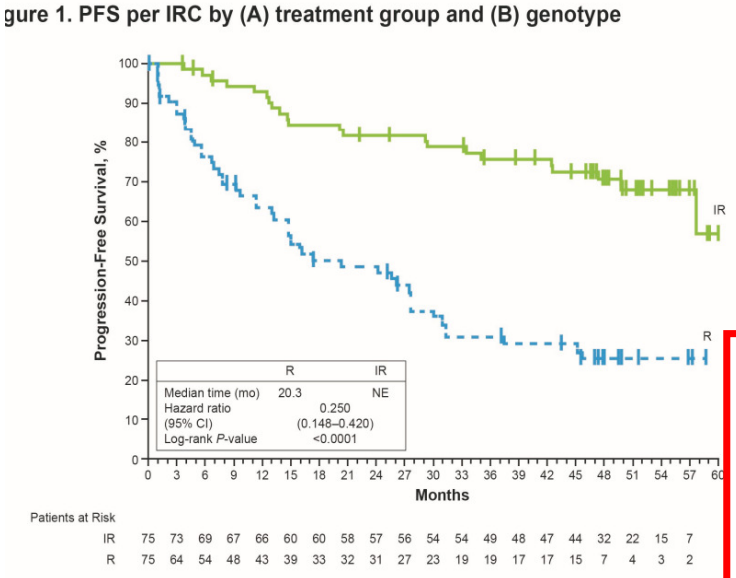
Conclusions: Addition of Bortezomib to DRC – no difference in PFS or ORR

Five-Year Follow-Up of Ibrutinib Plus Rituximab Vs Placebo Plus Rituximab for Waldenstrom's Macroglobulinemia: Final Analysis From the Randomized Phase 3 iNNOVATE™ Study

Phase 3 iNNOVATE study -

Primary analysis after 26.5 mo median F/U -Ibrutinib in combination with R (IR) - superior PFS vs placebo plus R (Dimopoulos, *N Engl J Med* 2018)

After 30.4 mo median follow-up, IR continued to show superiority over R (Buske, ASH 2018)



In the present analysis – FINAL ANALYSIS

150 pts (75 per arm) – Randomized 1:1

Confirmed symptomatic WM - Naive or previously treated

- Ibrutinib 420mg + R (375 mg/m^2/wk week 1–4 and 17–20).
- Placebo + R (375 mg/m^2/wk week 1–4 and 17–20).

- **Median follow-up 50 mo**
- **Median PFS not reached with IR vs 20.3 mth with R ([HR] 0.25 [0.15–0.42]; *P*<0.0001)**
- **PFS rates 68% vs 25% at 54 mo.**

Patients treated with IR also had a PFS benefit over those treated with R, regardless of their prior treatment status

PFS benefit of IR over R was also observed across prespecified subgroups

704 Initial Treatment with Lenalidomide Plus Rituximab for Mantle Cell Lymphoma (MCL): 7-Year Analysis from a Multi-Center Phase II Study

-Early efficacy and 5-year follow-up - multicenter phase 2 study of lenalidomide plus rituximab as initial treatment for MCL

- highly effective (ORR 92%, CR 64%) and well tolerated, with durable responses (5-year PFS and OS of 64% and 77%) NEJM 2015:373:1835; Blood 2018:132:2016)

This study - 7 Yr analysis

Both induction and maintenance with lenalidomide (LEN) and rituximab (RITUX).

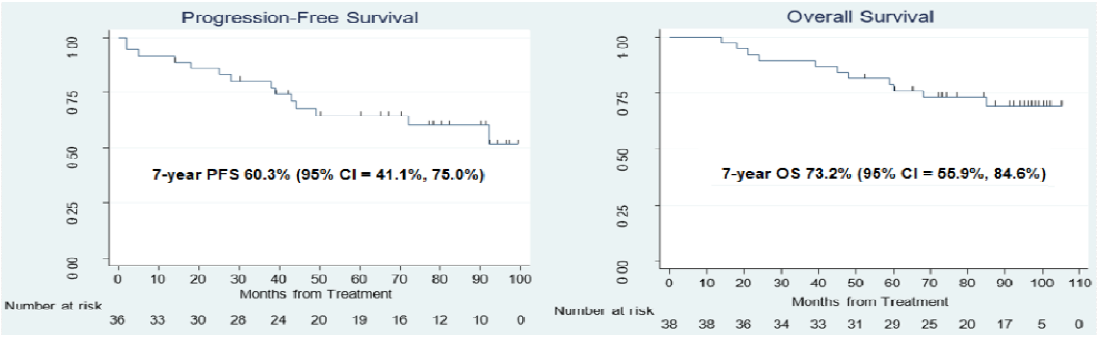
- Induction -LEN 20mg OD (Day 1-21 of 28-day cycle) - 12 cycles
- Followed by maintenance with dose reduction to 15 mg.
- RITUX weekly for 4 weeks during cycle 1, then once every other cycle.

Treatment continued until progression of disease, with option to stop therapy after 3 years.

- **7-year PFS rate estimated at 60.3% (95% CI = 41.1%, 75.0%)**
- **7-year OS rates 73.2% (95% CI = 55.9%, 84.6%)**
- **MIPI score ≤6.2 was predictive of increased overall survival (p = 0.04)**
  - **7-year OS rate 80.6% in this group versus 57.1% in patients with MIPI >6.2**
  - **no difference in PFS between the two groups**

Toxicity not significantly affected by continuous treatment, and close follow up was able to limit toxicity for those who wished to remain on therapy

Conclusion: Combination offers a ***chemotherapy-free initial approach*** which compares favorably in outcome to conventional outpatient chemotherapy-based regimens



Non Hodgkin Lymphoma
T cell

Lead:

Chandran / Anup

ASH 2020 Abstract No:40:
Multi-Center Phase II Study of Oral Azacytidine (CC-486) Plus CHOP As Initial Treatment for Peripheral T-Cell Lymphoma (PTCL)

Addition of hypomethylating agent oral azacitidine (CC486) to CHOP as initial therapy is feasible, safe, and induces high CR rate in PTCL-TFH subtype

Table: Disease Characteristics and Clinical Responses

Characteristic	No. of Patients	Percent
No. of Patients	21	100%
Sex		
Male	13	62%
Female	8	38%
Age, years		
Median (range)	66	
Range	22-77	
ECOG Performance Status		
0-1	13	62%
>1	8	38%
Ann Arbor Stage		
III-IV	19	90%
LDH		
Normal	11	52%
Elevated	10	48%
Bone Marrow Involvement		
Yes	7	33%
No	13	62%
PTCL Subtypes		
PTCL-TFH	17	81%
PTCL-NOS	3	14%
ATLL	1	5%
IPI Risk Category		
0-1	5	24%
2	7	33%
3	3	14%
4-5	6	29%
CD30 Expression		
Positive (≥ 5%)	5	24%
Negative (<5%)	16	76%
Interim Response (after cycle 3)	Evaluable n=20	
ORR	17	85.0%
CR	11	55.0%
End-of-Treatment Response	Evaluable n=17	
ORR	13	76.5%
CR	13	76.5%

Aberrant DNA methylation with PTCL lymphomagenesis- **Recurrent mutations affecting TET2, DNMT3A, IDH2 and RHOA**

Aza-R/R AITL (Lemonnier et al. Blood 2018;132:2305)

CHOP+Aza feasibility (Clozel et al. Cancer Discov 2013;3:1002) (Martin et al. Blood 2017;130:192)

Phase II study CHOP on day 1 of each cycle for 6 cycles.
Priming with oral azacitidine (CC-486) at 300 mg daily -6 to 0
14 days before CHOP cycles 2-6 8-21 / GCSF/PCP/VZV
9 or more CR out of 17 enrolled patients - worthy of further study.

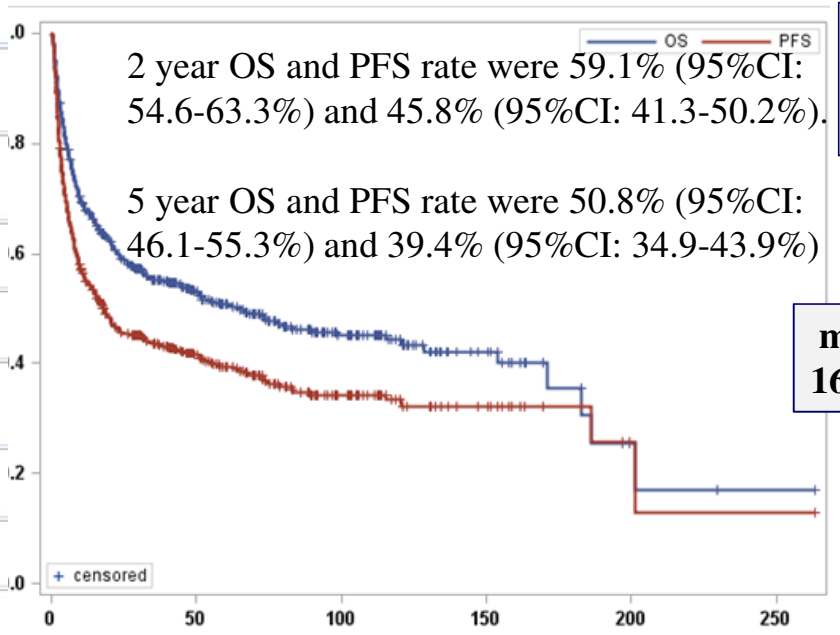
Median follow-up of 7 months (range 4-25 months)
Safe. Febrile neutropenia uncommon (14.3%)
Interim (3 cycles): ORR - 85% / CR - 55% (90%CI of 34.7%-74.1%).
End-of-treatment (EOT, n=17) CR - 76.5% (90%CI of 53.9%-91.5%) ;
86.7% for 15 PTCL-TFH

TET2, RHOA, DNMT3A, and IDH2 mutations :73%, 40%, 13% and 13%
TET2 mutations - CR (p=0.014), favorable PFS (p-0.012) and OS (p=0.042).
DNMT3A - adverse OS (p=0.028).

ASH 2020 Abstract No:41 : Successful Treatment of Mature T-Cell Lymphoma with Allogeneic Stem Cell Transplantation: The Largest Multicenter Retrospective Analysis

Disease Type (N)	Age at Transplant Median (range)	HCT-CI at Transplant Median (range)	IPI at Diagnosis Median (range)	Remission Status at Transplant	Conditioning Regimen Intensity	2 – yr PFS (95% CI)	5- yr PFS (95% CI)
PTCL-NOS (133)	52.1 (24-72)	1 (0-8)	2 (0-4)	60 CR 43 PR 10 SD 6 PD 14 UNK	51 MA 82 NMA/RIC	49.6% (40.5-58%)	43.9% (34.9-52.5%)
AITL (82)	52 (34-71)	2 (0-8)	2 (0-5)	45 CR 26 PR 2 SD 2 PD 7 UNK	27 MA 55 NMA/RIC	56.4% (44.7-66.6%)	47.3% (35.2-58.5%)
NK/T (20)	41 (20-62)	1 (0-5)	1 (0-4)	12 CR 4 PR 4 UNK	8 MA 12 NMA/RIC	30% (12.3-50.1%)	30% (12.3-50.1%)
Hepatosplenic (34)	33.5 (16-58)	2 (0-7)	3 (0-4)	11 CR 12 PR 4 SD 7 UNK	18 MA 16 NMA/RIC	54.7% (36.3-69.8%)	48.6% (29-65.6%)
CTCL: MF/SS (67)	51.5 (26-72)	1 (0-5)	2 (0-4)	24 CR 32 PR 3 SD 4 PD 4 UNK	11 MA 55 NMA/RIC 1 UNK	33.9% (22.6-45.5%)	18.6% (9.7-29.8%)
ALK-positive ALCL (18)	42 (19-58)	1 (0-4)	1.5 (0-3)	12 CR 3 PR 1 PD 2 UNK	9 MA 9 NMA/RIC	35.3% (14.5-57%)	35.3% (14.5-57%)
ALK-status UNK ALCL (7)	35 (23-49)	0 (0-2)	2 (1-4)	3 CR 3 PR 1 SD	6 MA 1 NMA/RIC	14.3% (0.7-46.5%)	14.3% (0.7-46.5%)
ALK-negative ALCL (26)	54 (25-69)	1 (0-5)	1.5 (0-3)	18 CR 7 PR 1 UNK	6 MA 20 NMA/RIC	34.9% (17.1-53.4%)	34.9% (17.1-53.4%)
Subcutaneous Panniculitic-like T-cell (11)	36 (26-49)	0 (0-4)	2 (2-3)	5 CR 4 PR 2 UNK	3 MA 7 NMA/RIC 1 UNK	55.6% (20.4-80.5%)	55.6% (20.4-80.5%)
Enteropathy-associated (7)	58.5 (48-69.1)	1.5 (0-6)	2 (0-4)	3 CR 2 PR 1 SD 1 UNK	1 MA 6 NMA/RIC	33.3% (4.6-67.6%)	33.3% (4.6-67.6%)
Primary Cutaneous gamma-delta TCL (6)	57 (57-57.26)	1.5 (0-9)	2 (1-5)	2 CR 4 PR	4 MA 2 NMA/RIC	33.3% (4.6-67.6%)	33.3% (4.6-67.6%)
Other (97)	51 (19-70)	1 (0-11)	3 (0-6)	50 CR 28 PR 2 SD 3 PD 14 UNK	38 MA 58 NMA/RIC 1 UNK	48.1% (37.5-57.9%)	42.2% (31.6-52.5%)

underwent allogeneic transplant for T-cell Lymphoma (n=508)



2 year OS and PFS rate were 59.1% (95%CI: 54.6-63.3%) and 45.8% (95%CI: 41.3-50.2%).

5 year OS and PFS rate were 50.8% (95%CI: 46.1-55.3%) and 39.4% (95%CI: 34.9-43.9%)

31% with TCL - disease free 3 years after aHCT (Smith et al. JCO2013)

1/1/2000-12/31/2019/ 12 academic institutions

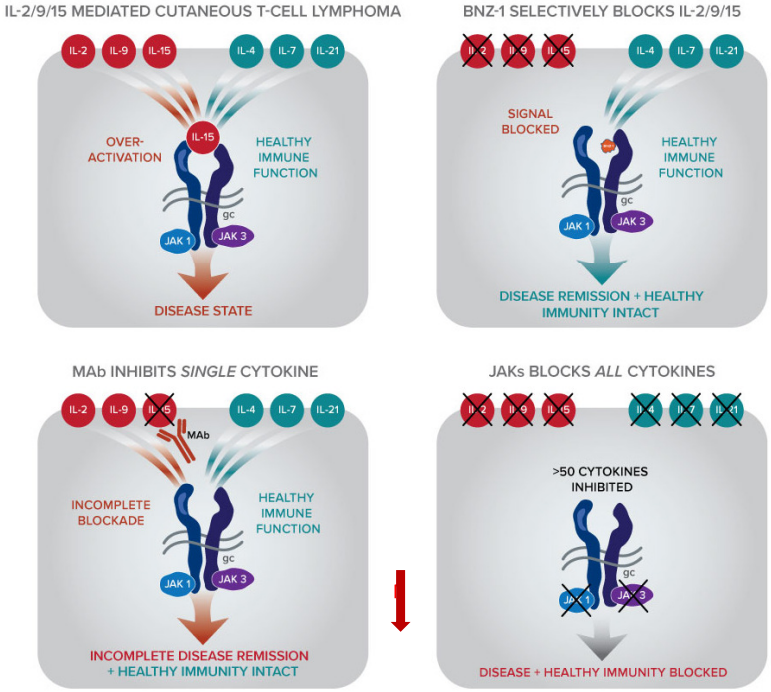
median FU-29.7 m(0.1-263 m), 163 pts -relapsed / 261 pts died

CTCL - higher relapse
OS was similar.
AITL trend improved survival

Disease status at the time of HCT was associated with PFS (p<0.001). Median PFS -CR (n=239), PR (n=164), SD (n=22) or PD (n=14) were 44.6 mo, 8.6 mo, 21 mo, 3.5 mo.
Degree of donor match was associated with cumulative TRM (p=0.0241). MRD, MUD, or MMD HCT, cumulative TRM at 12 months - 8% (95%CI: 5.5-12.2%), 13.1% (95%CI: 9.7-17.8%), 14.7% (95%CI: 8.7-24.6%)

ASH 2020 Abstract No:43:
Co-Inhibition of IL-2, IL-9 and IL-15 By the Novel Immunomodulator, Bnz-1, Provides Clinical Efficacy in Patients with Refractory Cutaneous T Cell Lymphoma in a Phase 1/2 Clinical Trial

BNZ-1, an IL-2, IL-9, and IL-15 inhibitor, may provide a novel treatment option for CTCL patients .



IL-2 and IL-15- pathogenesis of CTCL through activation of JAK/Stat signaling pathways

BNZ-1 -pegylated peptide antagonist -com γsignaling receptor: IL-2, IL-9 & IL-15

Multicenter, open-label Phase 1/2 study: sequential dose cohorts:0.5,1,2,4 mg/kg weekly intravenous BNZ-1: 15- 4 weeks [mycosis fungoides (MF) any stage/Sézary syndrome (SS)]

Activity in all doses: 2mg/Kg -19 cases enrolled

- **Incidence, severity and relationship of treatment-emergent adverse events**
- **Exploratory assessment of changes from baseline in CTCL disease severity (mSWAT)**

- **1 patient (5%) complete response,**
- **11 (58%) patients partial response (50% reduction over baseline)**
- **7 patients (37%) showed stable disease.**
- **No disease recurrence.**
- **Mean duration of response was calculated to be 9.2 months**

1) IL-2 and IL-15 inhibition x Tr propagation/survival
2) IL-2 and IL-9 inhibition T Regs
3) IL-15 inhibition anti-inflammatory effect

BNZ-1 -inflammatory nature of CTCL - reduction in mSWAT scores

ASH 2020 Abstract:

Final Analysis of the Ro-CHOP Phase III Study (Conducted by LYSA): Romidepsin Plus CHOP in Patients with Peripheral T-Cell Lymphoma

Emmanuel Bachy et al

PTCL – Aggressive NHL, Poor Prognosis. Romidepsin – HDACi – FDA approved in patients with PTCL who have received at least 1 prior therapy

Randomised, Phase 3 multicenter trial Untreated PTCL
Randomised based on IPI < 2 Vs 2 or more, 60 or less Vs > 60 yrs & histology - Nodal Vs Extranodal

CHOP Q3wkly with Romidepsin - Day 1 & Day 8 - 12 mg/m2.

