APTITUDE HEALTH®

EPICS

EPICS CONGRESS COVERAGE: ASH 2020 – FOCUS ON LEUKEMIA

December 8, 2020

FACULTY EXPERTS

EPICS

Chair
Elias Jabbour, MD

Naval Daver, MD

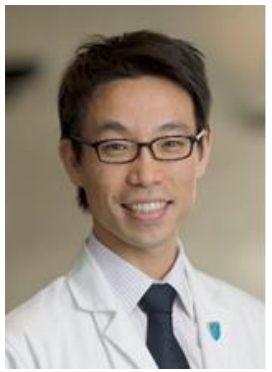
Eunice Wang, MD

Rami Komrokji, MD

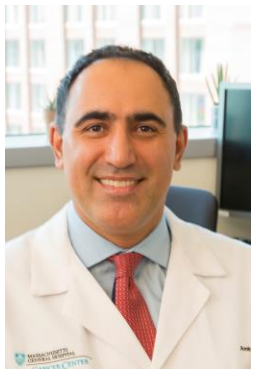
Guillermo Garcia-Manero, MD

Aaron Logan, MD, PhD

Jose Ribera, MD, PhD



Jae Park, MD



Amir Fathi, MD

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AGENDA

EPICS

Time EST	Topic	Speaker/Moderator
6.00 PM – 6.05 PM	Welcome and Introductions	Elias Jabbour, MD
6.05 PM – 6.20 PM	Advances in AML: Newly Diagnosed	Naval Daver, MD
6.20 PM – 6.45 PM	Discussion: Advances in AML: Newly Diagnosed	All Moderator: Elias Jabbour, MD
6.45 PM – 6.55 PM	Advances in AML: Relapsed/Refractory	Eunice Wang, MD
6.55 PM – 7.15 PM	Discussion: Advances in AML: Relapsed/Refractory	All Moderator: Elias Jabbour, MD
7.15 PM – 7.20 PM	Advances in Myelofibrosis	Rami Komrokji, MD
7.20 PM – 7.30 PM	Discussion: Advances in Myelofibrosis	All Moderator: Elias Jabbour, MD
7.30 PM – 7.40 PM	New Developments in Myelodysplastic Syndromes	Guillermo Garcia-Manero, MD
7.40 PM – 8.00 PM	Discussion: New Developments in Myelodysplastic Syndromes	All Moderator: Elias Jabbour, MD
8.00 PM – 8.05 PM	BREAK	All
8.05 PM – 8.15 PM	Advances in ALL: Newly Diagnosed	Aaron Logan, MD
8.15 PM – 8.40 PM	Discussion: Advances in ALL: Newly Diagnosed	All Moderator: Elias Jabbour, MD
8.40 PM – 8.50 PM	Advances in ALL: Relapsed/Refractory	Jose Ribera, MD
8.50 PM – 9.10 PM	Discussion: Advances in ALL: Relapsed/Refractory	All Moderator: Elias Jabbour, MD
9.10 PM – 9.15 PM	Advances in CML	Elias Jabbour, MD
9.15 PM – 9.25 PM	Discussion: Advances in CML	All Moderator: Elias Jabbour, MD
9.25 PM – 9.30 PM	Summary and Closing Remarks	Elias Jabbour, MD

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 693: Outcomes of TP53-Mutant Acute Myeloid Leukemia with Venetoclax and Decitabine. Kim et al
  - Background
    - 10-day decitabine (DEC10) efficacious in patients with AML and *TP53* mutations
    - DEC10 + venetoclax was investigated in a phase II trial in elderly patients
    - However, *TP53* mutations may cause resistance to venetoclax
  - Current analysis evaluated outcomes in patients in the phase II trial by *TP53* status
    - Mutant (n = 35); wild-type (n = 83)
    - OS with DEC10 + venetoclax lower in *TP53* mutant vs wild-type (5.2 months vs 19.4 months; HR, 4.67; *P* <.0001)

	DEC10 + Venetoclax	DEC10	*P* Value
ORR CR	66% 37%	52% 29%	- -
OS	5.2 months	4.9 months	.60

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 330: The First-in-Class Anti-CD47 Antibody Magrolimab Combined with Azacitidine Is Well-Tolerated and Effective in AML Patients: Phase 1b Results. Sallman et al
  - Study of 64 patients included 47 patients (73%) with *TP53* mutations (median baseline VAF burden of 73%)
  - 5% of patients had an AE leading to magrolimab dose reduction
  - "No significant increase" in irAEs with magrolimab

	***TP53* Wild-Type (n = 16)**	***TP53* Mutant (n = 47)**
OS	18.9 months	12.9 months

	All Patients (n = 43)	***TP53* Mutant (n = 29)**
ORR CR	63% 42%	69% 45%
MRD negativity in CR/CRi	35%	29%
DOR	9.6 months	7.6 months

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PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 1904: Results of Venetoclax and Azacitidine Combination in Chemotherapy Ineligible Untreated Patients with Acute Myeloid Leukemia with FLT3 Mutations. Konopleva et al
  - Pooled analysis of phase III VIALE-A trial and phase Ib trial of venetoclax/azacitidine, examining outcomes in patients with a *FLT3* mutation
  - Results showed decreased OS benefit with venetoclax in patients with *FLT3*-ITD

Efficacy in *FLT3* Mutated	Venetoclax/ Azacitidine	Placebo/ Azacitidine
CR + CRh	65%	18%
FLT3-ITD	61%	23%
FLT3-TKD	69%	20%
OS	13.3 months	8.6 months
FLT3-ITD	11.5 months	8.5 months
FLT3-TKD	19.2 months	10.0 months

