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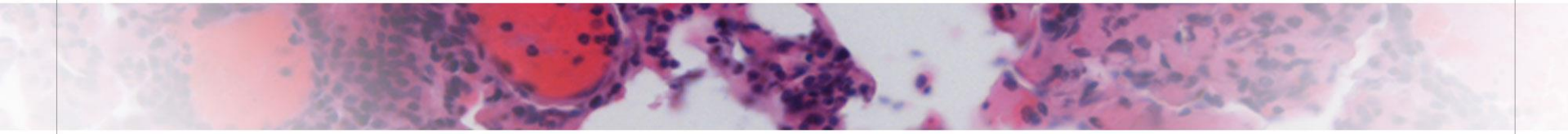

Prolonged Survival in Bi-Allelic TP53-Mutated (*TP53*^{mut}) MDS Subjects Treated with Oral Decitabine/Cedazuridine in the ASCERTAIN Trial (ASTX727-02)

On behalf of the ASCERTAIN Investigators Team

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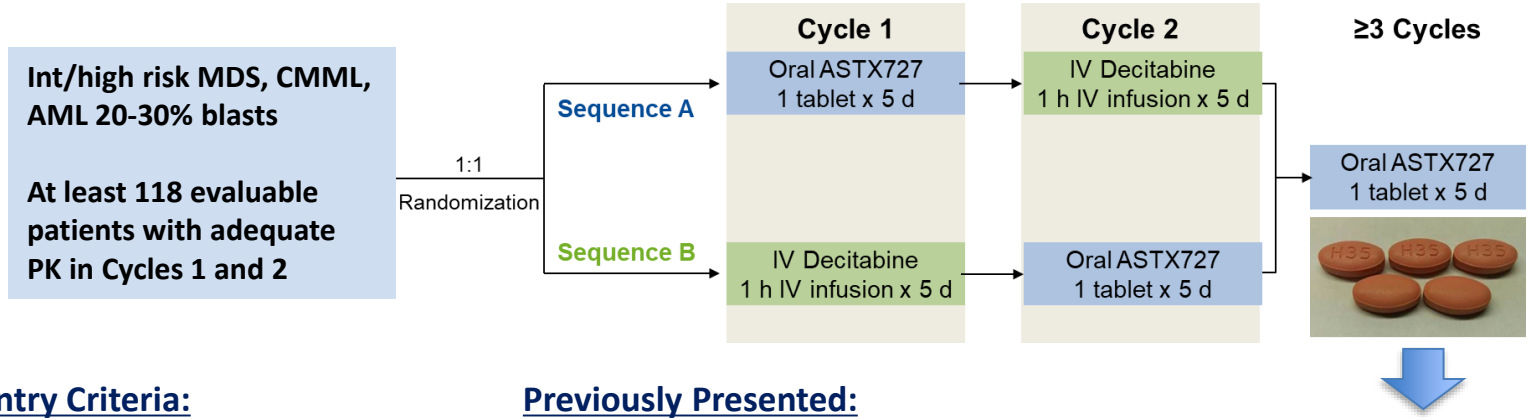
Introduction: *TP53* in MDS and oral decitabine/cedazuridine

- ***TP53* mutations are associated with poor prognosis in several malignancies**
  - $TP53^{mut}$ is associated with poor overall survival despite similar response rates in MDS (9.4 vs. 20.7 months in $TP53^{mut}$ vs. $TP53^{WT}$)[1].
  - More recently, the impact of monoallelic vs. biallelic *TP53* mutations has been described in MDS populations with biallelic populations having a markedly worse survival outcome (8.4 vs. 30 months in $TP53^{mut}$ vs $TP53^{WT}$)[2].
- **Oral decitabine/cedazuridine (ASTX727): fixed-dose combination of decitabine (DEC) with cytidine deaminase (CDA) inhibitor cedazuridine**
  - Phase III ASCERTAIN study in MDS, CMML, and RAEB-T demonstrated:
    - Pharmacokinetic equivalence to parenteral DEC dosed at 20 mg/m^2 for 5 days every 28 days[3].
    - Encouraging activity: CR rate of 22%, mOS ~32 months[4].
    - Consistent safety profile with no increase in GI adverse events
  - Study population provided an opportunity to study the impact of various gene mutations, including *TP53*.

