

Abstract #640

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A Phase 1/2 Study of the Oral Novel JAK1 Inhibitor INCB052793 as Monotherapy and in Combination With Standard Therapies in Patients with Advanced Hematologic Malignancies

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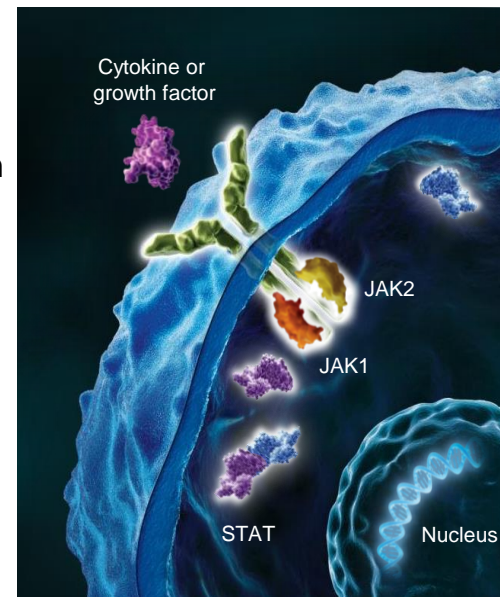
Rationale for Targeting JAK1

JAK signaling in AML/MDS

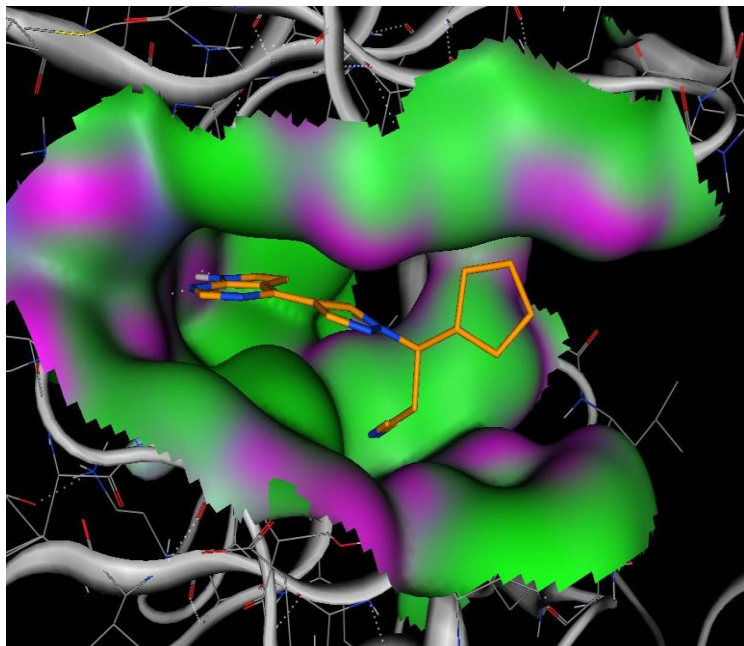
- Cytokine stimulation induces proliferation and growth of AML blasts; high levels of cytokines have been associated with poor prognosis in patients with AML
- Blocking JAK signaling can inhibit AML cell proliferation through STAT3/5 inhibition and induction of caspase-dependent apoptosis¹
- Patients with high-risk MDS who failed prior therapy with hypomethylating agents have no available standard-of-care; OS is often <6 months
 - Median OS: 5.6–5.8 months after AZA failure^{2,3}; 4.3 months after decitabine failure⁴
 - Median OS: 3.4 months for patients with MDS who developed secondary AML after AZA failure⁵

INCB052793: preclinical antitumor activity

- INCB052793 alone and combined with standard-of-care agents resulted in tumor inhibition in cellular and murine models of multiple myeloma⁶



