AZA + Glutaminase Inhibition with Telaglenastat (CB-839) for Advanced MDS: An Updated Interim Analysis

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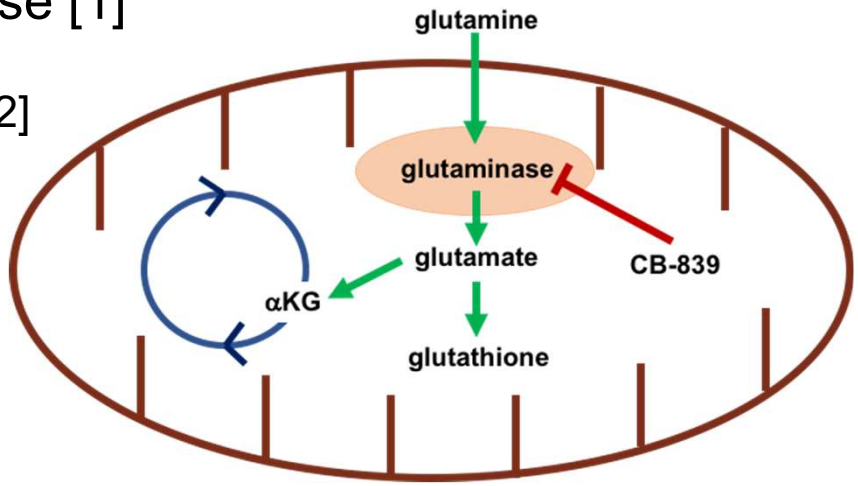
Background

- Malignant myeloid cells can utilize glutamine as an energy source [1]
- Glutamine is metabolized by glutaminase into glutamate in mitochondria
- Glutamate is a precursor to multiple intracellular molecules including:
  - alpha-ketoglutarate in the citric acid cycle
  - the intracellular antioxidant glutathione
- In vitro, removal of glutamine from cell culture medium leads to reduced ATP production and increased apoptosis of AML cells [1]
- CB-839 is an allosteric inhibitor of glutaminase [1]
  - CB-839 increases AML cell apoptosis in vitro and synergizes with AZA in an AML xenograft model [2]
- AZA + CB-839 for advanced MDS
  - NCT03047993
  - Initial findings presented at ASH 2019 [3]
  - We now present an updated interim analysis



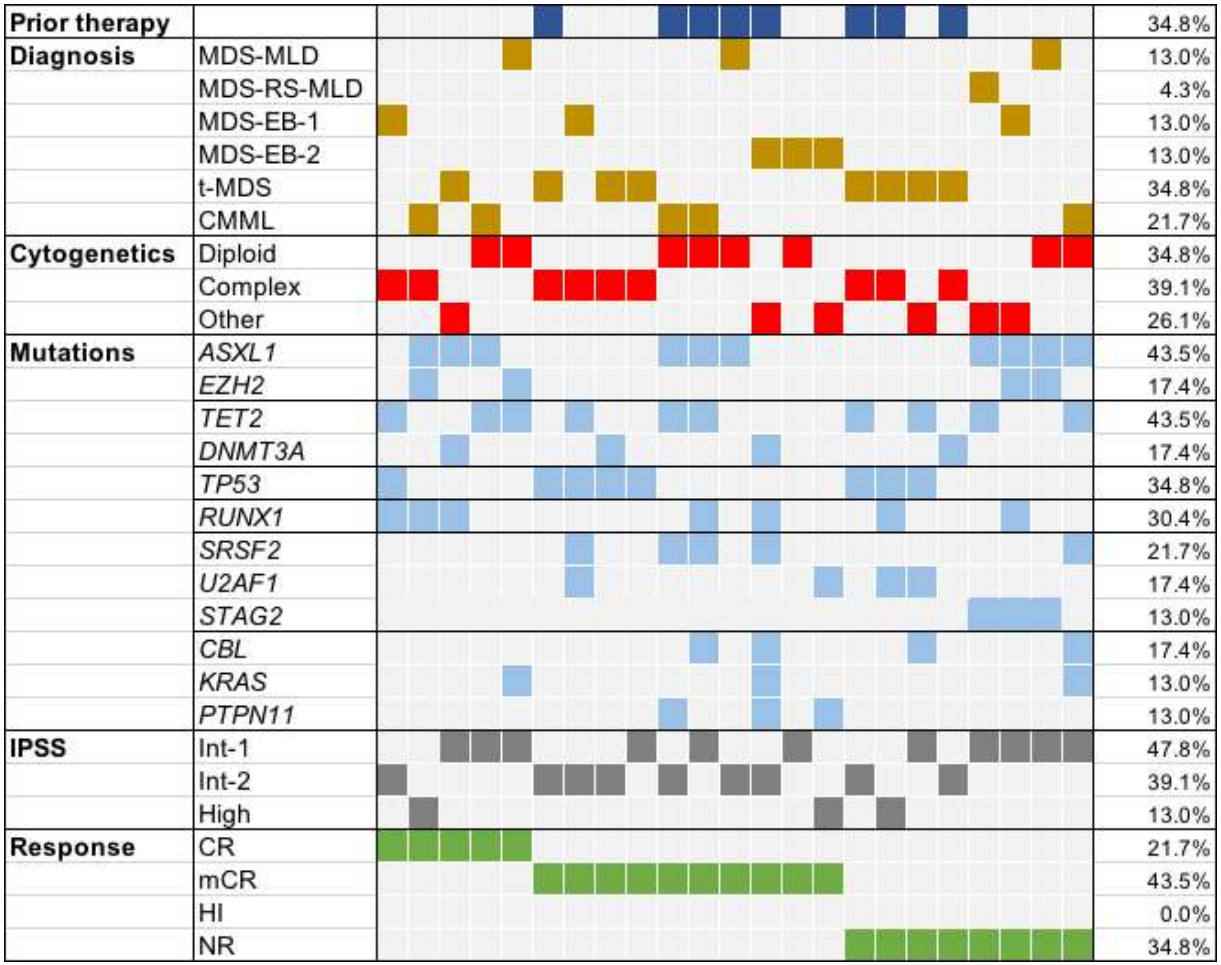
References:
1) Matre et al., *Oncotarget* 2016, 7(48):79722-79735
2) Cai et al., *Blood* 2016, 128(22):4064
3) Guerra et al., *Blood* 2019, 134(Supplement_1):567

