BLU-285—the breakthrough in treatment of patients with aggressive systemic mastocytosis and gastrointestinal stromal tumor

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In a recent phase I clinical trial an international consortium of gastrointestinal stromal tumors (GIST) researchers from Portland (USA), Leuven (Belgium) and Boston (USA) together with people from the drug developing company Blueprint Medicine report on a new promising small-molecule inhibitor for treating patients with aggressive systemic mastocytosis (SM) and GISTs.

GISTs form the largest group of mesenchymal tumors of the intestinal tract (1). They arise from the interstitial cells of the Cajal. More than 80% of GIST harbors mutations in the c-KIT cell surface transmembrane receptor tyrosine kinase. Most oncogenic c-KIT mutations are found in the juxta membranous domain in exon 11, the second most common mutation type is duplication in the extracellular domain in exon 9 (2). Mutations in exon 13, 14, and 17 are rather rare and associated with secondary resistance to therapy (3). With a frequency of 5–10% GIST have gain-of-function mutations in the *platelet-derived growth factor receptor* α (*PDGFRA*) gene (4). For both receptors the downstream oncogenic signaling is triggering the MAP kinase and the PI3K/AKT pathway (5).

It has been shown that therapeutic management with tyrosine kinase inhibitors (TKIs), mostly systemic treatment with imatinib or sorafenib, is majorly affected by the type and localization of the oncogenic mutation (5). Despite remarkable advances in personalized therapies in patients suffering from GISTs, therapy resistances often develop (4).

SM is a disorder of the mast cells where KIT exon 17 (D816V) is the primary driver of disease (6). Amino acid D816 is localized in the activation loop of the KIT tyrosine kinase receptor gene. Interestingly, the resistance associated mutant D842V in the *PDGFRA* is structurally identical to D816V in KIT. The region around the D842V mutation contains a conserved motif (Asp836-Phe837-Gly83) that corresponds to both, the active and inactive state of the PDGFRA kinase domain (7).

The currently Food and Drug Administration (FDA) approved drugs (imatinib, sunitinib, regorafenib) to treat GIST with KIT exon 9 and exon 11 mutations are type II inhibitors that trap the inactive conformation of the kinases occupying the hydrophobic pocket adjacent to the ATP binding site. The advantages over ATP-site compounds are improved kinase selectivity and slower off-rates. When mutations in the catalytic subunit of the kinase exist (exon 13: V654A or exon 14: T670I or exon 17: D816V) treatment becomes problematic (1,8). Moreover, GISTs having the D842V activating mutation in *PDGFRA* are fully resistant to imatinib and sunitinib since mutant proteins bind the drug less efficiently. Indio *et al.* (2018) have shown by gene expression profiling that the drug ineffectiveness is not due to resistance acquisition but rather caused by the D842V related specific gene signature (7).

Thus the idea came up to design a type I inhibitor that binds to the active protein kinase conformation which might overcome drug resistance. A number of companies have begun to develop therapeutic options that target some of the less frequent mutations in GIST. Extensive search finally yielded in BLU-285 (Avapritinib).

As reported from ASH Clinical News about Avapritinib (BLU-285) Prof. Daniel J. DeAngelo, Director of clinical

and translational research at Dana-Farber Cancer Institute in Boston, said that "*all patients had some response* …". This seems to be quite unique for a phase I clinical trial. Heinrich *et al.* reported enthusiastically about BLU-285 at the 2017 Connective Tissue Oncology Society Annual meeting in Maui (Hawaii) as a clinically very potent drug that is well-tolerated showing a broad mutational coverage, remarkable response rates and prolonged progression-free survival in PDGFRA-driven GIST.

Why this new drug is promising is summarized as follows:

(I) In their study the authors compare BLU-285 with other clinically used type I drugs (crenolanib, midostaurin) that have at least biochemical activity in the lower nanomolar range. However, in contrast to BLU-285 their targeted broad kinome signature leads to a more complex safety profile with many therapeutic side effects;

(II) BLU-285 showed a high potency against all disease-relevant KIT mutations. Intriguingly it was more potent to ATP-binding site mutants in exon 13 and 14, the preferential location of resistance mutations, when simultaneous JM domains mutants were present;

(III) BLU-285 was highly potent in nanomolar range *in vitro* in kit-mutant cell lines and in an *in vivo* subcutaneous allograft mouse model;

(IV) The clinical phase I study was performed as a dose-escalation study in patients with advanced unresectable GIST and advanced SM. In a patient with a primary gastric PDGFRA D842V mutant GIST that was progressing under imatinib, dasatinib and crenolanib a drastic tumor size reduction was observed after 8 weeks of daily orally administered BLU-285 in computed tomography and after further 8 weeks there was a rapid and sustained reduction in mutant allele load in blood plasma. In another patient suffering from SM the bone marrow mast cell infiltration, which is a marker for SM, decreased to baseline levels.

In summary, the authors give several evidences that BLU-285 might be highly effective against patient tumors that are characterized by c-KIT and *PDGFRA* mutations so far lacking effective therapy. As there are currently no other treatments, specifically for the PDGFRA D842V and the structurally homologous KIT D816V mutant tumors, available this report is undoubtedly a positive and promising development. Since the safety profile of BLU-285 seems to be highly favorable due to its high selectivity for KIT and PDGFRA kinases future clinical trials should also consider the potential of BLU-285 in combination therapy protocols.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Kang W, Zhu C, Yu J, et al. KIT gene mutations in gastrointestinal stromal tumor. Front Biosci (Landmark Ed) 2015;20:919-26.
2. Rubin BP, Heinrich MC. Genotyping and immunohistochemistry of gastrointestinal stromal tumors: An update. Semin Diagn Pathol 2015;32:392-9.
3. Nishida T, Blay JY, Hirota S, et al. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer 2016;19:3-14.
4. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357-64.
5. Pogorzelski M Falkenhorst J Bauer S. Molecular subtypes of gastrointestinal stromal tumor requiring specific treatments. Curr Opin Oncol 2016;28:331-7.
6. Arock M, Akin C, Hermine O, et al. Current treatment options in patients with mastocytosis: status in 2015 and future perspectives. Eur J Haematol 2015;94:474-90.
7. Indio V, Astolfi A, Tarantino G, et al. Integrated molecular characterization of gastrointestinal stromal tumors (GIST) harboring the rare D842V mutation in PDGFRA gene. Int J Mol Sci 2018;19.
8. Ustun C, DeRemer DL, Akin C. Tyrosine kinase inhibitors in the treatment of systemic mastocytosis. Leuk Res 2011;35:1143-52.

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