Interim Analysis of a Phase II Study of the Glutaminase Inhibitor Telaglenastat (CB-839) in Combination with Azacitidine in Advanced Myelodysplastic Syndrome (MDS).

Veronica A Guerra, Hagop Kantarjian, Jan Burger, Gautam Borthakur, Elias Jabbour, Naveen Pemmaraju, Tapan Kadia, Kimberley Sheppard, Guillermo Garcia-Manero, Marina Konopleva, Courtney D DiNardo.

Department of Leukemia
The University of Texas MD Anderson Cancer Center

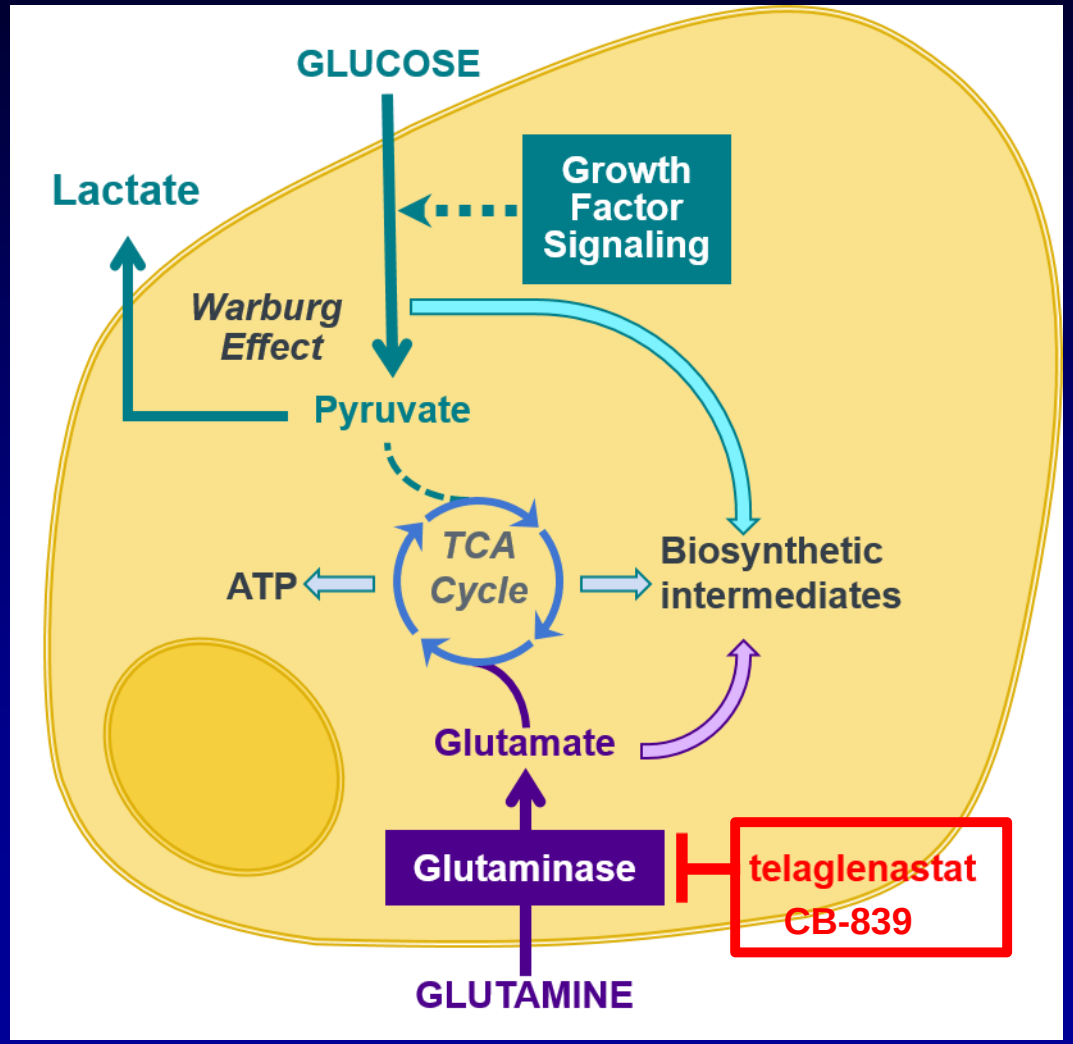
CB-839 + AZA in MDS: Background

- Glutaminase (GLS) catalyzes conversion of glutamine to glutamate
- Many tumor cells require continuous supply of glutamine and upregulate GLS
- GLS highly expressed in AML and high-risk MDS
- GLS inhibition = reduced cell growth ➡ apoptosis
- MDS with HMA failure poor prognosis, OS 4-6 months

Jaque et al. Blood 2015; 126 (11): 1346-1356
Wang et al. Blood 2015; 126 (23): 2566
Matés et al. Front. Biosci 2006; 11 (3): 3164-3180

