Venetoclax in combination with a pediatric-inspired regimen for the treatment of newly diagnosed adults with Philadelphia chromosome-negative acute lymphoblastic leukemia

Ibrahim Aldoss,[1] Jianying Zhang,[2] Kathryn Shimamoto,[3] Caner Saygin,[3] Marjorie Robbins,[4] Vaibhav Agrawal,[1] Ahmed Aribi,[1] Diren Arda Karaoglu,[3] Hoda Pourhassan,[1] Paul Koller,[1] Haris Ali,[1] Amanda Blackmon,[1] Salman Otoukesh,[1] Karamjeet Sandhu,[1] Brian Ball,[1] Andrew S. Artz,[1] Monzr M. Al Malki,[1] Amandeep Salhotra,[1] Jose Tinajero,[5] Zhaohui Gu,[6,7] Ian Lagman,[1] Michelle Velasquez,[1] Jacqueline Dang,[1] Pamela S. Becker,[1,8] Michelle Afkhami,[9] Lucy Ghoda,[6,8,10] Wendy Stock,[3] Stephen J. Forman,[1] Anthony Stein,[1] Guido Marcucci[1,6,8] and Vinod Pullarkat[1]

[1]Department of Hematology & Hematopoietic Cell Transplantation, City of Hope, Duarte, CA; [2]Department of Biostatistics, City of Hope, Duarte, CA; [3]Department of Medicine-Hematology and Oncology, University of Chicago, Chicago, IL; [4]Clinical Translational Project Development, City of Hope, Duarte, CA; [5]Department of Pharmacy, City of Hope, Duarte, CA; [6]Beckman Research Institute, City of Hope, Duarte, CA; [7]Computational and Quantitative Medicine, City of Hope, Duarte, CA; [8]Hematological Malignancies Translational Science, City of Hope, Duarte, CA; [9]Department of Pathology, City of Hope, Duarte, CA and [10]Department of Research Business Operations, City of Hope, Duarte, CA, USA

Correspondence: I. Aldoss
ialdoss@coh.org

Received: August 8, 2024.
Accepted: October 31, 2024.
Early view: November 7, 2024.

https://doi.org/10.3324/haematol.2024.286427

Supplementary Table 1. Treatment Regimen

Induction (Cycle 1)

Drug	Route	Dosage	Days	Important Notes
Intrathecal Cytarabine (IT Ara-C)	IT	70 mg	1	May be given prior to registration for patient convenience at the time of diagnostic bone marrow or venous line placement to avoid a second lumbar puncture.
Venetoclax *(INV)*	PO	400 mg (dose level 1) 200 mg (dose level -1)	1-14	Ramp up dose level 1: 100 mg on Day 1, 200 mg on Day 2, 400 mg on Day 3 then daily to Day 14. Ramp up dose level -1: 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3 then daily to Day 14. Appropriate dose adjustments will be made for concomitant use of CYP3A4 inhibitors (see **Section 7.3**).
Prednisone	PO	30 mg/m^2/dose BID	1-28	Total daily dose: 60 mg/m2/day. May give IV methylprednisolone at 80% of PO prednisone dose.
Vincristine	IV	1.5 mg/m^2	1, 8, 15 & 22	Maximum dose: 2 mg
Daunorubicin	IV	25 mg/m^2	1, 8, 15 & 22	
PEGaspargase*	IM or IV	2000 IU/m^2	4	*Calaspargase pegol may be utilized instead of PEGaspargase only for age < 22 years (described below). **Patients ≥ 22 y.o. must receive PEGaspargase.** Maximum dose: 3750 IU Dose delay to day 15 on PI discretion. For patients with BMI ≥ 30 Kg/m^2 or age ≥ 40 years, the dose will be 1000 IU/m^2 Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to PEGaspargase. Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity.
Calaspargase pegol*	IV	2,500 units/m^2	4	***Calaspargase pegol** may be utilized instead of PEGaspargase **ONLY for age < 22 years**. Patients ≥ 22 y.o. must receive PEGaspargase as described above. Maximum dose: 3750 IU Dose delay to day 15 on PI discretion. For patients with BMI ≥ 30 Kg/m^2, the dose will be 1000 IU/m^2 Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to calaspargase pegol. Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity.
Intrathecal Methotrexate (IT MTX)	IT	15 mg	8, 15*, 22* & 29	*CNS3 patients only Send CSF for cell count and cytospin. Patients should remain in a horizontal position for at least 60 mins following administration of IT chemotherapy to enhance drug delivery to the head.