Primary Endpoint –PFS
Secondary - OS, ORR, CR+CRu, Safety

ITT - 421, Median age - 65 yrs, Median F/U - 27.5 mo
63% - Stage 4, 81% - IPI>2
Median PFS - 12 mo Vs 10.2, HR - 0.81, p=0.09
Median OS - 51.8 mo Vs 42.9
ORR - 63 Vs 60%, CR+CRu - 41 Vs 37%
TEAE > 40%, Grade 3/4 TEAEs that occurred in ≥ 30%. Myelosuppression+, Dose interruption (36 Vs 20%), reduction (26 Vs 15%) and discontinuations (3 Vs 3%)

Conclusion - No change in standard

ASH 2020 Abstract :

Safety and Efficacy of Mitoxantrone Hydrochloride Liposome in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma and Extranodal NK/T-Cell Lymphoma: A Prospective, Single-Arm, Open-Label, Multi-Center, Phase Ⅱ Clinical Trial

Yan Gao et al

PTCL and Extranodal NK T cell lymphomas – rare.
Outcomes of relapsed and refractory – poor. Lack effective treatment options.
Preclinical studies - Liposome mitoxantrone – high accumulation in tumor tissues
Half life – significantly prolonged in Phase 1 trial

Prospective, single arm, open label, Phase 2 multicenter trial
PTCL after prior anthracyclines-based chemotherapy or ENKTCL failed - asparaginase-contained regimen.
Main exclusion criteria – prior cumulative dose of doxorubicin >360 mg/m2, history of significant cardiac malfunction or uncontrollable cardiovascular diseases.

PLM60 20mg/m2 Q 4 wkly x 6 cycles or until disease progression, or intolerable toxicity.
Primary endpoint - objective response rate (ORR)
Secondary – ORR(Investigators), DoR, PFS, OS, DCR

N=108, 98 evaluable for response. Objective response in 44 (40.7%)
CR – 22 (20.4%). ORR – 60%,
I ORR – 43.5%, Median DCR – 77.8%
Median DoR – 9.8 mo, DoR > 3 mo in 77.3%
Median PFS – 6.7 mo, 6 mo PFS – 55.3%
Median OS – 16.3 mo, 6-mo OS - 74.9%
Gr 3 or more toxicities – Leucocytopenia (50%), Neutropenia (45.4%)

Conclusion – Promising results

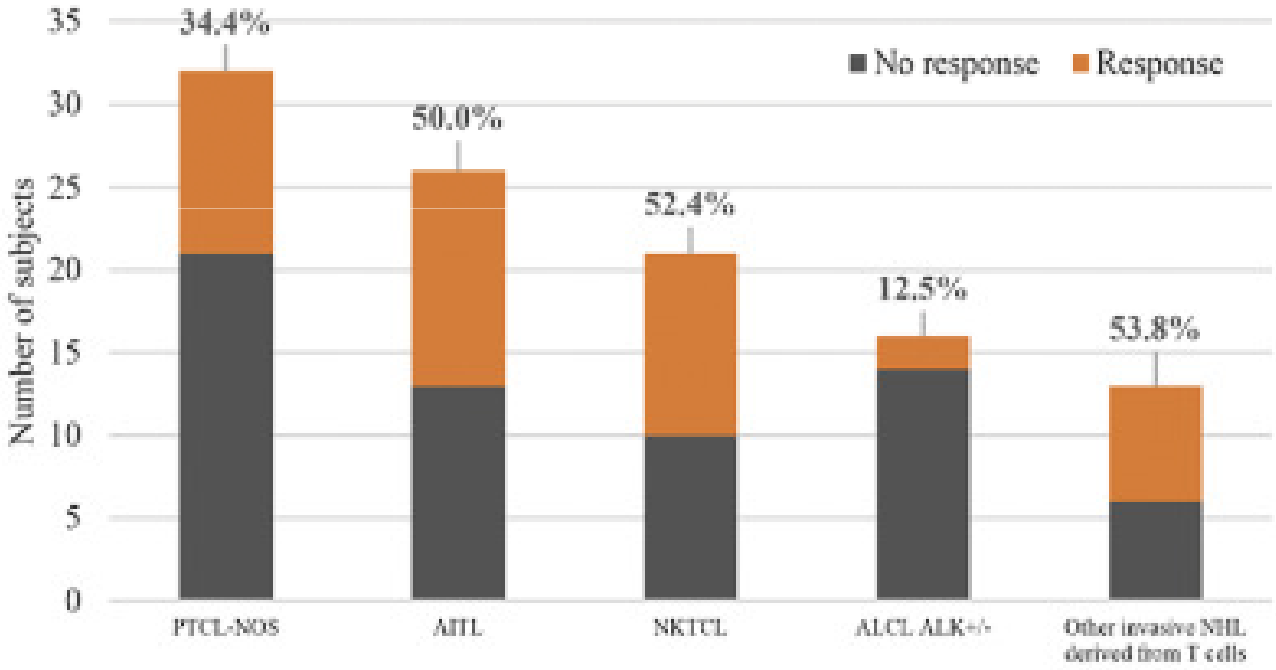


Figure 2. The response and maximum percentage changes from baseline in target lesions by cancer subtype

ASH 2020 Abstract :

A Phase II Study of Pembrolizumab in Combination with Romidepsin Demonstrates Durable Responses in Relapsed or Refractory T-Cell Lymphoma (TCL)

Swami P. Iyer et al

Few treatment options in relapsed refractory T cell lymphoma

Phase I/II trial.
Safety evaluated in the lead-in phase I study using a dose de-escalation strategy - Pembrolizumab at 200 mg on day 1 and Romidepsin 14 mg/m2 on days 1 and 8

Primary objectives - Safety, tolerability, and ORR.
Secondary objectives - complete remission rate (CRR), PFS, OS and DOR
Outcome assessment - Lugano Revised Response Criteria and correlated with PD-L1 expression by IHC and exploratory analysis for cell of origin.

N=20, Median age – 67 yrs, Male predominance. Phase 1 – 6 patients
Prior treatment – CHOP/CHOP like in 90%, Auto SCT in 2 pts, radiation in 4 and salvage therapies in 10
Phase II - 14 pts with 85% >60 years.
ORR - 50%, Median follow-up was 18 mo. 5 patients achieved CR and 2 PR. 3 CRs in Phase 1
Among 8 CRs – 4 off treatment for > 1 yr, 2 still on treatment for > 2 yrs, 1 underwent Haplo SCT
Most common Gr 3 or more ADR – Nausea, vomiting and fatigue
Hyperprogression in 2
IRAE – 4 pts - Grade 1 cytokine storm, Grade 3 gastritis, Grade 4 colitis and Grade 2 pneumonitis
Median PD-L1 expression in responders was 10. Higher PDL1 in patients with CR

Conclusion – Combination – Durable ORR and safe

Table 1 Demographics for Phase I and II	TCL (n= 20)
Age (Median; range in years)	67.5 (51-82)
<60 n (%)	3 (15)
≥60 n (%)	17 (85)
Gender, n (%)	Male: 13 (65) Female: 7 (35)
Race, n (%)	Caucasian: 10 (50) Black: 2 (10) Hispanic/Latino: 5 (25) Asian: 3 (15)
Bone marrow involvement, n (%)	5 (25)
Prior therapies, n (%)	≤2: 10 (50) ≥3: 10 (50)
Prior therapies CHOP/CHOP protocol CHOEP EPOCH BV with CHP or CHEP or Benda BV alone Others: CEOP, GDP/GND, DeVIC/ESHAP, Clinical studies: Romidepsin-ICE, Mogamulizumab	 8 3 3 4 3 4 6
Prior Radiation, n (%)	4 (20)
Prior SCT	2 (10)
Elevated LDH, n (%)	12 (80)
ECOG ≥3, n (%)	0 (0)
Stage 3 or 4, n (%)	17 (85)
Disease status, n (%)	Relapse: 3 (15) Refractory: 17 (85)
Histologic classification, n (%)	PTCL, NOS: 7 (35) PTCL with TfH: 3 (15) AITL: 2 (10) Mycosis Fungoides (MF) transformed: 3 (15) ALCL: 3 (15) NK/T cell: 2 (10)

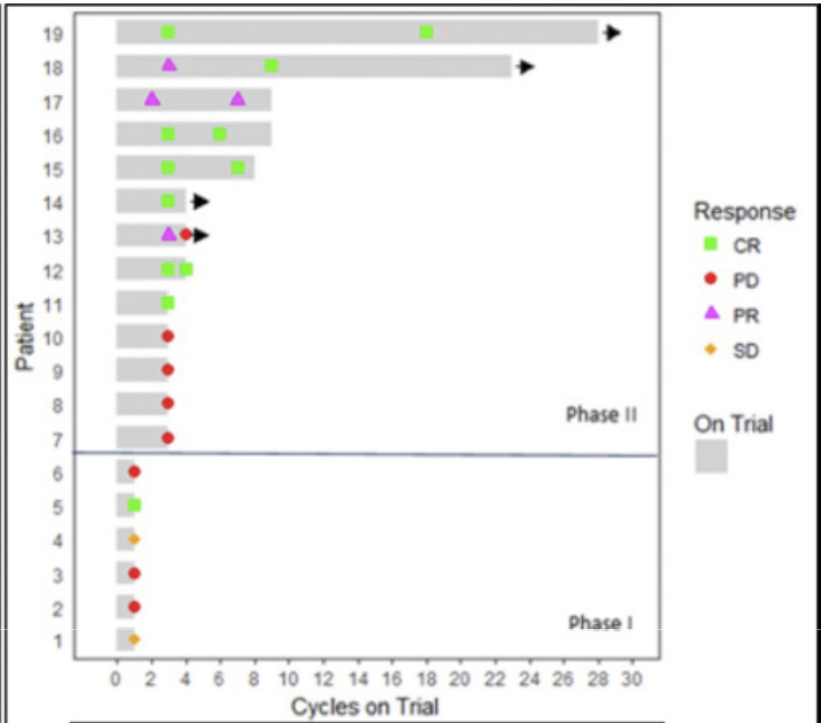


Figure 1A: Swimmer's plot (generated using R 3.4.4) sorted by the length on trial

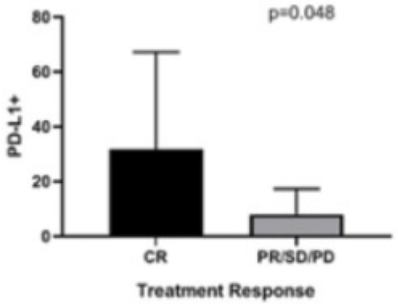
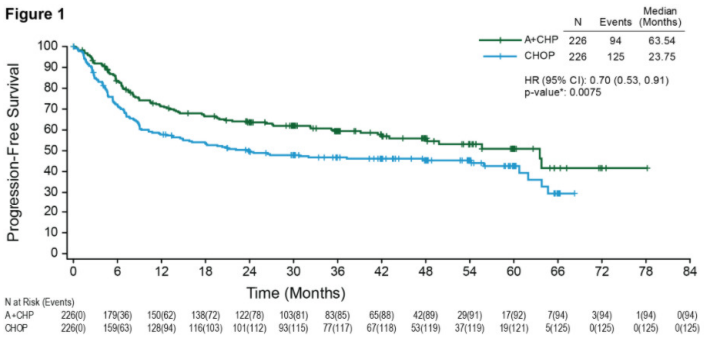


Figure 1B: Correlation of PDL1 expression by IHC with response

ASH 2020

The Echelon-2 Trial: 5-Year Results of a Randomized, Double-Blind, Phase 3 Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Frontline Treatment of Patients with CD30-Positive Peripheral T-Cell Lymphoma

A+CHP was the first treatment regimen to show an OS benefit over CHOP in patients (pts) with systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL)



This study report results with a median follow-up of 44.3 months for PFS and 55.5 months for OS.

Eligible adult pts with previously untreated CD30-positive PTCL (targeting 75% ± 5% with sALCL) were randomized to A+CHP or CHOP for six or eight cycles. Subsequent therapies, including BV or BV-containing regimens, were permitted

CONCLUSION

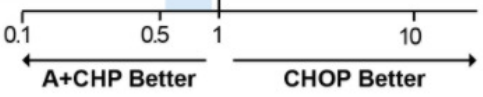
At 5 years, frontline treatment with A+CHP continues to provide clinically meaningful improvement in PFS and OS versus CHOP, including ongoing remission in ~60% of pts with sALCL, with a manageable safety profile, including continued resolution or improvement of PN.

	A+CHP(226)	CHOP(226)
PFS	**50.9%**	**42.7%**
OS	**68.7%**	**60.3%**
BV (second)	**10%**	**23%**
Median PFS	**63.5 m**	**23.8m**

90% ADVANCED STAGE, 70% sALCL
Only 2% had grade 03 PN

Figure 2

ITT Subgroups	Event/N A+CHP	Event/N CHOP	Hazard Ratio (95% CI)
Overall	94/226	125/226	0.70 (0.53, 0.91)
IPI Score			
0–1	14/52	27/48	0.42 (0.22, 0.81)
2–3	59/141	79/145	0.72 (0.51, 1.01)
4–5	21/33	19/33	1.14 (0.61, 2.15)
Age			
<65 years	51/157	74/156	0.64 (0.45, 0.92)
≥65 years	43/69	51/70	0.68 (0.45, 1.04)
Sex			
Male	60/133	79/151	0.83 (0.59, 1.16)
Female	34/93	46/75	0.44 (0.28, 0.70)
Baseline ECOG Status			
0	36/84	56/93	0.63 (0.41, 0.96)
1	38/90	50/86	0.61 (0.40, 0.94)
2	20/51	19/47	1.00 (0.53, 1.89)
Disease Stage			
I	3/12	2/9	2.15 (0.22, 20.88)
II	12/30	18/37	0.93 (0.43, 1.99)
III	26/57	36/67	0.63 (0.37, 1.05)
IV	53/127	69/113	0.66 (0.46, 0.95)
Disease Indication			
ALK-positive sALCL	7/49	16/49	0.40 (0.17, 0.98)
ALK-negative sALCL	46/113	61/105	0.58 (0.39, 0.85)
ATLL	2/4	2/3	0.69 (0.10, 4.94)
AITL	19/30	12/24	1.40 (0.63, 3.09)
EATL	1/1	2/2	not estimable
PTCL-NOS	19/29	32/43	0.80 (0.44, 1.46)
sALCL	53/162	77/154	0.55 (0.39, 0.78)
non sALCL	41/64	48/72	0.97 (0.63, 1.48)



ASH 2020 Abstract

Anti-PD-1 Antibody (Sintilimab) Plus Histone Deacetylase Inhibitor (Chidamide) for the Treatment of Refractory or Relapsed Extranodal Natural Killer/T Cell Lymphoma, Nasal Type (r/r-ENKTL): Preliminary Results from a Prospective, Multicenter, Single-Arm, Phase Ib/II Trial (SCENT)

ORIENT-4 trial demonstrated Sintilimab was effective and well tolerated in r/r-ENKTL. The efficacy of Chidamide, an oral HDACi was reported on rr-ENKTL(CHIPEL trial, 2017 ASH). This trial combined both for r/r ENKTL

In the phase II portion, patients received 6 cycles of Sintilimab (200 mg) plus Chidamide (RP2D of 30mg twice weekly) every 3 weeks. Patients with complete response (CR) or partial response (PR) received up to 1 year

PD-L1 protein expression was determined using tumor proportion score (TPS) and combined positive score (CPS). CPS ≥1 was considered positive. All patients' blood samples were collected for ctDNA assessment before treatment in each of cycles

- 37 eligible patients, Median age 48 years,70.3% patients with Stage IV.
- Response : 44% CR, 14%PR
- Median follow-up time was 7.3 (0.9-16.1) months. Estimated 1-year OS rate was 79.1%, 1-year PFS rate was 66.0%
- 48.7% patients had discontinued from study treatment (16 for PD)
- Patients with PD-L1 CPS≥30 exhibited benefit more from treatment.
- TRAEs were neutropenia (51.4%), thrombocytopenia (45.9%)

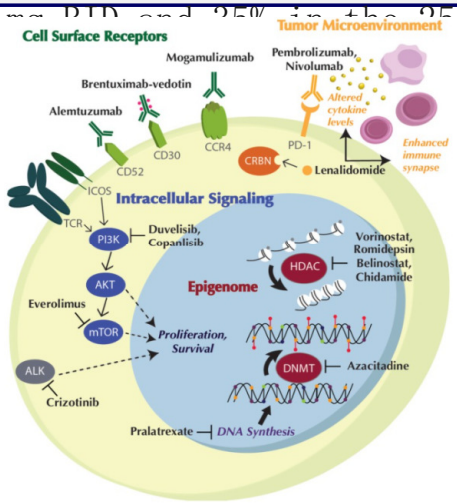
Conclusion

- Sintilimab plus Chidamide showed manageable safety profile and yielded effective antitumor activity, durable response in patients with r/r-ENKTL for the first time.
- It is a promising therapeutic option for this population, especially for those with CPS≥30.
- Epigenetic strategies synergize with anti-PD-1 antibody maybe enhanced antitumor responses to r/r-ENKTL, further investigation

ASH 2020 Abstract

Duvelisib in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma from the Phase 2 Primo Trial: Dose Optimization Efficacy Update and Expansion Phase Initial Results

Most approved therapies for R/R PTCL have ORR of < 30%. In the Phase 2, open-label, multi-center, PRIMO trial of Duvelisib (a dual PI3K-δ,γ inhibitor)- in R/R PTCL, the initial results of the dose-optimization phase showed a 54% ORR in the 75 mg BID and 25% in the 25 mg BID cohorts.



Pts were eligible if they had histologically confirmed R/R PTCL after ≥2 cycles of a prior standard regimen and a CD4 lymphocyte

In this study – DUV starting at 75 mg BID for 2 cycles to achieve more rapid tumor control, followed by 25 mg to try to maintain long-term disease control. For those at 25mg BID, it was permitted for the dose to be re-escalated to 75 mg BID if an assessment shows PD.

- 25 pts have been dosed, 20 of whom underwent at least 1 disease response assessment
- Median age 61 years. Forty-five percent (9/20) of pts remain on treatment
- 11 pts discontinued due to PD (n=7), adverse events (n=2) , or to under go transplant (n=2).
- Responses occurred in 8/20 pts
- The most frequent adverse events seen were neutropenia(25%), ALT increased (21%), Leucopenia (21%) and lymphopenia(21%).

CONCLUSION

- The mature dose-optimization phase results demonstrated a median DOR of 12.2 months for the 75 mg BID cohort.
- The preliminary results from the PRIMO dose-expansion cohort show an ORR of 40 % and CR rate of

Hodgkin Lymphoma

Lead:

Venkat / Rayaz

ASH 2020 Abstract No:370 :
Prevalence and Predictors of Neurocognitive Impairment in Long-Term Survivors of Childhood Hodgkin Lymphoma: A Report from the Childhood Cancer Survivor Study

Childhood HL survivors at increased risk of cardiac, pulmonary and endocrine morbidity and second cancers due to chemotherapy and radiotherapy. There is emerging evidence that HL survivors have neurocognitive impairment.

- The current study included 1,760 survivors (52.0% female, mean age 37.5 years, mean years from diagnosis 23.6) and 3,180 sibling controls (54.5% female, mean age 33.2 years) from the Childhood Cancer Survivor Study.
- Participants completed questionnaire assessing NC domains (task efficiency, emotional regulation, organization, and memory)
- Score worse than 90th centile for community control was considered impairment for a domain.