CB-839 + AZA in MDS: Background

- CB-839: selective, reversible oral GLS inhibitor
- Plasma concentrations >300nM → >90% GLS inhibition
- In preclinical studies the combination CB-839 + azacitidine was synergistic



Cai et al. Blood 2016; 128 (22): 4084

CB-839 + AZA in MDS : Endpoints

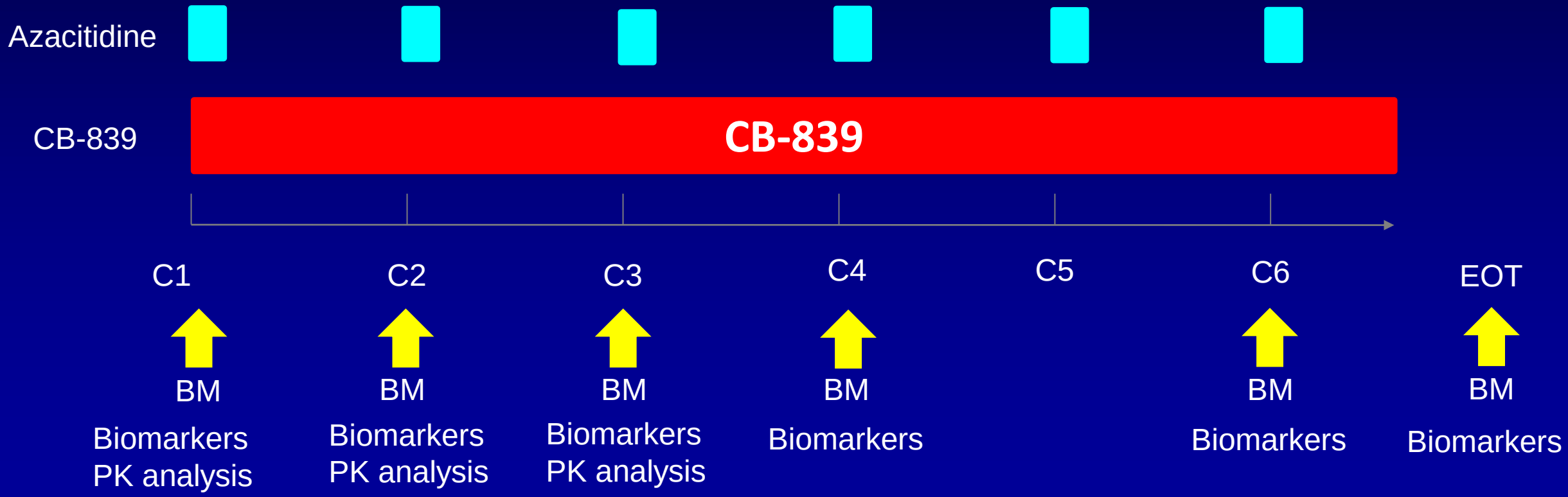
- **Primary endpoint**
  - **Phase I: Determine the recommended phase 2 dose of CB-839**
- **Secondary endpoints**
  - **Explore the pharmacokinetics and pharmacodynamics of CB-839 in combination with AZA**
  - **Determine the clinical activity by overall response rate (ORR) by IWG-MDS, overall survival (OS), event-free survival (EFS)**

CB-839 + AZA in MDS: Eligibility

- High-Risk MDS or intermediate-1 by IPSS with high-risk molecular features (TP53, ASXL1, EZH2 or RUNX1)
- Age ≥18
- ECOG PS 0-2
- Adequate organ function
  - Bilirubin ≤ 2 mg/dL, AST/ALT ≤ 3x ULN
  - Clearance creatinine > 30 mL/min

CB-839 + AZA in MDS : Study Design

- **Azacitidine 75 mg/m2/d IV/SC on days 1-7**
- **CB-839 600 mg twice daily orally on days 1-28**



