ALL, AML, MDS

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Disclosure of Conflicts of Interest

Prajwal Dhakal, MBBS has no relevant financial relationships to disclose.

Acute lymphoblastic leukemia

Ponatinib + BLIN

- **Philadelphia chromosome positive ALL**
- **Newly diagnosed, relapsed refractory**
- **Phase II**
- Ponatinib daily- 30 mg in Cycle 1 and 15 mg Cycle 2+
- Blinatumomab day 1-28 cycle 1-5
- IT Methotrexate + cytarabine
- 6-week cycle
- HCT- 1 ND in CR1 MRD +, 6 in R/R
- Ponatinib stopped - 1 stroke, 1 DVT
- BLIN stopped- 1 recurrent neurotoxicity

Characteristic N (%) / median [range]	Category	ND ALL N = 35	R/R ALL N = 14
Age (years)		57 [22-83]	38 [24-61]
CD19 expression		99.8 [74.9-100]	99.9 [98.6-100]
Line of therapy	Frontline 1^0 refractory Salvage 1 Salvage 2+	35 (100) 0 0 0	0 2 (14) 6 (43) 6 (43)
Response			
CR		21/23 (91)	11/13 (85)
CR/CRi		22/23 (96)	12/13 (92)
CMR after 1 cycle		21/33 (64)	10/14 (71)
CMR overall		28/33 (85)	11/14 (79)
2-yr EFS		93	42
2-yr OS		93	61

Short et al. JCO 40, no. 16_suppl (June 01, 2022) 7009-7009.

HyperCVAD + BLIN +/- INO

- **Phase II, newly diagnosed**
- **N- 58 patients, <60 years median age 34 (17-59 years)**
- Hyper-CVAD alternate high-dose MTX/Ara-C for up to 4 cycles, followed by 4 cycles of BLIN
- Beginning pt #39, INO on day 1 and 8 added to the 2 cycles of MTX/Ara-C and to 2 cycles of BLIN (4 total cycles with INO)
- All relapses in poor-risk features- no relapses beyond 2 years
- No relapses or deaths in INO group, estimated 1-year OS- 100%
- BLIN- recurrent grade 2 neurotoxicity
- No VOD

Total patients	**58, 45 evaluable**
CR	45 (100%)
MRD	76% after induction 95% overall
Current status	Relapse- 5 HCT- 18 in CR1 Died in remission- 2 In remission 33
Estimated 3-year OS	85%

Short et al. JCO 40, no. 16_suppl (June 01, 2022) 7034-7034.

INO + miniHCVD +/- BLIN

- **Phase II**
- **Newly diagnosed Ph- ve ALL 60+ years old**
- Total 80 pts; 30 patients 70+ yrs
  - 74 evaluable, 6 already MRD after 1 cycle chemo before enrollment
- INO + miniHCVD- 49 pts; BLIN added with pt #50
  - 4 cycle INO + miniHCVD→ 4 cycles BLIN
  - Maintenance- POMP 3 cycles followed by BLIN 1 cycle x 4
- Poor risk cytogenetics- 19 patients
- TP53 mutation- 24 patients
- 6 patient VOD, 1 after HCT

Total patients	**80, 74 evaluable**
CR	89%
MRD	80% after cycle 1 84% overall
Current status	Relapse- 11 HCT- 4 Died in remission- 31 In remission 33
30-day mortality	0
5-year OS	47%

Macaron et al. JCO 40, no. 16_suppl (June 01, 2022) 7011-7011.