INCB052793: Potent and Selective JAK1 Inhibitor¹⁻⁵



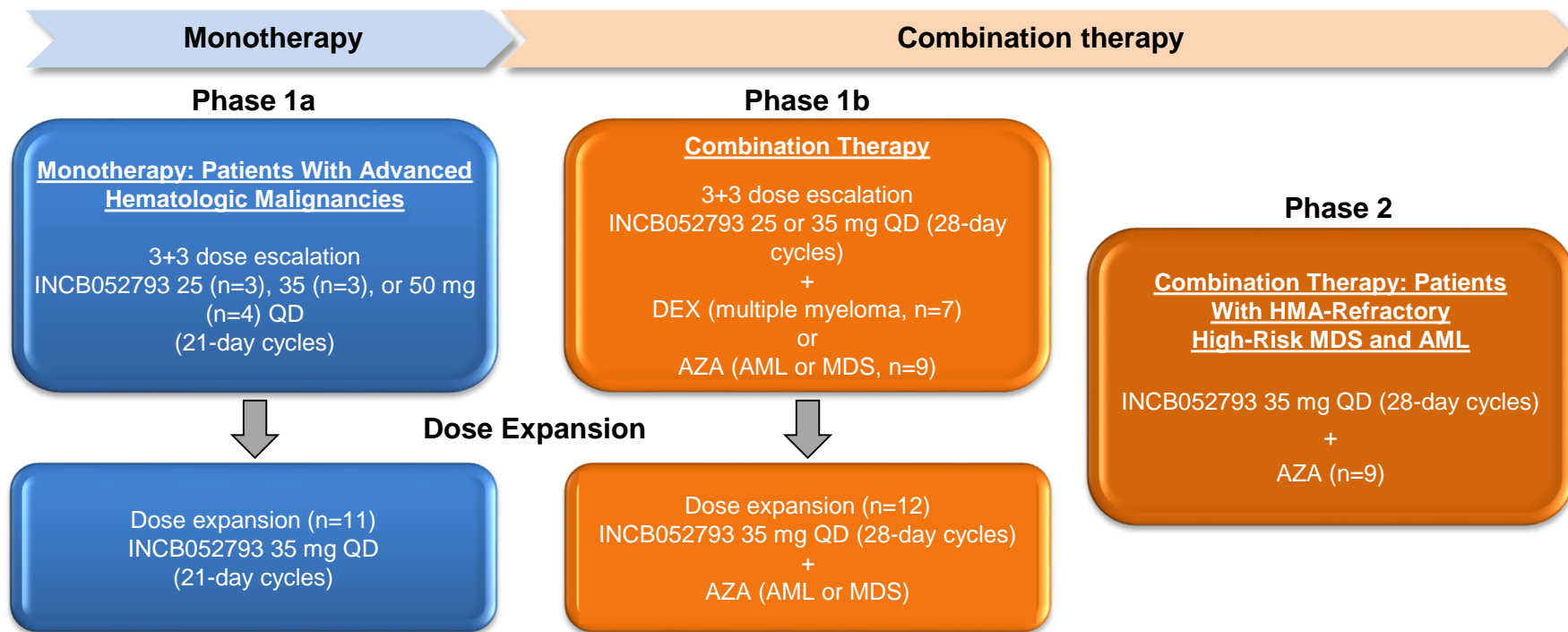
	Enzyme Assays	
	Mean IC50 (nM) ^{1,2}	Fold Selectivity for JAK1
JAK1	1.8 ± 0.32	-
JAK2	277 ± 101	154
JAK3	1548	860
TYK2	32	18
	Cellular Assays	
	Mean IC50 (nM) ^{1,2}	Fold Selectivity for JAK1
Whole Blood JAK1 (IL-6)	144 ± 8	-
Whole Blood JAK2 (TPO)	14110 ± 349	98

10 nM to 100 nM potentially inhibited production of proinflammatory factors (IL-17, IL-23 and MCP-1)

IL, interleukin; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein 1; TPO, thrombopoietin; TYK2, tyrosine kinase 2.

1. Data on file. Incyte Corporation; 2. Schindler C, et al. *J Biol Chem*. 2007; 282:20059-20063; 3. Baker SJ, et al. *Oncogene*. 2007;26(47):6724-6737; 4. O'Shea JJ, et al. *Nat Rev Drug Discov*. 2004;3(7):555-564; 5. Ozaki K, et al. *J Bio Chem*. 2004;277:29355-29358.

INCB052793-101: Phase 1/2 Study Design



Preliminary findings from data cutoff Nov 3, 2017.

AML, acute myeloid leukemia; AZA, azacitidine 75 mg/m² subcutaneously; DEX, dexamethasone 40 mg orally weekly; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; QD, once daily.

Study Objectives

Primary

- Phase 1a: safety and tolerability of INCB052793 in advanced hematologic malignancies; dose selection for expansion
- Phase 1b: safety and tolerability of INCB052793 in combination with standard therapies
- Phase 2: efficacy of INCB052793 plus AZA in HMA-refractory AML and high-risk MDS

Secondary

- Efficacy of INCB052793
- Safety and tolerability of INCB052793 plus AZA in HMA-refractory AML and high-risk MDS
- PK of INCB052793 monotherapy and combination therapy with AZA

Exploratory

- PD of INCB052793
- DOR, PFS, and OS of INCB052793 monotherapy and combination
- Biomarkers

AML, acute myeloid leukemia; AZA, azacitidine; DOR, duration of response; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; OS, overall survival; PFS, progression-free survival; PD, pharmacodynamics; PK, pharmacokinetics.