***Either PEGaspargase OR calaspargase pegol to be used depending on age of patient.**

- Calaspargase pegol < 22 years

- PEGaspargase ≥ 22 years

Extended Induction (if required) (Cycle 1A)

Extended Remission Induction Therapy is intended ONLY for patients with Day 29 M2 marrow (>5% lymphoblasts). Patients meeting these criteria are to begin Course 1A as soon as possible.

Drug	Route	Dosage	Days	Important Notes
Venetoclax (INV)	PO	400 mg (dose level 1) 200 mg (dose level -1)	1-7	Appropriate dose adjustments will be made for concomitant use of CYP3A4 inhibitors (see **Section 7.3**).
Prednisone	PO	30 mg/m^2/dose BID	1-14	Total daily dose: 60 mg/m2/day. May give IV methylprednisolone at 80% of PO prednisone dose.
Vincristine	IV	1.5 mg/m^2	1 & 8	Maximum dose: 2 mg
Daunorubicin	IV	25 mg/m^2	1	
PEGaspargase*	IM or IV	2000 IU/m^2	4	*Calaspargase pegol may be utilized instead of PEGaspargase only for age < 22 years (described below). **Patients ≥ 22 y.o. must receive PEGaspargase.** Maximum dose: 3750 IU For patients with BMI ≥ 30 Kg/m^2 or age ≥ 40 years, the dose will be 1000 IU/m^2 Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to PEGaspargase. Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity.
Calaspargase pegol*	IV	2,500 units/m^2	4	***Calaspargase pegol** may be utilized instead of PEGaspargase **ONLY for age < 22 years.** Patients ≥ 22 y.o. must receive PEGaspargase as described above. Maximum dose: 3750 IU Dose delay to day 15 on PI discretion. For patients with BMI ≥ 30 Kg/m^2, the dose will be 1000 IU/m^2 Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to calaspargase pegol. Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity.

***Either PEGaspargase OR calaspargase pegol to be used depending on age of patient.**

- Calaspargase pegol < 22 years
- PEGaspargase ≥ 22 years

Consolidation (Cycle 2)

Patients must begin remission consolidation therapy within 7 days from remission marrow or when peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever is later.

Therapy should be interrupted for patients who are febrile, neutropenic and proven infected, and resumed at the same point when the signs of infection have abated. Otherwise, therapy should not be interrupted for myelosuppression alone except on Day 29. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL.

Drug	Route	Dosage	Days	Important Notes
Venetoclax (INV)	PO	400 mg (dose level 1) 200 mg (dose level -1)	1-14	Appropriate dose adjustments will be made for concomitant use of CYP3A4 inhibitors (see **Section 7.3**).
Cyclophosphamide	IV	1000 mg/m^2	1 & 29	

Cytarabine	IV or SC	75 mg/m^2	1-4, 8-11, 29-32 & 36-39	
Mercaptopurine (6-MP)	PO	60 mg/m^2	1-14 & 29-42	Take at the same time each day. See Section 7.3 for dose adjustments based on TMPT status. Adjust dose using 50 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. Do not escalate dose based on blood counts during this course.
Vincristine	IV	1.5 mg/m^2	15, 22, 43 & 50	Maximum dose: 2 mg
PEGaspargase*	IM or IV	2000 IU/m^2	15 & 43	*Calaspargase pegol may be utilized instead of PEGaspargase ONLY for age < 22 years (described below). **Patients ≥ 22 y.o. must receive PEGaspargase.** Maximum dose: 3750 IU For patients with BMI ≥ 30 Kg/m^2 or age ≥ 40 years, the dose will be 1000 IU/m^2 Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to PEGaspargase. Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity.
Calaspargase pegol*	IV	2,500 units/m^2	15 & 43	***Calaspargase pegol** may be utilized instead of PEGaspargase **ONLY for age < 22 years.** Patients ≥ 22 y.o. must receive PEGaspargase as described above. Maximum dose: 3750 IU Dose delay to day 15 on PI discretion. For patients with BMI ≥ 30 Kg/m^2, the dose will be 1000 IU/m^2 Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to calaspargase pegol. Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity.
Intrathecal Methotrexate (IT MTX)	IT	15 mg	1, 8, 15* & 22*	*Omit dose on Days 15 and 22 for CNS3 patients. Send CSF for cell count and cytospin. Patients should remain in a horizontal position for at least 60 mins following administration of IT chemotherapy to enhance drug delivery to the head.