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 27: Phase 3, Multicenter, Open-Label Study of Gilteritinib, Gilteritinib Plus Azacitidine, or Azacitidine Alone in Newly Diagnosed FLT3 Mutated (FLT3mut+) Acute Myeloid Leukemia (AML) Patients Ineligible for Intensive Induction Chemotherapy. Wang et al
  - Randomized trial of gilteritinib/azacitidine vs azacitidine (gilteritinib monotherapy arm closed)
  - Initial data from 15 patients in safety cohort of gilteritinib/azacitidine reported
    - CRc in 10 patients (67%) including CR in 5 patients (33%)
    - DOR was 10.4 months in CRc patients
    - Grade ≥3 TEAEs included neutropenia and febrile neutropenia, each in 8 patients (53%)
  - Post-meeting update: On December 21, 2020, it was announced that this trial did not meet the primary endpoint of OS

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 1945: Venetoclax, FLT3 Inhibitor and Decitabine in FLT3mut Acute Myeloid Leukemia: Subgroup Analysis of a Phase II Trial. Maiti et al
  - Analysis of 12 patients with newly diagnosed AML and 13 patients with relapsed/refractory AML

	Newly Diagnosed	Relapsed/ Refractory
CRc CR	92% 75%	62% 23%
OS (median f/u, 14.5 months)	Not reached	6.8 months
DOR (24-month)	80%	58%

  - Grade 3 febrile neutropenia, 40%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 25: Phase II Study of Venetoclax Added to Cladribine + Low Dose AraC (LDAC) Alternating with 5-Azacytidine Demonstrates High Rates of Minimal Residual Disease (MRD) Negative Complete Remissions (CR) and Excellent Tolerability in Older Patients with Newly Diagnosed Acute Myeloid Leukemia (AML). Kadia et al
  - 55 patients, median age of 68 years (range, 57–84 years)
  - CRc, 50 patients (93%), with MRD negativity in 42 patients (84%)
    - CR, 42 patients (78%), with MRD negativity in 39 patients (93%)
  - 1-year RFS, 66%
  - 1-year OS, 70%
  - Grade 3 infection in 14 patients

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 332: Interim Analysis of the Phase 1b/2 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. Lachowiez et al
  - 68 patients enrolled (29 newly diagnosed, 39 relapsed/refractory [2 cohorts])
  - Efficacy in newly diagnosed patients
    - CRc, 90% (MRD negativity in 96%)
    - 1-year OS, 94%
  - Efficacy in relapsed/refractory patients
    - CRc, 67% (MRD negativity in 69%)
    - 1-year OS, 68%
    - 46% bridged to transplant
  - Grade 3/4 AEs: neutropenia (50%), bacteremia (35%), pneumonia (28%)

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 635: Five-Year Final Results of a Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed High-Risk/Secondary Acute Myeloid Leukemia (AML): Outcomes By Age Subgroup and Among Responders. Lancet et al
  - Median follow-up, 60.65 months

	CPX-351	7+3	HR	95% CI
OS (overall) (N = 309) Median 5-year	 9.33 months 18%	 5.95 months 8%	 0.70	 0.55–0.91
OS (post-transplant) (n = 92) Median 3-year	 Not reached 56%	 10.25 months 23%	 0.51	 0.28–0.90
OS by age subgroup 60-69 years 70-75 years	 9.59 months 8.87 months	 6.87 months 5.62 months	 0.73 0.52	 0.54–0.99 0.34–0.77

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 24: A Phase 1 Study of Gilteritinib in Combination with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed AML: Final Results. Pratz et al
  - 79 patients; 44 patients (56%) with a *FLT3* mutation
  - CR, 39.5%
  - DOR, 8.0 months
  - DFS, 13.3 months
  - OS, median not reached with a median follow-up of 35.8 months
  - The most common grade ≥3 TEAE was febrile neutropenia (63%)

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 692: CC-486 Prolongs Survival for Patients with Acute Myeloid Leukemia (AML) in Remission after Intensive Chemotherapy (IC) Independent of the Presence of Measurable Residual Disease (MRD) at Study Entry: Results from the QUAZAR AML-001 Maintenance Trial. Roboz et al

OS by MRD Status at Entry	CC-486	Placebo	HR	95% CI
MRD-negative (n = 244)	30.1 months	24.3 months	0.81	0.59–1.12
MRD-positive (n = 219)	14.6 months	10.4 months	0.69	0.51–0.93

  - MRD response
    - CC-486, 37%
    - Placebo, 19%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

> 991: Clinical Outcomes of Patients with Secondary Acute Myeloid Leukemia (sAML) Treated with Hypomethylating Agent Plus Venetoclax (HMA-Ven) or Liposomal Daunorubicin Cytarabine (CPX-351). Salhotra et al

	Venetoclax/HMA (n = 27)	CPX-351 (n = 20)	*P* Value
CR	78%	50%	.047
MRD-negative remission	52%	25%	.064
OS	13.2 months	Not reached	.395

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: NEWLY DIAGNOSED

EPICS

- 636: Enasidenib (ENA) Monotherapy with Addition of Azacitidine in Non-Responders Is Effective in Older Patients with Newly Diagnosed IDH2 Mutated Acute Myeloid Leukemia (AML): A Completed Phase 2/1b Sub-Study of the Beat AML Master Trial. Stein et al
  - Patients on phase II study of enasidenib monotherapy who did not achieve a CR/CRi after 5 cycles were transferred to phase Ib substudy of enasidenib plus azacitidine
  - Data from 17 patients reported, with a median follow-up of 12.7 months
  - CR/CRi, 41%
    - CR, 18%
  - DOR, median not reached
  - OS, 8.9 months
  - Differentiation syndrome (all grades) in 2 patients (17%)

ADVANCES IN AML: NEWLY DIAGNOSED DISCUSSION (1/4)

