Memorial Sloan Kettering
Cancer Center

MDM2 (HDM)Inhibition

Eytan M. Stein, MD
Associate Attending Physician
Director, Program for Drug Development in Leukemia
Leukemia Service
Memorial Sloan Kettering Cancer Center
New York, New York

Disclosures

Advisory Board: Novartis, PinotBio, Janssen, Bristol Myers Squibb, Agios, Jazz, Menarini, Genentech, Genesis, Abbvie, Neoleukin, Gilead, Syndax, OnCusp, CTI Biopharma, Foghorn, Servier, Calithera, Daiichi, Aptose, Syros, Astellas, Ono Pharma, Blueprint *Honoraria:* Kura. *Safety Monitoring:* Epizyme, Cellectis. *Research Funding*: Eisai, Bristol Myers Squibb *Equity*: Auron.

MDM2 (HDM)

- MDM2 is a negative regulator of p53.
- Functions as an E3 ubiquitin ligase that targets p53 for degradation.
- Inhibits p53 transcriptional activation.
- Inhibiting MDM2 allows for increased amount/activity of p53 thereby leading to apoptosis in myeloid malignancies
  - MDM2 inhibitors would be predicted to have minimal/no activity in p53 *mutant* myeloid malignancies.
- When MDM2 inhibitors are used in the clinic, a common pathway of resistance is that p53 mutations arise.