Brexucabtegene-autoleucelcel (KTE-X19)

- Anti CD-19 CAR T-cell therapy, approved for R/R ALL
- **Phase I/II, ZUMA-3**
- **R/R ALL**
- 2- year follow-up; median 26.8 months (20.7-32.6)
- Grade 3/4 AE (initially reported in Shah et al. Lancet 2021)
  - Anemia- 27, Fever- 20, Infection- 14
  - CRS- 13, neurologic events- 14
  - Brain herniation-1
  - Septic shock- 1

Total patients	**55**
CR Total 26-50 % blasts 51-75% blasts 76-100 % blasts	 56% 83 % 86% 57%
CRi	15%
DOR	18.6 months (9.6-NE)
RFS	11.7 months (6.1-20.5)
Median OS	25.4 (16.2- NE)
HCT	11 patients

Shah et al. JCO 40, no. 16_suppl (June 01, 2022) 7010-7010.

T-ALL

- Phase I, donor derived CD7 CAR-T
  - Total 20 patients, 19 followed
  - median follow-up 15.8 months (range 13-18.3)
  - ORR 95% CR 85% at day 30 post infusion
  - 7 went to HCT
  - 1-year PFS 51.6% 1-year OS 72.6%
  - Short term SE- CRS, GVHD
  - Long onset SE- G4 intestinal GVHD, G5 pneumonia, G4 pseudomonas, G3 CMV encephalitis
- Phase I, autologous CD7-targeted CAR T-cell therapy
- Phase I, donor-derived CD5 CAR T cells in patients who relapsed after CD7 CAR-T therapy

Pan et al. JCO 40, no. 16_suppl (June 01, 2022) 7023-7023
Zhao et al. JCO 40, no. 16_suppl (June 01, 2022) 7035-7035.
Pan et al. JCO 40, no. 16_suppl (June 01, 2022) 7028-7028

Acute myeloid leukemia

Crenolanib + 7+3

- **Phase II, newly diagnosed FLT3 + AML**
- 7 + 3 (DNR/Ida) + crenolanib
  - Crenolanib 100 TID starting day 9 until 72 hrs prior to next chemo
- FLT3-ITD- 33 pts; FLT3 TKD- 8; TKD + ITD- 3
  - 11 - concomitant *NPM1*/*DNMT3A* mutations
  - 11 - secondary AML-type mutations
  - 2 - *TP53*
- Grade ≥3 AE
  - Febrile neutropenia (50%)
  - diarrhea (18%)
  - Nausea (6%)
  - Rash (6%)
- No QTc prolongation

Total patients	**44**
Age	57 (19-75)
CR/CRi	73% after 1 cycle 86% after 2 cycles
HCT	22 patients
Median EFS	45 months
Median OS	NR 57% alive with median f/up 45 months (range 4.4-54.9)
Cumulative relapse	15%

Wang et al. JCO 40, no. 16_suppl (June 01, 2022) 7007-7007.

Quizartinib + DAC +VEN

- **Phase I/II, newly diagnosed, R/R FLT3+ AML**
- Total patients 28; ND- 5 ; R/R- 23
- DAC x 10 days in Cycle 1, 5 days cycle 2+
- VEN x 14-21 days
- QUIZ (30 or 40 mg/day) daily continuously
- QUIZ 30 mg daily determined as RP2D
- Grade 3/4 non-hematologic toxicities- lung infection (42%), neutropenic fever (30%).
- Median follow-up- 13 months
- Median OS for R/R- 7.6 months; 1-year OS- 30%
- HCT- 8/18 responding R/R pts (5/8 prior GILT)
- Median OS with HCT- 19; w/o HCT- 8 months (p=0.2)

Subgroups	CRc in R/R pts
Prior GILT	12/16
No prior GILT	6/7
Prior HMA + VEN	8/11
No prior HMA +VEN	10/12
DNMT3A +; DNMT3A-	8/12; 10/10
NPM1 +; NPM1 -	7/9; 11/13
RAS/MAKP+; RAS/MAPK*	2/5; 16/17

Yilmaz et al. JCO 40, no. 16_suppl (June 01, 2022) 7036-7036.