Methods

- Safety and tolerability
- PK assessments: INCB052793 monotherapy and combination therapy with AZA
- Efficacy: investigator-assessed response and pre-specified response criteria
 - Patients with multiple myeloma: disease assessments on Day 1 of each cycle for first 12 months, every 12 weeks (4 cycles) thereafter, and EOT
 - Patients with AML, MDS, or MPN: bone marrow assessments at baseline; 3, 6, and 12 months after Day 1; every 12 months thereafter; and EOT
- MTD definition: 1 dose level below that at which $\geq 1/3$ of patients in a cohort experienced DLTs
- Selection of recommended phase 2 dose: based on safety and PD effect during dose-escalation

AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; DLT, dose-limiting toxicity; EOT, end of treatment; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics.

Key Eligibility Criteria

Inclusion

Phase 1a monotherapy

- Any relapsed or refractory hematologic malignancy

Phase 1b combination therapy

- Newly diagnosed or previously treated AML, MDS (IPSS Int-1 or higher), or MDS/MPN overlap syndrome
- Multiple myeloma relapsed from or refractory to ≥ 2 prior treatment regimens

Phase 2 combination therapy

- AML or high-risk MDS with prior HMA treatment failure

Exclusion

- Prior treatment with a selective JAK1 inhibitor (prior ruxolitinib permitted for phase 1 only)

Patient Demographics and Baseline Characteristics

Characteristic	Phase 1a	Phase 1b			Phase 2
	INCB052793 Monotherapy (n=11)	INCB052793 + DEX (n=7)	INCB052793 (25 mg) + AZA (n=5)	INCB052793 (35 mg)* + AZA (n=16)	INCB052793 + AZA (n=9)
Median age (range), y	56 (52–68)	64 (41–81)	64 (39–75)	66 (27–82)	70 (60–78)
Male, n (%)	9 (82)	7 (100)	2 (40)	9 (56)	7 (78)
Primary diagnosis, n (%)					
AML	0	0	4 (80)	8 (50)	6 (67)
CLL/DLBCL	3 (27)	0	0	0	0
Hodgkin's lymphoma	1 (9)	0	0	0	0
MDS	0	0	0	7 (44)	3 (33)
MDS/MPN	4 (36)	0	1 (20)	1 (6)	0
Multiple myeloma	3 (27)	7 (100)	0	0	0
Previous HMA treatment	1 (9)	0	1 (20)	9 (56)	9 (100)
Azacitidine	1(9)	0	0	7 (44)	5 (56)
Decitabine	0	0	1 (20)	3 (19)	5 (56)

* Includes patients from dose-escalation and dose-expansion studies.

AML, acute myeloid leukemia; AZA, azacitidine 75 mg/m² subcutaneously; CLL, chronic lymphocytic leukemia; DEX, dexamethasone 40 mg orally weekly; DLBCL, diffuse large B-cell lymphoma; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

Selection of Recommended Phase 2 Dose for INCB052793

- No dose limiting toxicities were observed at any dose level
- 35 mg QD was selected as recommended phase 2 dose based on:
 - Pharmacodynamic effect: pSTAT3 inhibition (IL-6) in peripheral blood mononuclear cells was observed at all dose levels
 - Thrombocytopenia observed in solid tumor patients at higher doses

INCB052793-Related Non-Hematologic AEs (Any Grade) Observed in ≥15% of Patients in Any Individual Cohort

Treatment-Related AE, n (%)	INCB052793 Monotherapy (n=11)	INCB052793 + DEX (n=7)	INCB052793 + AZA (n=30)
Nausea	3 (27)	0	8 (27)
Aspartate aminotransferase increased	0	1 (14)	9 (30)
Fatigue	1 (9)	1 (14)	8 (27)
Alanine aminotransferase increased	0	0	8 (27)
Vomiting	3 (27)	0	3 (10)
Constipation	0	0	5 (17)
Pneumonia	0	2 (29)	0
Sepsis	0	2 (29)	0

- Fatal AEs included respiratory failure (INCB052793 monotherapy; n=1), respiratory arrest (INCB052793 + DEX; n=1), and acute respiratory distress syndrome (INCB052793 + AZA; n=1)
- No fatal AEs were deemed INCB052793-related