Preclinical Rationale for MDM2 Inhibition

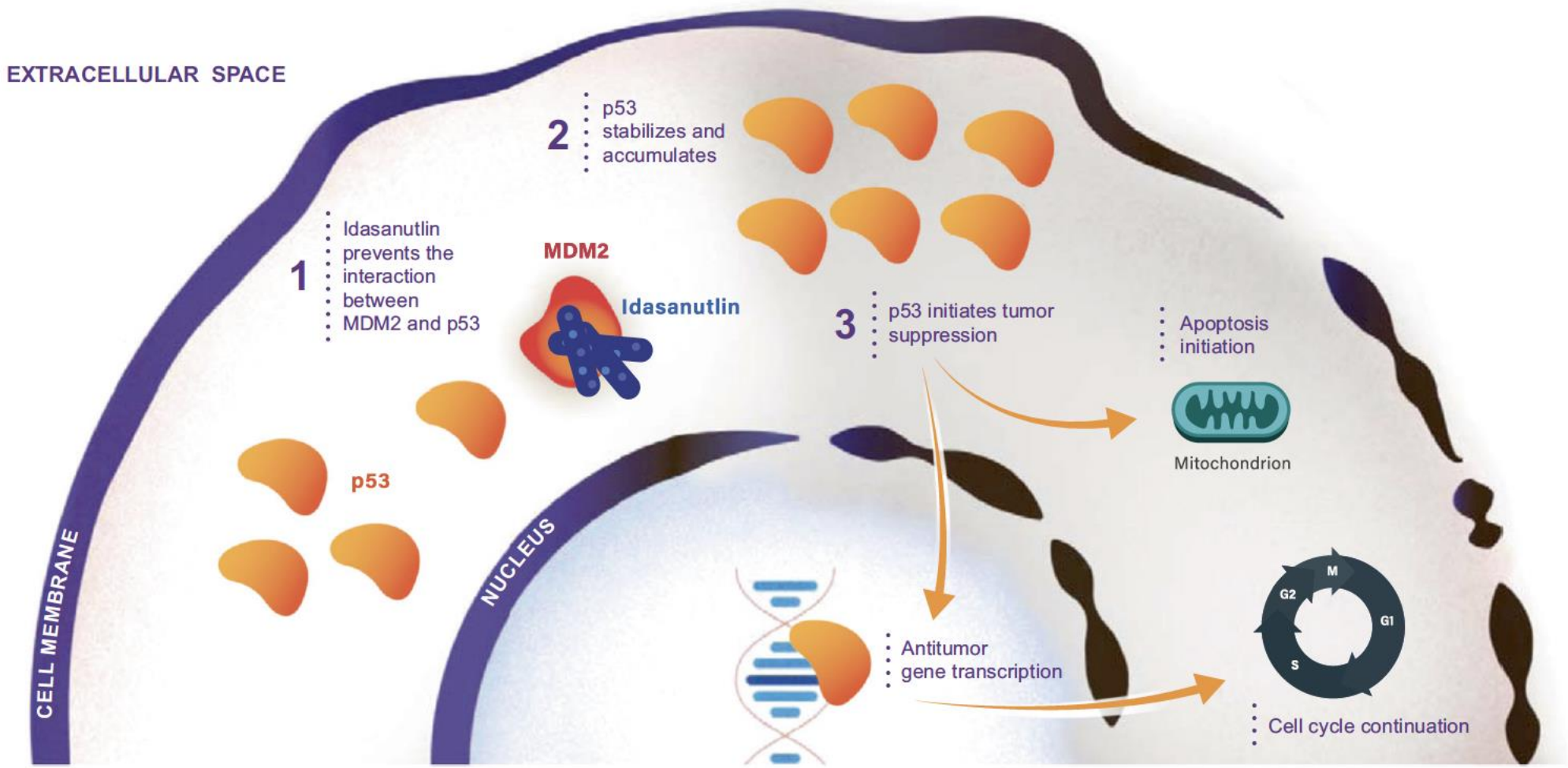
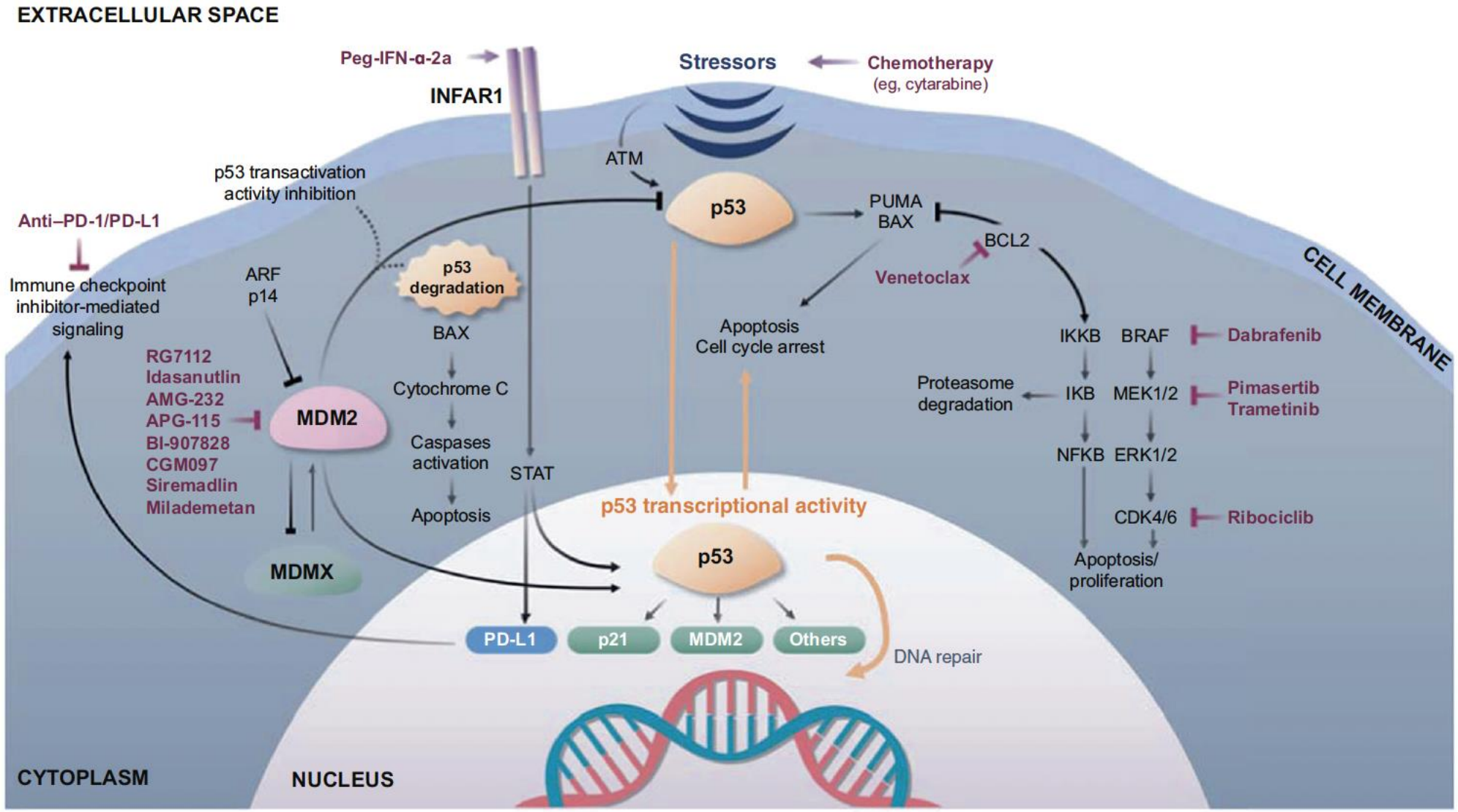