EPICS

- In older patients who are not candidates for intensive therapy, the NCCN guidelines list venetoclax/HMA as the preferred approach, even for patients with *FLT3* or *IDH* mutations
  - However, for patients with *FLT3* mutations, especially *FLT3*-ITD, the experts prefer to use a combination with a next-generation FLT3 inhibitor, eg, gilteritinib/HMA upfront, rather than using venetoclax/azacitidine and waiting for the patient to relapse before using a FLT3 inhibitor
    - This preference is reinforced by the results from Konopleva et al. ASH 2020, #1904, showing reduced benefit with venetoclax/azacitidine in patients with *FLT3*-ITD mutations, and consistent with other data showing *FLT3* mutations as a marker for lack of response or resistance to venetoclax/azacitidine
  - In the setting of an elderly, unfit patient with an *IDH* mutation, however, expert opinion is that venetoclax/HMA is an appropriate option, reserving an IDH inhibitor for second-line therapy

ADVANCES IN AML: NEWLY DIAGNOSED DISCUSSION (2/4)

EPICS

- It was thought by the experts that FLT3 inhibitor-based combinations can be used upfront in *FLT3* wild-type patients, which might help prevent relapses with venetoclax/HMA
  - However, they believe that more broadly acting agents (eg, magrolimab) might be more effective
- For a patient with secondary AML and no *TP53* mutation, the experts would use venetoclax/HMA
- Regarding CPX-351, expert opinion is that long-term data were impressive (Lancet et al. ASH 2020, #635), especially in patients undergoing transplant, even though the study was not designed to address this endpoint
  - CPX-351 was seen as a good option over standard 3+7 therapy for patients with secondary AML; on the other hand, CPX-351 did not show benefit over 3+7 in patients with prior HMA therapy (≥4–6 cycles). The experts also mentioned that despite initially good tolerability, myelosuppression can be a long-term issue with CPX-351

ADVANCES IN AML: NEWLY DIAGNOSED DISCUSSION (3/4)

EPICS

- Experts were enthusiastic about the data from QUAZAR AML-001 showing increased MRD clearance with CC-486 compared with placebo (Roboz et al. ASH 2020, #692), as this was the first demonstration of MRD conversion in AML
  - However, it was noted that 19% of patients in the placebo arm also demonstrated an MRD response, raising questions over the reliability of MRD measurement in the study
- In general, the experts still view MRD as an emerging concept in AML, and the effect of transplant on the outcome of patients with MRD-positive disease still needs to be determined
- The experts cautioned that there are currently no data indicating that CC-486 can substitute for oral azacitidine (eg, in combination with venetoclax); however, this is a question that many community physicians are asking about
- Maintenance therapy was viewed by the experts as feasible in most patients with AML to prolong remission, unless oral medications are not feasible, given that IDH inhibitors, FLT3 inhibitors, and CC-486 are all orally administered

ADVANCES IN AML: NEWLY DIAGNOSED DISCUSSION (4/4)

EPICS

- The experts were also enthusiastic over the potential of magrolimab, given the favorable toxicity profile and activity in patients with *TP53* mutations; for some of these patients, transplant can even be delayed
  - Other than hemolytic anemia in the first cycle, this agent was viewed as well tolerated, even in combination with other agents such as azacitidine
  - The activity of magrolimab in *TP53* wild-type patients was also seen as impressive; one possible trial could be a comparison of magrolimab/azacitidine with venetoclax/azacitidine
- The response rate of eprenetapopt (formerly APR-246) in patients with *TP53* mutations was seen by the experts as good, although there were questions about the durability of the responses
- For both magrolimab and eprenetapopt, the experts think a combination with azacitidine will be needed for maximum efficacy

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: RELAPSED/REFRACTORY

EPICS

- 29: Outcomes with Sequential FLT3-Inhibitor (FLT3i) Based Therapies in Patients (pts) with FLT3-Mutated Acute Myeloid Leukemia (AML) Exposed to Prior FLT3i Based Therapies. Yilmaz et al
  - Retrospective analysis of patients receiving FLT3i as a single agent or with low- or high-intensity chemotherapy
  - Frontline cohort (receiving first FLT3i in the first-line setting), n = 56
  - Salvage cohort (receiving first FLT3i in the relapsed/refractory setting), n = 183

Response	1st FLT3i	2nd FLT3i	3rd/4th FLT3i
Frontline cohort	77%	31%	25%
Salvage cohort	45%	21%	10%

Survival	1st FLT3i	2nd FLT3i	3rd/4th FLT3i
Frontline cohort	16.7 months	6.0 months	1.4 months
Salvage cohort	7.9 months	4.0 months	4.1 months

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: RELAPSED/REFRACTORY

EPICS

- 334: Clinical Outcomes in Patients with Relapsed/Refractory Acute Myeloid Leukemia Treated with Gilteritinib Who Received Prior Midostaurin or Sorafenib. Perl et al
  - Retrospective analysis of outcomes in phase I/II CHRYSALIS and phase III ADMIRAL trials (focus on ADMIRAL here)

	Gilteritinib	Chemotherapy	HR	*P* Value
OS				
No prior TKI	9.6 months	6.0 months	-	-
Prior TKI	6.5 months	4.7 months	0.625	.0008
CRc				
No prior TKI	55%	22%	-	-
Prior TKI	48%	21%	-	-

	No Prior TKI	Prior TKI
OS (CHRYSALIS and ADMIRAL)	8.7 months	7.0 months

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: RELAPSED/REFRACTORY

EPICS

- 335: Patterns of Secondary Resistance Differ in Patients (pts) with Acute Myeloid Leukemia (AML) Treated with Type I Versus Type II FLT3-Inhibitors (FLT3i's). Alotaibi et al
  - Type I FLT3i: midostaurin, gilteritinib, crenolanib (n = 21)
    - RAS pathway, n = 6 (29%)
    - Epigenetic modifiers, n = 3 (14%)
    - *FLT3*-TKD mutation no longer detected in 6 patients (28%)
  - Type II FLT3i: sorafenib, quizartinib (n = 46)
    - *FLT3*-D835, n = 14 (30%)
    - *FLT3*-TKD mutation no longer detected in 12 patients (26%)