Trial design

- Single arm, phase Ib/II trial of CB-839 + AZA in patients with:
  - IPSS Int-1 risk MDS with high-risk mutation (*ASXL1*, *TP53*, *RUNX1, EZH2*)
  - IPSS Int-2 or high risk MDS
- Prior HMA therapy permitted
- Primary outcomes
  - Phase Ib – safety and RP2D -> CB-839 600mg bid + standard 7d AZA
  - Phase II – clinical efficacy of CB-839 + AZA
- Data cutoff for current interim analysis: July 24, 2020
  - At time of data cutoff
    - 23 patients had been enrolled
    - 6 patients remained on study

Patient characteristics

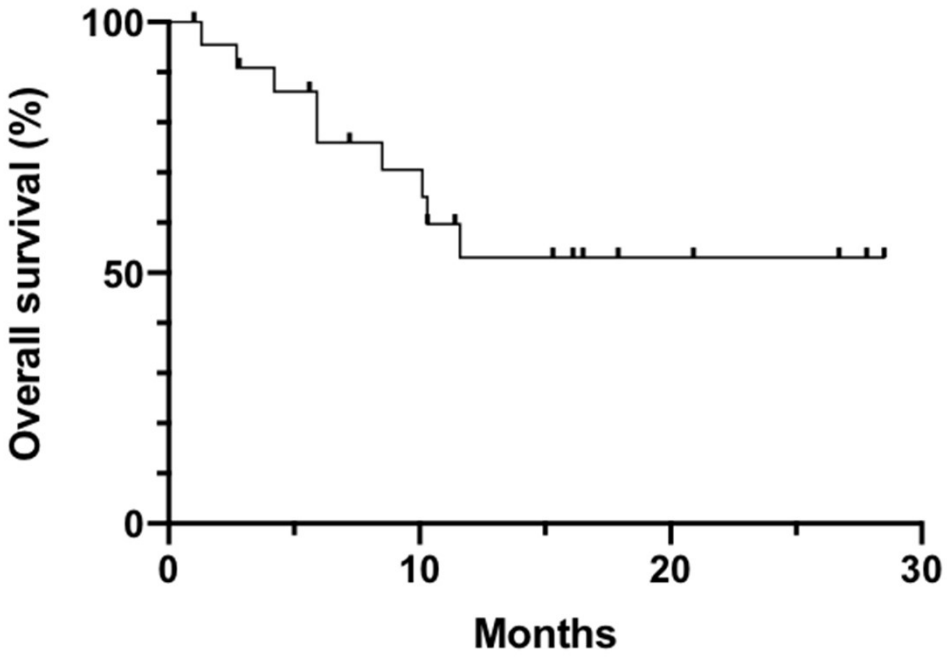
Characteristic (N=23)	N (%); Median [Range]
Age, years	71 [49-83]
Sex	
Female	5 (22)
Male	18 (78)
Prior treatment(s)	
Frontline	15 (65)
Prior therapy	8 (35)
Diagnosis, n (%)	
MDS	18 (78)
CMML	5 (22)
Performance status (ECOG)	
0-1	18 (78)
2	5 (22)
Transfusion-dependent	8 (35)
Pre-treatment	
ANC ($x10^9$/L)	1.25 [0.02-8.55]
Hemoglobin (g/dL)	9.3 [7.1-13.1]
Platelets ($x10^9$/L)	39 [6-520]
BM blast %	7 [0-15]
Cytogenetics	
Diploid	8 (35)
Complex	9 (39)
Other	6 (26)
IPSS	
Int-1	11 (49)
Int-2	8 (39)
High	3 (13)