Fig. 1 Activation of p53 by MDM2 inhibition. Inhibiting the MDM2-p53 interaction with an MDM2 antagonist leads to reactivation of p53 in cancers with wild-type or functional p53.

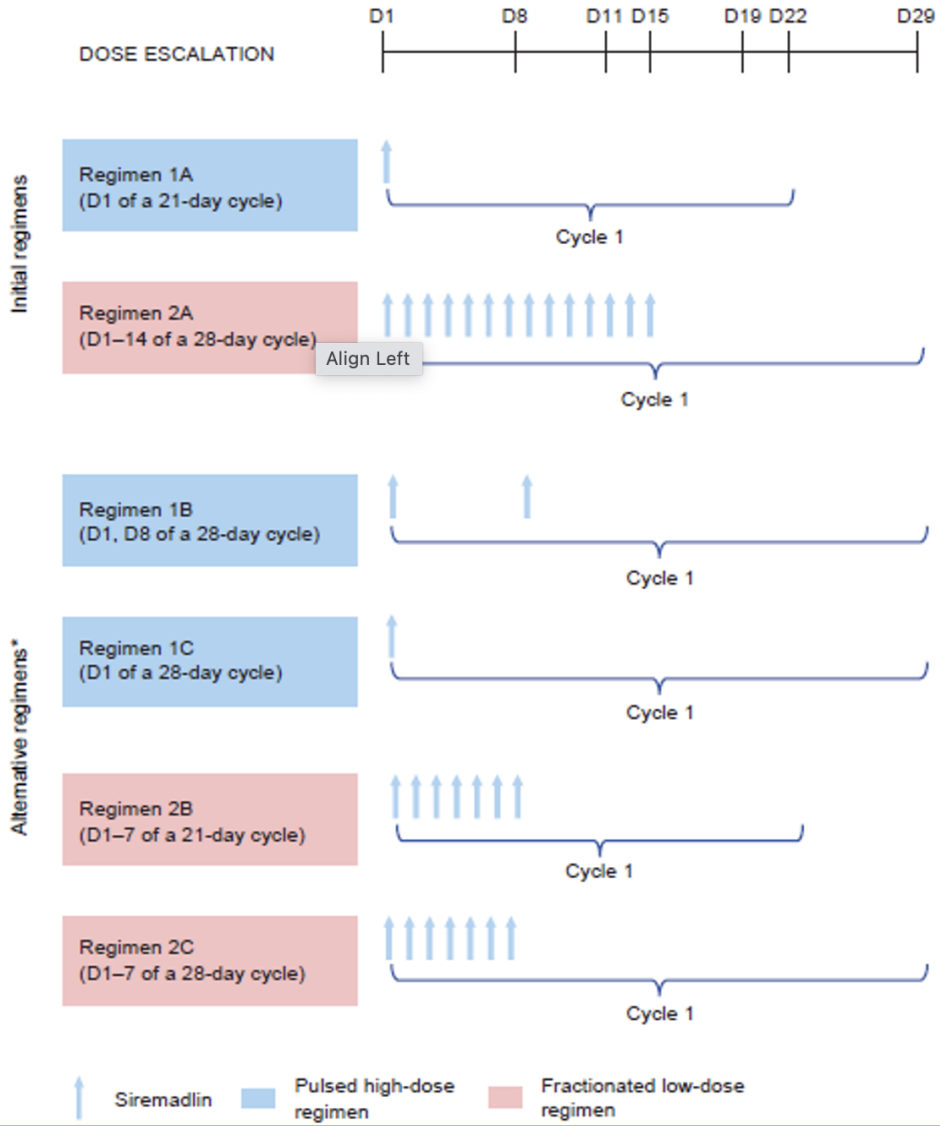
Konolpeva M, et. al , Leukemia 2020