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: RELAPSED/REFRACTORY

EPICS

- 333: Efficacy and Safety of Venetoclax in Combination with Gilteritinib for Relapsed/Refractory FLT3-Mutated Acute Myeloid Leukemia in the Expansion Cohort of a Phase 1b Study. Daver et al
  - Data from 43 patients reported
  - Median 2 prior lines of therapy (range, 1–5 lines)
  - ≥1 prior FLT3i in 28 patients (65%)
  - Modified CRc with prior FLT3i, 82%
  - Time to best response, 0.9 months
  - OS in all *FLT3* mutations, 12.3 months
  - 1 incidence of clinical TLS and 3 cases of laboratory TLS

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: RELAPSED/REFRACTORY

EPICS

- 28: Phase II Study of CPX-351 Plus Venetoclax in Patients with Acute Myeloid Leukemia (AML). Kadia et al
  - Data from 20 patients reported (18 evaluable for response)
  - ORR, 44%
    - CR, 6%
  - 1-year RFS, 86%
  - Grade 3/4 infections in 7 patients
  - 3 deaths (pneumonia, respiratory failure, sepsis)

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: RELAPSED/REFRACTORY

EPICS

- 331: Flotetuzumab As Salvage Therapy for Primary Induction Failure and Early Relapse Acute Myeloid Leukemia. Aldoss et al
  - Data from 44 patients presented
  - Median 2 prior lines of therapy (range, 1–3 lines)
  - CR/CRh/CRi, 32%
  - In responders, the median DOR was 8.13 months, and the median OS was 10.7 months
  - All patients experienced CRS/IRR (grade ≥3 in 1 patient); most CRS events occurred in the first week of treatment
  - Grade ≥3 confusion in 3 patients (7%)

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: RELAPSED/REFRACTORY

EPICS

- 170: Safety and Efficacy of Decitabine Plus Ipilimumab in Relapsed or Refractory MDS/AML in the Post-BMT or Transplant Naïve Settings. Garcia et al

	Prior Transplant (n = 25)	No Prior Transplant (n = 22)
Prior regimens (range)	3 (0–5)	1 (0–3)
ORR	19%	56%
OS	7.6 months	18.3 months
DLT at ipilimumab 10 mg/kg	Grade 3 acute GVHD	Grade 4 non-GVHD

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN AML: RELAPSED/REFRACTORY

EPICS

- 115: Preliminary Data on a Phase 1/2A First in Human Study of the Menin-KMT2A (MLL) Inhibitor KO-539 in Patients with Relapsed or Refractory Acute Myeloid Leukemia. Wang et al
  - Data reported from 12 patients
  - Median 3 prior lines of therapy (range, 2–7 lines)
  - 2 CR in 8 evaluable patients
  - Grade ≥3 AEs: 5 total; 1 incidence each of pancreatitis, lipase increase, neutropenia, TLS, DVT
  - Phase I dose escalation continues

ADVANCES IN AML: RELAPSED/REFRACTORY DISCUSSION (1/2)

EPICS

- The experts interpreted the analysis of gilteritinib following prior midostaurin or sorafenib (Perl et al. ASH 2020, #334) as showing that the efficacy decreases with subsequent lines of FLT3 inhibitors. Therefore, in patients with a prior FLT3 inhibitor, combination therapy (eg, gilteritinib/venetoclax) is seen as a better approach than single-agent gilteritinib
  - For a young, fit patient with relapsed disease and a *FLT3* mutation, treatment choices would include gilteritinib/venetoclax with or without azacitidine if the patient previously received high- or intermediate-dose cytarabine within 9–12 months, and FLAG-IDA with a FLT3 inhibitor in patients with a late relapse (>12 months) or if they only received low-dose cytarabine previously
- A wide variety of resistance mechanisms to single-agent FLT3 inhibitors was noted by the experts, including *BCR-ABL* fusions, *IDH, RAS*, and *FLT3* D835 mutations; however, a high rate of *TP53* mutations has not been observed
  - "Explosive" disease involving a *FLT3* wild-type clone has also been seen with second-generation FLT3 inhibitors
  - Therefore, combinations are seen as key to avoid these resistance mechanisms

ADVANCES IN AML: RELAPSED/REFRACTORY DISCUSSION (2/2)

EPICS

- Preliminary data with the menin-MLL inhibitor KO-539 (Wang et al. ASH 2020, #115) were seen by the experts as encouraging, given the new mechanism of action and tolerability
  - However, the small patient cohort presented at ASH makes it difficult to make a definitive statement
  - One of the experts mentioned that a patient who responded to this agent did not have *MLL*-rearranged disease, so thought it was good to keep the initial trial agnostic for specific molecular aberrations
  - Potential exists to combine with venetoclax/azacitidine, 7+3, CPX-351, and magrolimab
- The high response rate seen with decitabine/ipilimumab (Garcia et al. ASH 2020, #170) was encouraging to the experts, although the need for biomarkers was mentioned
- Expert opinion is that data from ASH 2020 indicated that venetoclax could have utility in a wide range of malignancies, including AML, myelofibrosis, MDS, and Ph-positive ALL

PROGRAM OVERVIEW: ABSTRACTS ADVANCES IN MYELOFIBROSIS

EPICS

> 53: Favorable Overall Survival with Imetelstat Treatment Correlates with Other Clinical Benefits in Intermediate 2 or High Risk Myelofibrosis Relapsed/Refractory to Janus Kinase Inhibitor. Mascarenhas et al

	Imetelstat 4.7 mg/kg (n = 48)	Imetelstat 9.4 mg/kg (n = 59)
OS	19.9 months	28.1 months
PFS	14.8 months	20.7 months
Symptom response at week 24	6%	32%
Spleen response at week 24	0	10%

- Phase III IMpactMF (primary endpoint of OS) enrolling patients with relapsed/refractory MF to open 1Q2021
  - Imetelstat 9.4 mg/kg Q21D vs BAT