CB-839 + AZA in MDS : Patient characteristics

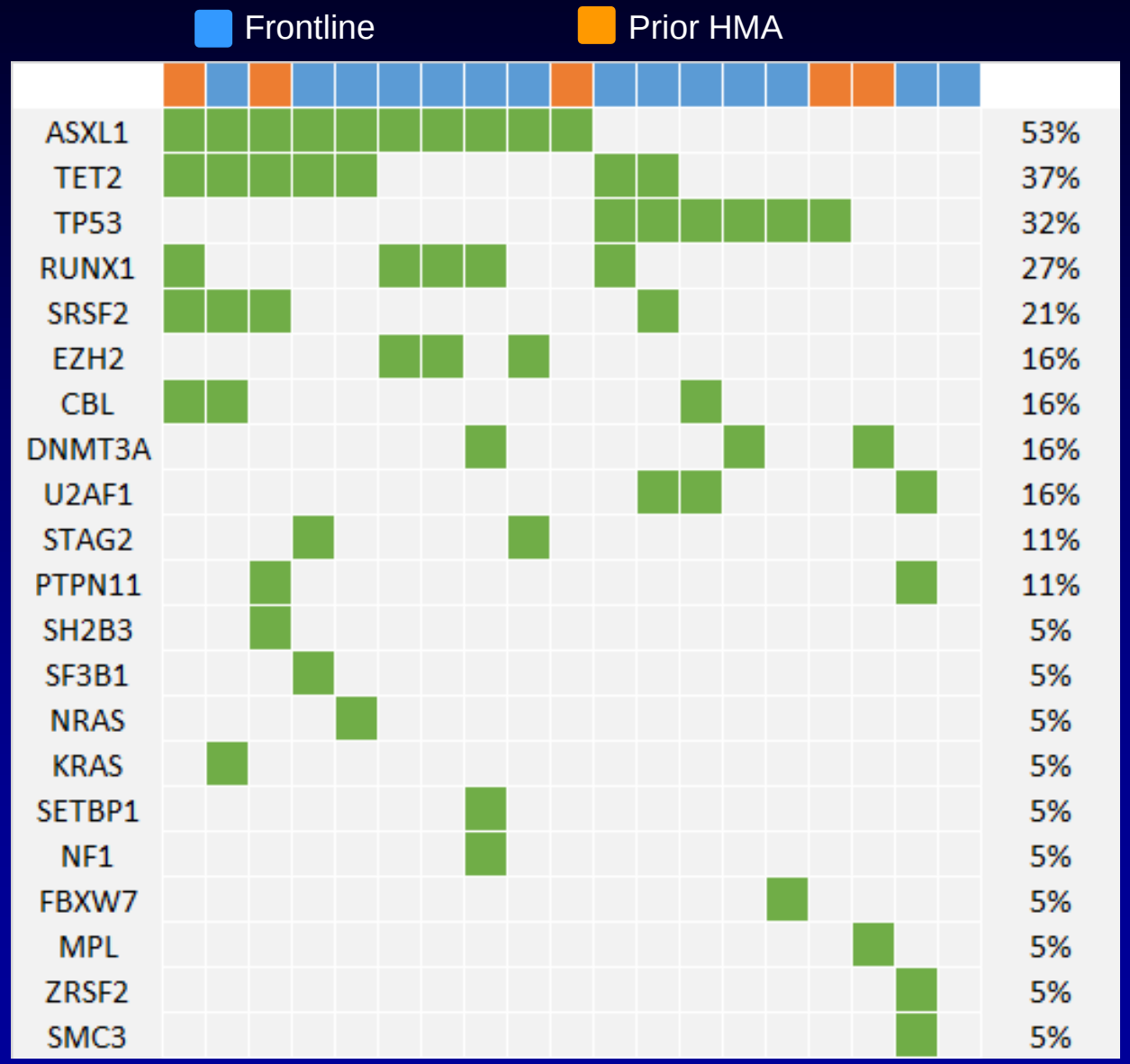
Characteristics		N=19 (%) / median [range]
Age		68 [47-82]
Sex	Male	15 (79)
Treatment	Frontline	14 (74)
	Prior HMA	5 (26)
Diagnosis	t-MDS	5 (26)
	MDS-EB-1	4 (21)
	MDS-EB-2	3 (16)
	CMML	5 (26)
	MDS-MLD	2 (11)
Hemoglobin		9.3 [7.1-13.1]
Platelets		70 [11-520]
ANC		1.04 [0.01-8.5]
PS <2		18 (95)
BM Blast %		6 [0-14]

CB-839 + AZA in MDS :Patients Characteristics

Characteristics	N (%)
Cytogenetics	
Diploid	7 (37)
Complex	7 (37)
Other	5 (26)
IPSS Score	
Intermediate-1	9 (47)
Intermediate-2	9 (47)
High Risk	1 (5)

CB-839 + AZA in MDS: Somatic Mutations

Mutations	N (%)
ASXL1	10 (53)
TET2	7 (37)
TP53	6 (32)
RUNX1	5 (26)
SRSF2	4 (21)