	Task Efficiency Impairment	Emotional Regulation Impairment	Organization Impairment	Memory Impairment
Model 1:				
HL vs. Siblings	**1.37 (1.01, 1.85)**	**1.56 (1.23, 1.99)**	**1.32 (1.01, 1.73)**	**1.72 (1.21, 2.44)**
Model 2:				
Female (vs. Male)	1.16 (0.82, 1.63)	**1.44 (1.08, 1.92)**	0.83 (0.61, 1.15)	**2.00 (1.33, 3.00)**
Non-White (vs. White)	**2.08 (1.24, 3.50)**	**1.65 (1.02, 2.66)**	1.33 (0.78, 2.25)	1.50 (0.81, 2.75)
Former Smoker (vs. Never)	**1.53 (1.03, 2.29)**	**1.42 (1.01, 2.00)**	0.95 (0.64, 1.43)	**1.87 (1.21, 2.90)**
Current Smoker (vs. Never)	**1.93 (1.21, 3.07)**	**2.49 (1.70, 3.65)**	1.24 (0.78, 1.97)	**1.73 (1.01, 2.97)**
Late Relapse or SMN (vs. None)	**1.57 (1.06, 2.33)**	1.27 (0.91, 1.78)	1.33 (0.91, 1.95)	1.14 (0.72, 1.81)
Anthracyclines (Yes vs. No)	1.27 (0.74, 2.16)	**0.55 (0.35, 0.85)**	0.92 (0.56, 1.52)	1.58 (0.85, 2.95)
Corticosteroids (Yes vs No)	1.30 (0.89,1.90)	1.19 (0.87, 1.62)	1.12 (0.80, 1.60)	0.87 (0.57,1.34)
Chest RT >0 to ≥30 Gy (vs. None)	0.87 (0.54, 1.40)	1.01 (0.67, 1.52)	0.92 (0.60, 1.42)	1.11 (0.65, 1.89)
Chest RT >30 gy (vs. None)	1.10 (0.66, 1.85)	1.15 (0.74, 1.79)	1.07 (0.66, 1.72)	1.25 (0.68, 2.31)
Models 3:				
≥Grade 2 Pulmonary (vs. Grade 1/None)	**1.86 (1.15, 3.02)**	1.09 (0.69, 1.72)	1.00 (0.58, 1.72)	1.61 (0.94, 2.77)
≥Grade 2 Cardiovascular (vs. Grade 1/None)	**1.63 (1.14, 2.33)**	**1.63 (1.22, 2.19)**	**1.53 (1.09, 2.14)**	**2.10 (1.39, 3.16)**
≥Grade 2 Neurologic (vs. Grade 1/None)	**3.69 (2.22, 6.13)**	**1.72 (1.04, 2.84)**	1.75 (0.99, 3.09)	**5.46 (3.22, 9.28)**
≥Grade 2 Endocrine (vs. Grade 1/None)	**1.62 (1.12, 2.33)**	**1.39 (1.04, 1.86)**	0.91 (0.66, 1.26)	**1.53 (1.004, 2.33)**

Bold indicates p<0.05

- Survivors experienced significantly more neurocognitive impairment compared to sibling controls.
- Smoking and chronic health conditions were associated with neurocognitive impairment while treatment exposures showed little association.
- Mitigation or prevention of smoking and chronic health conditions may improve neurocognitive functioning in HL survivors

ASH 2020 Abstract No: 595

Increased Tumor Specific Cytotoxic T Cell Responses and Reversion to a Favorable Cytokine Profile after Treatment in Patients with Newly Diagnosed High Risk Hodgkin Lymphoma Treated on Children's Oncology Group Trial-AHOD1331Study

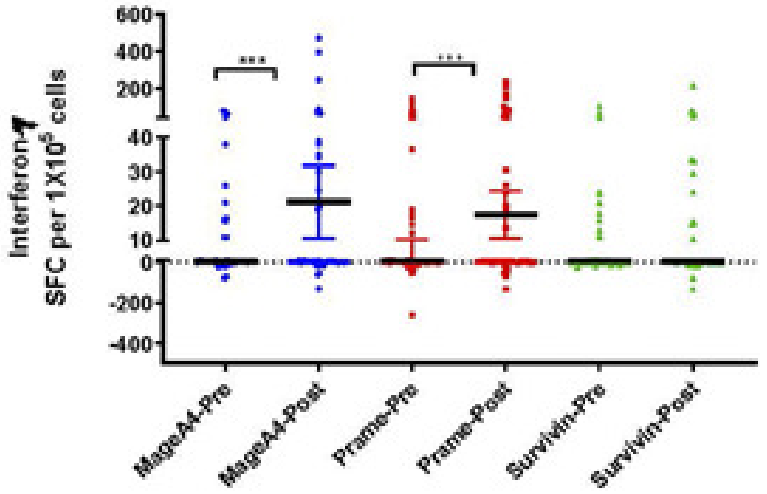
Immune system and microenvironment play an important role in HL. However little is known about the effect of treatment on peripheral blood immune cells and tumor specific T-cells in HL.

- PB samples collected before and after treatment in children (2-22 years) with HL.
- RCT comparing ABVE-PC and Bv-AVEPC.
- Pre and Post TH1/TH2 cytokine tested. Tumor specific T cell responses tested.

B. Table. Differences in cytokines at diagnosis (pre) and after treatment(post) Wilcoxon Ranked Sum test (N=175 patients)

Variable	Median(post-pre)	Std Dev	P-value
Proinflammatory Cytokines			
IL_1B	17.54	174.9	0.9645
IL2	2.23	28.0850	0.3926
IL4	0.69	4.6997	0.1376
IL6	18.71	268.6	**0.0021**
IL7	57.28	752.4	0.4406
IL8	-323.10	4042.2	0.3051
IL12	2.06	36.2982	0.2571
GCSF	235.00	957.5	**<0.0001**
GMCSF	1.29	12.4949	0.0576
INF-g	26.29	106.0	**<0.0001**
MCP1(MCAF)	76.68	477.8	**<0.0001**
MIP1b	279.17	2763.2	0.2859
TNFa	-12.14	231.8	**<.0001**
Immunosuppressive cytokines			
IL5	4.57	85.1036	0.1194
IL10	-4.11	31.8368	0.1266
IL13	-1.54	6.7284	**<0.0001**
IL17a	9.75	68.7399	0.2713

A. Figure. T cell responses to tumor associated antigens Mage/ p=<0.0001 by 2-way ANOVA)



ASH 2020 Abstract No: 595

Increased Tumor Specific Cytotoxic T Cell Responses and Reversion to a Favorable Cytokine Profile after Treatment in Patients with Newly Diagnosed High Risk Hodgkin Lymphoma Treated on Children's Oncology Group Trial-AHOD1331Study

- There was a significant decrease in peripheral blood helper T cells (CD3+CD4+) and an increase in cytotoxic T cells (CD3+/CD8+) after treatment.
- Increased T cell responses to MAGE4 and PRAME post therapy suggests that recovery post anti-HL treatment can promote tumor antigen specific T cell immunity in vivo.
- Reduced IL-13 and increased Interferon-γ following treatment suggest a favorable milieu for T cell expansion.
- Correlations between immune responses and clinical outcomes will be performed once outcome data are available.
- The impact of Bv will be evaluated by comparing the differences of the immune responses by treatment arm.
- The results will help identify immune markers of response that can guide future immunotherapies for HL.

ASH 2020 Abstract No:472 : Consolidation with Nivolumab and Brentuximab Vedotin after Autologous Hematopoietic Cell Transplantation in Patients with High-Risk Hodgkin Lymphoma

The AETHERA study demonstrated that post-HCT consolidation with brentuximab vedotin (BV) in high-risk HL pts improved PFS. Nivolumab monotherapy as post-HCT consolidation in HL has also shown improvement in PFS. Therefore, logical to combine both.

- Multi-centre phase 2 study.
- Prior BV or PD1 blockade were allowed if pts were not refractory.
- Starting between day 30-75 after HCT, pts received 1.8 mg/kg of BV and 3mg/kg nivo q21 days for a planned 8 cycles.
- If 1 drug was discontinued due to toxicity, the other could be continued

ASH 2020 Abstract No:472 : Consolidation with Nivolumab and Brentuximab Vedotin after Autologous Hematopoietic Cell Transplantation in Patients with High-Risk Hodgkin Lymphoma

Table 1: Baseline Characteristics

Variable	N (%)
Male gender	34 (58%)
Age, median (range)	30 (18-72)
Primary refractory	18 (31%)
Relapse within 1 year	35 (59%)
Late relapse	6 (10%)
B sx at relapse	14 (24%)
Extranodal dz at relapse	23 (39%)
2 or more salvage regimens	15 (25%)
Disease status at HCT	
Complete response	48 (81%)
Partial response	11 (19%)
Disease status at baseline	
Complete response	53 (90%)
Partial response	6 (10%)
Modified AETHERA risk factors	
1	21 (36%)
2	23 (40%)
3+	14 (24%)
Frontline regimen	
A(B)VD	50 (85%)
ABVD/MOPP	1 (2%)
BV+AVD	2 (3%)
ABVE+PC	6 (10%)
Prior radiation	14 (24%)
Prior BV	30 (51%)
Prior PD-1 blockade	25 (42%)
HCT conditioning regimen	
BEAM	47 (80%)
GemBuMelVorinostat	7 (12%)
Other	5 (8%)

Figure 1: Progression-free survival in all patients (n=59)

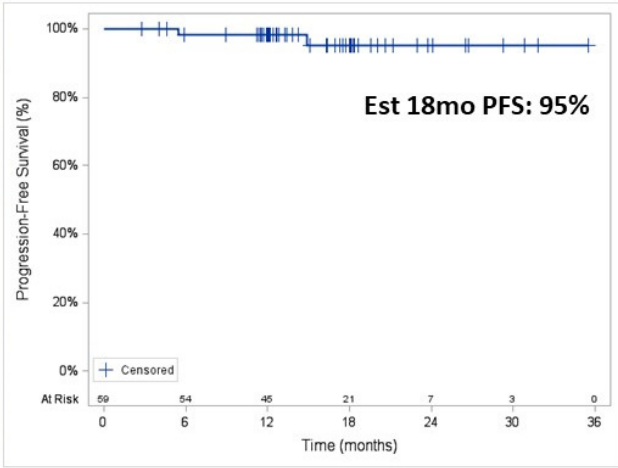
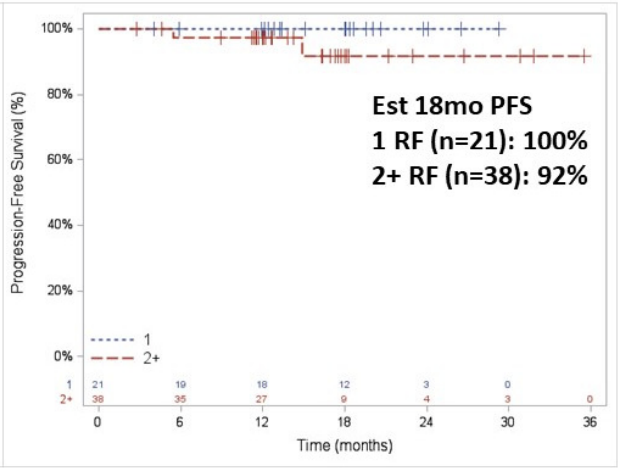


Figure 2: Progression-free survival by number of high-risk factors



IrAEs were observed more frequently than in the pre-HCT setting and PN and neutropenia were common.

ASH 2020 Abstract No:1157 :

PVAG Regimen (Prednisone, Vinblastine, Doxorubicin, Gemcitabine) Used in Real-Life Setting in First Line Therapy for Elderly Classical Hodgkin Lymphoma Patients: A Retrospective Study of Lysa Centers

Older cHL patients : aggressive disease + a poor tolerance to chemotherapy esp. bleomycin-induced lung toxicity.
PVAG regimen developed by the German Hodgkin Study Group (GHSG).

- 49 elderly patients received first-line chemo with PVAG
- Prednisone 40 mg/m^2 D1-5, Vinblastine 6 mg/m^2 D1, Doxorubicin 50 mg/m^2 D1, Gemcitabine 1000 mg/m^2 D1 q3wk
- Profile: Median age : 76 years (range, 61-87) with 69% ≥70 years old
- 35% presented in PS 2-4. IPS ≥3 in 65%. 43% had a CIRS-G score over 6.

SAFETY

Hematological toxicity

Febrile neutropenia – 12%
Grade III-IV neutropenia – 45%
thrombopenia – 16%
anemia – 35%

Non - Hematological toxicity

Grade III-IV mucositis – 6%
nausea – 4%
neuropathy – 10%
Ac. Cardiac toxicity – 6%

- 11 deaths - HL(8%) , infection (2), toxic death(1)

- **Univariate analysis**: OS was adversely affected by grade 3-4 CIRS-G in ≥2 categories (HR: 3.63, 95%CI 1.23-10.71, P=0.019).
- Age, IPS, B symptoms, lymphopenia, anemia, ↓albumin, CIRS-G>6 did not affect outcome.

EFFICACY

- CR – 52% and PR – 13%
- 35% - SD / PD

- Median followup: 33.2 months
- 26 (53%) patients progressed / relapsed.
- mPFS: 21.6m. 3-yr PFS: 48.6% (95%CI 36.3-65.1)
- mOS: 66.5m. 3-yr OS: 73.7% (95%CI 61.2-88.8).

Conclusion

- PVAG regimen has favorable safety profile in older patients (older than the pivotal trial popln)
- Immunotherapy combn needs evaluation.

ASH 2020 Abstract No:2918

Enhanced Outcome Prediction in Early Stage Classical Hodgkin Lymphoma Using Pre-Treatment Biomarkers and Interim PET (BioPET); Sub-Analysis of UK NCRI RAPID Trial

Unmet need: iPET helps in risk-adapted treatment for early stage HL. But RFS is inferior for patients with a negative iPET who omit RT. The association of candidate genes with EFS in this setting was analysed.

- RAPID trial: iPET –ve: randomised to IFRT vs no further treatment. iPET +ve – further ABVD + RT
- 227 patients – (21 with events)
- Baseline biopsy was analysed using **Quantigene 2.0 plex (Gene expression assay)**
- 57 candidate genes known to be associated with treatment response and survival – analysed

Candidate genes - ranked as per variability of expression. The association was evaluated by regression analyses (Cox and binary logistic),

Events observed in

10/121 PET score 1	2/33 PET score 3
4/53 PET score 2	1/10 PET score 4
	4/10 PET score 5

Two genes significant for PET outcome - score 3-5
PRF1 - ↑ risk (OR=1.49, 95% CI: 1.05-2.13, p=0.03)
BCL2L1 ↓ risk (OR=0.65, 95% CI: 0.44-0.96, p=0.03)
No genes associated with PET score 4-5 (small numbers)

3 genes significant cHL-EFS analaysis
- CD22 (HR=0.54, 95%CI: 0.41-0.72, p<0.001);
- BID (HR=4.04, 95%CI: 1.79-9.14, p=0.001;
- IL15RA (HR=0.39, 95%CI: 0.16-0.97, p=0.04);

Model: cut-off value 0.69: time-depndnt ROC curve analysis
True positive :67.7% & False positive:9.5%
Independent of EORTC and GHSG risk scores

Combined PET + EFS analysis
(DS 4-5 or event; n=36) vs (DS 1-3+no event; n=191)
5 genes asso. with failure:CD22, BCL2, SH2D1A, ITGA4, CD3D
CD22 (HR=0.66, 95% CI: 0.51-0.85, p=0.02) significant.

Conclusion: iPET + selected pre-treatment genes - promising utility for enhanced prediction of cHL-EFS in early stage cHL that is independent of EORTC and GHSG

ASH 2020 Abstract No:1158 :

Effect of Pembrolizumab Monotherapy Versus Brentuximab Vedotin on Patients with Relapsed/Refractory Classical Hodgkin Lymphoma (R/R cHL): Exploratory Analysis of the Randomized, Phase 3 Keynote-204 Study By Prior Lines of Therapy

KEYNOTE-204 study: R/R cHL, the PD-1 inhibitor pembro was superior to BV. (PFS & safety)

- Age ≥18 y, had measurable disease and ECOG PS 0-1, post–ASCT & ineligible for ASCT included.
- pembro 200 mg IV Q3W vs BV 1.8 mg/kg IV Q3W.
- Stratified: Status after 1L therapy(primary refractory vs relapse<12 m vs relapse ≥12 m) and prior auto-SCT (yes vs no)

- Current analysis - blinded independent central review.
- 304 randomized pts – clinical and radiology records

		1 prior therapy (n=55)		≥2 prior therapies (n=249)	
Baseline parameter	Age	49yr (22% >65yr)		34yr (10.8% >65yr)	
	Prior ASCT	Nil		112 pts (45.0%)	
	Primary refractory	18 (32.7%)		105 (42.2%)	
	ASCT ineligiblity	chemorefractory- 21, Other reason- 34			
		Pembro (n=27)	BV (n=28)	Pembro (n=124)	BV (n=125)
Efficacy analysis	Discontinued Rx	23 pts (85.2%)	25 pts (92.6%)	87 (71.9%)	121 (96.8%)
	Median f/u	24m	23.6m	27.1m	27.6m
	Median PFS	16.4m vs 8.4m (HR 0.70; 95% CI 0.031-1.59)		12.6m vs 8.2m (HR 0.66; 95% CI 0.47-0.92);	
	12m PFS	58.9%	37.4%	52.8%	35.3%
	Secondary PFS (excluded ASCT)	11.7m vs 8.3m (HR 0.62; 95% CI 0.28-1.40)		12.6m vs 8.2m (HR 0.63; 95% CI 0.45-0.88)	
	ORR%	66.7%	53.6%	65.3%	54.4%
	Duration of Response	20.7m	14.1m	20.5m	11.2m
	Subsequent SCT	7-ASCT	9-ASCT 1-allo SCT	23-ASCT 14-allo SCT	25-ASCT 12-allo SCT
Safety analysis	Adv events	21 (77.8%)	20 (74.1%)	89 (73.6%)	97 (77.6%)
	Most common AE	Hypothyroid - 22.2%	Neuropathy-22.2%	Hypothyroid - 14.9%	Neuropathy-17.6%
	Gr III AE	1(3.7%)	8 (29.6%)	29(23.1%)	30(24.0%)

ASH 2020 Abstract No:1158 :

Effect of Pembrolizumab Monotherapy Versus Brentuximab Vedotin on Patients with Relapsed/Refractory Classical Hodgkin Lymphoma (R/R cHL): Exploratory Analysis of the Randomized, Phase 3 Keynote-204 Study By Prior Lines of Therapy

Conclusion

- pembro monotherapy had significant improvement in PFS and ORR vs BV regardless of number of prior therapies.
- In particular, these data suggest that pembro monotherapy may be a promising option as 2L+

ASH 2020 Abstact No. 1152
The Outcomes of Nivolumab Fixed Dose 40 Mg Therapy in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma

Currently, the recommended dose of nivolumab for patients with relapsed or refractory classical Hodgkin lymphoma (r/r cHL) is 3 mg/kg

Experimental studies provided the rationale for possible reduction of nivolumab dose in patients with solid tumors (Agrawal et al. 2016)

Patients and methods

- This study included 42 patients (14 male/28 female) with r/r cHL who were treated with nivolumab 40 mg every 2 weeks.
- Median age - 36 (22-53) years.
- Median no. prior therapy lines was 4 (2-7). Prior treatment - BV in 14 pts (33%), HDC/ASCT - 9 pts (21%), & allo-HSCT - 1 pt (2%).
- At nivolumab initiation - 38 pts (90.5%) – PD & 4 pts (9.5%) - PR.
- B-symptoms were present in 23 pts (55%),
- ECOG status -- grade 0-I in 25 (59.5%), grade II - 12 (29%), grade III - 4 (9.5%) & grade IV in 1 (2%).