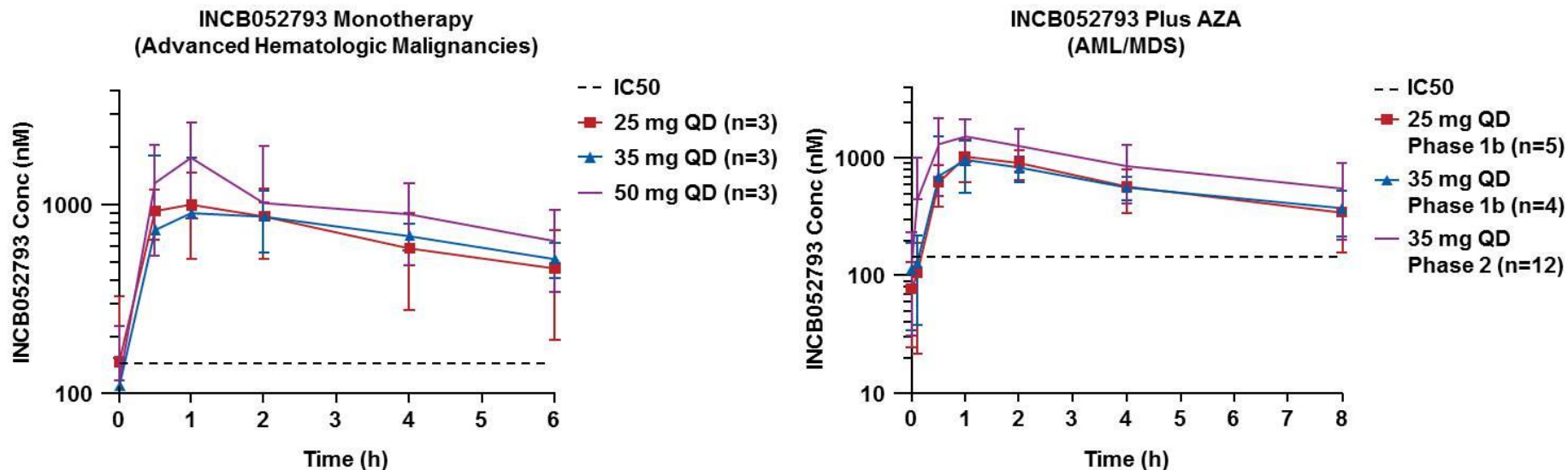
Treatment-Emergent Hematologic AEs Observed in $\geq 15\%$ of Patients in Any Individual Cohort

Treatment-Emergent AE, n (%)	INCB052793 Monotherapy (n=11)		INCB052793 + DEX (n=7)		INCB052793 + AZA (n=30)		Historical AZA in AML (n=236) ¹
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Grade ≥ 3
Anemia	4 (36)	2 (18)	3 (43)	2 (29)	11 (37)	7 (23)	37 (16)
Thrombocytopenia	5 (11)	3 (11)	4 (7)	3 (7)	15 (30)	14 (30)	56 (24)
Neutropenia	2 (11)	0	2 (7)	2 (7)	10 (30)	10 (30)	62 (26)
Febrile neutropenia	1 (9)	1 (9)	0	0	17 (57)	16 (53)	66 (28)