CB-839 + AZA in MDS : Response Rates

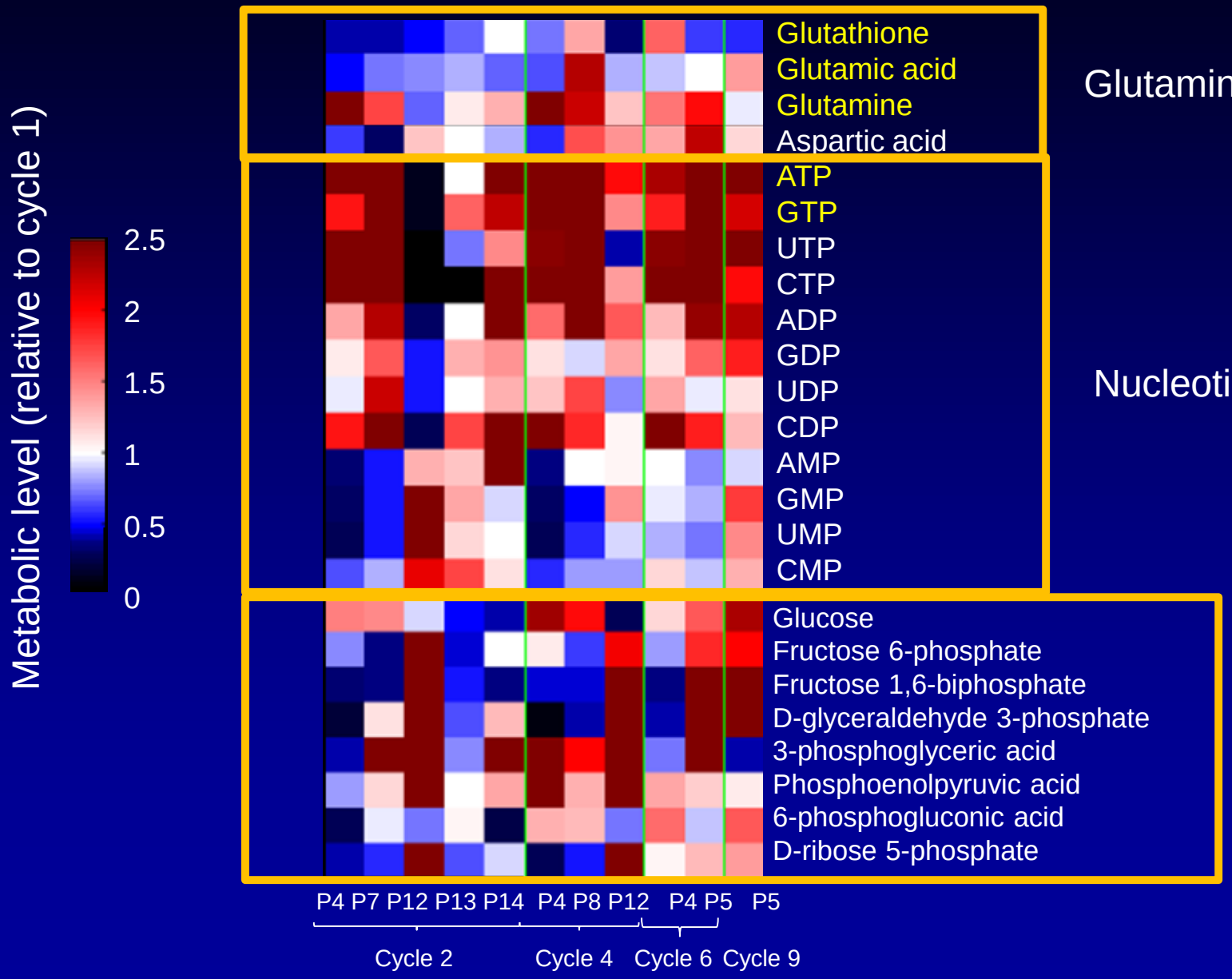
Response	All patients N=19 (%)	Frontline N=14 (%)	Prior HMA N=5 (%)
ORR	12 (63)	8 (57)	4 (80)
CR	2 (11)	2 (14)	
mCR	9 (47)	6 (43)	3 (60)
HI	1 (5)		1 (20)
Stable Disease	6 (32)	5 (36)	1 (20)
No response	1 (5)	1 (7)	
CG Response	5/12 (42)	5/10 (50)	0/2 (0)

- Time to CG response: 3 months [2.7-3.2]

CB-839 + AZA in MDS: Response Rates for key MDS subsets

Response	Complex CG N=7 (%)	ASXL1 N=10 (%)	TP53 N=6 (%)
ORR	**6 (86)**	**6 (60)**	**5 (83)**
CR	1 (14)	1 (10)	1 (17)
mCR	5 (71)	4 (40)	4 (67)
HI		1 (10)	
Stable Disease	1 (14)	4 (40)	
No response			1 (17)
CG response	**4/7 (57)**	**2/4 (50)**	**3/6 (50)**