MDS - myelodysplastic syndromes; mut – mutations; WT – weight; CMML – chronic myelomonocytic leukemia; RAEB-T - refractory anemia with excess blasts in transformation; CR – complete response; mOS – median overall survival; GI - gastrointestinal

[1] Takahashi, K, et al. *Oncotarget*. 2016
[2] Bernard, et al. *Nat Med*. 2020
[3] Garcia-Manero, et al. [ASH Abstract 846] *Blood*. 2019;134 (suppl 1)
[4] Savona, et al, Int. MDS Symposium, 2021

Methods/Study Design: ASCERTAIN



Major Entry Criteria:

- Candidates for IV decitabine
- ECOG PS 0-1
- Life expectancy of ≥3 months
- Adequate organ function
- One prior cycle of HMA is allowed

Previously Presented:

- Demonstrated PK AUC equivalence to IV DEC at 20 mg/m^2
- Oral safety profile consistent with IV, no marked GI toxicity[3]
- Clinical activity similar (CR rate 22%, mOS ~32 months)[4]

Current Analyses:

- 133 subjects enrolled and whole blood collected for NGS analyses
- NGS (179 genes) analyses available for 125 subjects
- Focus on genes from 2022 MDS NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®)[5] (30 genes)

IV – intravenous; ECOG – Eastern Cooperative Oncology Group; PS – performance status; HMA - hypomethylating agent; PK – pharmacokinetics; AUC – are under the curve; NGS – next-generation sequencing;

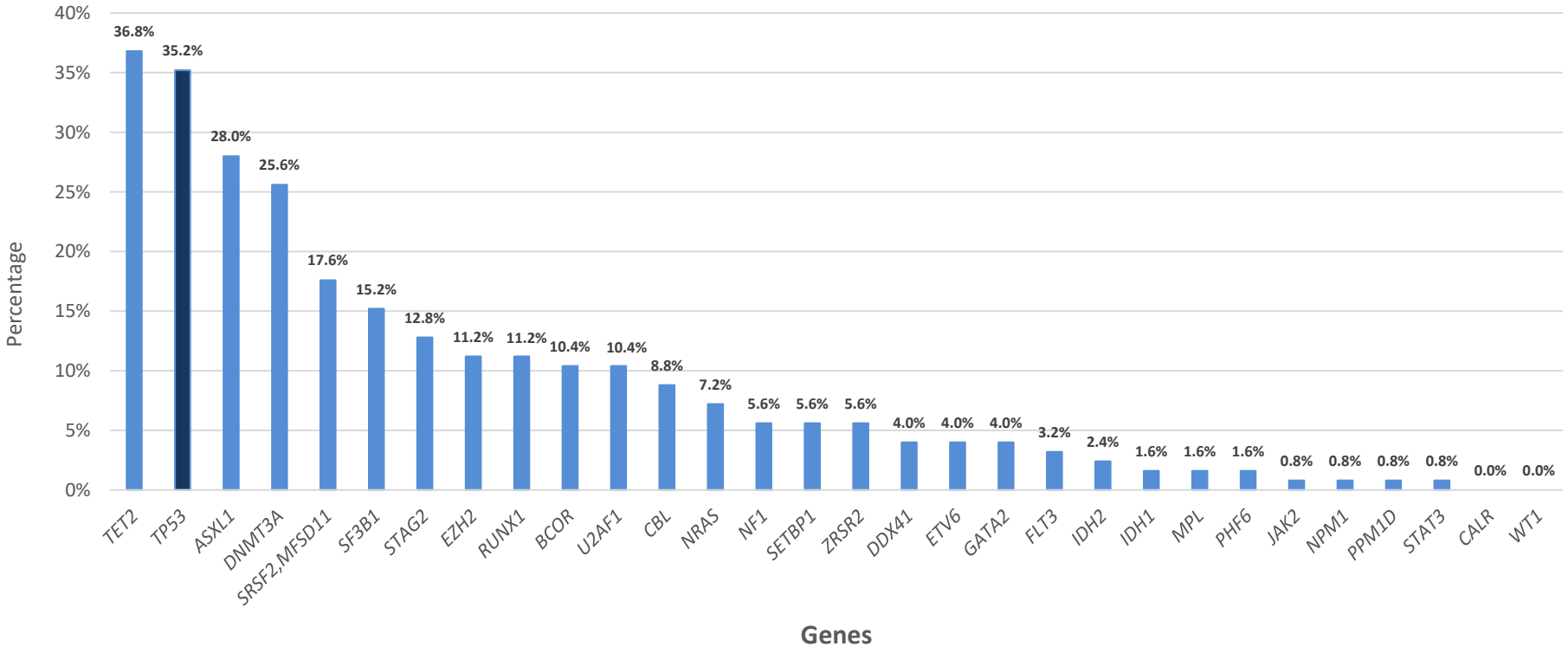
[3]Garcia-Manero, et al, [ASH Abstract 846] Blood. 2019;134 (suppl 1).
[4]Savona, et al. MDS symposium 2021.
[5]NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelodysplastic Syndromes 3.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed [Nov 8, 2022]. To view the most recent and complete version of the guideline, go online to NCCN.org.