- Primary endpoint was the ORR determined by PET/CT) every 3 months.
- Secondary endpoints -PFS & OS.

Results

- The median number of nivolumab cycles was 24 (2-38).
- The ORR was 66%. (CR) - 39%, PR - 27%, SD - 5%, PD - 2%, indeterminate response (IR) - 27%.
- With a median follow-up of 27.5 mon (11.3-34.5), 41 pts (97.6%) were alive,
- The median OS – Not Reached.
- The 2-year PFS was 44.5% (95% CI 28.2-59.6)
- The AE of any severity were observed in 30 pts (71%). Grade 3 or higher AE - 4 (9.5%), including grade 3 arthralgia, grade 3 anemia, grade 4 pneumonia and pneumonitis, grade 4 increased level of alanine aminotransferase & MDS in 1 pt.

Conclusions:

- Study demonstrated the efficacy and safety of nivolumab 40 mg therapy.
- The presented results are comparable to previously published data of nivolumab 3 mg/kg therapy in patients with r/r cHL.
- Thus, this creates a basis for further direct comparative study of nivolumab efficacy in different dose

ASH 2020 Abstract No. 2077
A Phase 2 Trial of Ibrutinib and Nivolumab in Patients with Relapsed or Refractory Classical Hodgkin's Lymphoma

We hypothesized that the addition of ibrutinib to nivolumab would lead to deeper & more durable responses in cHL by normalizing the Th1/Th2 balance thus reversing immune escape of RS cells.

This is a single arm, phase II, single institutional clinical trial testing the clinical activity of nivolumab in combination with ibrutinib in patients ≥18 years of age.

Patient received at least one prior line of therapy & who were either not candidates for or had a prior ASCT. Prior treatment with nivolumab was allowed.

Ibrutinib was administered at 560 mg daily until progression in combination with nivolumab 3 mg/kg IV every 3 weeks for 16 cycles.
The primary objective - CRR prior to cycle 7 assessed per Lugano criteria.

Results:

- 10 patients, the median age - 41 years (range 20-84) & 4 patients (40%) were male.
- The median number of prior lines of treatment - 4.5 (range 1-11), 5 patients (50%) had prior ASCT, 8 patients (80%) had prior brentuximab, and 5 patients (50%) had prior nivolumab. Four of the five patients with prior nivolumab had progressed while receiving therapy while the remaining patient had stable disease upon completing nivolumab with a median time from the last nivolumab treatment of 15.6 months (range 0.7-23.2).
- Of the 10 patients who received treatment,
- 1 patient came off study after 2 cycles due to persistent grade 2 transaminitis lasting for several weeks attributed to nivolumab requiring high dose oral steroids.
- 1 patient came off study after cycle 9 due to grade 3 hematuria attributed to ibrutinib
- 1 patient came off study due to a pericardial effusion after 8 cycles of ibrutinib maintenance.
- In the remaining patients, treatment was generally well tolerated with most AEs being grade 1-2 (Table 1).
- The median number of total cycles received was 9 (range 2-22).
- Of the 9 patients evaluable for response, 6 patients responded (ORR = 66%), 4 of whom had a complete response (CRR = 44%) with a median time to response of 2 months (Table 2, Fig.1).
- In intention-to-treat analysis, the ORR was 60% and CRR was 40%
- Overall, at a median follow up of 9.5 months, both the median PFS and duration of response have not yet been reached,

Table 1. Treatment Emergent Adverse Events (TEAEs) occurring in greater than 1 patient and all grade ≥ 3 TEAEs for 10 pts.

	All events	Grade 1-2	Grade ≥ 3
hyperglycemia	5	5	0
myalgias	5	5	0
hypertension	4	4	0
lymphopenia	3	1	2
thrombocytopenia	3	3	0
fatigue	3	3	0
rash	3	2	1
hypoglycemia	3	3	0
cough	3	3	0
anemia	3	3	0
congestion	3	3	0
hypocalcemia	3	3	0
Soft tissue infection	3	3	0
hypoalbuminemia	2	2	0
leukopenia	2	2	0
Weight gain	2	2	0
dyspepsia	2	2	0
GERD	2	2	0
UTI	2	1	1
hematuria	2	1	1
vomiting	2	2	0
diarrhea	2	2	0
insomnia	2	1	1
bleeding	2	2	0
pruritis	2	2	0
Pericardial effusion	1	0	1
sepsis	1	0	1
oophorectomy	1	0	1

Table 2. Patient Characteristics and response parameters.

	All	No prior nivolumab	Prior nivolumab
Number of pts	10	5	5
Median Age	41 (20-69)	42 (20-84)	40 (24-69)
Median lines of prior treatment	4.5 (1-11)	3 (1-5)	6 (2-11)
Median Follow Up (months)	9.5	12.4	9.5
ORR	6 (60%)	3 (60%)	3 (60%)
CRR	4 (40%)	3 (60%)	1 (20%)
Median TTR (days)	62.5 (56-71)	62 (56-71)	63 (61-64)
Median TTF (months)	27.3	27.3	6.8
Median DoR (months)	NR	NR	NR
Median PFS (months)	NR	NR	NR

ORR, Overall Response Rate; CRR, Complete Response Rate; DoR, Duration of Response; TTR, Time to response; TTF, Time to Treatment Failure; NR, Not reached; PFS, Progression Free Survival.

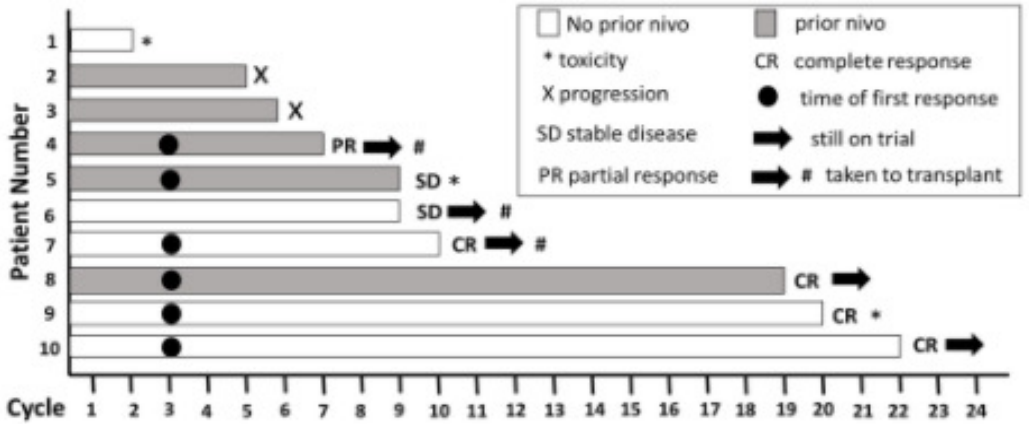


Figure 1. Swimmer's plot of patient outcomes for 10 pts.

Conclusions:

- Although the numbers are small and further recruitment is ongoing (target n=17), the combination of ibrutinib and nivolumab was generally well tolerated and with high response rate with more than half of responding patients achieving a CR.
- In addition, responses were seen in patients with prior nivolumab treatment.

ASH 2020 Abstract No:470 : Phase II Study of Pembrolizumab Plus GVD As Second-Line Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma

- No one standard second line treatment (SLT) exists and options include regimens containing platinum, gemcitabine, and more recently brentuximab vedotin (BV). CR rates associated with these regimens range from 50-70%. Due to the increasing use of BV in the front-line setting, development of SLT regimens that are both highly effective and BV-sparing are needed.

Methods

- Transplant eligible patients (pts) with RR cHL following failure of 1-line of therapy were eligible.
- Treatment consisted of 2 - 4 cycles of pembrolizumab (200mg IV, day 1), gemcitabine (1000mg/m2 IV, days 1 and 8), vinorelbine (20mg/m2 IV, days 1 and 8) and liposomal doxorubicin (15mg/m2, days 1 and 8), given on 21-day cycles.
- Pts who achieved CR by PET (Deauville ≤3) after 2 or 4 cycles proceeded to HDT/AHCT. HDT/AHCT was carried out according to institutional standards and BV maintenance was allowed following HDT/AHCT.
- The primary endpoint was CR rate after 2 or 4 cycles of pembrolizumab-GVD.

Results

- Among 39 patients enrolled, 34 are evaluable for response.
- median age - 36 (range 21-71), 43% are male, 23 (62%) had advanced stage disease, & 15 (41%) had primary refractory disease.
- RR cHL risk factors (B-symptoms, extranodal disease, & RR disease within 1 year of initial treatment), 4(11%) had no risk factors (RFs), 21 (57%) - 1 RF, 9 (24%) - 2 RFs, & 3 (8%) - all 3 RFs.

- Grade 3 AEs included rash (n=1), elevated AST/ALT (n=3), oral mucositis (n=2), and neutropenia (n=3).
- Among 34 evaluable pts, 31 (91%) achieved CR after 2 cycles & 3 achieved PR. An additional 1 pt achieved CR after 4 cycles of pembrolizumab-GVD, therefore in total, 32 of 34 (94%) achieved CR following pembrolizumab-GVD.
- 32 have undergone HDT/AHCT following 2 (n=27) or 4 (n=5) cycles of treatment. 1 pt is awaiting HDT/AHCT; 1 pt refused HDT/ASCT and received pembrolizumab maintenance instead.
- 2 pts received involved site radiation therapy to initial area of relapsed disease prior to planned HDT/AHCT and 10 pts received post-HDT/ASCT maintenance with BV.
- Median follow-up post-HDT/AHCT is 9 mon (range 0.03-20.9 mon) and all pts remain in remission to date.

Conclusion

- Second-line therapy with pembrolizumab-GVD is a highly effective and well-tolerated regimen that can efficiently bridge pts with RR cHL to HDT/AHCT.
- Given the high CR rate observed with pembrolizumab-GVD, an expansion cohort evaluating 8 cycles of pembrolizumab maintenance (instead of HDT/AHCT) for patients who achieve CR after 4 cycles of pembrolizumab-GVD is planned

Multiple Myeloma

Lead:

Pankaj / Nikita

ASH Updates
Multiple myeloma

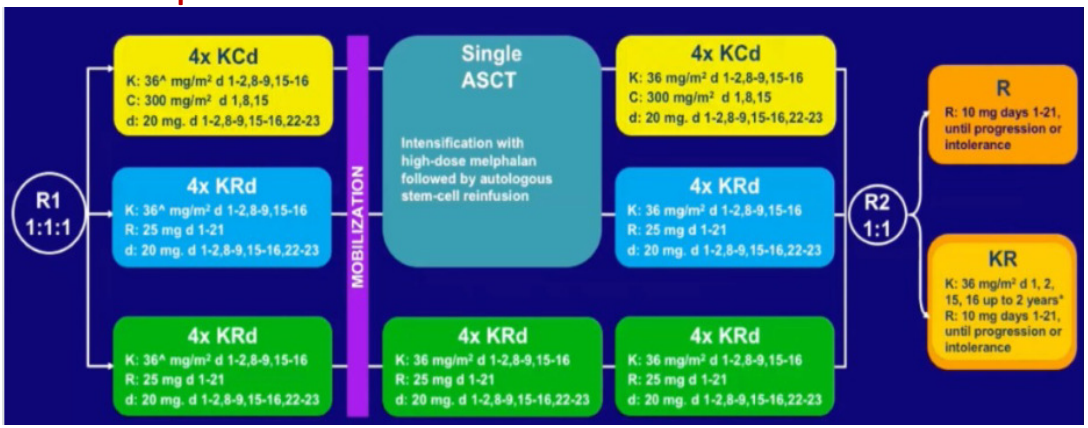
Hematology Cancer Consortium

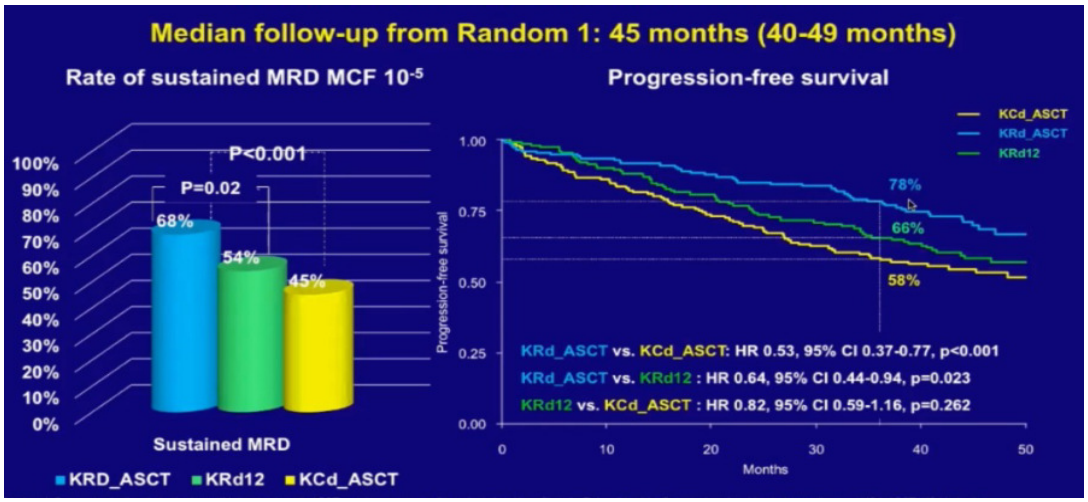
12 December 2020

ASH 2020:Abstract no. 141

Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized Forte Trial

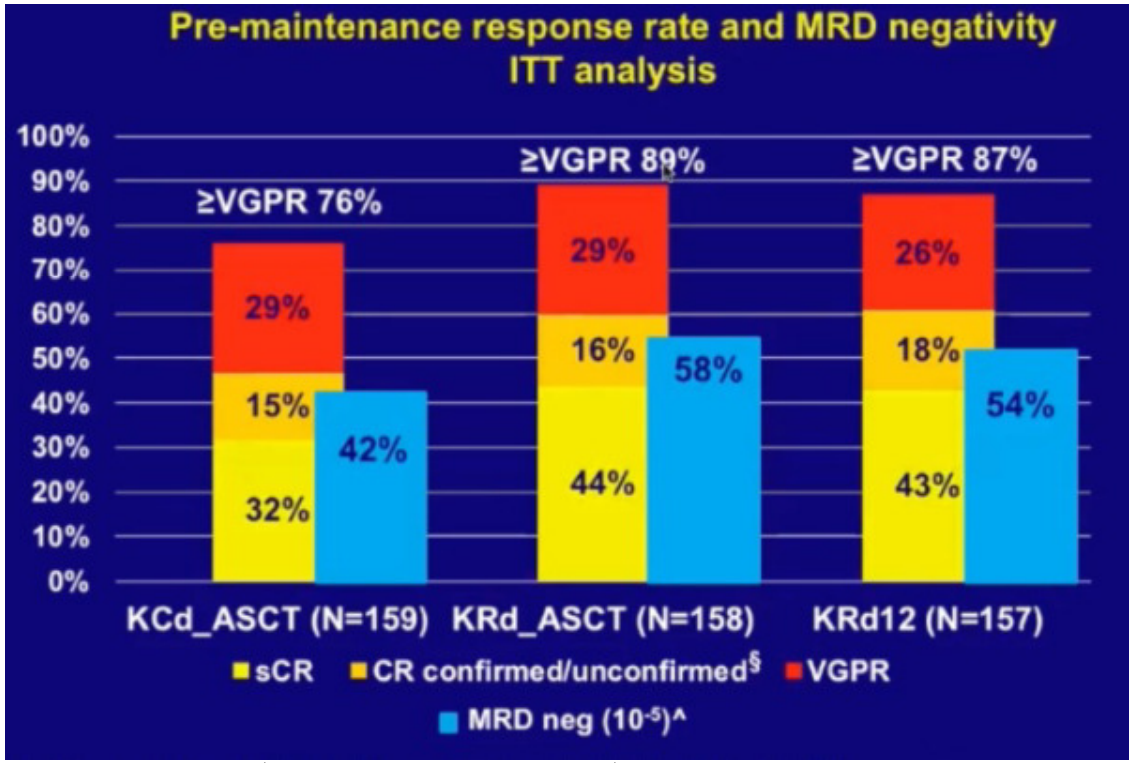
Study to compare the KCd+ASCT Vs KRdx12 Vs KRd+ASCT
Objectives: PFS after Random 1&2; Safety of KR Vs R
474 NDMM patients





Random 1: KCd+ASCT Vs KRdx12 Vs KRd+ASCT: Efficacy

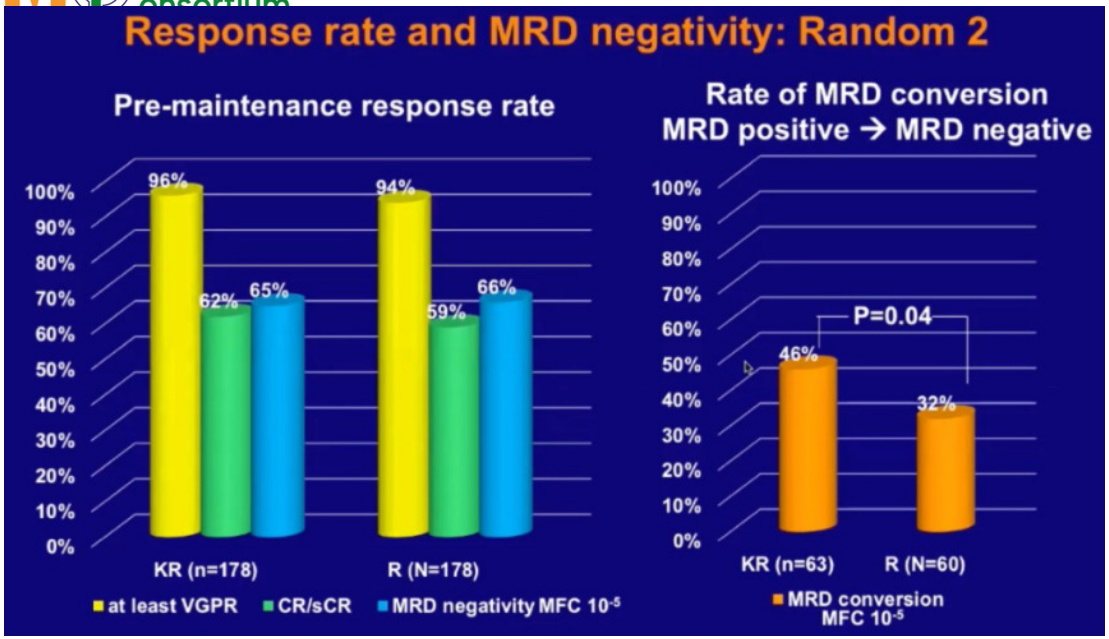
OR-2.53; p-0.004 — VGPR — OR-2.11; p-0.015