CB-839 + AZA in MDS: Metabolic Analysis



Glutamine/Aspartate utilization

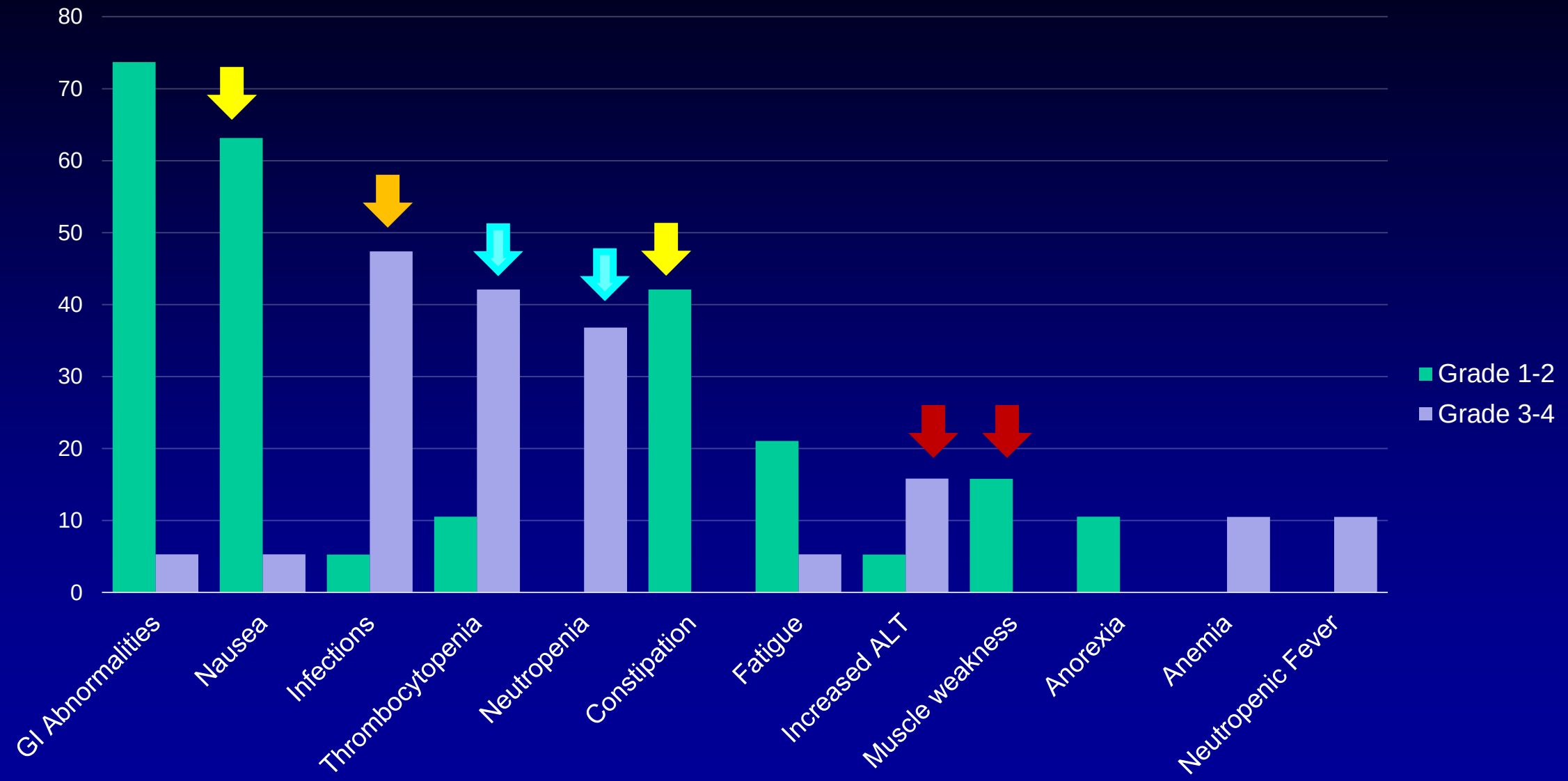
Nucleotides

Glycolysis/PPP Pathway

CB-839 inhibits Glutamine utilization

Metabolic level in PB MS, relative to baseline
Stefano Tiziani lab (UT Austin)

CB-839 + AZA in MDS : Adverse Events



Adverse events >10%

CB-839 + AZA in MDS : Disposition

N= 19 patients
Follow-up 10.5 months

Median number cycles: 3 [1-10]

Time to best response: 1 cycle [1-4]