PROGRAM OVERVIEW: ABSTRACTS ADVANCES IN MYELOFIBROSIS

EPICS

- 55: CPI-0610, a Bromodomain and Extraterminal Domain Protein (BET) Inhibitor, in Combination with Ruxolitinib, in JAK-Inhibitor-Naïve Myelofibrosis Patients: Update of MANIFEST Phase 2 Study. Mascarenhas et al
  - Data from 78 patients reported
  - Primary endpoint: SVR35 (≥35% reduction from baseline at 24 weeks)
  - SVR35 achieved in 42 of 63 evaluable patients (67%)
    - Median SVR, –50%
  - Secondary endpoint of symptom response (≥50% reduction in TSS at 24 weeks) achieved by 34 of 60 patients (57%)
  - Most AEs were grade 1/2
    - Grade 3/4 toxicities included anemia (29%), thrombocytopenia (8%)

PROGRAM OVERVIEW: ABSTRACTS ADVANCES IN MYELOFIBROSIS

EPICS

- 3006: Long-Term Safety of Fedratinib in Patients with Intermediate- or High-Risk Myelofibrosis (MF). Pardanani et al
  - Safety data from 28 patients receiving ≥24 cycles of fedratinib in 2 trials (TED12037 and TED12015)

AEs of Special Interest (Any grade/Grade 3/4)	>24 to 30 Cycles (n = 28)	>30 to 36 Cycles (n = 22)	>36 Cycles (n = 17)
Cardiac failure	7% / 0	5% / 0	6% / 0
Infections	4% / 0	5% / 0	12% / 1%
Neurologic events	4% / 0	14% / 1%	29% / 0

ADVANCES IN MYELOFIBROSIS (ABSTRACT 53, 55, 3006) DISCUSSION

EPICS

- Expert opinion is that ruxolitinib remains the JAK inhibitor of choice for first-line therapy, and that symptom improvement is better with ruxolitinib than other available agents
- Fedratinib is seen as a first-line option for patients with borderline anemia or thrombocytopenia
  - The activity of fedratinib in patients previously treated with ruxolitinib has led to this agent being used as a second-line option in the absence of clinical trials (ie, the JAKARTA trial was in a JAK inhibitor-naive population)
- New agents, including navitoclax and inhibitors of LSD1 or BET, were seen by the experts as being developed as first-line options in combination with ruxolitinib
- Imetelstat and momelotinib were viewed as being positioned for post failure of ruxolitinib therapy
  - It was thought that imetelstat has the potential to demonstrate an OS benefit in this setting
- Unmet needs identified by the experts for patients with myelofibrosis included ruxolitinib failures, management of cytopenia, high-risk mutations, and accelerated-phase disease

PROGRAM OVERVIEW: ABSTRACTS
NEW DEVELOPMENTS IN MYELODYSPLASTIC SYNDROMES

EPICS

- 536: Phase 3 Study of Lenalidomide (LEN) Vs Placebo in Non-Transfusion Dependent (TD) Low Risk Del(5q) MDS Patients - Interim Analysis of the European Sintra-REV Trial. Lopez Cadenas et al
  - Data from 61 patients reported (40 lenalidomide, 21 placebo)

	Lenalidomide	Placebo	HR	*P* Value
Time to transfusion dependency	6.3 years	2.8 years	0.388	.028
Erythroid response	72.5%	0	-	<.001
Cytogenetic response	80%	0	-	<.001

  - Median OS not reached in either arm (median follow-up of 2.1 years)
  - Main AE was grade 3/4 neutropenia (47% with lenalidomide and 5% with placebo)
  - No increase in AML evolution observed

PROGRAM OVERVIEW: ABSTRACTS
NEW DEVELOPMENTS IN MYELODYSPLASTIC SYNDROMES

EPICS

- 653: Efficacy and Safety of Pevonedistat Plus Azacitidine Vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes (MDS) from Study P-2001 (NCT02610777). Sekeres et al
  - Phase II trial; data from 67 patients reported

	Pevonedistat/ Azacitidine	Azacitidine	HR/RR	*P* Value
EFS	20.2 months	14.8 months	0.539	.045
OS	23.9 months	19.1 months	0.701	.240
ORR CR	79% 52%	57% 27%	- -	0.65 0.50
DOR	34.6 months	13.1 months	-	-
RBC/platelet transfusion independence	69%	47%	1.46	.228

  - Grade 3/4 AEs: 30/32 with pevonedistat/azacitidine and 29/35 with azacitidine

PROGRAM OVERVIEW: ABSTRACTS
NEW DEVELOPMENTS IN MYELODYSPLASTIC SYNDROMES

EPICS

- 656: Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study. Garcia et al
  - Data from 78 patients reported

Efficacy	
ORR CR	79% 40%
OS	27.5 months

Grade 3/4 AE	
Neutropenia	82%
Febrile neutropenia	49%
Thrombocytopenia	42%
Anemia	23%

PROGRAM OVERVIEW: ABSTRACTS
NEW DEVELOPMENTS IN MYELODYSPLASTIC SYNDROMES

EPICS

- 657: Efficacy and Safety of Sabatolimab (MBG453) in Combination with Hypomethylating Agents (HMAs) in Patients with Acute Myeloid Leukemia (AML) and High-Risk Myelodysplastic Syndrome (HR-MDS): Updated Results from a Phase 1b Study. Brunner et al
  - Sabatolimab is a TIM3 immune checkpoint inhibitor
  - Trial enrolled 41 patients with MDS, as well as 48 patients with AML and 12 patients with CMML
  - ORR in MDS (n = 39), 64%
    - CR, 23%
  - ORR in very high-risk MDS (n = 16), 75%
    - CR, 31%
  - 12-month PFS in MDS, 52%
  - 24% of patients with an irAE any grade, of which 4 were grade ≥3