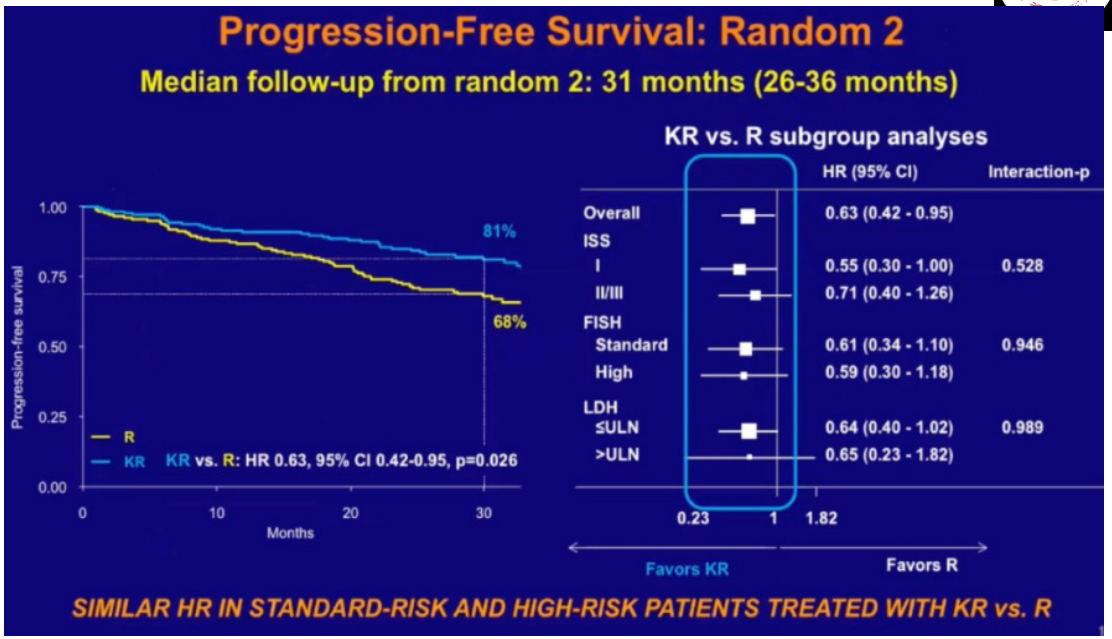


OR-1.65; p-0.035 — SCR — OR-1.6; p-0.048

OR-2.02; p-0.009 — MRD — OR-1.73; p-0.042

ASH 2020:Abstract no. 141……





Conclusion

- KRd_ASCT significantly prolonged PFS (3y PFS – 78%) in comparison to KRd 12 Vs KCd_ASCT
- Benefit of KRd_ASCT was observed in all subgroups of patients:
  - KRd_ASCT in ISS I, FISH Std Risk, LDH ≤ ULN:
    - 3y PFS 80-84%
  - KRd_ASCT in ISS II/III, FISH high Risk, LDH > ULN:
    - 3y PFS 69-72%

- KR Significantly prolonged PFS Vs R (30m PFS – 81%) The benefit of KR was observed in all subgroups of patients
  - KR in ISS I, FISH Std Risk, LDH ≤ ULN:
    - 30m PFS 83-85%
  - KR in ISS II/III, FISH high Risk, LDH > ULN:
    - 30m PFS 60-78%
- Maintenance with KR was manageable with no increase in Rx discontinuation due to toxicity

ASH 2020:Abstract no. 417

ANCHOR (OP-104): Melflufen Plus Dexamethasone (dex) & Daratumumab (dara) or Bortezomib (BTZ) in RRMM Refractory to an IMiD &/or a PI - Updated Efficacy & Safety

Melflufen – Investigational first in class peptide drug conjugate that targets aminopeptidases & rapidly releases alkylating agents into tumor cells

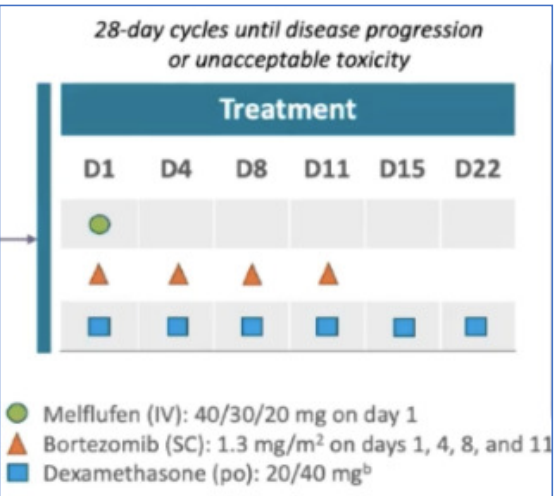
Phase I/ II open label multicenter study

Objective

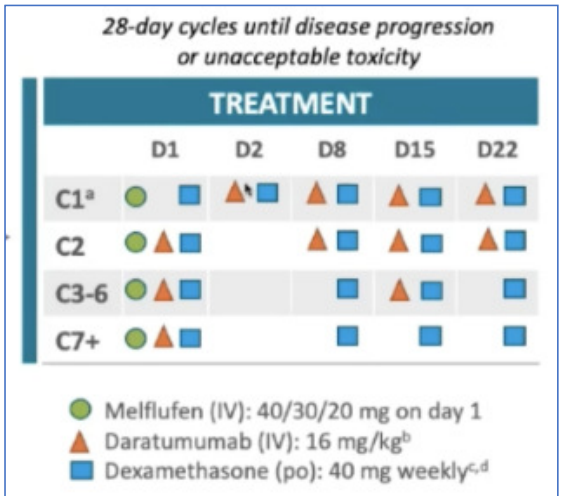
Phase I: Optimal dose of Melflufen in combination

Phase II: Overall Response Rate

Melflufen+Dexa+V



Melflufen+Dexa+Dara



Melflufen + Dexa + V (N=13)

Grade ≥3 TRAEs[a,b]	Patients, n (%) 30 mg (n=6)	40 mg (n=7)	Total (N=13)
Any Grade ≥3 TRAE	5 (83)	7 (100)	**12 (92)**
Thrombocytopenia[c]	3 (50)	7 (100)	**10 (77)**
Neutropenia[d]	2 (33)	5 (71)	**7 (54)**
Anemia	2 (33)	4 (57)	**6 (46)**

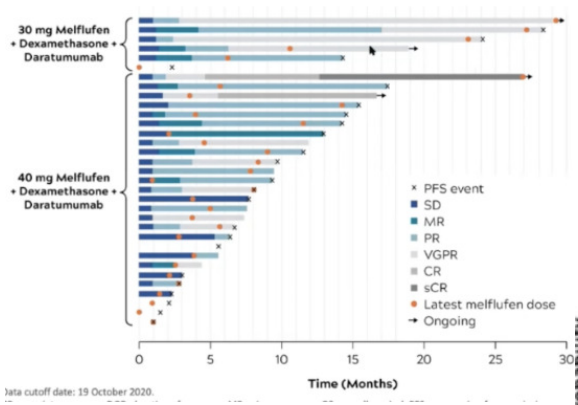
Subgroup	Best Confirmed Response, Patients, n >CR	VGPR	PR	MR	SD	PD	NA	Patients, % ORR	CBR
Melflufen 30 mg (n=6)	0	1	2	0	2	0	1[a]	50	50
Melflufen 40 mg (n=7)	1	3	1	0	1	0	1[b]	71	71
Total (N=13)	**1**	**4**	**3**	**0**	**3**	**0**	**2**	**62**	**62**

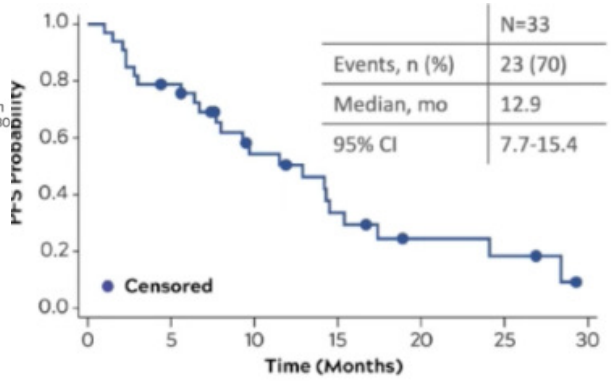
ASH 2020:Abstract no. 417

Melflufen + Dexa + Dara (N=33)

	30 mg (n=6)	40 mg (n=27)
Any TEAEs leading to melflufen dose reduction, n (%)	3 (50)	18 (67)
Time to first dose reduction due to AE, median, mo (95% CI)	6.2 (1.4-NR)	3.7 (2.7-4.6)
Most common AEs leading to dose reduction, n (%)		
Thrombocytopenia[a]	2 (33)	15 (56)
Neutropenia[b]	1 (17)	7 (26)
Most common AEs leading to treatment discontinuation of any study drug,[c] n (%)		
Thrombocytopenia[a]	1 (17)	11 (41)
Neutropenia[b]	1 (17)	2 (7)
Sepsis	1 (17)	1 (4)
Anemia	0 (0)	2 (7)

Subgroup	Best Confirmed Response, Patients, n							Patients, %	
	>CR	VGPR	PR	MR	SD	PD	NA	ORR	CBR
Melflufen 30 mg (n=6)	0	4	1	0	0	0	1[a]	83	83
Melflufen 40 mg (n=27)	2	6	11	1	2	1	4[b]	70	74
Total (N=33)	2	10	12	1	2	1	5	73	76





Conclusion

- Melflufen + Dexa + V/Dara (triplet) is well tolerated as Melflufen + Dexa (doublet) with similar safety profile
  - Grade 3/4 TRAEs were mostly hematological & clinically manageable with dose reductions
- Both combinations demonstrated encouraging activity
  - ORR with Melflufen + Dexa + Daratumumab – 73%
  - ORR with Melflufen + Dexa + Bortezomib – 62%
- Median PFS – 12.9 months (Melflufen + Dexa + Dara)
- In combination with Dara: recommended dose – 30mg
- For Meflufen + Dexa + Bortezomib – RP2D is pending

Abnormal Metaphase Cytogenetics Adds to Currently Known Risk-Factors for Venous Thromboembolism in Multiple Myeloma: Derivation of the *PRISM* score. ASH abstract no : 148

Limitations of VTE prediction tools

No uniform treatment for patients & No disease specific variables

AIM:

- To make a simple VTE predictive tool – disease specific, patient specific, treatment specific variables
- Assess impact of VTE on OS

METHODOLOGY & RESULTS

- Consecutive pts. with ND MM from 2008-2018, Cleveland Clinic, Ohio (934 totally)
- Excluded 5 who had VTE within 6 mo of MM, 146 who were on VTE therapy/>1 prophy regimen
- **783 for model development**
- Median age -63 years [22-91],
- 55% were males, 20% black race
- ISS - III 32%,
- High-risk FISH 23%,
- Abnormal metaphase cytogenetics 18%,
- Creatinine >2 mg/dl in 19% of patients.

Thromboprophylaxis
60% - Aspirin
3% - LMWH
37% - No prophylaxis

Median time to VTE – 3.2 months
Cumulative incidence of VTE
at 6 and 12 months was 8.2% and 11.5%

Multivariate analysis – 5 risk factors

PRISM score

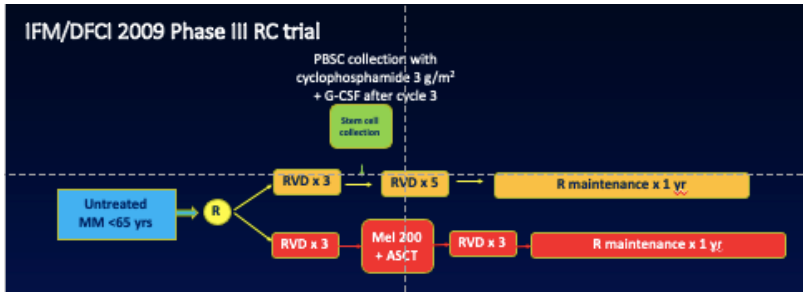
Prior VTE	- 8
Race Black.	-1
IMid use.	-2
Surgery within 3 mo	-5
Metaphase CTG	- 2

Groups	Score	Pts (%)	CI of VTE at 12m
Low	0	17.8%	2.7%
Intermediate	1-6	74%	10.8%
High	>6	8.1%	36.5%

Occurrence of VTE no impact on OS

Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial

ASH abstract no : 143



	RVD arm (n=350)	Transplant arm (n=350)	p
CR	49%	59%	0.02
VGPR	29%	29%	
PR	20%	11%	
At least VGPR	78%	88%	0.001
MRD neg by FCM	228(65%)	280(80%)	0.001
4 yr PFS (months)	35	47	<0.001
4 yr OS (months)	83	81	NS

Extended follow up to evaluate the long-term outcome in the 2 arms and the impact of 2nd line treatments on PFS2 and OS

Methodology

Choice of 2nd line treatment and decision to perform an ASCT at relapse was based on investigator's discretion.

PFS2 - time from randomization to progression on next line therapy or death from any cause

Second PFS - time from date of 1st progression to progression on next line therapy or death.

Results

Grp	Prog	Treated	Pom	Carf	Dara	PFS2	2nd PFS	Med OS	8yr OS
RG (350)	270 (77.1%)	262	105 (40.1%)	14	12	95 mo	36 mo	NR	60.2%
TG (350)	227 (64.9%)	217	107 (46.5%)			NR	25 mo	NR	62.2%
					p	*0.76.*	*0.003.*		*0.81*

2nd PFS	ISS - 3	HR –CTG*	2nd hemat malignancy
RG	73	48	5/350
TG	75	47	7/350

**t(4;14), t(14;16), del(17p*

RG- RVD alone group
TG – TG group

PFS, PFS2, 2nd PFS significantly longer in the MRD neg group.

MRD appears to predict outcome and might be used after induction to identify pts who probably do not require early ASCT

ASH 2020:Abstract no. 721

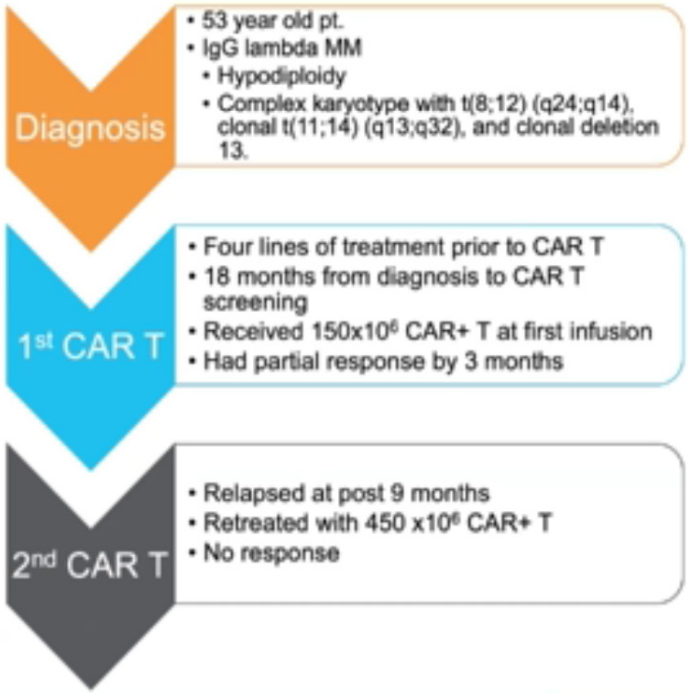
Biallelic Loss of BCMA Triggers Resistance to Anti-BCMA CAR T Cell Therapy in Multiple Myeloma

Background

- CAR T-cell therapy targeting B cell maturation antigen (BCMA) has provided deep (73% - 100%) responses in relapsed/refractory MM.
- **Median PFS has been less than 12 months**
- In small number of patients **re-treated** at the time of progression with the same CAR T product, **responses have been infrequent.**
- **development of resistance** that may preclude effectiveness of the 2nd infusion, and may also underly relapse following response to the initial CAR-T cell therapy

Methods

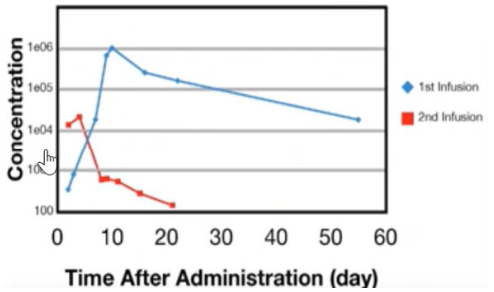
Longitudinal single cell transcriptomic and bulk genomic analysis

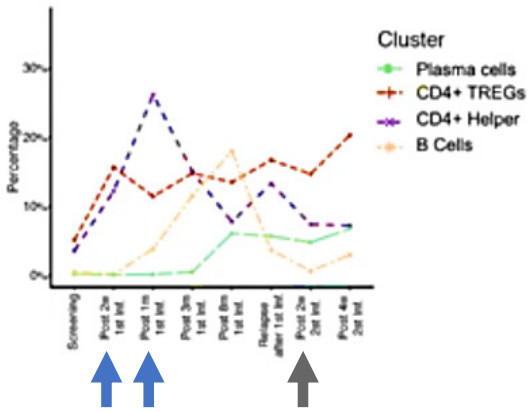


Results

BM niche

No expansion of CAR T-cells after 2nd infusion





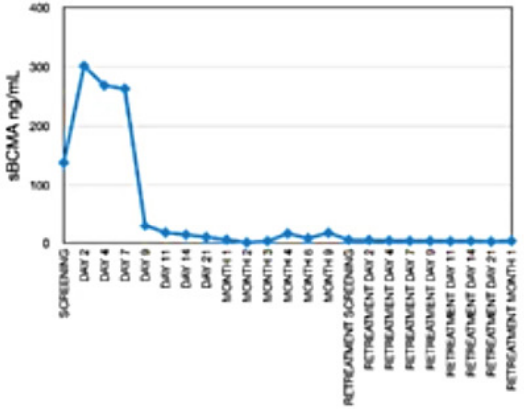
ASH 2020:Abstract no. 721

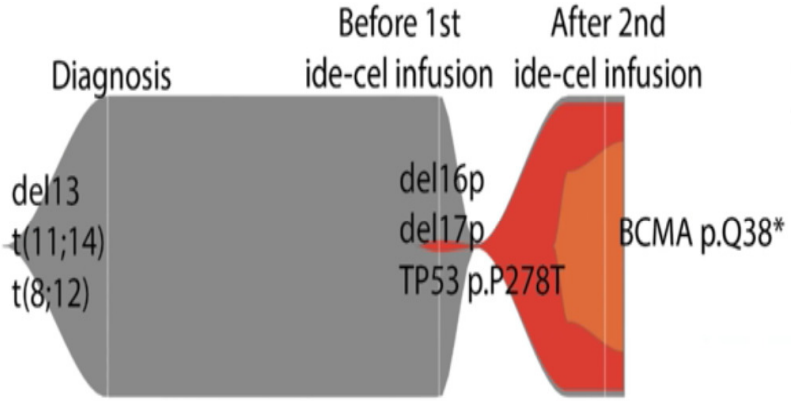
Biallelic Loss of BCMA Triggers Resistance to Anti-BCMA CAR T Cell Therapy in Multiple Myeloma

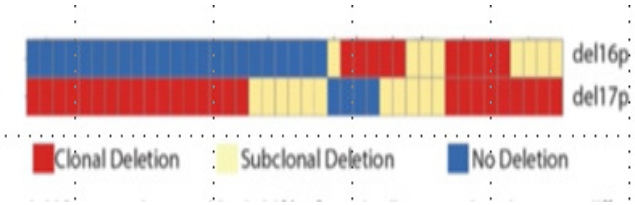
Results

Tumor intrinsic factors

High soluble BCMA levels after 1st infusion







30-40% del17p patients have del16p

Conclusion

- These results highlight the need to investigate **sBCMA as a potential indicator of BCMA loss at relapse**, and to carry out detailed transcriptomic or genomic analysis to confirm mutations.
- MM cells are **able to survive without BCMA expression**.
- With the growing number of BCMA targeting therapeutic modalities under development, there maybe more such occurrences.