CR/mCR/HI
N=11

Alive N=7
On study: N=3

HSCT N= 4
Alive, N= 2
Died, N= 2

Died N= 2
In mCR N=1
Progression N=1

Stable Disease
N=7

Alive N=5
On study: N=3

HSCT N= 1
Alive, N= 1

Died: N=2

No Response
N=1

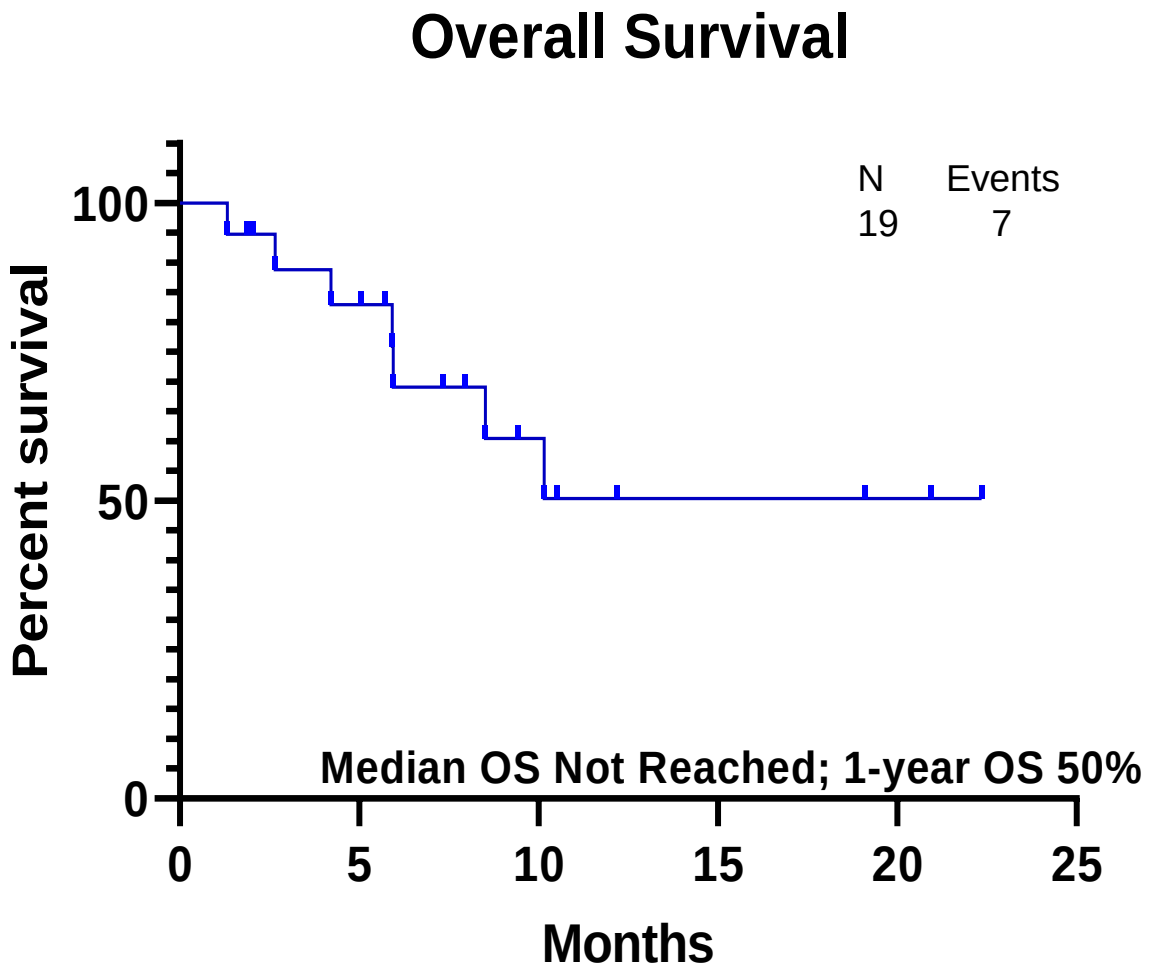
Died: N=1

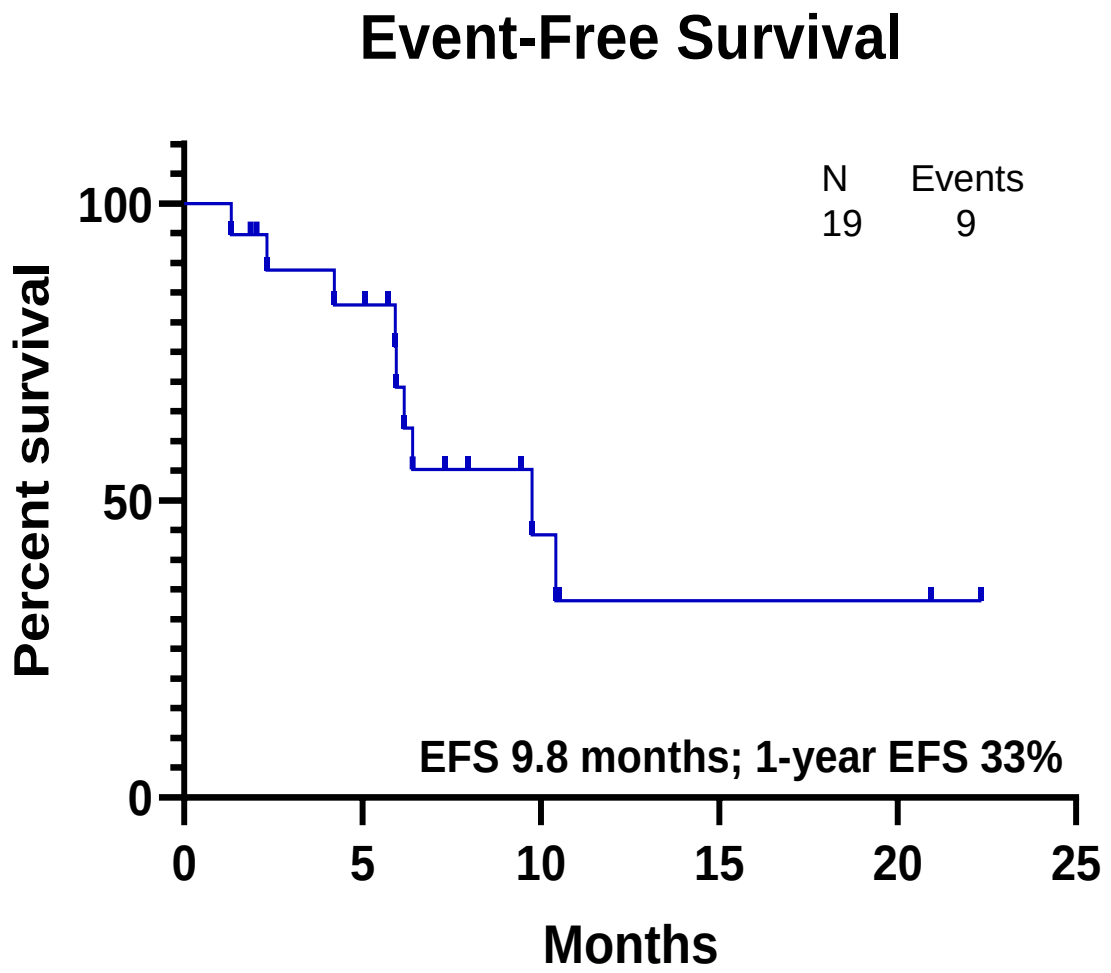
Cause of death N=7
- Infection N=2
- Unknown N=2
- Progression N=1
- Post HSCT N=2