PROGRAM OVERVIEW: ABSTRACTS
NEW DEVELOPMENTS IN MYELODYSPLASTIC SYNDROMES

EPICS

- 658: Treatment with Imetelstat Provides Durable Transfusion Independence (TI) in Heavily Transfused Non-Del(5q) Lower Risk MDS (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis Stimulating Agents (ESAs). Platzbecker et al
  - Data from 38 patients reported, with a median of 8 units RBC/8 weeks (range, 4–14 units)
  - 8-week transfusion independence, 42%
    - Time to onset, 8.3 weeks
  - 1-year transfusion independence, 29%
  - Hematologic improvement-erythroid, 68%
  - Main grade 3/4 AEs
    - Thrombocytopenia, 61%
    - Neutropenia, 55%
    - Anemia, 21%

PROGRAM OVERVIEW: ABSTRACTS
NEW DEVELOPMENTS IN MYELODYSPLASTIC SYNDROMES

EPICS

- 2858: Preliminary Results from a Phase 1 Study of APVO436, a Novel Anti-CD123 x Anti-CD3 Bispecific Molecule, in Relapsed/Refractory Acute Myeloid Leukemia and Myelodysplastic Syndrome. Watts et al
  - Data from 32 patients reported (7 patients with MDS)
    - Median 3 prior lines of therapy (range, 1–13 lines)
  - 2 patients (disease not specified) achieved a CR
    - Bone marrow blast reductions from 29% to 0 and from 33% to 4%, respectively
  - Grade ≥3 CRS/IRR in 5 patients (16%)

NEW DEVELOPMENTS IN MYELODYSPLASTIC SYNDROMES DISCUSSION (1/2)

EPICS

- The experts discussed OS benchmarks in patients with high-risk MDS
  - The AZA-001 trial (Fenaux et al. *Lancet Oncol*. 2009;10:223) reported a median OS of 24.5 months with azacitidine, but this has not been reproduced; expert opinion is that 17 months is a more realistic measure, and that an increase in OS from 17–25 months would be meaningful
  - Phase I data with venetoclax/azacitidine showed a median OS of 27.5 months, which shows potential to represent a new standard, based on the above discussion
- Expert opinion is that pevonedistat may have an additive effect in combinations, and that the addition of pevonedistat to azacitidine appeared to be associated with an increased number of cycles of therapy delivered. It is not known if there are patient subsets that derive the most benefit with pevonedistat; however, it was thought that this agent may not be affected by *TP53* mutation status
- The mechanism of action of the telomerase inhibitor imetelstat in MDS was a mystery to the experts, given that preclinical data showed that shortening telomeres led to MDS in mouse models
  - Nevertheless, the transfusion independence with imetelstat (Platzbecker et al. ASH 2020, #658) was seen by experts as impressive

NEW DEVELOPMENTS IN MYELODYSPLASTIC SYNDROMES DISCUSSION (2/2)

EPICS

- The experts are looking forward to phase III data with eprenetapopt, pevonedistat, and magrolimab in MDS, which are anticipated in late 2020 or 2021
- While ongoing trials will provide better first-line options than single-agent azacitidine or decitabine, expert opinion is that trials are needed for patients whose disease progresses on HMA therapy
- It was noted that in the near future, a molecular-based classification scheme for MDS will be presented

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: NEWLY DIAGNOSED

EPICS

- 267: First Results of an Open Label Phase II Study to Evaluate the Efficacy and Safety of Inotuzumab Ozogamicin for Induction Therapy Followed By a Conventional Chemotherapy Based Consolidation and Maintenance Therapy in Patients Aged 56 Years and Older with Acute Lymphoblastic Leukemia (INITIAL-1 trial). Stelljes et al
  - 36 patients included
  - Median age, 65 years (range 56–80 years)

Efficacy	
CR/CRi after ≥1 induction	100%
MRD-negative remission	21/28 (78%)
1-year OS	87%
1-year EFS	87%

Grade 3/4 AEs	Induction 1	Induction 2	Induction 3
Leukocytopenia	60%	15%	13%
Thrombocytopenia	52%	5%	6%
Elevation of GOT/GPT	14%	0	6%
Elevated bilirubin	10%	0	0

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: NEWLY DIAGNOSED

EPICS

- 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. Short et al
  - Data from 37 patients reported

Efficacy	
CR after induction MRD negative	81% 71%
CR at any time MRD negative	100% 97%
2-year RFS	71%
2-year OS	80%

Grade 3/4 AEs	
CRS	3%
Neurotoxicity	13%
ALT/AST elevation	24%
Hyperglycemia	21%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: NEWLY DIAGNOSED

EPICS

- 1014: Reduced-Intensity Chemotherapy With Mini-Hyper-CVD Plus Inotuzumab Ozogamicin, With or Without Blinatumomab, in Older Adults With Newly Diagnosed Philadelphia Chromosome-Negative ALL: Results From a Phase II Study. Short et al
  - Data from 70 patients reported
    - Median age, 68 years (range, 60–81 years)

Efficacy	
ORR CR	98% 88%
MRD response	96%
OS Median 3-year	 62 months 56%

Grade 3/4 AEs	
Thrombocytopenia	81%
Infections	70%
Hyperglycemia	53%
VOD	9%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: NEWLY DIAGNOSED

EPICS

- 583: Ultrasensitive Next-Generation Sequencing-Based Measurable Residual Disease Assessment in Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia after Frontline Therapy: Correlation with Flow Cytometry and Impact on Clinical Outcomes. Short et al
  - Retrospective analysis of MRD in 67 patients using 2 different methods
    - MFC (sensitivity of 10^{-4})
    - NGS (sensitivity of 10^{-6})

MFC vs NGS	MRD– by MFC	MRD– by NGS
5-year relapse rate	27%	8%

Outcome by NGS MRD	
5-year OS	
MRD–	100%
MRD+	55%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: NEWLY DIAGNOSED

