blood®

AMERICAN SOCIETY OF HEMATOLOGY®

ASH Abstracts
2020

Reprinted from:

2020 ASH Annual Meeting Abstracts
Blood 2020

Selected abstract
Abstract #465

62nd ASH Annual Meeting and Exposition
December 5-8, 2020

Abstract 465

Interim Results of the Phase I/II Study of the Ponatinib, Venetoclax and Dexamethasone for Patients with Relapsed or Refractory Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

Nicholas J. Short, MD[1], *Marina Konopleva, MD, PhD[1], Elias Jabbour, MD[1], Tapan M. Kadia, MD[1], Naval Daver, MD[2], Robin Cook, RN[1*], Nitin Jain, MD[1] and Farhad Ravandi, MBBS[1]*

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

[2]Department of Leukemia, The University of Texas, M.D. Anderson Cancer Center, Houston, TX

Background: Patients (pts) with relapsed/refractory (R/R) Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) have poor outcomes, and there is no clear standard of care. While the pan-BCR-ABL tyrosine kinase inhibitor (TKI) ponatinib is highly active in Ph+ ALL, single-agent responses are short-lived. Ph+ ALL is highly dependent on Bcl-2 for survival, suggesting a possible therapeutic role for venetoclax in this disease. Preclinical studies suggest that ponatinib and venetoclax result in synergistic anti-leukemia activity through inhibition of the Lck/Yes novel (LYN) tyrosine kinase by ponatinib and its downstream prevention of Mcl-1 upregulation (Leonard JT et al. *Sci Trans Med* 2016;8(354)). We therefore designed a phase I/II study to evaluate the safety and efficacy of the combination of ponatinib, venetoclax, and dexamethasone in pts with R/R Ph+ ALL.

Methods: Adults ≥18 years of age with R/R Ph+ ALL or chronic myeloid leukemia in lymphoid blast phase who had received at least 1 prior BCR-ABL TKI were eligible. For cycle 1, pts without recent ponatinib exposure (i.e. within 2 weeks) received a 7-day run-in of ponatinib monotherapy with ponatinib given at a dose of 45 mg daily on days 1–35, venetoclax daily on days 8–35 (up to 400 mg in dose level 1; up to 800 mg in dose level 2), and dexamethasone 40 mg IV/PO daily on days 8–11. Pts with recent ponatinib exposure received all three agents beginning on day 1 of cycle 1. For cycles 2+, all pts received venetoclax 400–800 mg daily on days 1–28, ponatinib daily on days 1–28, and dexamethasone 40 mg IV/PO daily on days 1–4. The dose of ponatinib was adjusted according to the remission status, with pts who had not achieved CR/CRi receiving 45 mg daily, those in CR/CRi but still with detectable *BCR-ABL1* by PCR receiving 30 mg daily, and those in complete molecular response (CMR) receiving 15 mg daily. Each cycle was 28 days. All pts received 8 administrations of intrathecal chemotherapy. Up to 8 doses of rituximab were added for CD20+ disease. The primary safety objective was to determine the maximum tolerated dose (MTD) of venetoclax in combination with ponatinib and dexamethasone, and the primary efficacy objective was to determine the CR/CRi rate of the regimen.

Results: To date, 8 pts have been enrolled, and 6 pts have been treated and are evaluable for safety and efficacy. Three pts received venetoclax 400 mg daily, and 3 pts received venetoclax 800 mg daily. The median number of courses given was 3 (range, 1–8). No dose-limiting toxicities have been observed, and the MTD has not yet been reached. Non-hematologic grade 3–4 adverse events included: ALT/AST elevation and febrile neutropenia in 2 pts each, and GI hemorrhage, altered mental status, lower extremity weakness, and infection in 1 pt each. There were no early deaths.

The characteristics of the treated pts and their responses are shown in **Table 1.** The median age was 53 years (range, 27–73 years). All pts had received prior allogeneic hematopoietic stem cell transplant. The median number of prior therapies was 3.5 (range, 2–4) and median number of prior TKIs was 2 (range, 1–3). Five pts (83%) had received prior ponatinib and 4 (67%) had received blinatumomab. Three pts (50%) had extramedullary disease, and 3 of 5 pts (60%) who underwent *ABL1* kinase domain testing had a detectable T315I mutation.

Overall, 3 pts (50%) achieved CR. Notably, all pts who achieved CR received the 800 mg daily dose of venetoclax. Two responses were in pts who had received prior ponatinib, and 2 were in pts who had received prior blinatumomab. One pt who received venetoclax 400 mg daily had bone marrow blast decrease from 94% to 6% after cycle 1 along with full neutrophil recovery and platelet recovery to 97 x 10^9/L (though not meeting formal criteria for partial remission). Among the 3 pts who achieved CR, all achieved CMR and remain on study. At last follow-up, all responding pts remain

**signifies non-member of ASH*

in ongoing CMR with remission durations of 1 month, 5 months, and 8 months, respectively. With a median duration of follow-up of 8.6 months, the median OS has not been reached, and the estimated 9-month OS rate is 60%.