Preclinical Rationale for MDM2 Inhibition



Konolpeva M, et. al , Leukemia 2020

Phase 1 Study of Siremadlin – Novel MDM2 Inhibitor



Memorial Sloan Kettering Cancer Center

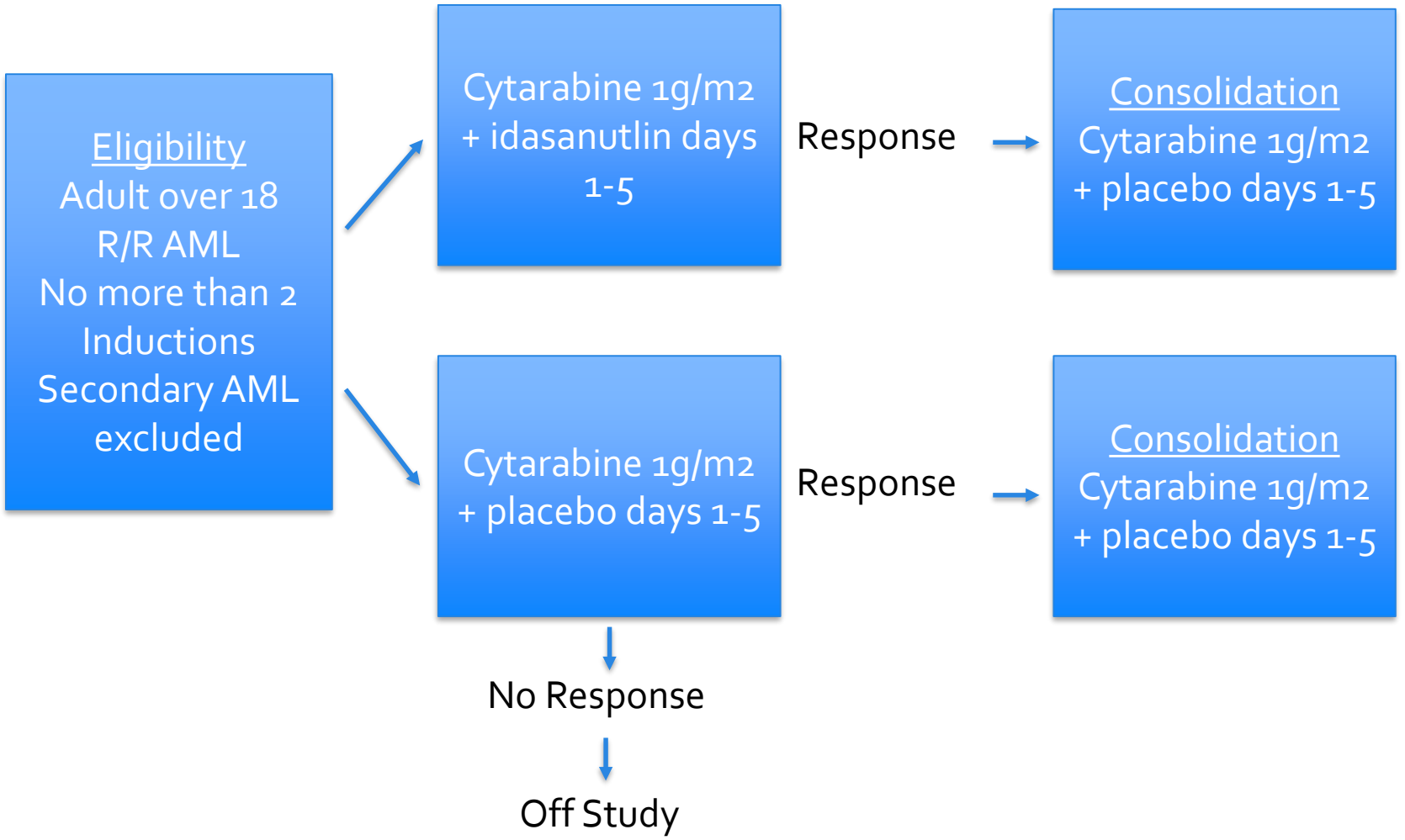
Stein EM, et. al, Clinical Cancer Research,2022