EPICS

- 2795: Interim Results of a Multicenter, Single-Arm Study to Assess Blinatumomab in Adult Patients with Minimal Residual Disease of B-Precursor Acute Lymphoblastic Leukemia (GMALL-MOLACT1-BLINA). Goekbuget et al
  - Study amended to include patients with MRD-positive disease at a level of $<10^{-4}$
  - Data from 65 patients reported
  - 70% of patients achieved MRD negativity with a sensitivity $<10^{-4}$
  - OS (not quantified) appeared similar in patients who had baseline MRD of 10^{-4} to 10^{-3} and 10^{-3} to 10^{-2}

ADVANCES IN ALL: NEWLY DIAGNOSED DISCUSSION (1/3)

EPICS

- The experts think that antibody-based therapies, particularly inotuzumab ozogamicin and blinatumomab, will play a role in first-line therapy, especially in elderly patients. It is currently not clear if inotuzumab ozogamicin can replace chemotherapy, but at least allows for reduced intensity of chemotherapy
  - It was thought that definitive phase III data were still needed with inotuzumab ozogamicin and blinatumomab in the first-line setting, as most of the data are from single-arm trials
  - The change in outcomes with the use of antibody-based therapies may eventually lead to new risk classifications of ALL

ADVANCES IN ALL: NEWLY DIAGNOSED DISCUSSION (2/3)

EPICS

- The experts also see a need to treat patients with detectable MRD, even at levels below the current cutoff of 10^{-3} in the MRD indication for blinatumomab
  - Even 10^{-4} was seen by experts as a high level of MRD, and waiting for a patient to reach 10^{-3} would risk losing the patient to relapse
  - The GMALL trial showed that even in patients with "low" MRD levels, there will be relapses
  - As NGS-based approaches, which have a sensitivity of 10^{-6}, become more widely used, the experts think that physicians should be prepared to treat MRD at even lower levels
  - Expert opinion is that the level of MRD could influence subsequent treatment (eg, avoiding transplant at low levels of MRD)
  - It was recommended to have multiple assessments of MRD, including at the end of induction and after consolidation
  - Blood-based testing was seen as a useful approach, given its high sensitivity and approximately 90% concordance with bone marrow (Muffly et al. ASH 2020, #975). Additionally, MRD can be detected in blood approximately 2 months prior to fulminant relapse, which may give additional lead time to intervene

ADVANCES IN ALL: NEWLY DIAGNOSED DISCUSSION (3/3)

EPICS

- The experts think that new agents may yield deep MRD responses that overcome the unfavorable prognosis in high-risk subsets, such as Ph-like ALL, although more research is needed
- In patients with Ph-positive ALL, the experts see TKIs, immunotherapy, and BCL-2 inhibitors as components of future curative regimens, and that most patients can potentially be cured without transplantation or CAR T cells

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: RELAPSED/REFRACTORY

EPICS

- 268: Superior Event-Free Survival with Blinatumomab Versus Chemotherapy in Children with High-Risk First Relapse of B-Cell Precursor Acute Lymphoblastic Leukemia: A Randomized, Controlled Phase 3 Trial. Locatelli et al
  - Following induction and 2 cycles of high-risk consolidation chemotherapy (HC), 108 patients were randomized to receive either blinatumomab or the third cycle of HC (HC3)

	HR (Blinatumomab vs HC3)	*P* Value or 95% CI
EFS	0.33	<.001
OS	0.43	0.18–1.01

	Blinatumomab	HC3
Cumulative incidence of relapse (24 months)	25%	71%
MRD remission	90%	54%

Grade 3/4 AEs	Blinatumomab	HC3
CRS	0	0
Neurotoxicity	6%	2%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: RELAPSED/REFRACTORY

EPICS

- 160: ALLCAR19: Updated Data Using AUTO1, a Novel Fast-Off Rate CD19 CAR in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukaemia and Other B-Cell Malignancies. Roddie et al
  - CAR T construct designed to reduce toxicity
  - 25 patients enrolled; 20 patients treated

	Any Grade	Grade 2	Grade ≥3
CRS	10 (50%)	7 (35%)	0
Neurotoxicity	4 (20%)	1 (5%)	3 (15%)[a]

[a]Grade 3 only.

Efficacy	n = 19
ORR CR (MRD–)	84% 84%
12-month DOR	68%
12-month OS	63%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: RELAPSED/REFRACTORY

EPICS

- 163: Preliminary Results of Balli-01: A Phase I Study of UCART22 (allogeneic engineered T-cells expressing anti-CD22 Chimeric Antigen Receptor) in Adult Patients with Relapsed or Refractory (R/R) CD22+ B-Cell Acute Lymphoblastic Leukemia (B-ALL). Jain et al
  - Initial cohort of 5 patients treated
    - Median 3 prior therapies (range, 2–6 therapies)
  - 2 CRi at day 28; 1 patient reached CR (MRD+) at day 42
  - CRS, grade 1 (n = 2) and grade 2 (n = 1)
  - ICANS, none reported

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: RELAPSED/REFRACTORY

EPICS

- 269: Pre-CAR Blinatumomab Is Associated with Increased Post-CD19 CAR Relapse and Decreased Event Free Survival. Taraseviciute et al
  - Retrospective analysis of 420 patients

	No Prior Blinatumomab (n = 345)	Prior Blinatumomab (n = 75)
Failure to achieve CR	7%	18%
RFS	44.9 months	20.3 months
EFS	22.6 months	5.8 months

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: RELAPSED/REFRACTORY

EPICS

- 468: Disease Burden Impacts Outcomes in Pediatric and Young Adult B-Cell Acute Lymphoblastic Leukemia after Commercial Tisagenlecleucel: Results from the Pediatric Real World CAR Consortium (PRWCC). Schultz et al
  - Patients were classified by disease burden
    - High burden (HB) disease: ≥5% bone marrow lymphoblasts, peripheral blood lymphoblasts, CNS3 and/or extramedullary disease
      - n = 94
    - Low burden (LB) disease: detectable disease not meeting the HB criteria
      - n = 41
    - No detectable disease (NDD)
      - n = 46

