Call for Grants

The intent of this document is to encourage organizations with a focus in continuing medical education (CME) for healthcare professionals to submit an application for funding that is related to therapeutic approaches to front line treatment of Philadelphia Chromosome positive Acute Lymphoblastic Leukemia (Ph+ ALL) and patient risk factors for relapse in Ph+ALL.

Please note that applications must be submitted in English

Date: 12/15/2021
From: Global Medical Affairs, Takeda Oncology
Re: Philadelphia Chromosome positive Acute Lymphoblastic Leukemia Front Line Treatment and Risks for Relapse
Therapeutic Area: Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Background: The mission of the Takeda Oncology Call for Grants program is to partner with qualified organizations to meet unmet educational needs, encourage improvement in patient outcomes, and/or promote excellence in patient care. The initiatives funded are independent, meaning that projects are the full responsibility of the recipient organization. Takeda has no influence over any aspect of the project and only asks for reports about the results and impact of the projects in order to share them publicly.

Eligibility: Collaborations within institutions, and between different organizations, are encouraged. All partners must have a relevant role, with the requesting organization being the primary contact with Takeda and responsible for ensuring the grant agreement is adhered to. All funding will be awarded to the requesting organization. For collaborative applications, all partners must submit a letter describing their competencies, experience and roles within the project.

Education Topics of Interest:

- Overview of Ph+ALL disease state, including its high mutation burden resulting in rapid treatment resistance and high relapse rates
- Therapeutic approaches for front line Ph+ ALL, including available and emerging agent's potential efficacy and safety profiles
- Importance of response to first line treatment including achievement of complete molecular remission and suppression of potential mutations
- Prevalence of BCR-ABL1 T315I mutations in Ph+ ALL and impact on treatment resistance, and survival outcomes
- Risk factors for relapse of Ph+ ALL

The goal of this call for grants is to educate healthcare providers on the front line treatment of Ph+ALL and the importance of achieving a durable first response to treatment.

Summary of healthcare gaps:

Approximately 25% of adults with Acute Lymphoblastic Leukemia (ALL) have an acquired chromosomal abnormality known as the Philadelphiachromosome. This genetic mutation is generated by the reciprocal translocation of the ABL1 gene located on chromosome 9 to the BCR located on chromosome 22, resulting in

the formation of the BCR-ABL1 oncoprotein (NCCN Guidelines for ALL V2. 2021). This subtype of ALL, knows as Ph+ ALL is rare and considered to be an aggressive disease with poor long term overall survial. (Ronson A, et al. 2017). The presence of the Ph chromosome in adults increases with age, and individuals with Ph+ ALL typically have a worse prognosis than those without this abnormality (NCCN Guidelines for ALL V2. 2021) In particular, those with the Ph chromosome have been shown to have a lower 5-year survival rate. Patients with Ph-negative ALL have a 5-year survival rate of 73%, while those with Ph-positive ALL had a 50% 5-year survival rate (Sasaki K et al. Am J Hematol. 2021; 96:650–58).

NCCN and ESMO guidelines utilize BCR-ABL tyrosine kinase inhibitors (TKIs) to target this genetic mutation. Despite these recommended regimens having a potential need for a BCR-ABL TKI, there are no randomized head-to-head trials comparing the efficacy and safety of different BCR-ABL TKIs for adults with newly diagnosed Ph+ ALL; as such, there currently is no consensus opinion on the optimal BCR-ABL1 TKI for initial induction therapy in either NCCN or ESMO guidelines (NCCN Guidelines for ALL V2. 2021; Short NJ, et al. 2018; Hoelzer D, et al. 2016.) In fact, no TKIs are currently approved in the US for the treatment of newly diagnosed Ph+ ALL in adult patients (Gleevec (imatinib) [package insert] 2020; Sprycel (dasatinib) [package insert 2021; Tasigna (nilotinib) [package insert] 2020; Bosulif (bosutinib) [package insert 2020; Iclusig (ponatinib) [prescribing information] 2021). NCCN and ESMO guidelines include allogeneic SCT as a treatment option for consolidation therapy if an appropriate donor is obtained; however, in the current TKI era, there is a reexamination of the role of SCT, especially among patients who achieve a deep molecular response to initial therapy (NCCN Guidelines for ALL V2; Hoelzer D, et al. 2016). SCT is associated with a transplant-related mortality rate up to 40%, depending on the intensity of the conditioning regimen and rates of acute and chronic graft-versus-host disease approaching 50% (Short NJ, et al. 2018). The minimum goal when treating Ph+ALL is to induce a hematologic complete reponse (CR). Once a CR is achieved, the next major goal is to reach MRD-negativity (Soverini S, et al. 2019). Achieving MRD negativity is associated with improved outcomes (Jabbour E, et al. 2018).