Gene Mutations Analyzed based on 2022 NCCN Guidelines® for MDS[5]

Mutated Gene[b]	Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes[c]	Overall Incidence	Clinical Significance
TET2	Nonsense or Frameshift or Splice Site Missense: any in codons 1134–1444 or 1842–1921	20%–25%	Associated with normal karyotypes. More frequent in CMML (40%–60%). Common in clonal hematopoiesis of indeterminate potential (CHIP) and CCUS.
DNMT3A	Nonsense or Frameshift or Splice Site Missense in codons G543, R635, A741, R736, H739, S770, M880, R882, W893, P904, A910	12%–18%	More frequent occurrence in AML, particularly R882 mutations. Common in CHIP and CCUS.
ASXL1	Nonsense or Frameshift	15%–25%	Independently associated with a poor prognosis in MDS and CMML. More frequent in CMML (40%–50%). Common in CHIP and CCUS.
EZH2	Nonsense or Frameshift	5%–10%	Independently associated with a poor prognosis in MDS and MDS/MPN. More frequent in CMML (12%).
SF3B1	Missense: E622, Y623, R625, N626, H662, T663, K666, K700E, I704, G740, G742, D781	20%–30%	Strongly associated with ring sideroblasts and more frequent in MDS-RS (80%). Independently associated with a more favorable prognosis.
SRSF2	Missense or In-Frame Deletion: involving codon P95	10%–15%	More frequent in CMML (40%) and associated with a poor prognosis.
U2AF1	Missense: S34, Q157	8%–12%	Associated with a poor prognosis.
ZRSR2	Nonsense or Frameshift	5%–10%	Associated with a poor prognosis.
RUNX1[d]	Nonsense or Frameshift	10%–15%	Independently associated with a poor prognosis in MDS.
TP53[d]	Nonsense or Frameshift or Splice Site Missense: any in codons except P47S and P72R	8%–12%	Independently associated with a poor prognosis. More frequent with complex karyotypes (50%) and del(5q) (15%–20%). May predict resistance or relapse to lenalidomide.
STAG2	Nonsense or Frameshift or Splice Site	5%–10%	Associated with a poor prognosis.
NRAS[d]	Missense: G12, G13, Q61	5%–10%	Associated with a poor prognosis, particularly in patients predicted to have lower-risk MDS. More frequent in CMML and JMML (~15%).
CBL[d]	Missense: any in codons 366–420	<5%	More frequent in CMML (10%–20%) and JMML (15%).
NF1[d]	Nonsense or Frameshift or Splice Site	<5%	More frequent in CMML (5%–10%) and in JMML (30%) where it is often germline.
JAK2	Missense: V617F	<5%	More frequent in MDS/MPN-RS-T (50%); can occur in conjunction with *SF3B1*.
CALR	Frameshift: after codon 352	<5%	Observed in MDS/MPN-RS&T where it can occur in conjunction with *SF3B1* mutations.
MPL	Missense: W515L/K	<5%	Observed in MDS/MPN-RS&T where it can occur in conjunction with *SF3B1* mutations.