Phase 1 study of Siremadlin - Novel MDM2 Inhibitor

	High-dose 1A		High-dose 1B		Low-dose 2A	Low-dose 2C	All patients
	RDE (250 mg) *N* = 15	Other doses (350–400 mg) *N* = 12	RDE (120 mg) *N* = 24	Other doses (150 mg) *N* = 6	(20–30 mg) *N* = 7	RDE (45 mg) *N* = 27	*N* = 91
Best overall response, n (%)							
CR	1 (6.7)	1 (8.3)	1 (4.2)	0	0	2 (7.4)	5 (5.5)
CRi	2 (13.3)	0	0	1 (16.7)	0	4 (14.8)	7 (7.7)
TF	9 (60.0)	7 (58.3)	15 (62.5)	5 (83.3)	6 (85.7)	16 (59.3)	58 (63.7)
TF-resistant disease	5 (33.3)	6 (50.0)	15 (62.5)	4 (66.7)	4 (57.1)	16 (59.3)	50 (54.9)
TF-indeterminate cause	4 (26.7)	1 (8.3)	0	1 (16.7)	2 (28.6)	0	8 (8.8)
Unknown	0	0	2 (8.3)	0	0	1 (3.7)	3 (3.3)
Overall response rate (CR+CRi+PR), n (%) [95% CI]	3 (20.0) [4.3–48.1]	1 (8.3) [0.2–38.5]	1 (4.2) [0.1–21.1]	1 (16.7) [0.4–64.1]	0 [0–41.0]	6 (22.2) [8.6–42.3]	12 (13.2) [7.0–21.9]

Stein EM, et. al, Clinical Cancer Research,2022

Idasantulin – MIRROS Trial – Relpased and Refractory AML



Primary Outcome
Overall Survival in ITT (p53 WT)