Pre-MEASURE

- CIBMTR database
- Retrospective analysis of adults with AML in CR1 who underwent a first alloHCT from 2013-2017
- Evaluate post alloHCT relapse based on pre-alloHCT minimal residual disease (MRD)
- Total pts- 448
- 147 (33%) relapsed at median 5.6 months post-alloHCT.
- MRD + in 129 (29%) pre-HCT patient samples; 1.35 mutation/patient
- 173 mutations- FLT3-ITD (n= 43), NPM1 (n = 48), and IDH2 (n = 46).
- 3-yr RFS 36% (95% CI 28-45) with MRD + vs 56% (51-62) with MRD-
- HR for relapse if MRD+ : 2.3 (95% CI 1.6-3.1)

	3- yr relapse probability
MRD + NPM1/FLT3 mutation	55% RFS 26% (16-37%)
MRD + with RIC/NMA conditioning	57%
MRD – with RIC/NMA conditioning	35%
MRD + with MAC conditioning	35%
MRD + FLT3/NPM1 mutation with RIC/NMA conditioning	67% RFS 19% (8-33%)

Hourigan et al. JCO 40, no. 16_suppl (June 01, 2022) 7006-7006.

Magrolimab + AZA

- **Phase Ib, newly diagnosed TP53-mut not suitable for intensive chemotherapy**
- Magrolimab IV 1 mg/kg priming dose D1, 4, then ramp up to 30 mg/kg Q2W + Azacitidine SC 75 mg/m2 D1-7
- Grade 3/4 AE
  - Febrile neutropenia (37.5%), neutropenia (20.8%)
  - Anemia (29.2%; Grade 3, 26.4%; Grade 4, 2.8%)
  - Thrombocytopenia (29.2%)
  - Pneumonia (26.4%)
- Treatment stopped
  - HCT- 9 pts (12.5%)
  - PD 26 (36.1%)
  - Death 8 (11.1%)
  - AE 13 (18.1%)
  - Other 14 (19.4%)

Total patients	**72**
Age	57 (19-75)
Adverse cytogenetics	57 (79.2%)
AML-MRC	34 (47.2%)
t-AML	15 (20.8%)
CR/ CRi or CRh	33.3/ 8.3%
Duration of CR	7.7 mos (95% CI 4.7-10.9)
Duration of CRi	8.7 mos (95% CI 5.3-10.9)
Median OS	10.8 mos (95% CI 6.8-12.8)

Daver et al. JCO 40, no. 16_suppl (June 01, 2022) 7020-7020.

Cedazuridine/decitabine+VEN

- **Phase II, R/R AML or untreated elderly/unfit for chemo**
- Oral treatment
- Cedazuridine/decitabine- 100mg/35 mg (ASTX727) day 1-5 + VEN day 1-28
- Notable mutations in FL
  - RUNX1 (33%)
  - ASXL1 (33%)
  - DNMT3A (7%)
  - TET2 (40%)
  - TP53 (20%)
- Grade 3/4 AE, mostly myelosuppression-related; others- ischemic stroke- 1, septic shock- 1, debilitation- 1

	Frontline (n=15)	**R/R (n=13)**
Median age **80+ yrs**	81 9 pts	72 5 pts
CR	4	2
CRi	4	2
MLFS	1	2
Median OS (f/up- 5 months)	NR (range 0.6-7.3)	7.2 (range 0.8-7.3)

Ravandi et al. JCO 40, no. 16_suppl (June 01, 2022) 7037-7037.

Myelodysplastic syndrome

Magrolimab + AZA

- **Phase Ib, untreated Intermediate/high-/very high- risk MDS**
- t-MDS- 22%
- Poor-risk cytogenetics- 62% (27% complex)
- Magro priming dose with ramp up to 30mg/kg weekly or Q2W maintenance dose
- Aza day 1-7 every 28 days
- Median no. of cycles- 6 (range 1-27)
- Grade 3/4 TEAEs
  - anemia (47%), neutropenia (46%), thrombocytopenia (46%), and WBC count decreased (30%)
- 6 pts discontinued due to AE
- 60-day mortality - 2%.