ETV6[d]	Nonsense or Frameshift	<5%	Independently associated with a poor prognosis.
GATA2[d]	Nonsense or Frameshift or Splice Site Missense: in codons 349–398		Associated with a poor prognosis.
DDX41[d]	Nonsense or Frameshift or Splice Site Missense: in codon R525H		Constitutional (germline) mutations in this gene can occur.
IDH1	Missense: R132	<5%	More frequent in AML.
IDH2	Missense: R140Q, R172	<5%	More frequent in AML. Associated with a poor prognosis.
SETBP1	Missense: E858, T864, I865, D868, S869, G870	<5%	Associated with disease progression. More frequent in aCML (24%); CMML (5%–10%) and JMML (7%).
PHF6	Nonsense or Frameshift or Splice Site	<5%	More frequent in cases with excess blasts, but no association with survival.
BCOR	Nonsense or Frameshift or Splice Site	<5%	Associated with a poor prognosis. More frequent in CMML (5%–10%).
FLT3	Internal Tandem Duplication or Missense: in codon D835		Associated with a poor prognosis.
WT1	Nonsense or Frameshift or Splice Site		Associated with a poor prognosis.
NPM1	Frameshift: W288fs*12		Associated with a poor prognosis.
STAT3	Missense: any codons 584–674	<5%	Occurs in LGL associated with MDS; associated with immune bone marrow failure.
PPM1D	Nonsense or Frameshift	~5%	Associated with therapy-related MDS, but not associated with adverse prognosis independent of *TP53*. Common in CHIP and CCUS.

- *TP53, EZH2, RUNX1, CBL, DNMT3A, SF381,* and *ASXL1* were selected for further analysis based on previously reported negative impact on overall survival (OS) and leukemia-free survival (LFS).

Mutation Frequency of Specific Genes in ASCERTAIN



Mutational Burden and Outcomes

Mutation	Mutational Frequency; N, (%) (Expected Frequency)	CR % Mut/WT	ORR (CR+Cri+PR+ HI) % Mut/WT	LFS (p value, Chi-Square)	OS (p Value Using Chi-Square)
TET2	46, (36.8%) (20-25%)	17.4/25.3	56.5/62.0	0.622	0.373
TP53	44, (35.2%) (8-12%)	14.0/26.8	58.1/61.0	Worse, p=0.032	Worse, p=0.023
ASXL1	35, (28.0%) (15-25%)	22.9/22.2	65.7/57.8	P=0.054	P=0.341
DNMT3A	32, (25.6%) (12-18%)	28.1/20.4	53.1/62.4	P=0.127	P= 0.055
SRSF2_MFSD11	22, (17.6%) (10-15%)	13.6/24.3	50.0/37.9	P=0.695	P=0.924
SF3B1	19, (15.2%) (20-30%)	15.8/23.6	31.6/65.1	P=0.291	P= 0.700
STAG2	16, (12.8%) (5-10%)	18.8/22.9	50.0/61.5	P=0.245	P=0.913
EZH2	14, (11.2%) (5-10%)	28.6/21.6	85.7/56.8	P=0.941	P=0.710
RUNX1	14, (11.2%) (10-15%)	7.1/24.3	42.9/62.2	P=0.260	P= 0.926
BCOR	13, (10.4%) (<5%)	23.1/22.3	38.5/62.5	P=0.104	P= 0.317
U2AF1	13, (10.4%) (8-12%)	30.8/21.4	61.5/59.8	P=0.690	P=0.755
CBL	11, (8.8%) (<5%)	18.2/22.8	72.7/58.8	P=0.063	Worse, P=0.012