Secondary Outcomes
CR
Overall Response Rate
MRD assessment

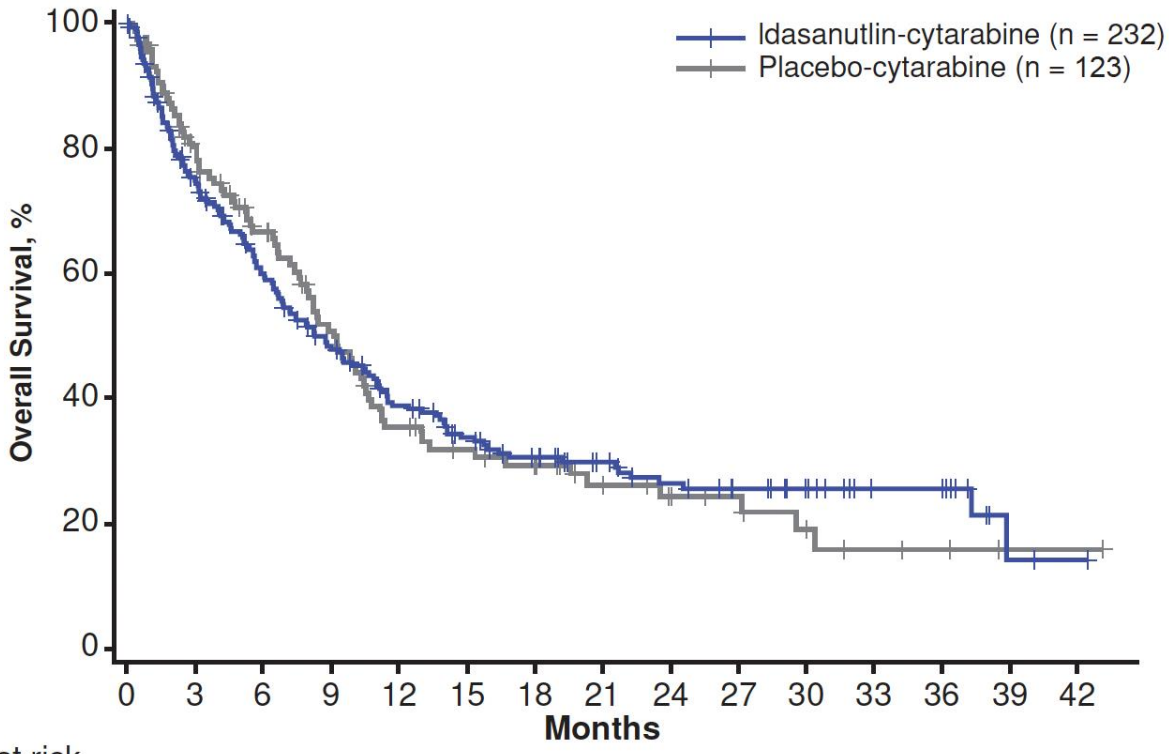
Randomized Study of Idasanutlin/Chemo in R/R AML

	Idasa-C (n = 232)	Placebo-C (n = 123)	Odds ratio or hazard ratio (95% CI)	*p* value (HR)
ORR [CR, CRp, CRi], n (%)	90 (38.8)	27 (22.0)	2.25 (1.36-3.72)	.0008
CR, n (%)*	47 (20.3)	21 (17.1)	1.23 (0.70-2.18)	.408
CRp, n (%)	23 (9.9)	4 (3.3)	—	—
CRi, n (%)	20 (8.6)	2 (1.6)	—	—
Median EFS, wk†	6.3	4.4	0.65	.0005
	n = 28	n = 10		
DOR, median (95% CI), mo‡	13.9 (6.4, 21.1)	29.4 (8.2, NE)	—	—