CB-839 + AZA in MDS : Treatment Discontinuation

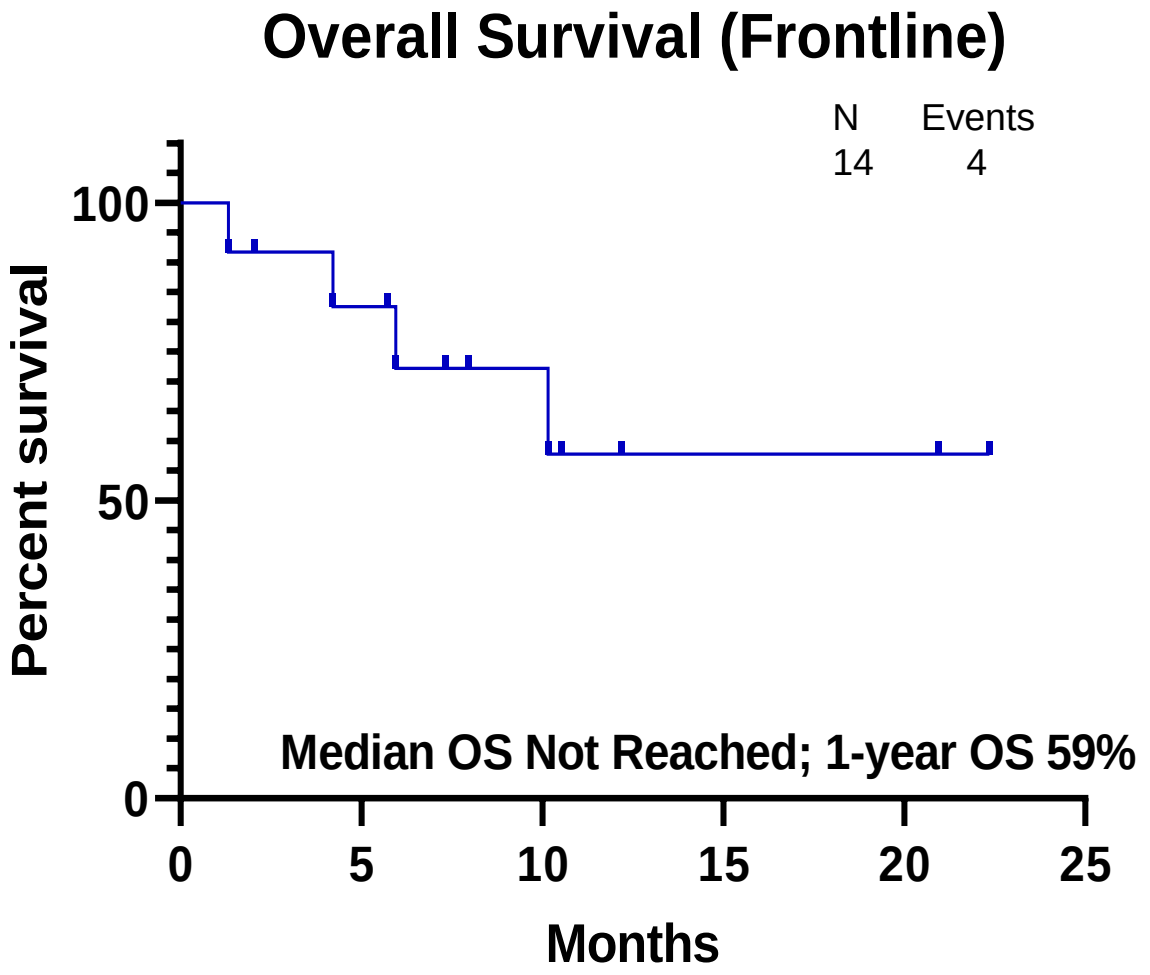
Cause of Discontinuation	N=13
HSCT	**5 (26)**
Death	3 (16)
Disease progression	3 (16)
Physician decision	1 (5)
No response	1 (5)