- *TP53*^{mut} and *CBL*^{mut} associated with inferior outcomes (LFS, OS)

TP53^{mut} Population Demographically Similar to *TP53*^{WT}

Factor		*TP53*^{mut} (N=44)	*TP53*^{WT} (N=81)	Overall (N=125)
Age, years (median, range)		70 (45-84)	71 (44-88)	71 (44-88)
Sex: M (%)		28 (63.6%)	54 (66.7%)	82, (65.6%)
Disease: MDS,CMML (%)		40, 4 (91%, 9%)	69, 12 (85%, 15%)	109, 16 (87%, 13%)
IPSS (CMML pts no category)	HR	9 (20%)	10 (12%)	19 (15%)
	Int-2	13 (30%)	12 (15%)	25 (20%)
	Int-1	17 (39%)	44 (54%)	61 (49%)
	LR	1 (2%)	3 (4%)	4 (3%)
ECOG PS	0	17 (39%)	34 (42%)	51 (41%)
	1	27 (61%)	47 (58%)	74 (59%)

IPSS – International Prognostic Scoring System; HR – hazard ratio; Int – intermittent; LR – low risk

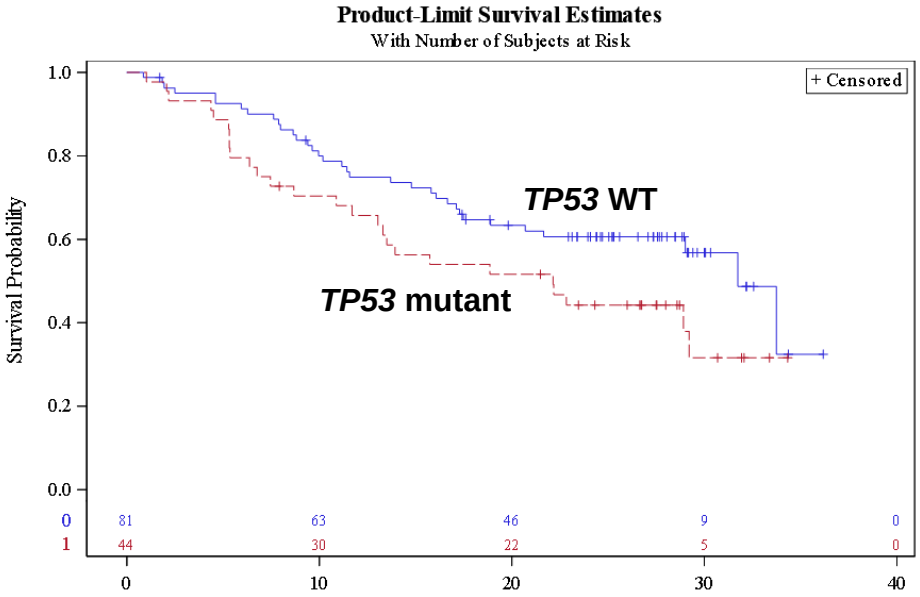
Further Analysis of Selected Genes