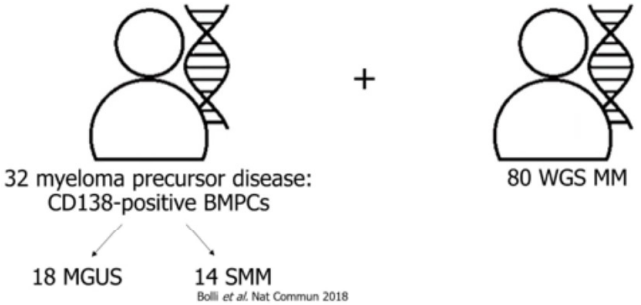
?Dual antigen targeting therapies. ?Are del17p patients likely to develop resistance to BCMA targeting therapies?

ASH 2020:Abstract no. 602

Whole-Genome Sequencing Reveals Evidence of Two Biologically and Clinically Distinct Entities: Progressive *Versus* Stable Myeloma Precursor Disease

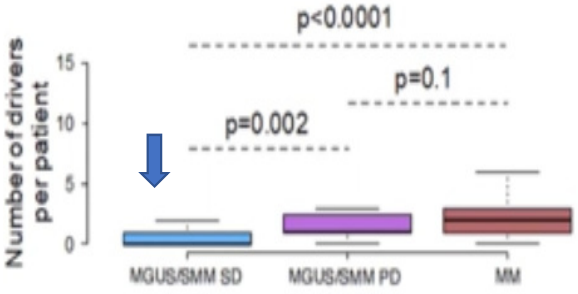
Objective

To analyse the genomic basis of disease progression from SMM/MGUS to MM.

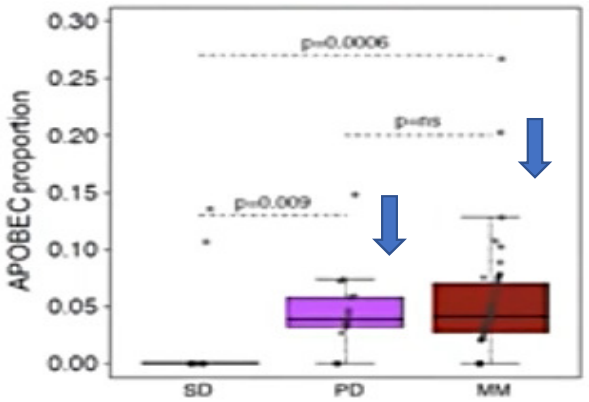


Key differences between the stable and progressive cohorts

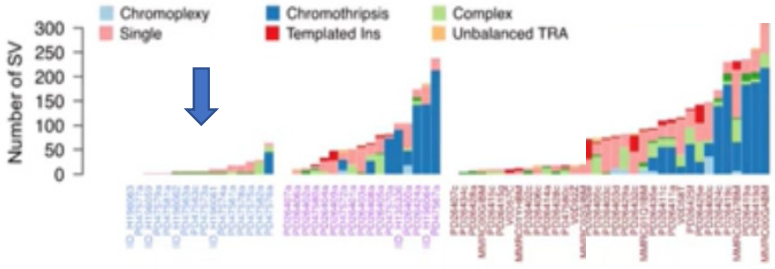
a. Stable disease cohort had a lower mutational burden



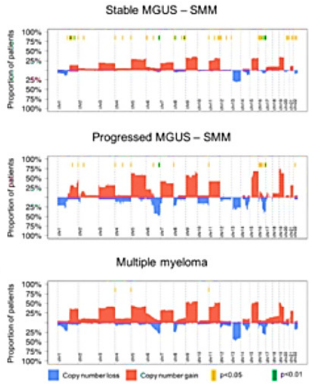
b. APOBEC mutational activity seen in PD and MM



c. Patients with stable disease have lower burden of structural variants and complex events.



d. Patients with stable disease have lesser number of known MM aneuploidies

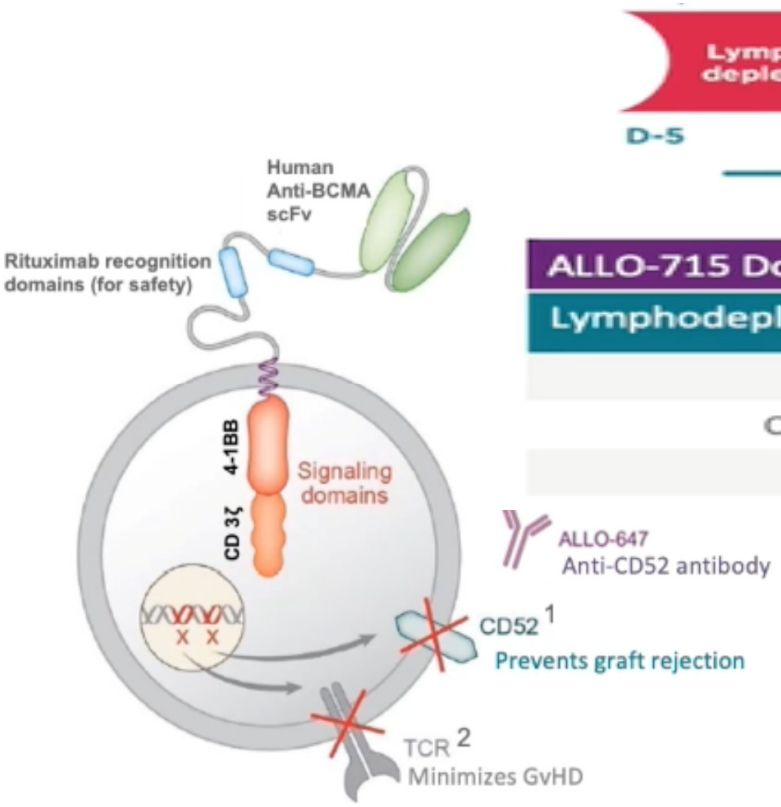


Conclusion

- Genomic landscape of stable precursors differs from progressive precursors and multiple myeloma
- Novel evidence
- Biologically and clinically distinct entities of asymptomatic monoclonal gammopathies

ASH 2020 Abstract No:129 :

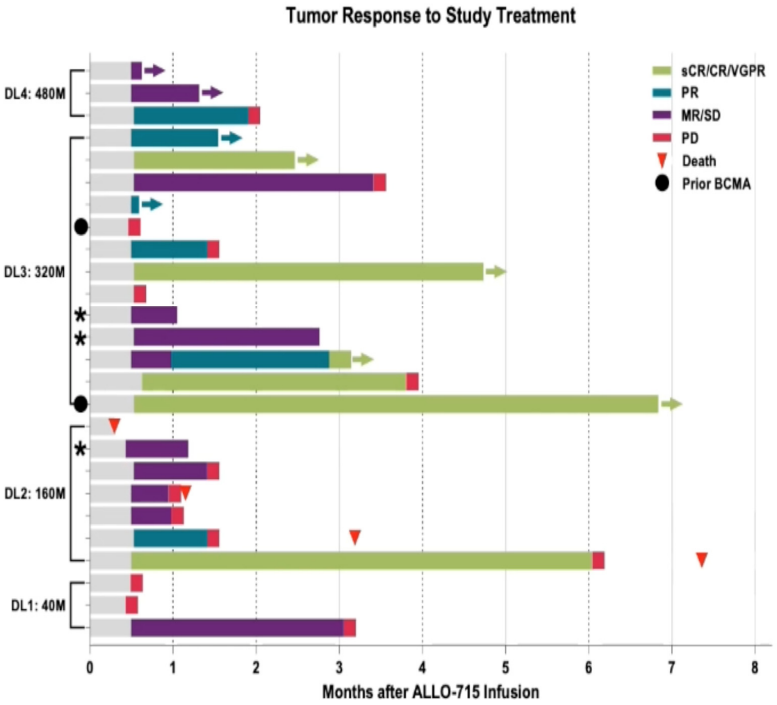
Universal: An Allogeneic First-in-Human Study of the Anti-Bcma ALLO-715 and the Anti-CD52 ALLO-647 in Relapsed/Refractory Multiple Myeloma



ALLO-715 Dose Escalation: 40, 160, 320, 480 x 10^6 CAR+ T cells	
Lymphodepletion Regimens (FCA*, CA†)	**Doses**
Fludarabine	30 mg/m²/day x 3 days
Cyclophosphamide	300 mg/m²/day x 3 days
ALLO-647	13 to 30 mg x 3 days

Characteristics		Safety Population (N = 31)
Age, median (range), years		65 (46, 76)
Gender, %	Male	61
	Female	39
ECOG, %	0	48
	1	52
ISS Stage ≥2, %		74
High-risk cytogenetics*, %		48
Extramedullary disease, %		23
High tumor burden†, %		39
Time since initial diagnosis, median (range), years		5.4 (0.9, 20.1)
Number of prior anti-myeloma regimens, median (range)		5 (3 – 11)
Prior autologous SCT, %		94
Penta-exposed, %		94

ASH 2020 Abstract No:129 :
Universal: An Allogeneic First-in-Human Study of the Anti-Bcma ALLO-715 and the Anti-CD52 ALLO-647 in Relapsed/Refractory Multiple Myeloma



Response is dose dependent
6/9-ongoing response, longest 6 months

AE of Interest* (N=31)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cytokine Release Syndrome†	5 (16)	9 (29)	–	–	–	14 (45)
ICANS†	–	–	–	–	–	–
Graft-versus-Host Disease	–	–	–	–	–	–
Infection‡	2 (7)	6 (19)	4 (13)	–	1 (3)	13 (42)
Infusion Reaction to ALLO-647	4 (13)	3 (10)	–	–	–	7 (23)

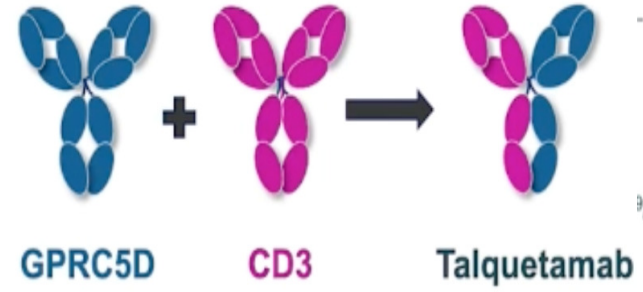
Cell Dose & LD Regimen	FCA						CA	
	DL1 (40M)	DL2 (160M)	DL3 (320M)			DL4 (480M)	DL2 (160M)	DL3 (320M)
	Low ALLO-647 (N=3)	Low ALLO-647 (N=4)	Low ALLO-647 (N=6)	High ALLO-647 (N=4)	ALL ALLO-647 (N=10)	Low ALLO-647 (N=3)	Low ALLO-647 (N=3)	Low ALLO-647 (N=3)
ORR†, n (%)	–	2 (50)	3 (50)	3 (75)	6 (60)	1 (33)	–	2 (67)
VGPR+ Rate†, n (%)	–	1 (25)	3 (50)	1 (25)	4 (40)	–	–	1 (33)

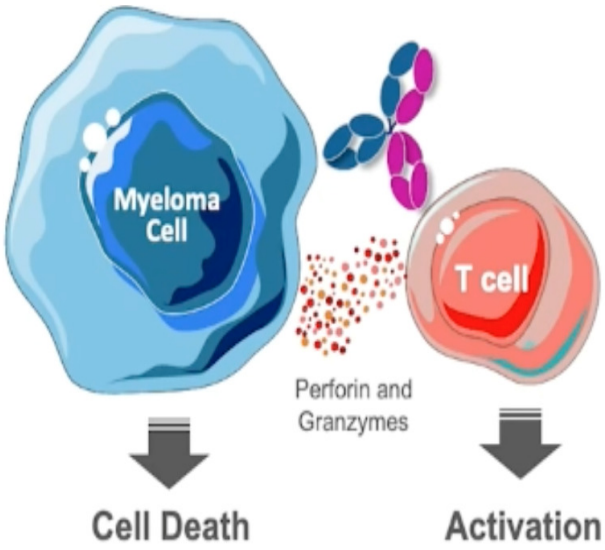
VGPR+ = sCR, CR, or VGPR

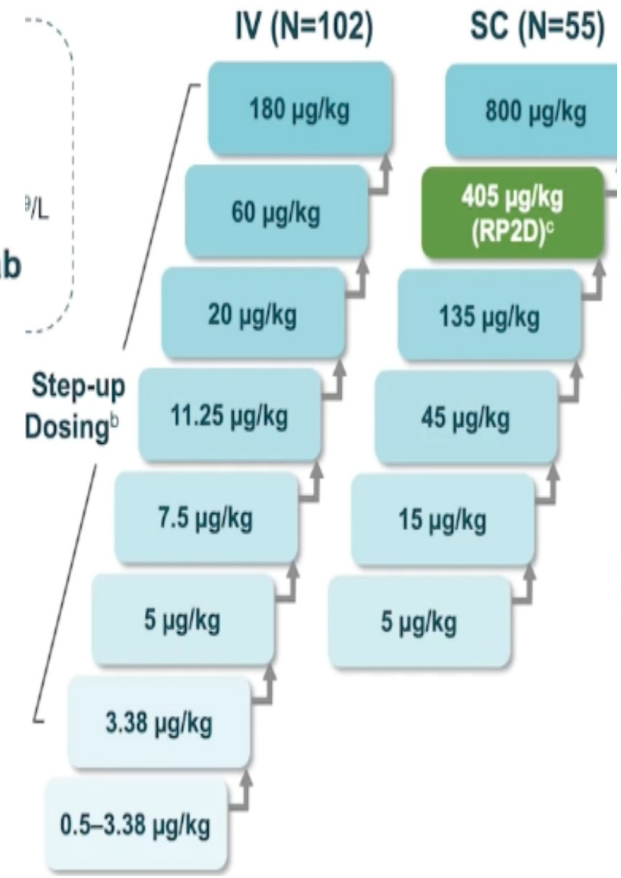
5/6 in VGPR + -MRD negative

ASH 2020 Abstract No:290 :

A Phase 1, First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D (GPRC5D) x CD3 Bispecific Antibody, in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)