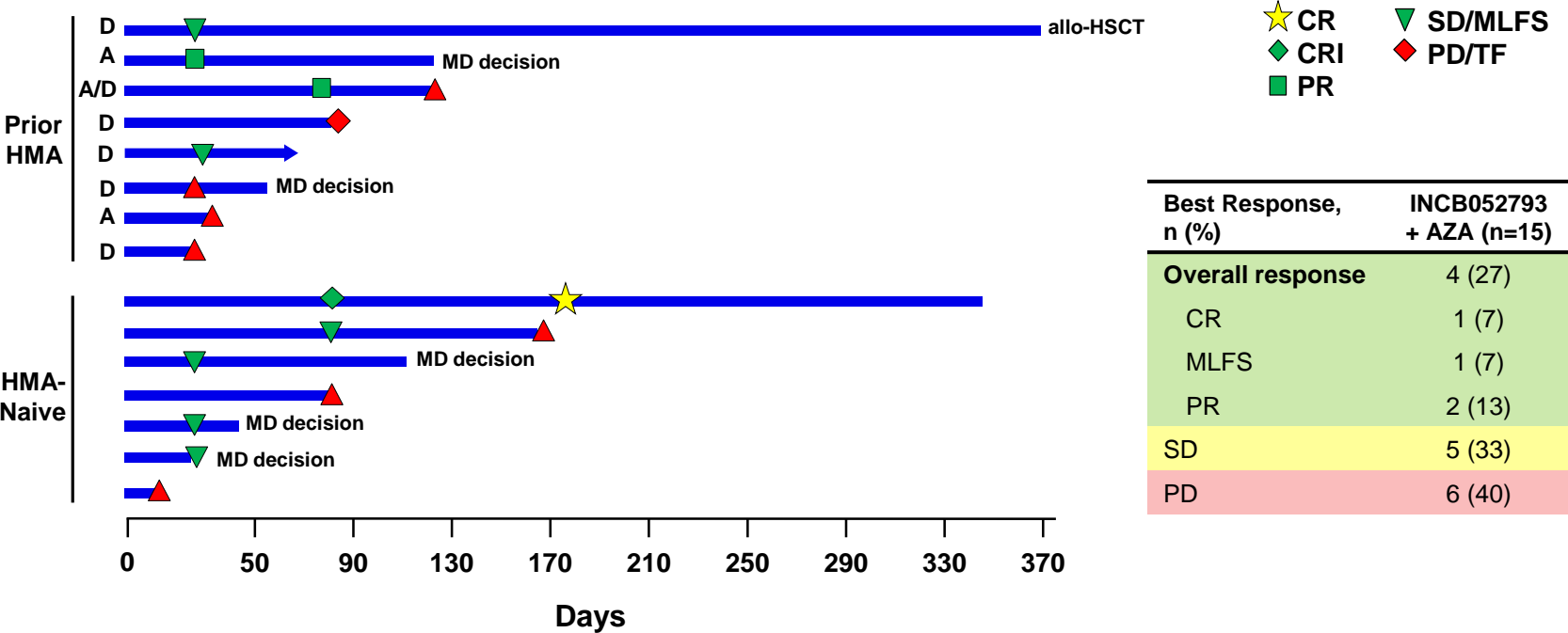
AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine 75 mg/m² subcutaneously; DEX, dexamethasone 40 mg orally weekly.

1. Dombret H, et al. *Blood*. 2015;126(3):291-299.

Pharmacokinetic Analyses



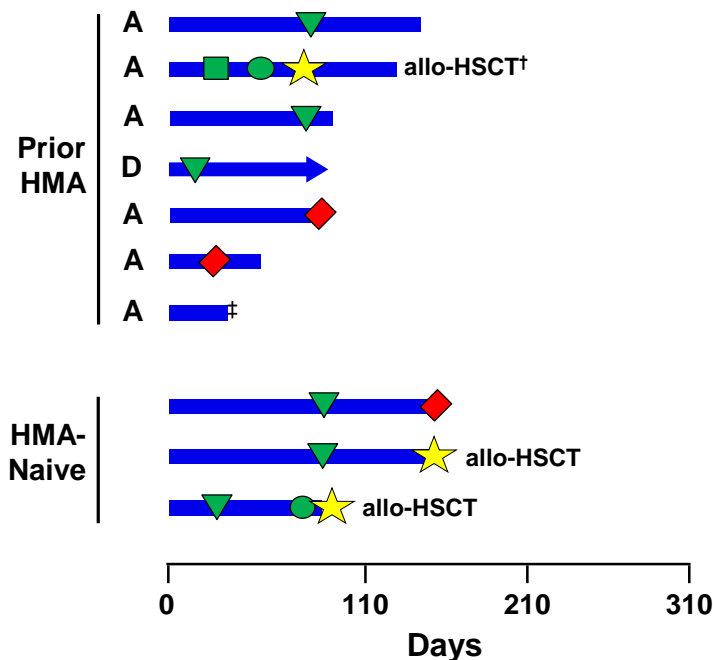
Best Response at Data Cutoff: AML*



* Per International Working Group response criteria for AML.

A, azacitidine; allo-HSCT, allogeneic hematopoietic stem sell transplant; AML, acute myeloid leukemia; AZA, azacitidine 75 mg/m² subcutaneously; CR, complete remission; CRI, complete remission with incomplete blood count recovery; D, decitabine; HMA, hypomethylating agent; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial remission; SD, stable disease; TF, treatment failure.