- *TP53* mutations (N=44) were associated with a worse OS (HR 1.7, 95% CI of 1.00-2.87) and LFS (HR 1.63 with 95% CI 0.98-2.72) compared to *WT* gene status.
- *CBL* mutations (N=11) were associated with worse OS (HR 2.54, 95% CI 1.19-5.43) and LFS (HR 2.01, CI 0.95-4.26) compared to *WT* gene status.
- *DNMT3A* mutations (N=32) trended toward better OS outcome (HR 0.50, 95% CI 0.25-1.028, p=0.060).
- The $TP53^{mut}$ population was further analyzed by allelic status:
  - Biallelic if more than one *TP53* copy OR 17p deletion and at least one *TP53* mutation (*LOH analyses were not conducted).
  - $TP53^{mut}$: 30 monoallelic, 14 biallelic (by this definition).

CI – confidence interval; OR – overall response; LOH – loss of heterozygosity

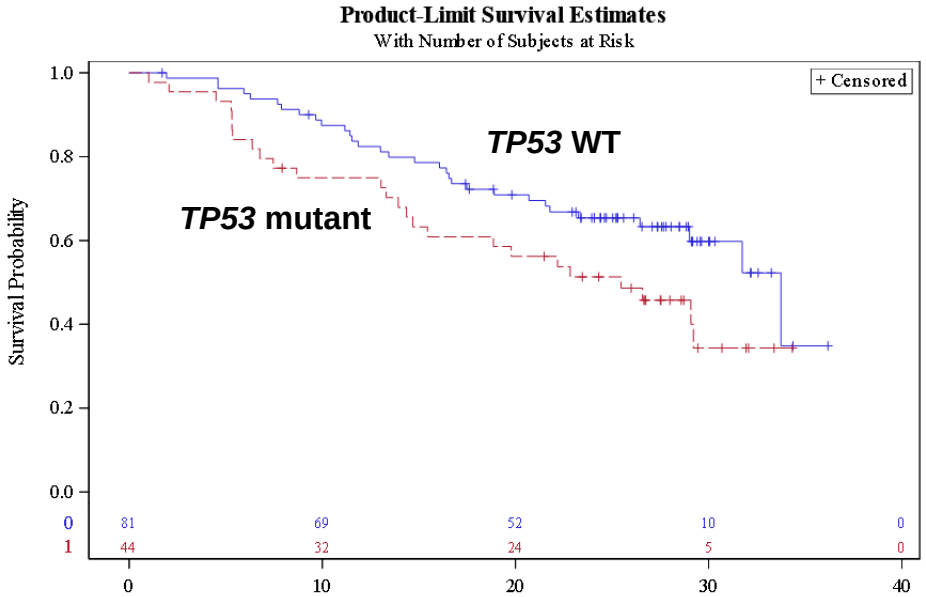
Survival and LFS Outcomes in *TP53* Mutant Patients

Leukemia-Free Survival



LFS: WT 31.7 months (21.7, NE)
Mut 22.1 months (11.7, 29.2)