	HB	LB	NDD
1-year OS	58%	85%	95%
1-year EFS	34%	69%	72%

Grade ≥3 AE	HB	LB	NDD
CRS	32%	10%	0
Neurotoxicity	9%	5%	4%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: RELAPSED/REFRACTORY

EPICS

- 465: Interim Results of the Phase I/II Study of the Ponatinib, Venetoclax and Dexamethasone for Patients with Relapsed or Refractory Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Short et al
  - Data from 9 patients reported
    - Median 3 prior therapies (range, 2–4 therapies)
    - 7 patients (78%) with prior ponatinib
  - CR/CRi in 5 patients (56%)
    - 4 of 7 patients (57%) with prior ponatinib achieved a CR/CRi
  - 1-year OS, 63%
  - 6-month RFS, 100%
  - Grade 3 thromboembolic event in 1 patient

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: RELAPSED/REFRACTORY

EPICS

- 466: Venetoclax and Navitoclax in Pediatric Patients with Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma. Rubnitz et al
  - Data from 18 patients reported
    - 13 patients with B-ALL

Efficacy	n = 13
CR/CRi//CRp MRD– (n = 8)	8 (62%) 5 (63%)
DOR	3.5 months
OS	11.4 months

Grade 3/4 AEs	n = 18
Febrile neutropenia	50%
Neutropenia	33%
Hyperglycemia	17%

PROGRAM OVERVIEW: ABSTRACTS
ADVANCES IN ALL: RELAPSED/REFRACTORY

EPICS

- 977: Blinatumomab in Children with Relapsed or Refractory B-Precursor Acute Lymphoblastic Leukemia (R/R-ALL): Final Results of 110 Patients Treated in an Expanded Access Study (RIALTO). Locatelli et al
  - Median follow-up of 11.5 months

Efficacy	n = 110
CR	
All patients	63%
≥5% blasts at baseline	59%
<5% blasts at baseline	92%
MRD response	
≥5% blasts at baseline	47%
<5% blasts at baseline	92%
RFS	8.5 months
OS	14.6 months

ADVANCES IN ALL: RELAPSED/REFRACTORY DISCUSSION (1/2)

EPICS

- The experts discussed the sequencing of blinatumomab and CAR T cells in relapsed/refractory ALL
  - Expert opinion is that since immunotherapies are more effective with a low tumor burden and less effective with each relapse, blinatumomab should be used early in first relapse
  - Currently, transplant is needed after blinatumomab, and for patients who relapse, CAR T cells can be offered, although in the future, CAR T-cell therapy might be moved prior to transplant
- A major effort in CAR T-cell therapy in ALL is reducing AEs
  - One of the experts mentioned that with experience, physicians are getting better at earlier intervention to address toxicity, including earlier use of tocilizumab, which does not appear to inhibit CAR T-cell expansion
  - The experts think that patients receiving commercial CAR T-cell therapy are undergoing treatment in earlier lines of therapy with a lower disease burden, which may contribute to less toxicity
- It was also mentioned that more rapid CAR T manufacturing approaches, such as the 24-hour platform (Yang et al. ASH 2020, #159), can help bring CAR T cells to more patients, especially those with rapidly progressing disease

ADVANCES IN ALL: RELAPSED/REFRACTORY DISCUSSION (2/2)

EPICS

- CAR T cells are thought by experts to be more effective with a lower bulk of disease, and experts raised the possibility of trials to explore CAR T cells as consolidation therapy. The experts have observed CAR T expansion in patients with low (ie, MRD-level) disease burden
- It was thought by the experts that patient subsets of interest for CAR T cells include those with poor-risk genetics, *MLL* rearrangements, a complex karyotype, or low hypodiploidy
- The experts see a diminishing role for chemotherapy in adult patients with relapsed/refractory ALL, although the use of chemotherapy allows for a lower dose of inotuzumab ozogamicin, which lowers the risk of veno-occlusive disease with transplant
  - Agents targeting B-cell receptor signaling were mentioned by experts as a potential approach to replace chemotherapy

PROGRAM OVERVIEW: ABSTRACTS ADVANCES IN CML

EPICS

- 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 (TKIs). Hochhaus et al
  - 233 patients randomized 2:1 to asciminib or bosutinib
    - ≥3 prior TKIs in 48% of patients receiving asciminib and 60.5% of patients receiving bosutinib

	Asciminib	Bosutinib	*P* Value
MMR at 24 weeks (primary endpoint)	25.5%	13.2%	.029
$MR^{4.5}$ at 24 weeks	9%	1%	-

  - Grade ≥3 AEs, 51% in the asciminib arm and 60.5% in the bosutinib arm
  - 5 arterial occlusive events reported in the asciminib arm (3%)

ADVANCES IN CML (ABSTRACT LBA-4) DISCUSSION

EPICS

- In discussing where asciminib may fit in the treatment algorithm for patients with CML, one of the experts mentioned patients with non–*BCR-ABL1* T315I failures and an elevated cardiovascular risk
  - However, most of the experts would prefer ponatinib as third-line therapy, and would use bosutinib in patients with cardiovascular comorbidities
  - Another competing consideration for patients who fail 2 TKIs is transplantation
- The experts discussed the design of the ASCEMBL trial
  - The rationale for using bosutinib as the reference arm instead of ponatinib was not clear to the experts
  - Additionally, the experts were not sure about the primary endpoint of MMR at 24 weeks, and whether or not this is a good surrogate for survival
- Regarding the rate of cardiovascular events in the asciminib arm, one of the experts raised concern over the frequency (5/156 patients; 3.2%); however, a different panelist thought that this was low as a percentage of patients, and also lower than would be expected with ponatinib