Outcome	All (n=95)	TP53-wt	TP53-mut
ORR	75	79	68
CR (95% CI)	33 (23-43)	31 (20-44)	40 (21-61)
Marrow CR %	32	38	20
Duration of CR, median (95% CI) mos	11.1 (7.6-13.4)	12.9 (8-NR)	7.6 (3.1-13.4)
RBC transfusion independence	14%	10%	24%
PFS, median(95% CI) mos	11.6 (9-14)	11.8 (8.8-16.6)	11 (6.3-12.8)
OS, median (95% CI) mos	NR (16.3-NR)	NR (21.3-NR)	16.3 (10.8-NR)

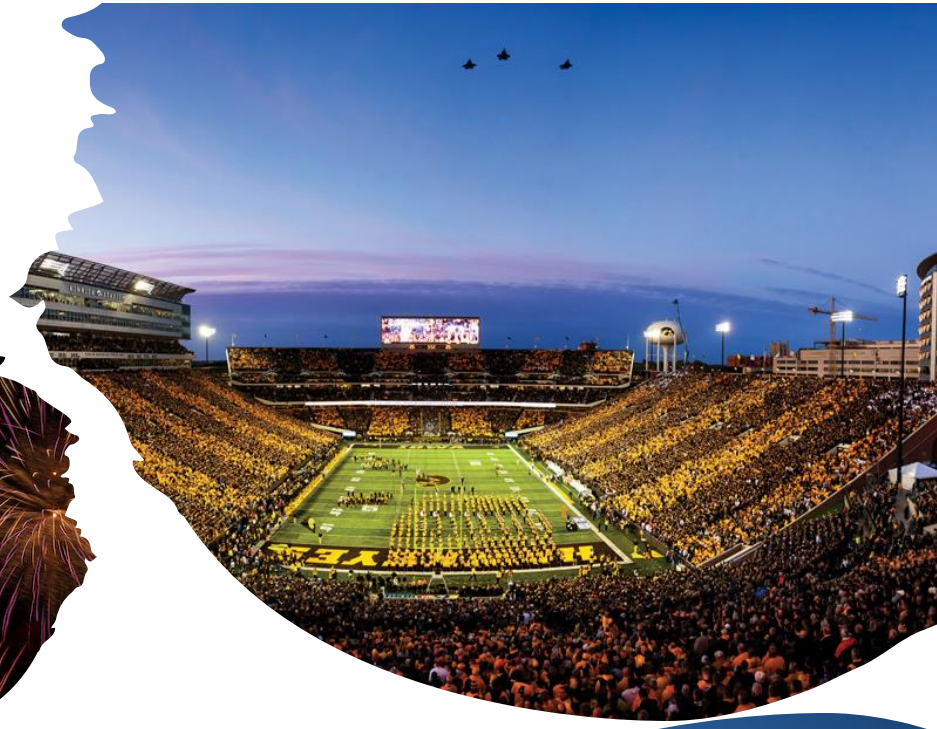
Sallman et al. JCO 40, no. 16_suppl (June 01, 2022) 7017-7017.

Ivosidenib

- **Phase I**
- ***IDH1*-mutant R/R MDS after intensive chemotherapy or HMA**
- **IVO 500 mg daily**
- Total patients- 16
  - 5 on treatment and free from leukemic transformation
  - 11 discontinued- 6 disease progression, 1 HCT, 1 sepsis (fatal but not related to IVO)
- Grade 3/4 AE- 11 pts; treatment related 8 pts, treatment related grade 3/4- 2 pts, serious- 7 pts
- Differentiation syndrome (Grade 2)- 2 pts
- QTc prolongation (Grade 1/2)- 2 pts
- CR- 7 pts; marrow CR- 5 pts; PR- 1 pt
- Hematologic improvement in ≥1 lineages- 11 pts

Sallman et al. JCO 40, no. 16_suppl (June 01, 2022) 7053-7053.

Thank you !!



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