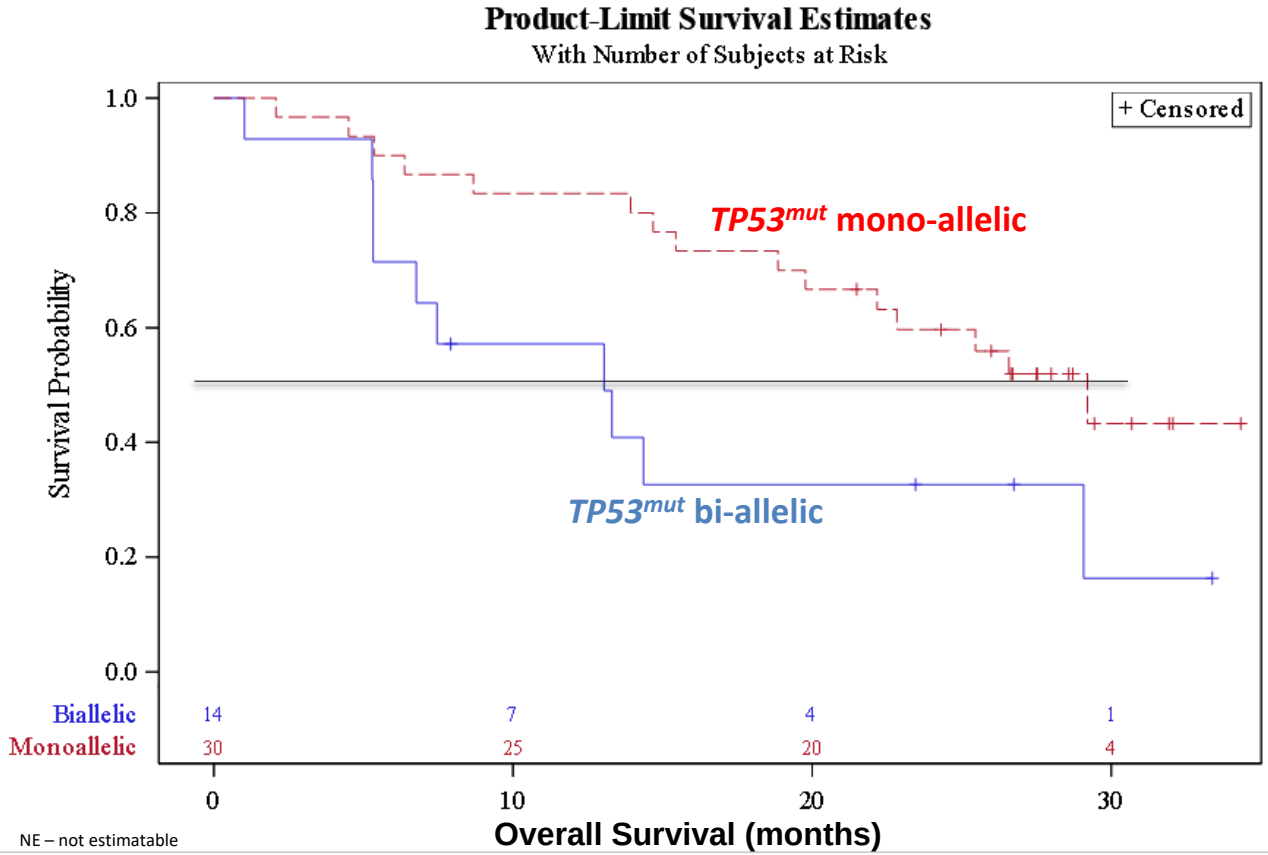
Overall Survival



OS: WT 33.7 months (29.0, NE)
Mut 25.5 months (14.4, NE)

NE – not estimatable

Survival in *TP53*^{mut} (Mono- vs. Bi-allelic)



NE – not estimatable

Mono-allelic OS:
mOS: 29.2 months
95% CI (19.7 months, NE)

Bi-allelic OS:
mOS: 13.0 months
95% CI (5.3 months, 29.0)

Conclusions

- ASCERTAIN previously demonstrated equivalent PK exposure of oral decitabine/cedazuridine (ASTX727) compared with IV DEC
  - encouraging efficacy (CR rate and OS); safety profile consistent with IV DEC.
- The ASCERTAIN MDS/CMML population was notable for higher percentages of subjects with *TP53* and *DNMT3A* mutations.
- Both the *TP53*^{mut}and *CBL* groups had a worse OS compared to WT.
  - Within the *TP53*^{mut} patients, those identified as biallelic had a worse outcome compared to monoallelic (13.0 months vs. 29.2 months, respectively) consistent with previous published work.
- The observed mOS in patient with biallelic *TP53*^{mut} (13.0 months) exceeds previously described historical control (8.4 months), though limited by small patient numbers and lack of LOH studies.
- Oral decitabine/cedazuridine remains the only orally available HMA with PK exposures equivalent to its parenteral form.

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