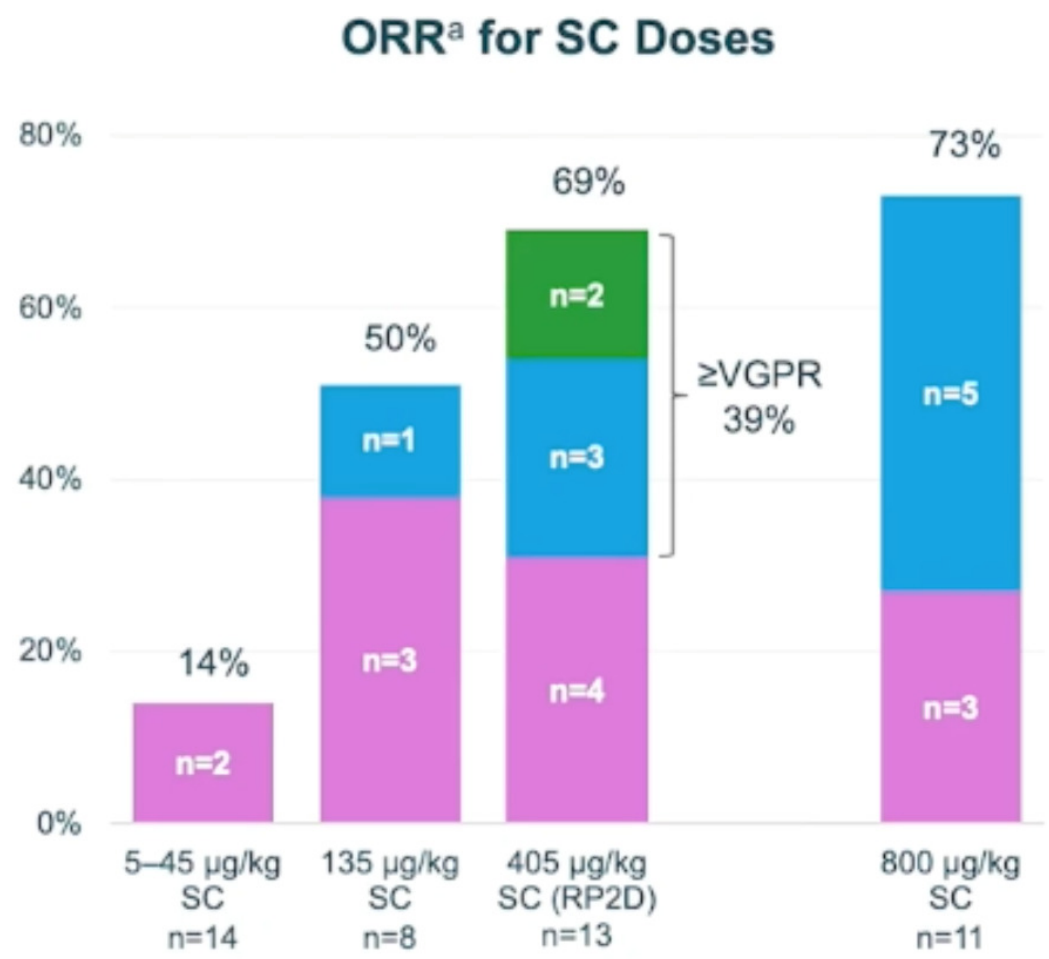


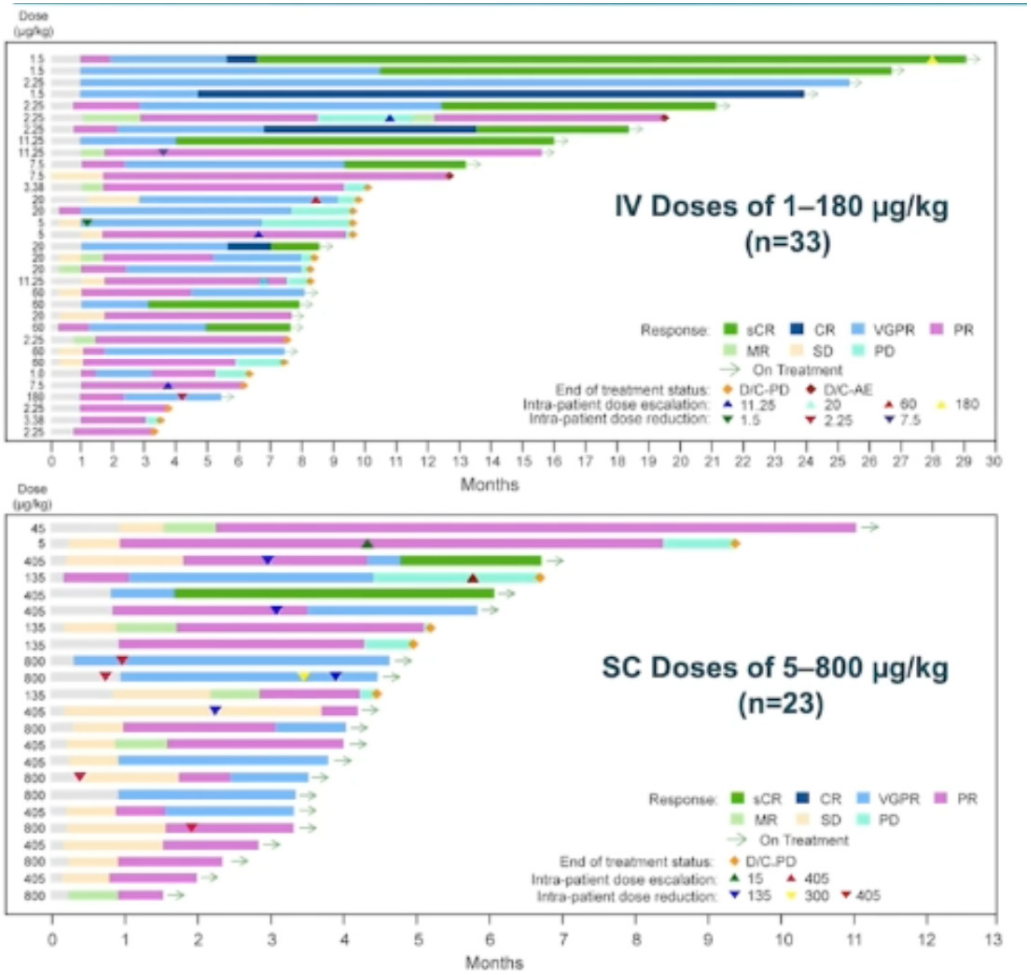


DLT-Lipase elevation, skin rash

AEs (≥25% of Total)	Total (N=157) 3.6-mo (0.1–28.1) mF/U		405 µg/kg SC RP2D (n=19) 2.7-mo (0.1–6.5) mF/U	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic, n (%)				
Anemia	76 (48)	43 (27)	5 (26)	0
Neutropenia	74 (47)	48 (31)	9 (47)	8 (42)
Lymphopenia	62 (40)	57 (36)	3 (16)	3 (16)
Leukopenia	50 (32)	25 (16)	4 (21)	3 (16)
Thrombocytopenia	50 (32)	20 (13)	4 (21)	1 (5)
Nonhematologic, n (%)				
CRS	84 (54)	5 (3)	13 (68)	0
Dysgeusia	60 (38)	NA	9 (47)	NA
Fatigue	46 (29)	1 (1)	3 (16)	0
Headache	43 (27)	2 (1)	3 (16)	0
Pyrexia	42 (27)	1 (1)	2 (11)	0
Diarrhea	39 (25)	4 (3)	3 (16)	0

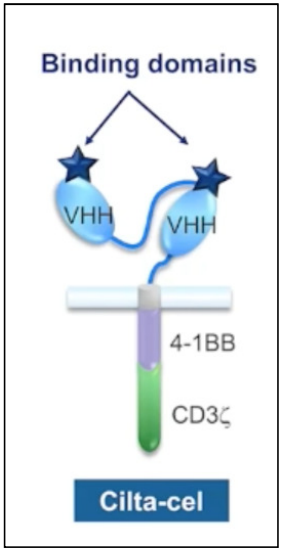
ASH 2020 Abstract No:290 :
A Phase 1, First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D (GPRC5D) x CD3 Bispecific Antibody, in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

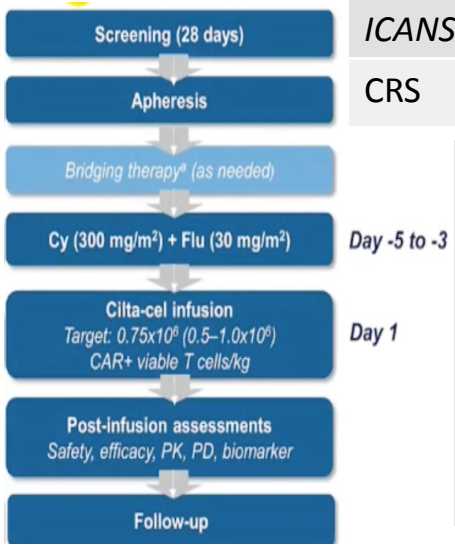




ASH 2020: Abstract No.177:
CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/ Refractory Multiple Myeloma

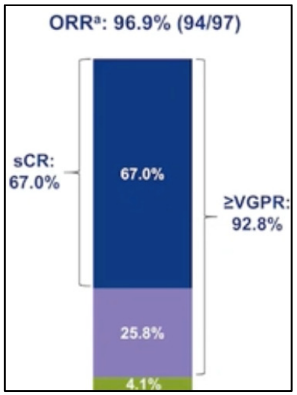
- **Ciltacabtagene autoleucel (Cilta-cel)- chimeric antigen T-cell therapy**
- **2 BCMA single-domain antibodies designed to confer activity**
- **Primary objective: ORR**
- **Phase 1b, n=24; Phase 2, n=59**





Median turnaround time-29 days
No patient discontinued due to manufacturing failures

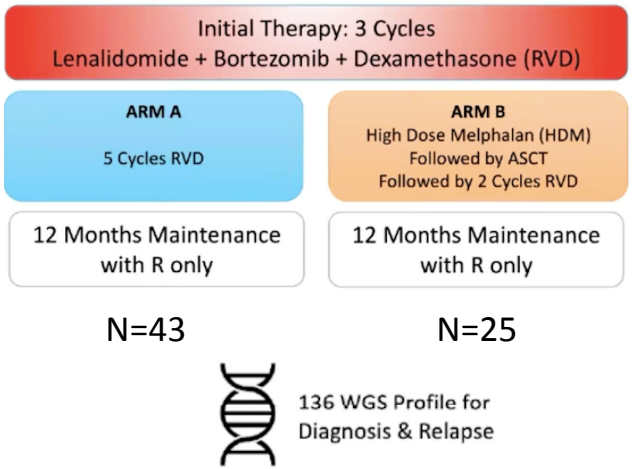
Toxicity	Grade 3/4
Hematologic	99%
Infection	19.6%
Neurotoxicity *ICANS*	9.3% *2.1%*
CRS	4.1%



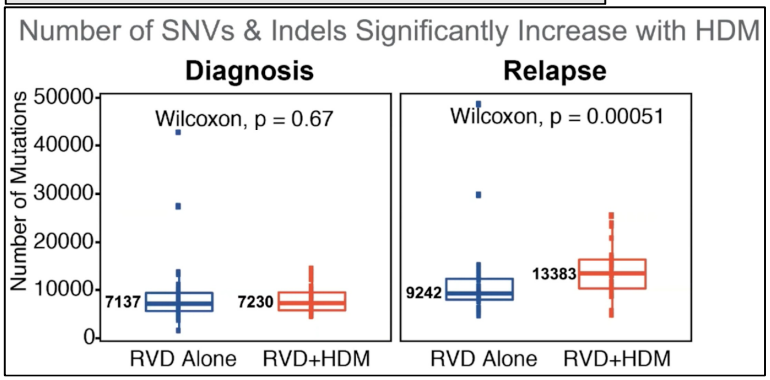
Baseline Characteristic	N=97
Median age (range) in years	61 (43-78)
Tumor BCMA expression ≥ 90%	92%
High-risk cytogenetics	24%
Prior lines of treatment, median (range)	6 (3-18)
Triple class refractory	88%
Penta-refractory	42.3%
Refractory to last line	99%

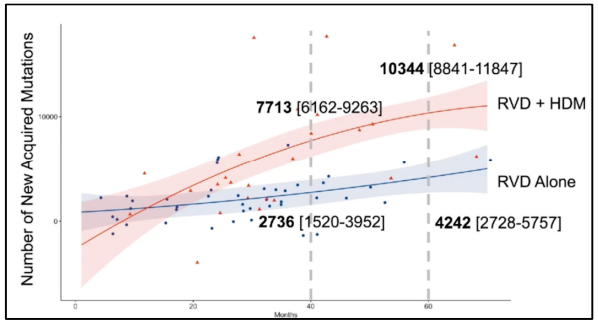
Overall MRD negative 10^{-5}: In evaluable patients (93%), in all treated- 54.6%
Median time to first response: 1 mon (0.9-8.5)
Median f/u-12.4 mon
Median PFS- NR
12-mon PFS-76.6%; 12-mon OS-88.5%
CRS grades mostly 1 or 2
Cita-cel ongoing studies: earlier line settings and outpatient administration

ASH 2020: Abstract No.61: High-Dose Melphalan Significantly Increases Mutational Burden in Multiple Myeloma Cells at Relapse: Results from a Randomized Study in Multiple Myeloma



Both arms matched for age, sex, ISS, cytogenetics, best response and time to progression





A polynomial model: RVD may add >10,000 (~2.45X more than RVD alone) new mutations in 5 years after diagnosis

- **HDM increased subclonal mutation frequency at relapse**
- **72% HDM treated patients accumulated mutations in the DNA damage**
- **Repair (DDR) pathways vs. 17% in RVD alone (p<0.0001)**
- **HDM increased clonal heterogeneity at relapse**
- **At relapse, increased mutations in the HDM group was observed in the**
- **regions of RNA (transcriptional strand bias)**

- **No significant difference in copy number alterations between the 2 arms**
- **HDM did not significantly affect "driver" gene mutations**
- **DDR pathway mutations may cause resistant clones to HDM- future studies: HDM with PARPi in CR-?additional benefit**

Chronic Myeloid Leukemia

Lead:

Aby / Hasmukh

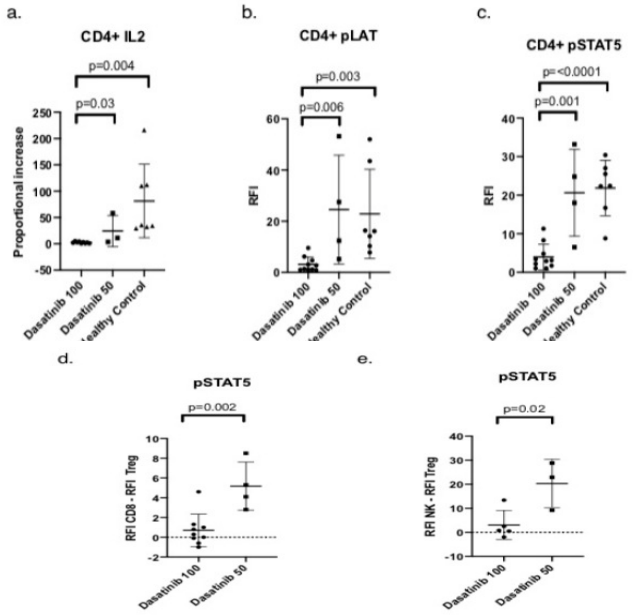
ASH 2020 Abstract No:2144 :

Inhibition of Immune Cell Subsets Is Differentially Affected By Dasatinib Dosage in Patients with Chronic Phase CML

Immune cells(Tregs, Nkcells, CD8+T- cells) influence CML disease response.
To study effect of the immune cells by Dasatinib- multikinase inhibitor at different doses

Methodology

Expression of the cytokines, TNFa, IFNg and IL-2, after treatment of cells with OKT3.
Relative fluorescence intensity (RFI) was calculated



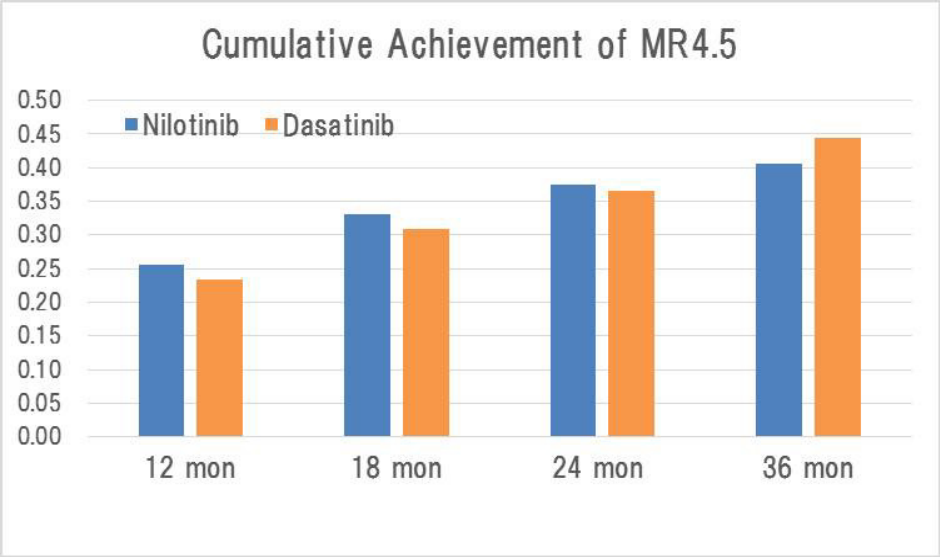
	Dasatinib 100mg N=10	Dasatinib 50mg N=4	Remark
CD4+IL2	↓	↓	Inhibits key sign paths in T & NK cells Reduced Treg activity
CD4+pLAT	↓	↑	
CD4+pSTAT5	↓	↑	
CD8+/Treg (pSTAT5)	↓	↑	
NK/Treg (pSTAT5)	↓	↑	

Conclusion- Dasatinib (50 mg)improves Effector cell function
Dasatinib (100mg)increased T reg inhibition

ASH 2020 Abstract No:45:

Nilotinib Vs. Dasatinib in Achieving MR$^{4.5}$ for Newly Diagnosed Chronic Myeloid Leukemia: Results of the Prospective Randomized Phase 3 Study, JALSG CML212

- ✓ **Which 2nd gen TKI is better to achieve DMR for de novo CML-CP? Nilotinib(300mg)/ Dasatinib (100mg) Primary end point- Rate of cumulative achievement of MR4.5 by 18 mon**
- ✓ **Secondary- Safety/continuity/PFS/EFS,OS**
- ✓ **82 centres. 454 patients (227 in each arm. Sokal Score Risk stratification)**



	Nilotinib	Dasatinib
Sokal score- High	18.9%	18.5%
MR4.5 at 18 months	33%	30.8%
EFS at 36 mths	67.2%	65.4%
OS at 36 months	98.8%	99%
CCYR at 36 months	78.4%	78.9%
Adverse effects G3 or 4	Lipase (11%)	Neutro (12%) Thrombo(16%

Conclusion- Nilotinib and Dasatinib are equally effective for de novo CML-CP patients in achieving MR4.5

652 Phase 1 Trial of Vodobatinib, a Novel Oral BCR-ABL1 Tyrosine Kinase Inhibitor (TKI): Activity in CML Chronic Phase Patients Failing TKI Therapies Including Ponatinib

The activity and safety of vodobatinib was evaluated in ponatinib treated (PT) and ponatinib naïve (PN) chronic phase (CP)-CML subjects in an exploratory analysis, in multi centre study including India.

Vodobatinib, a novel 3rd generation (3G) TKI effective against wild-type and mutated BCR-ABL1 with limited off-target activity.

- Multiple escalating doses of vodobatinib (once daily) in 28-day cycles were evaluated in a 3+3 study design.
- The primary objective was determination of the maximal tolerated dose (MTD) or recommended phase 2 dose (RP2D) along with safety.
- Secondary objective was to evaluate anti-leukemic activity.
- Mutation profile: Single mutation in 9 (01 had T315I), double mutation in 02

Efficacy	Ponatinib treated (PT) N = 16	Ponatinib naïve (PN) N = 15
Cytogenetic Response		
Achieved CCyR	4** (25%)	7# (47%)
Maintained* CCyR	4 (25%)	3 (20%)
Achieved PCyR	3 (19%)	0 (0%)
Stable disease ##	3 (19%)	1 (7%)
Progressive disease	2 (12%)	4 (26%)

*Where CCyR = Complete Cytogenetic Response, PCyR = Partial Cytogenetic Response; MCyR = Major Cytogenetic Response (PCyR + CCyR); * pts with intolerance, ## Stable disease: Pt with less than MCyR maintaining hematological response; **2 pts were refractory and 2 were intolerant with loss of response; #5 pts were refractory and 2 were intolerant with loss of response;*

Table 3: Overall Efficacy Outcomes: Molecular Response

Efficacy	Ponatinib treated (PT) N = 16	Ponatinib naïve (PN) N = 15
Molecular Response		
Achieved DMR	2 (12%)	1 (7%)
Achieved MMR	3 (19%)	4 (26%)
Maintained* DMR	0 (0%)	1 (7%)

*DMR = Deep Molecular Response (<0.01 % IS BCR-ABL); MMR = Major Molecular Response (<0.1 % IS BCR-ABL); * pts with intolerance*

31 CP-CML pts received vodobatinib at doses of 12 to 240 mg; 16 pts (9 males) in ponatinib treated (PT) cohort [7 (44%) ponatinib was the immediate prior TKI] and 15 pts (7 males) in the ponatinib naïve (PN) cohort.

Efficacy: Median duration of treatment was 17.3 (0.6-36) and 14.8 (0.5- 42) months in the Ponatinib treated and naive groups, respectively

Safety: Grade ≥ 3 TEAEs were reported in 10 (63%) pts, Three pts died on study: 1 due to disease progression in the PT group; 1 due to pneumonia (suspected COVID-19) and 1 due to intracranial hemorrhage in the PN group.