***Either PEGaspargase OR calaspargase pegol to be used depending on age of patient.**

- Calaspargase pegol < 22 years
- PEGaspargase ≥ 22 years

Supplementary Table 2. All Grades and ≥ Grade 3 at Least Possibly Related Treatment Related Adverse Events (TRAE) to Either Study Drug and All Grades at Least Possibly Related TRAE to Venetoclax

Adverse Event	All Grades: AE at Least Possibly Related to Either Study Drug		All Grades : AE at Least Possibly Related to Venetoclax		Grade 3 or Higher: AE at Least Possibly Related to Either Study Drug	
	Count	Percentage	Count	Percentage	Count	Percentage
White blood cell decreased	23	95.8%	23	95.8%	23	95.8%
Neutrophil count decreased	20	83.3%	19	79.2%	20	83.3%
Lymphocyte count decreased	17	70.8%	12	50%	17	70.8%
Anemia	23	95.8%	20	83.3%	20	83.3%
Constipation	13	54.2%				
Thrombocytopenia	22	91.7%	19	79.2%	19	79.2%
Elevated LDH	10	41.7%	8	33.3%	1	4.2%
APTT prolonged	7	29.20%	1	4.2%	1	4.20%
Hypofibrinogenemia	7	29.2%			1	4.2%
Bruising	2	8.3%	1	4.2%		
Elevated ALT	22	91.7%			8	33.3%
Elevated AST	18	75%			5	20.8%
Hyperbilirubenemia	21	87.5%			9	37.5%
Elevated alkaline phosphatase	20	83.3%			1	4.2%
Pancreatitis	3	12.5%			3	12.5%
Thromboembolic event	3	12.50%			1	4.2%
Lipase increased	1	4.2%				
Nausea	19	79.2%	10	41.7%	5	20.8%
Vomiting	13	54.2%	6	25%		
Weight gain	4	16.7%				
Weight loss	1	4.2%				
Gastroesophageal reflux disease	1	4.2%				
Gastritis	1	4.2%				
Flatulence	3	12.50%	1	4.20%		
Dysgeusia	1	4.2%				
Diarrhea	1	4.2%				
Anorexia	6	25%	2	8.3%		
Bloating	4	16.7%	1	4.2%		
Dehydration	1	4.2%			1	4.2%
Peripheral neuropathy	18	75%			1	4.20%
Paresthesia	10	41.7%				
Myalgia	1	4.2%				

Headache	5	20.8%				
Insomnia	6	25%				
Hyperlipidemeia	1	4.2%			1	4.2%
Hypertriglyceridemia	5	20.8%			3	12.5%
Hypoalbuminemia	16	66.7%			2	8.3%
Hypoglycemia	3	12.5%				
Hyperglycemia	19	79.2%			4	16.7%
Hyponatremia	4	16.7%				
Hyperphosphatemia	16	66.7%	16	66.7%		
Glucosuria	1	4.2%				
Adrenal insufficiency	1	4.2%				
Generalized muscle weakness	3	12.5%				
Febrile neutropenia	3	12.5%	3	12.5%	3	12.5%
Fatigue	7	29.2%	6	25%		
Sepsis	4	16.7%	2	8.3%	4	16.7%
perianal abscess	1	4.2%				
Pneumonia	2	8.3%	2	8.3%	2	8.3%
Fever	2	8.3%	2	8.3%	2	8.3%
Enterocolitis infectious	2	8.3%			1	4.2%
Diastolic cardiomyopathy	1	4.2%				
Hypertension	5	20.8%			1	4.2%
Hypotension	2	8.3%	1	4.2%	2	8.3%
Dyspnea	2	8.3%				
Edema limbs	5	20.80%				
Dry mouth	1	4.2%				
Facial edema	1	4.2%				
Sore throat	1	4.2%				
Mucositis	3	12.5%	2	8.40%		
neck stiffness	1	4.2%				
Pain	7	29.2%	1	4.2%		
Skin rash or changes	2	8.40%				
Proteinuria	4	16.7%				
Hiccups	2	8.3%				
Hyperhidrosis	1	4.2%				
Dizziness	1	4.2%				
Visual changes	2	8.40%	1	4.20%		

Supplementary Figure 1. Oncoprint. Oncoprint illustrating the frequency of pre-treatment mutations and fusions for patients with Ph-like ALL and non-Ph-like ALL.