Relapse in patients with Ph+ ALL treated with a TKI-based regimen is mediated largely by the development of BCR-ABL1 kinase domain mutations that confer resistance; different BCR-ABL1 TKIs may be associated with different mutational profiles and mutations can develop within the first month of TKI treatment (Short NJ, et al. 2018) The T315I mutation is the most frequent cause of TKI resistance in Ph+ ALL and is associated with poor outcomes. One small study showed that patients with T315I mutations (n=3) had a shorter median time to progression (median, 3.4 months; range, 1.8-10.6 months) compared with patients with no mutations (n=25; median, 11.3 months; range, 0.6-47.1 months), or patients with P-loop mutations (n=13; median, 12.8 months; range, 1.0-32.3 months) (Ravandi F, et al. 2015). In one study with a follow-up time of about 5.5 years, patients with the T315I mutation experienced significantly quicker median time to relapse compared with patients without the T315I mutation (7 months vs not reached) (Rousselot P, et al. 2016). For patients with Ph+ ALL, the outcomes are particularly poor and the unmet need for a therapy to treat this patient population is high.

References

Bosulif (bosutinib) [package insert]. New York, NY: Pfizer Inc; 2020.

Gleevec (imatinib) [package insert]. East Hanover, NJ: Novartis; 2020.

Hoelzer D, Bassan R, Dombret H, Fielding A, Ribera J, Buske C. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2016/9;27: v69-v82.)

Iclusig (ponatinib) [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Ltd; 2021

Jabbour E, DerSarkissian M, Duh MS, McCormick N, Cheng WY, McGarry LJ, Souroutzidis A, Huang H, O'Brien S, Ravandi F, Kantarjian HM. Efficacy of Ponatinib Versus Earlier Generation Tyrosine Kinase Inhibitors for

Front-line Treatment of Newly Diagnosed Philadelphia-positive Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk. 2018 Apr;18(4):257-265. doi: 10.1016/j.clml.2018.02.010. Epub 2018 Feb 17.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia V2. 2021. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). 2021;(Version 2.2021 – July 19, 2021.
Ravandi F, O'Brien SM, Cortes JE, Thomas DM, Garris R, Faderl S, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2015/8/26;121(23): 4158-4164.
Ronson A, Tvito A, Rowe JM. Treatment of Philadelphia Chromosome-Positive Acute Lymphocytic Leukemia. Current Treatment Options in Oncology. 2017/3;18(3)
Rousselot P, Coudé MM, Gokbuget N, Gambacorti Passerini C, Hayette S, Cayuela J, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood. 2016/8/11;128(6): 774-782
Sasaki K, JAbbour E, Short N, Jain N, Ravandi F, Pui C, Kantarjian H. Acute lymphoblastic leukemia: A population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980–2017American Journal of Hematology. 2021; 96:650–58.
Short NJ, Kantarjian H, Pui C, Goldstone A, Jabbour E. SOHO State of the Art Update and Next Questions: Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Clinical Lymphoma Myeloma and Leukemia. 2018/7;18(7): 439-446.
Soverini S, Bassan R, Lion T. Treatment and monitoring of Philadelphia chromosome-positive leukemia patients: recent advances and remaining challenges. J Hematol Oncol. 2019 Apr 23;12(1):39.
Sprycel (dasatinib) [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2021.
Tasigna (nilotinib) [package insert]. East Hanover, NJ: Novartis; 2020.

Target audience: We welcome applications that primarily target hematologic oncologists and general oncologists who treat Ph+ ALL patients and work in centers specializing in the management of acute leukemias. Other healthcare specialties such as advanced practitioners, nurses, and pharmacists including those in academic settings that interact with Ph+ ALL patients will also be considered.

Educational format:. Live, virtual live, and online formats as well as novel and unique ideas with meaningful validation are accepted.