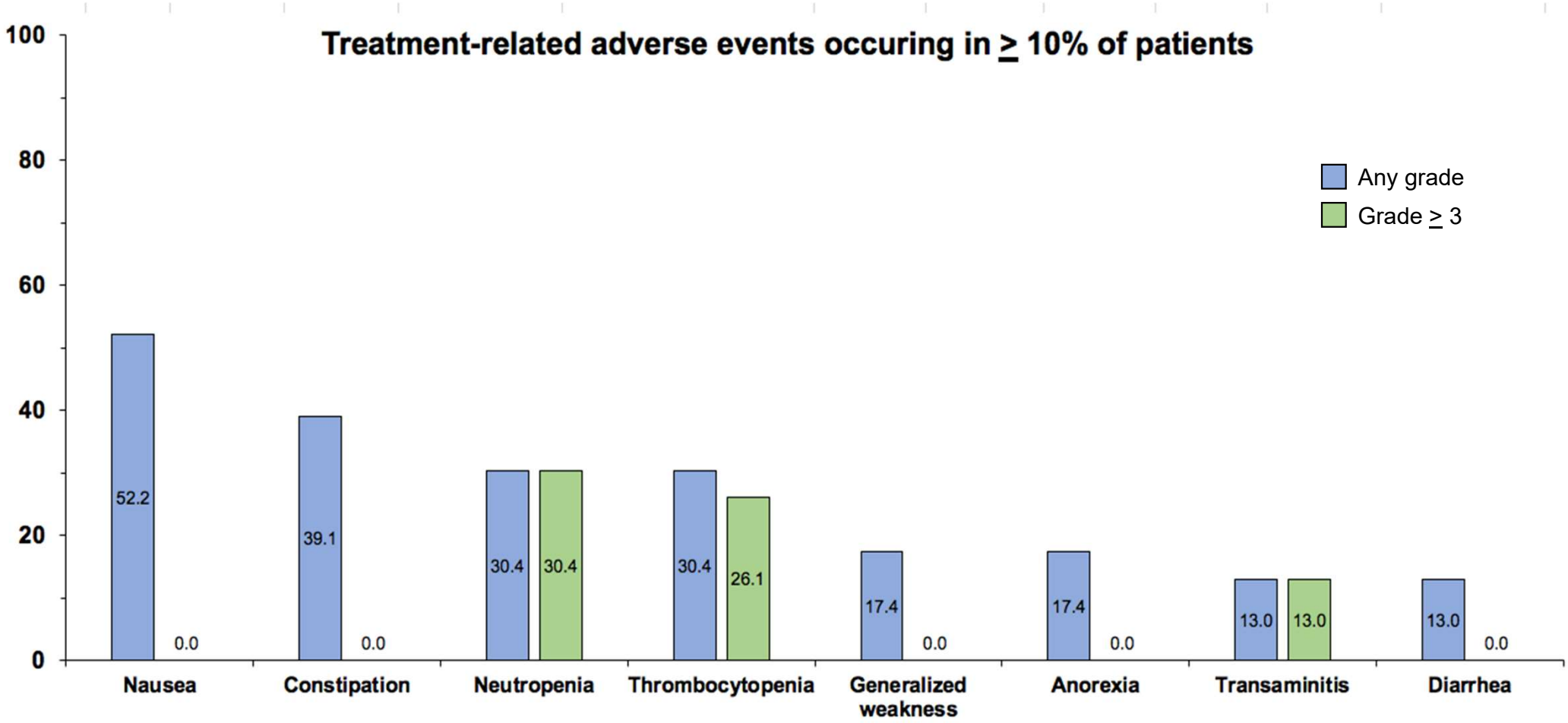
Outcomes

Best response attained on study (N=23)	**N (%)**
Objective response	15 (65)
CR	5 (22)
mCR +/- HI	10 (43)
HI	0
No response	8 (35)
Proceeded to allogeneic SCT	5 (22)
Early mortality	
30-day	0
60-day	1 (4.3)

Objective response rate	**N (%)**
Previously-treated	5/8 (63)
TP53-mutated	5/8 (63)
Complex cytogenetics	6/9 (67)



Safety


Treatment-related adverse events occuring in ≥ 10% of patients
100
80
60
40
20
0
Any grade
Grade ≥ 3
52.2
0.0
39.1
0.0
30.4
30.4
30.4
26.1
17.4
0.0
17.4
0.0
13.0
13.0
13.0
0.0
Nausea
Constipation
Neutropenia
Thrombocytopenia
Generalized weakness
Anorexia
Transaminitis
Diarrhea

Conclusions

- AZA + CB-839 is a safe combination for patients with MDS
  - Most common grade ≥ 3 non-hematologic treatment-related AE was transaminitis (13%), which could be effectively managed with dose-reduction of CB-839 from 600mg bid to 400mg bid
- AZA + CB-839 displays clinical efficacy, including in patients with high-risk disease, with an overall response rate of 65%
- Responding patients on therapy demonstrate reduced leukemic stem cells and increased progenitor cells, suggestive of myeloid differentiation (please see abstract for details)
- Trial enrollment is nearing completion