Conclusions: The chemotherapy-free, oral combination of ponatinib, venetoclax and dexamethasone appears safe and has promising early efficacy in this heavily pretreated population of pts with R/R Ph+ ALL, with all 3 pts who received venetoclax 800 mg daily achieving CMR. The MTD has not yet been reached, and the study continues to accrue.

Table 1. Patient characteristics and responses

Pt#	Age (years)	Extramedullary leukemia	Prior HSCT	Prior ponatinib	Prior blinatumomab	*ABL1* KD mutation(s)	Venetoclax dose	# of cycles received	Response	MRD response
1	35	No	Yes	Yes	Yes	T315l, F359V	400 mg	3	No response	N/A
2	27	No	Yes	Yes	Yes	T315l, E255V	400 mg	3	No response	N/A
3	73	Yes	Yes	Yes	No	T315l	400 mg	2	No response	N/A
4	72	No	Yes	No	Yes	Q252H, V299L	800 mg	7+	CR	CMR
5	36	Yes	Yes	Yes	Yes	Not evaluated	800 mg	8+	CR	CMR
6	71	Yes	Yes	Yes	No	E255V	800 mg	2+	CR	CMR

Disclosures: Short: *AstraZeneca:* Consultancy; *Takeda Oncology:* Consultancy, Honoraria, Research Funding; *Amgen:* Honoraria; *Astellas:* Research Funding. **Konopleva:** *Reata Pharmaceutical Inc.;:* Patents & Royalties: patents and royalties with patent US 7,795,305 B2 on CDDO-compounds and combination therapies, licensed to Reata Pharmaceutical; *Forty-Seven:* Consultancy, Research Funding; *Ablynx:* Research Funding; *Stemline Therapeutics:* Consultancy, Research Funding; *Sanofi:* Research Funding; *Calithera:* Research Funding; *Rafael Pharmaceutical:* Research Funding; *Ascentage:* Research Funding; *Agios:* Research Funding; *AstraZeneca:* Research Funding; *F. Hoffmann La-Roche:* Consultancy, Research Funding; *Genentech:* Consultancy, Research Funding; *Cellectis:* Research Funding; *AbbVie:* Consultancy, Research Funding; *Kisoji:* Consultancy; *Eli Lilly:* Research Funding; *Amgen:* Consultancy. **Jabbour:** *Genentech:* Other: Advisory role, Research Funding; *AbbVie:* Other: Advisory role, Research Funding; *Adaptive Biotechnologies:* Other: Advisory role, Research Funding; *Takeda:* Other: Advisory role, Research Funding; *Pfizer:* Other: Advisory role, Research Funding; *BMS:* Other: Advisory role, Research Funding; *Amgen:* Other: Advisory role, Research Funding. **Kadia:** *Pfizer:* Honoraria, Research Funding; *Astra Zeneca:* Research Funding; *Pulmotec:* Research Funding; *Abbvie:* Honoraria, Research Funding; *Cyclacel:* Research Funding; *Ascentage:* Research Funding; *Incyte:* Research Funding; *BMS:* Honoraria, Research Funding; *Amgen:* Research Funding; *Celgene:* Research Funding; *Astellas:* Research Funding; *Genentech:* Honoraria, Research Funding; *JAZZ:* Honoraria, Research Funding; *Cellenkos:* Research Funding; *Novartis:* Honoraria. **Daver:** *Daiichi Sankyo:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Gilead:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Amgen:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Trovagene:* Research Funding; *Fate Therapeutics:* Research Funding; *ImmunoGen:* Research Funding; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Celgene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Jazz:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Trillium:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Syndax:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *KITE:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Agios:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Bristol-Myers Squibb:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pfizer:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Karyopharm:* Research Funding; *Servier:* Research Funding; *Genentech:* Research Funding; *AbbVie:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Astellas:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novimmune:* Research Funding. **Jain:** *Genentech:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *AbbVie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pharmacyclics:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *BMS:* Research Funding; *AstraZeneca:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pfizer:* Research Funding; *ADC Therapeutics:* Research Funding; *Incyte:* Research Funding; *Servier:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Cellectis:* Research Funding; *Verastem:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Adaptive Biotechnologies:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Precision Bioscienes:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Fate Therapeutics:* Research Funding; *Aprea Therapeutics:* Research Funding; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *TG Therapeutics:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Ravandi:** *Amgen:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria; *Celgene:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria, Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *Xencor:* Consultancy, Honoraria, Research Funding; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Astellas:* Consultancy, Honoraria, Research Funding; *Orsenix:* Consultancy, Honoraria, Research Funding; *Macrogenics:* Research Funding.

Aschauer Straße 30, 81549 München, Germany
Tel: +49 89 203043-1474, Fax: +49 89 203043-1480
www.springerhealthcare.com

Part of the Springer Nature group

Printed in Germany

ICY20DV005124