Outcomes measures: The educational evaluation plan must be designed to objectively measure improvements in HCP knowledge and competence (level 3 and above). Ideally, the evaluation plan will include quantitative and qualitative evidence that the educational program has had an impact on HCP behavior.

Submission requirements: When responding, please follow the established guidelines for the Takeda medical education grant submission process. All applications must be submitted at https://www.tsupportportal.com/

The education must be accredited by the appropriate accrediting bodies, be fully compliant with ACCME criteria and the Standards for Commercial Support and must be in accordance with the U.S. Food and Drug Administration's Guidance on Industry-Supported Scientific and Educational Activities. If accepted,

must attest to the terms, conditions and purposes of an educational grant as described in the Takeda letter of agreement.

Geographic region: United States

Length of proposed project: 12 months (the enduring component should be available for at least 12 months)

Expected approximate monetary range of awarded proposals:
The total available budget related to this call for grants is approximately $300,000. Grants of varying budgets up to $300,000 will be considered. The total budget for this call for grants may be distributed among more than 1 provider. The amount of the grant Takeda Oncology will fund for any project will depend on the Review Committee's evaluation of the proposal and costs involved and will be stated clearly in the approval notification**.**

Preference will be given to proposals that address ALL of the following:

1. **Overview of requesting organization:** Please describe the organization requesting the grant, including its history, current mission, a list of key officers and staff who will direct the program; and descriptions of any other participating organizations/partners. Describe any experience your organization has in working in this area.
2. **Abstract:** Please provide a summary of your proposed project, including a brief assessment of needs in the target population.
3. **Agenda and Faculty:** Submissions with proposed agenda and faculty will be prioritized
4. **Goals and implementation plan:** Provide a clear description of program goals, implementation plan, target audience, and an anticipated timeline of project activities and milestones. Please indicate whether the project will be integrated into an existing program; if yes, please describe the existing program, how this project will be integrated, and the additional impact that is expected if funding is awarded.
5. **Budget:** Please provide a detailed itemized budget for the proposed project. Please also include a narrative justification for the requested amount.
6. **Reach and impact:** Please describe the planned reach for your program, as well as the estimated impact the program will have on your intended audience. Please involve any currently available baseline data.
7. **Collaboration:** If your project is collaborative in nature, please describe the roles and capabilities of each partner.
8. **Evaluation:** Specify how you will define and measure success for each of the proposed activities; indicate how the program will be measured and evaluated, and how results will be reported.
9. **Reporting:** Please specify the descriptive and evaluative reporting results that you will provide. For projects that are funded for longer than six-months, interim reporting is required. A final report is due at the end of the funded activities, including reporting of funding used to inform reconciliation of unused funding.
10. **Sustainability/replicability:** Describe any plans to broadly disseminate the proposed program's results and ensure sustainability beyond the funding period. Describe how the proposed program could serve as a model in other geographic regions or to serve different populations.
11. **Terms and conditions:** Please take note that every Call for Grants released by Takeda Oncology is governed by the following terms and conditions:
    i. All grant applications received in response to this Call for Grants will be kept confidential reviewed in accordance with all Takeda policies and guidelines.
    ii. This CGA does not commit Takeda to fund any Call for Grants submission, or the costs associated with such submissions.
    iii. Takeda reserves the right to cancel, in part or in its entirety, this Call for Grants.

iv. For compliance reasons, and in fairness to all providers, all communications about this Call for Grants must come exclusively to Takeda's Department of Medical Education. Failure to comply will automatically disqualify providers.

v. Failure to follow the instructions within this Call for Grants will result in a denial

12. Additional submission requirements:

- Letter of commitment from any partner organizations
- IRS 501(c)(3) letter (if applicable)
- Current operating budget

Key dates: Call for Grants release date: [12/15/2021]
Full proposal deadline: [01/21/2022]
Review of proposals by review committee starts: [01/24/2021]
Anticipated proposal notification date: week of [02/14/2021]

Grants will be distributed following the execution of a fully signed Letter of Agreement.

How to submit: Instructions on submitting can be found at:
http://www.takedaoncology.com/partnerships/grants--donations/

Questions: If you have any questions, please direct them in writing to Sarah Willette, Manager Congresses, Outreach and Medical Education (sarah.willette@takeda.com) with the subject line "(Call for Grants: Multiple Myeloma)".