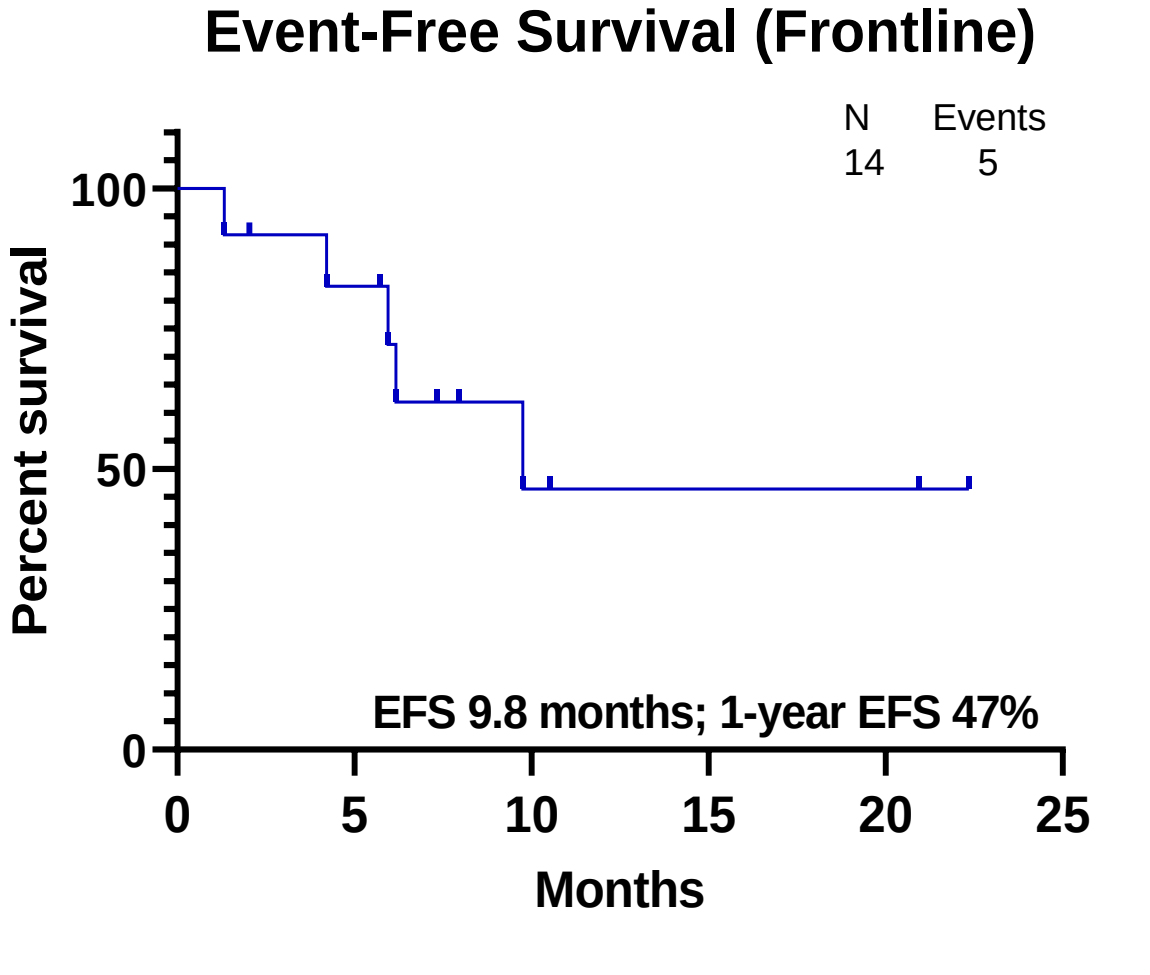
CB-839 + AZA in MDS : OS and EFS





CB-839 + AZA in MDS : OS and EFS (Frontline)





CB-839 + AZA in MDS : Conclusions

- CB-839 + Azacitidine is safe and well tolerated in advanced MDS
  - ORR 63%; CR 11% and mCR 47%
  - 1-year OS 50%; 1-year EFS 33%
  - ORR 80% prior HMA; 83% in TP53 patients, 86% in complex karyotype
- Safe regimen
  - CB-839 600 mg BID orally continuously has acceptable safety profile
  - Reversible transaminitis rate: 16%
- Longer follow-up is needed

Acknowledgments

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