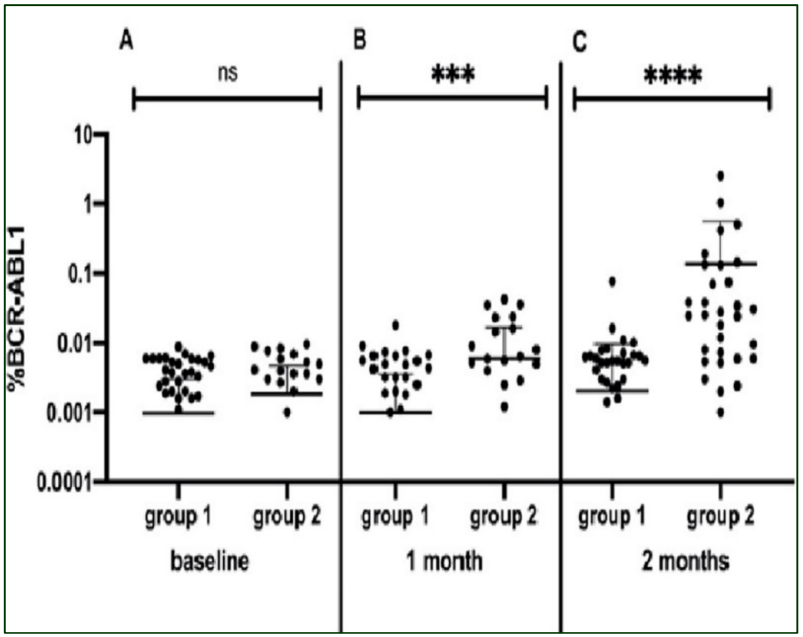
Conclusion: Comparable and promising efficacy was noted in both PT (50% CCyR) and PN (67% CCyR) groups, meriting further study of vodobatinib as a potential new agent for treatment of previously treated CP-CML.

ASH 2020 Abstract No:2157 :

BCR-ABL1 Levels at First Month after TKI Discontinuation Predict Subsequent Maintenance of Treatment-Free Remission: A Study from the "Gruppo Triveneto LMC"

Success of TFR in CML ranges at present between 30-70%. At present it is difficult to predict outcomes of TFR strategy in a patient. This study attempts to predict eventual outcomes of TFR by monitoring baseline BCR-ABL transcript value and trends of BCR-ABL transcript after suspension of TKI.

BCR-ABL measured at therapy discontinuation, monthly for first 6 months, 2 monthly for the next 6 months and 3 monthly thereafter.110 patients (Imatinib)56(2nd gen TKI)-Total 166 patients.



	MMR group(n=120)	MMR loss group(n=46)	
Mean BCR-ABL(Base)	0.0010	0.0018	p=0.052
Mean BCR-ABL(1 month)	0.0010	0.0060	p=0.0005
Mean BCR-ABL(2 month)	0.0020	0.1354	p=0.0001

To determine a threshold value of BCR-ABL1 RNA at one month after discontinuation, the ROC analysis was performed, defining an AUC=0.6430
Cut off---0.0051%.
The chosen range has 92.2% specificity, 31.7% sensitivity and a likelihood ratio of 4.087.

Chance of a successful TFR could be foreseen already at one month after TKI discontinuation, both for patients stopping imatinib or 2G-TKI.

ASH 2020 Abstract No:1237

Long-Term Outcome of Chronic Phase Chronic Myeloid Leukemia Patients Treated with Nilotinib Front-Line

Nilotinib has shown superior response rates and rates of deep molecular remission compared to Imatinib. However long term outcomes of patients on Nilotinib is awaited. This study retrospectively analyzed long term outcomes of upfront 600mg Nilotinib in 202 patients in "real-life" setting in CML-CP.

The patients receiving Nilotinib from Oct-2007 to June 2020 included in the study.

Primary End point- 1.Rate of molecular responses(long-term)
2. Vascular safety of Nilotinib

Secondary Endpoint-1.Kinetics of Mol response
2. Survival & Safety of Nilo

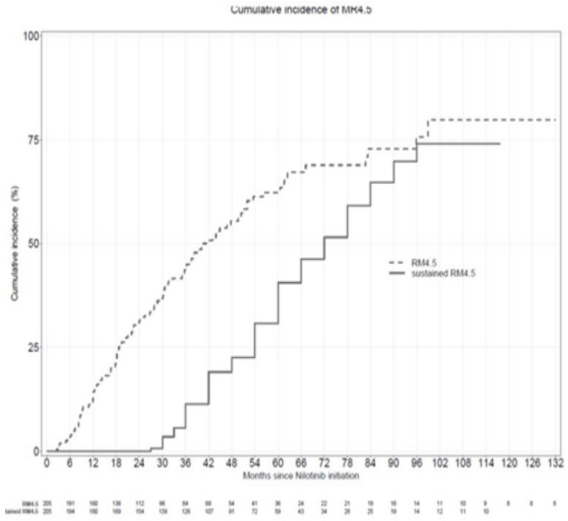


Figure: CI of MR4.5 and sustained MR4.5 (≥2 years) in NIL first-line CP CML pts.

Total 202 pts Median Age -50.4 years. 26% CV risk .Median F/U-61.5 (1-147.5).
113(55%) –Off Nilotinib (toxicity/TFR/resistance). TFR tried in 51% of pts at 10 yr
28 (14%) -arterial event at median of 26 (0.6-98.5) months.
46(22.5%) pts reached TFR criteria& stopped NIL after median-58.5 (27-126)mon

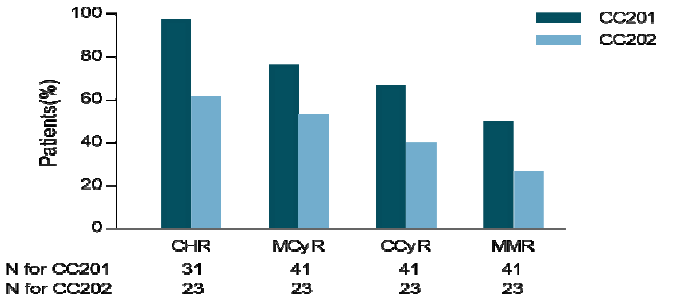
	1year	2 year	5 year
MMR	64%	79%	95%
MR4.5	14%	31%	62%
Sustained MR4.5	-	30%	45.5%
After TFR no MMR loss	70.7%	-	65.26%
PFS	-	94.92%	89.5%
OS	-	95.75%	94.8%

Nilotinib – high rates of sustained MR 4.5 in high proportion allowing TFR. Vascular toxicity in elderly is a concern.

ASH 2020 Abstract No:651 :
651 Novel BCR-ABL1 Tyrosine Kinase Inhibitor (TKI) HQP1351 (Olverembatinib) Is Efficacious and Well Tolerated in Patients with T315I-Mutated Chronic Myeloid Leukemia (CML): Results of Pivotal (Phase II) Trials

HQP1351 (olverembatinib) - an orally active third-generation BCR-ABL TKI designed for treatment of patients with CML withT315I mutation, which confers resistance against all first- and second-generation TKIs

Figure 1. Overview of efficacy in patients with CML-CP (Study CC201) and CML-AP (Study CC202)



Two single-arm, multicenter, open-label pivotal studies in TKI resistant CML with T315I mutation

HQP1351-CC201 (41 patients, CML-CP) and HQP1351-CC202 (23 patients, CML-AP)
HQP1351 was given at 40mg once every other day for 28 consecutive days per cycle over 24 months

	CML-CP (41)	CML-AP (23)
3m PFS	100%	100%
6m PFS	96.7%	95.5%
CHR	96.8% (30/31)	78.3% (18/23) MaHR
CCyR	75.6% (31/41)	52.2% (12/23) MCyR
MMR	48.8% (20/41)	26.1% (6/23)

Toxicities predominantly haematologic in both studies

Skin pigmentation, metabolic and electrolyte imbalances and proteinuria were among the non-haematologic toxicities.

HQP1351 was highly and durably efficacious in the CML patients with T315 mutation; the probability and depth of clinical response may increase with prolonged treatment period.

LBA-4 Efficacy and Safety Results from ASCEMBL, a Multicenter, Open-Label, Phase 3 Study of Asciminib, a First-in-Class STAMP Inhibitor, vs Bosutinib (BOS) in Patients (Pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Previously Treated with ≥2 Tyrosine Kinase Inhibitors

Hypothesis- Asciminib could provide superior efficacy to BOS beyond 2nd line(failure or intolerance)
Primary endpoint-major molecular response (MMR) rate at 24 wks
Median follow up-15 month (data cutoff- May 2020)

Baseline characters	Asciminib 40mg BID (N=157)	Bosutinib 500mg OD(n=76)
Reason to discontinue last TKI		
Lack of efficacy	95 (60.5)	54(71.1)
Lacko of tolerability	59 (37.6)	22(28.9)
Patient disposition		
Treatment ongoing	97(61.8)	23(30.3)
Discontinued treatment	59(37.6)	53(69.7)
Reason for discontinuation		
Lack of efficacy	33(21)	24(31.6)
Physician decision	10(6.4)	6(7.9)
Adverse events	8(5.1)	16(21.1)
Patient decision	4(2.5)	3(3.9)
Death	1(0.6)	0
LFU	1(0.6)	1(1.3)
Progressive disease	1(0.6)	3(3.9)

RESULTS-

1. MMR rate at 24 wks was 25.5%(40) with asciminib and 13.2%(10) with BOS, meeting the primary objective.

2. CCyR rate at 24 wks was 40.8% with asciminib vs 24.2% with BOS.

TOLERANCE

1.Treatment discontinuation due to adverse effects- Asciminib (5.8%) than BOS (21.1%)

2.Grade –3 AE(>10%)-thrombocytopenia (17.3%; 6.6%), neutropenia (14.7%; 11.8%), diarrhea (0%, 10.5%), and increased ALT (0.6%, 14.5%)

Conclusion-Asciminib has shown significant and clinically meaningful superiority resistant/intolerant (R/I) CML patients especially in those who received ≥2 prior TKIs.

ASH 2020 Abstract No-46

Bosutinib (BOS) Versus Imatinib for Newly Diagnosed Chronic Phase (CP) Chronic Myeloid Leukemia (CML): Final 5-Year Results from the Bfore Trial

- **Hypothesis- Bosutinib(400mg) is superior to imatinib(400mg) in molecular response**
- **Primary endpoint-major molecular response (MMR) rate at 12 month (published in jco 2018)**
- **Median follow up-5-year update**

STUDY	TKI	EMR(%)	MMR (%)	MR4.5 (%)
BFORE	IMA	60	64	36.6
	BOS	80	74	47.4
DASISION	IMA	64	64	33
	DASA	84	76	42
ENESTend	IMA	66	60	31.4
	NILO	90	77	53.5

RESULTS

1.Efficacy is similar to other 2GTKI(table)

2. Difference is more in high sokal group

3. Transformations to accelerated/blast phase (AP/BP) occurred in 6 (AP 3; BP 3) BOS- and 7 (AP 6; BP 1) IMA-treated pts.

4. Progression/death - 6.7 % and 9.3%

TOLERANCE

1. Most TEAEs occurred during the first year of treatment
2. Diarrhea (75%), nausea (37.3%), thrombocytopenia (35.8%) and increased ALT (33.6%)
3. The most frequent AEs leading to permanent treatment discontinuation were increased ALT (4.9%)

Conclusion- First-line BOS continued to show superior efficacy vs IMA in terms of earlier and deeper molecular response

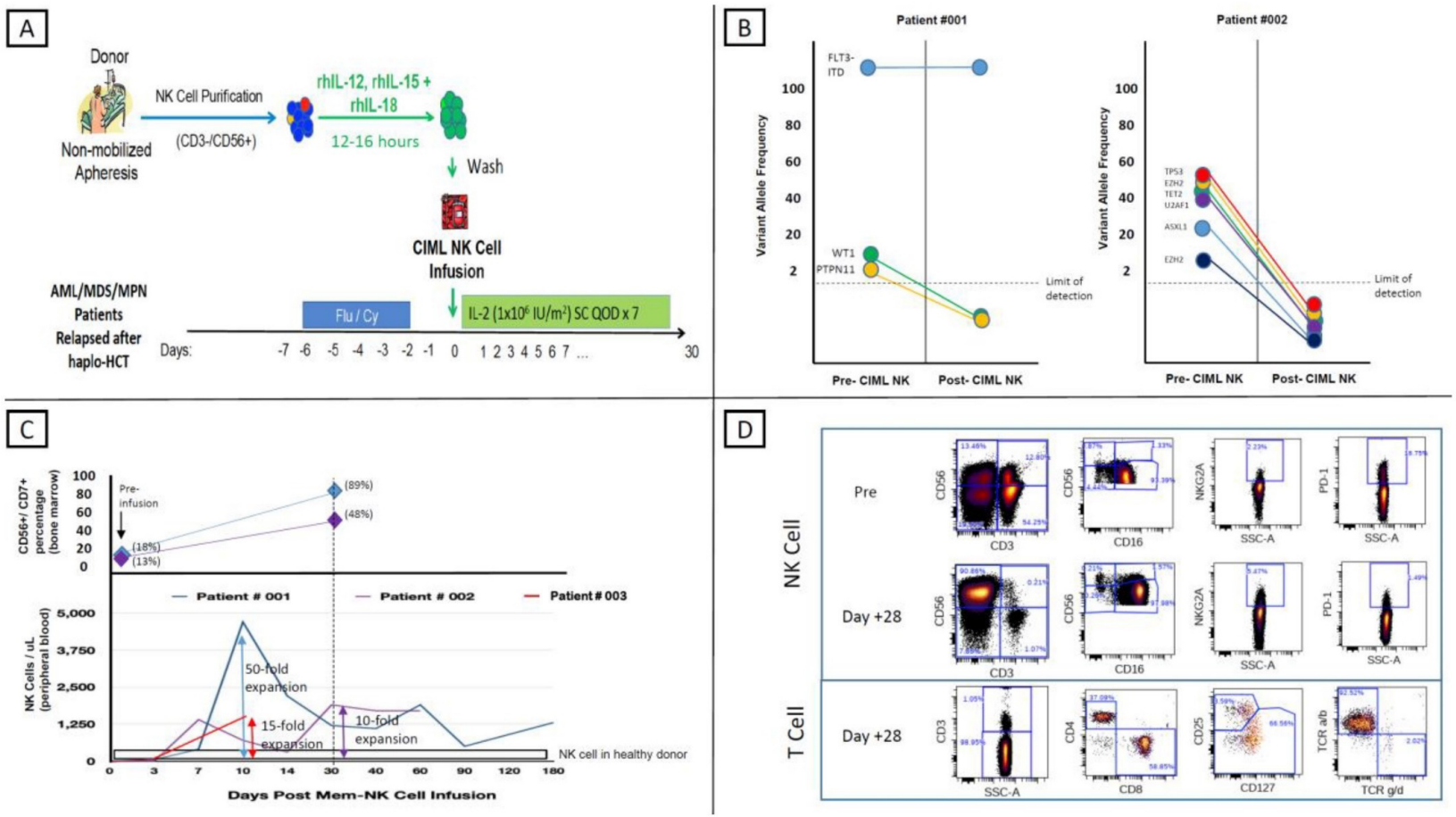
NK cell

Lead:

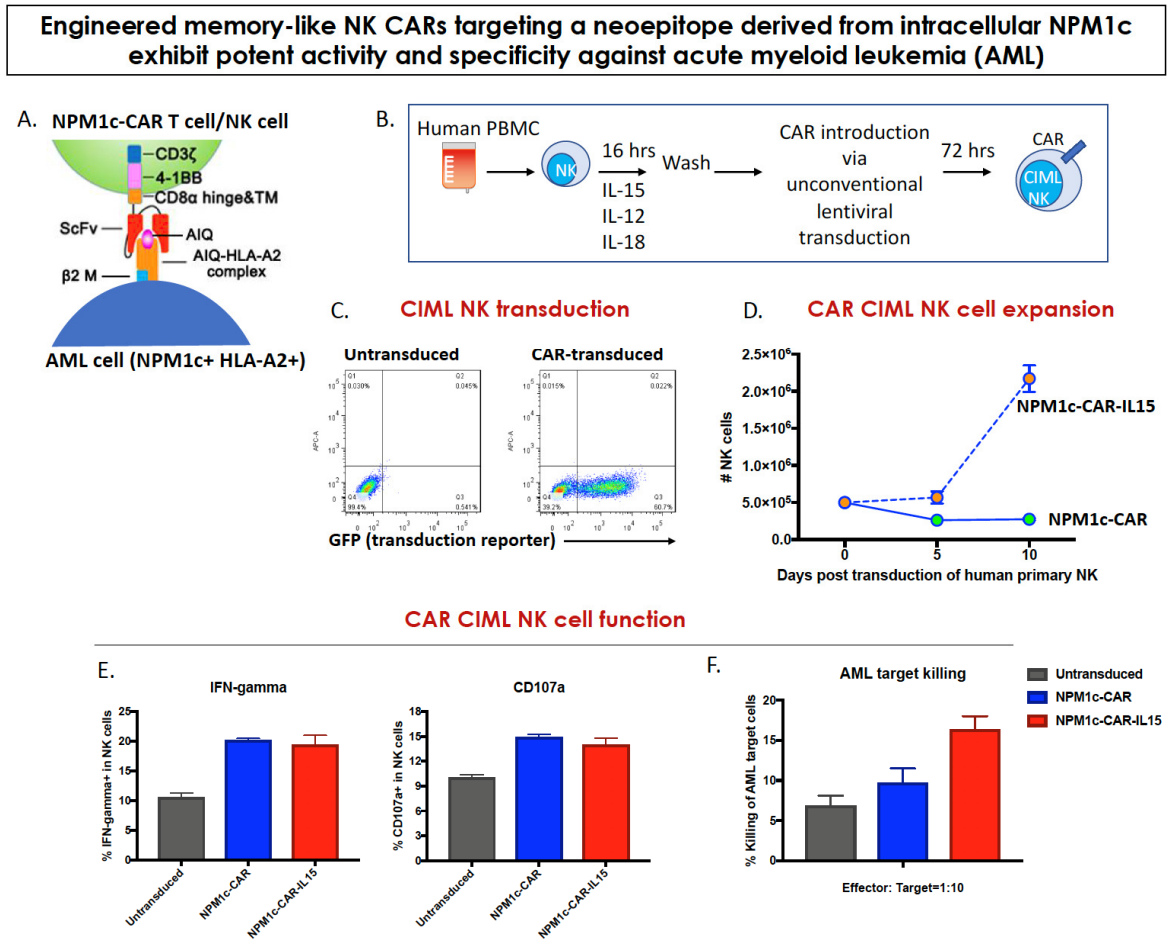
Uday Kulkarni

ASH 2020 Abstract no 66

66 Cytokine-Induced Memory-like NK Cells Exhibit Massive Expansion and Long-Term Persistence after Infusion Post-Haploidentical Stem Cell Transplantation: A Report of the First Three Cases in a Phase I Trial



ASH 2020 Abstract no 611
Engineered Memory-like NK Cars Targeting a Neoepitope Derived from Intracellular NPM1c Exhibit Potent Activity and Specificity Against Acute Myeloid Leukemia



ASH 2020 Abstract no 685
Systems-Level Analysis of the Immune Repertoire in Neutropenia Reveal Arrested NK Cell Differentiation and Exhaustion