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EDITORIAL



# Blinatumomab bridges the gap between leukemia and immunity

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On December 3, 2014, the US Food and Drug Administration (FDA) granted accelerated approval to blinatumomab (BLINCYTO®, from Amgen Inc.) – which had received breakthrough therapy designation a few months earlier – for the treatment of Philadelphia chromosome (Ph)-negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia (ALL)[1] (source https://www.cancer.gov/about-cancer/treatment/drugs/fda-blinatumomab). This decision was based on data from the MT103–211 trial (NCT1466179), a multicenter open-label single-arm Phase II study enrolling 185 individuals with relapsed or refractory ALL.[2,3] In this context, 32% of patients (95% CI: 26–40%) achieved a complete remission following 2 cycles of blinatumomab (with a median duration of response of 6.7 months; range, 0.46–16.5 months).[2,3] Toxicity was evaluated on a total of 212 subjects with relapsed or refractory ALL receiving blinatumomab in the context of the MT103–211 trial and other studies. Common side effects (affecting more than 20% of patients) included (but were not limited to) pyrexia, headache, and febrile neutropenia. In addition, around 50% of the individuals on blinatumomab manifested neurologic adverse effects that required treatment interruption or discontinuation, and 11% of blinatumomab-treated patients experienced cytokine-release syndrome of life-threatening or fatal severity.[2-4] Owing to such severe toxicities, the FDA requested specific warnings on the product label as well as the implementation of a Risk Evaluation and Mitigation Strategy Exit Disclaimer (REMS), a procedure to communicate to healthcare providers the dangers potentially associated with the administration of blinatumomab (source https://www.cancer.gov/about-cancer/treatment/drugs/fda-blinatumomab). Subsequent studies including NCT02003612 (in which outcomes from the MT103–211 trial were compared with outcomes from an historical cohort of B-precursor $Ph^-$ relapsed/refractory ALL patients),[5,6] and a Phase I/II trial testing blinatumomab in pediatric patients with relapsed/refractory ALL,[7] as well as data from the MT103–211 trial at 5-year follow-up[8] further corroborated the promising clinical potential of blinatumomab.

On July 12, 2017 the US FDA granted full approval to blinatumomab for the treatment of adults and children with relapsed/refractory B-cell precursor ALL, regardless of Ph status (source https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm566708.htm). This decision was based on data from: (1) the TOWER trial (NCT02013167), a multicenter, open-label Phase III study in which 405 patients with relapsed/refractory B-cell precursor ALL were randomized (2:1) to receive blinatumomab (n = 271) or investigator's choice chemotherapy (n = 134);[9] and (2) the ALCANTARA trial (NCT02000427), a multicenter single-arm Phase II study enrolling a total of 45 individuals with relapsed/refractory $Ph^+$ B-cell precursor ALL[10] (source https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm566708.htm).

In the context of the TOWER study, median overall survival was 7.7 months for patients on blinatumomab versus 4.0 months for patients receiving chemotherapy (hazard ratio for death 0.71; 95% CI: 0.55 - 0.93; $p = 0.01$).[9] Both complete remissions with full hematologic recovery and complete remissions with full, partial, or incomplete hematologic recovery were more frequent among blinatumomab-treated patients (34% and 44% respectively) than among patients on investigator's choice chemotherapy (16% and 25%, respectively; $p < 0.001$ in both cases).[9] Moreover, blinatumomab was associated with a higher rate of event-free survival at 6 months (31%) as compared with chemotherapy (12%), as well as with a longer median duration of remission (7.3 *vs.* 4.6 months). Although serious adverse events were documented in 62% of blinatumomab-treated patients and 45% of chemotherapy-treated subject, exposure-adjusted event rates were 349.4 per 100 patient-years in the blinatumomab group and 641.9 per 100 patient-years in the chemotherapy group.[9] As expected from previous clinical observations,[2-4] cytokine release syndromes were restricted to blinatumomab-treated patients (4.9%), accounting for 1% of treatment discontinuations and 5% of interruptions.[9]

In the context of the ALCANTARA study, median relapse-free survival and overall survival of 6.7 and 7.1 months, respectively, was achieved.[10] Sixteen out of 45 patients (36%) achieved complete remission with full, partial, or incomplete hematologic recovery after 2 cycles of blinatumomab, including 40% of the patients bearing a *T315I* substitution (which is associated with highly aggressive disease and dismal clinical outcome).[10,11] Moreover 88% of patients in complete remission achieved

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minimal residual disease (MRD)-negativity. In line with previous clinical data,[2-4] common adverse events included pyrexia (58%), febrile neutropenia (40%), and headache (31%). Moreover, 3 patients experienced grade 3 neurologic toxicities, which required treatment discontinuation in 1 case, and 3 patients manifested grade 1–2 cytokine release syndromes.

Blinatumomab is a so-called "bispecific T-cell engager" (BiTE), *i.e.*, a fusion protein consisting of 2 single-chain variable fragments from different antibodies, one of which is specific for CD3.[12-15] Besides recognizing CD3, blinatumomab binds to CD19, hence generating a physical link between $CD3^+$ T cells - including (but not limited to) cytotoxic T lymphocytes – to cells from the B lineage, including cancer cells in patients with B-cell malignancies.[16,17] CD19 has been successfully used as a target for other immunotherapeutic agents for hematological malignancies, including adoptively transferred chimeric antigen receptor (CAR)-expressing cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells.[18-24] The engagement of CD3 and CD19 by blinatumomab triggers T cell activation in the absence of conventional MHC-restricted TCR engagement, *de facto* underlying the clinical efficacy of this BiTE for the treatment of B-cell precursor ALL.[25,26] However, blinatumomab also engages $CD4^+CD25^+FOXP3^+$ regulatory T ($T_{REG}$) cells, resulting in immunosuppressive effects that are detrimental for patients.[27-29] In line with this notion, low amounts of circulating $T_{REG}$ cells have recently been associated with an improved propensity of patients with B-precursor ALL to respond to blinatumomab.[28] Preliminary findings from a Phase I study suggest that blinatumomab may also be beneficial for patients with relapsed/refractory non-Hodgkin lymphoma (NHL).[30] However, additional clinical investigation is required to elucidate the true therapeutic potential of blinatumomab in NHL patients. Moreover, it will be interesting to see whether blinatumomab can be safely and efficiently combined with other immunomodulatory regimens that may overcome the immunosuppressive effects of $T_{REG}$ cells, including (but perhaps not limited to) metronomic cyclophosphamide,[31,32] radiation therapy at specific dose and administration schedules,[33-35] Toll-like receptor agonists,[36-39] immunostimulatory cytokines,[40-44] and/or immune checkpoint blockers.[45,46] Irrespective of these incognita and potential developments, the recent decision from the US FDA solidified an important bridge between the immune system of patients with B-cell precursor ALL and their disease.

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