Best Response at Data Cutoff: MDS*



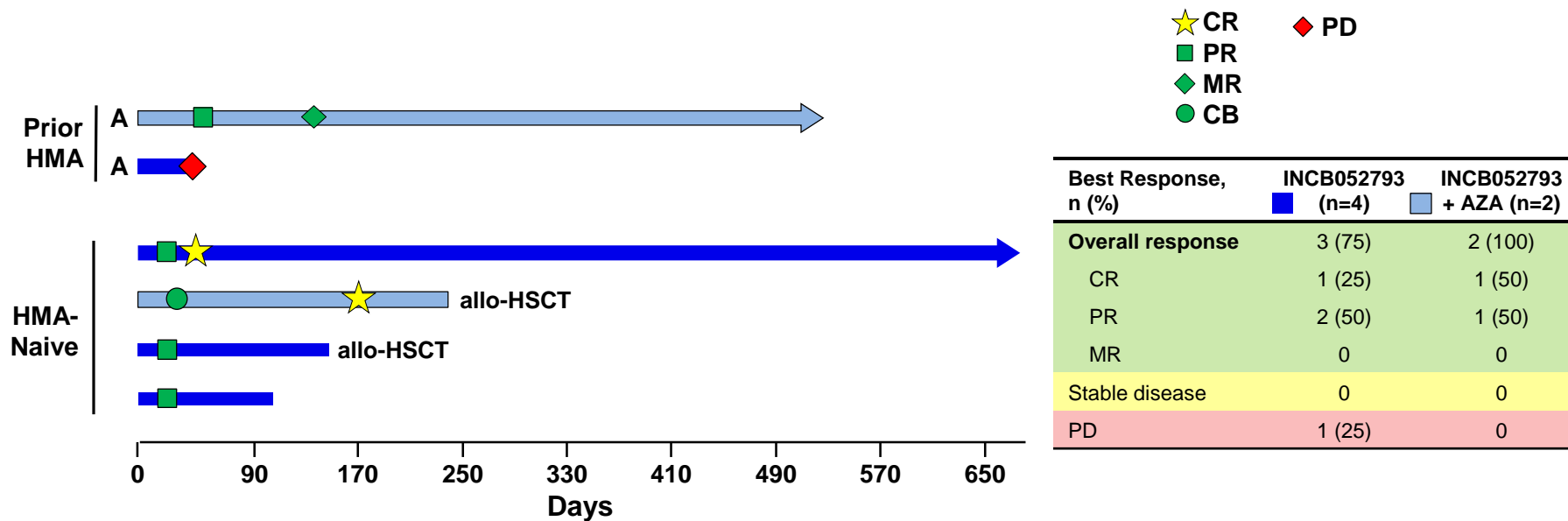
★ CR
 ■ PR
 ● MCR
 ▼ SD
 ◆ PD

Best Response, n (%)	INCB052793 + AZA (n=10)
Overall response	3 (30)
CR	3 (30)
PR	0
MCR	0
SD	4 (40)
PD	2 (20)
Missing [‡]	1 (10)

* Per International Working Group response criteria for MDS. [†] Patient received end of treatment donor leukocyte infusion. [‡] Patient withdrawn due to AE.

A, azacitidine; AE, adverse event; allo-HSCT, allogeneic hematopoietic stem cell transplant; AZA, azacitidine 75 mg/m² subcutaneously; CR, complete remission; D, decitabine; HMA, hypomethylating agent; MCR, marrow complete remission; MDS, myelodysplastic syndrome; PD, progressive disease; PR, partial remission; SD, stable disease.

Best Response at Data Cutoff: MDS/MPN*



* Per International Working Group response criteria for MDS and International Consortium Proposal of Uniform Response criteria for MDS/MPN in adults. A, azacitidine; allo-HSCT, allogeneic hematopoietic stem cell transplant; AZA, azacitidine 75 mg/m² subcutaneously; CB, clinical benefit; CR, complete remission; HMA, hypomethylating agent; MR, marrow response; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; PD, disease progression; PR, partial remission.

Conclusions

- Preliminary findings from this phase 1/2 trial indicate that INCB052793 has clinical activity, especially in combination with AZA, in patients with advanced myeloid malignancies, including patients relapsed from/refractory to HMA treatment
- No signals of activity were observed in multiple myeloma or lymphoid malignancies, with 2 of 7 patients having a minimal response
- These data indicate that INCB052793 might (re)-sensitize HMA-refractory or relapsed patients to the effects of HMAs
- Enrollment is ongoing for the phase 2 portion of the study

Acknowledgments

- We thank the patients and their families