Konopleva M, et. al, Blood Advances 2022

Randomized Study of Idasanutlin/Chemo in R/R AML

Figure 2



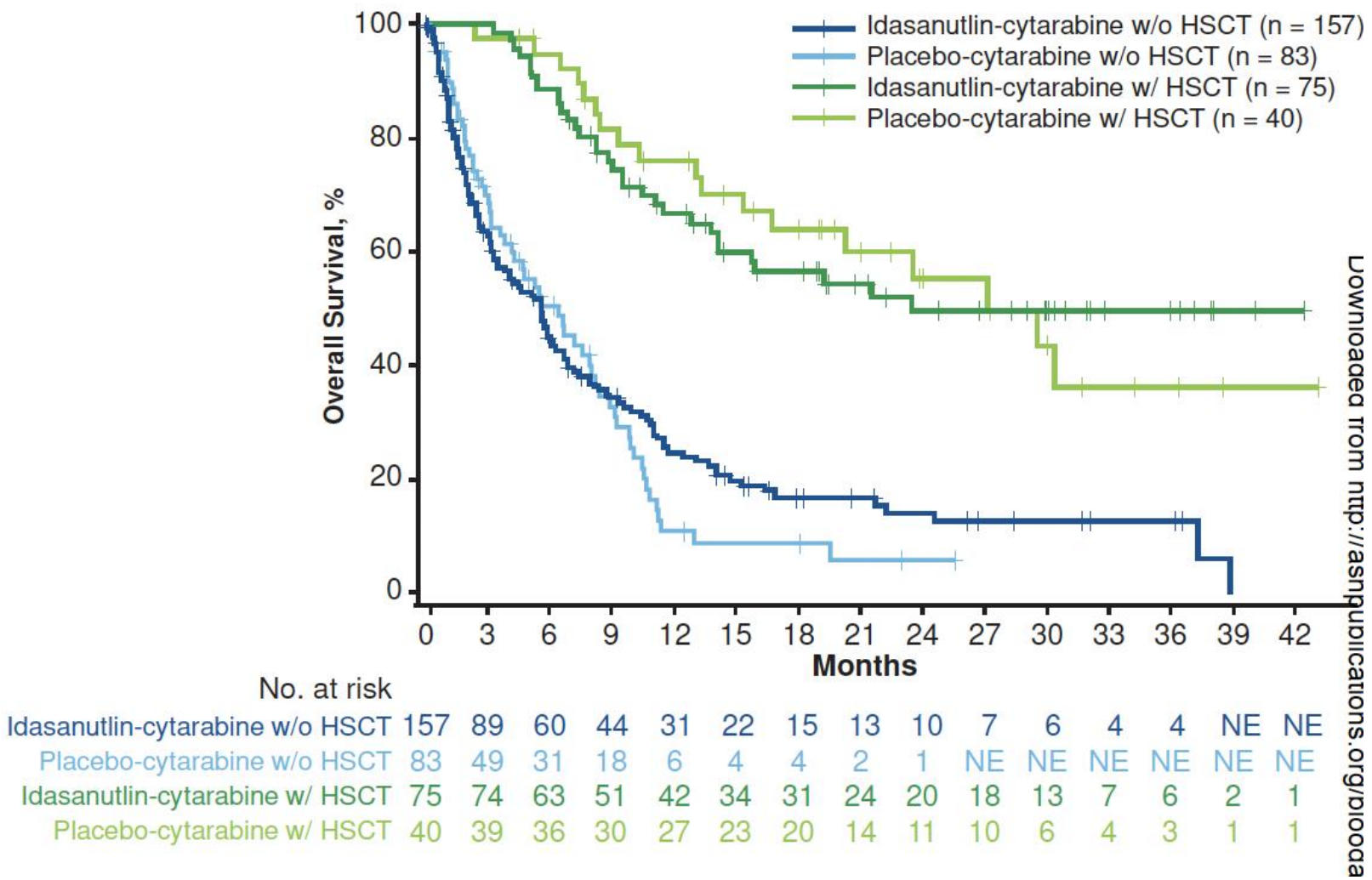
No. at risk

Idasantulin-cytarabine	232	163	123	95	73	56	46	37	30	25	19	11	10	2	1
Placebo-cytarabine	123	88	67	48	33	27	24	16	12	10	6	4	3	1	1

Konopleva M, et. al, Blood Advances 2022

Randomized Study of Idasanutlin/Chemo in R/R AML

3A



Konopleva M, et. al, Blood Advances 2022

Randomized Study of Idasanutlin/Chemo in R/R AML

- **Authors of the MIRROS trial offer the following reasons that no benefit to Idasanutlin with chemo in R/R AML.**
  - **Increased toxicity (neutropenia) in the idasanutlin arm**
  - **Higher rate of gastrointestinal AEs in the idasanutlin arm**
  - **Higher use of salvage chemotherapy in placebo arm**
  - **Higher use of consolidation in placebo arm**

- **What authors don't say is that perhaps MDM2 inhibition is only relevant in a subset of patients with WT p53. To improve outcomes there needs to be a a better patient selection strategy.**

Konopleva M, et. al, Blood Advances 2022

Conclusions

- MDM2, a negative regulator of p53, can be inhibited and leads to "reactivation" of WT p53 to induce apoptosis in myeloid leukemia cells.
- Single agent MDM2 inhibitors are active in relapsed and refractory AML, which is a remarkable feat!
- However, in a randomized phase III study adding an MDM2 inhibitor to cytarabine for patients with relapsed and refractory AML, there was no benefit in overall survival compared to cytarabine and placebo (despite increased overall response rates).
- Multiple studies are evaluating the use of various MDM2 inhibitors in a variety of clinical settings. Both with intensive chemotherapy for newly diagnosed AML and with HMA/venetoclax
- The key to success? Finding the right patient population amongst those pts who are p53 wild type!

Thank You!

steine@mskcc.org