OncoImmunology 2:6, e24567; June 2013; © 2013 Landes Bioscience

Novel multifunctional antibody approved for the treatment of breast cancer

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Keywords: breast carcinoma, cancer immunotherapy, monoclonal antibodies, trastuzumab, T-DM1

Abbreviations: FDA, Food and Drug Administration; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; NHL, non-Hodgkin's lymphoma; T-DM1, trastuzumab emtansine.

During the past 15 years, monoclonal antibodies (mAbs) have become an important tool for the treatment of hematopoietic and solid malignancies. The mAbs that have been approved by regulatory agencies for use in cancer patients as well as those that are currently being developed in this sense target antigens that are overexpressed on the surface of cancer cells and mediate antineoplastic effects via multiple, often non-mutually exclusive, mechanisms.[1–3] Thus, while trastuzumab (Herceptin™, Roche) mainly (but not only) inhibits the signal transduction cascade elicited by the v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (ERBB2, best known as HER2), rituximab (Rituxan™, Genentech) exerts antitumor effects mostly by engaging the host immune system against CD20-expressing cancer cells, hence activating both antibody-dependent and complement-dependent cellular cytotoxicity.[4,5] These mAbs are often used in combination with radio- and/or chemotherapeutic regimens, and are generally associated with relatively mild and transient side effects.[3,6]

Along with the development of mAbs that would exert antineoplastic effects as such, i.e., "naked" mAbs, the therapeutic potential of mAbs that specifically shuttle cytotoxic agents or radioisotopes to malignant cells, hence minimizing unwarranted toxic phenomena, has been intensively investigated. The efficacy of these "immune conjugates" largely relies on their internalization by cancer cells via receptor-mediated endocytosis, resulting in the highly specific delivery of their cytotoxic moiety.[7] Nowadays, no less than 3 distinct immune conjugates are approved by the US Food and Drug Administration (FDA) for use in cancer patients,[1,2] including ibritumomab tiuxetan (Zevalin™, IDEC pharmaceuticals), an ^{90}Y- or ^{111}In-conjugated murine IgG1 targeting CD20 that is currently employed for the treatment of relapsed or refractory, low grade or follicular B-cell non-Hodgkin's lymphoma (NHL);[8] tositumomab (Bexxar™, GlaxoSmithKline), an ^{131}I-conjugated fully human IgG1 specific for CD20 that is being used against CD20-expressing relapsed or refractory, low-grade, follicular or transformed NHL;[9] and brentuximab vedotin (Adcetris™, Seattle Genetics), a CD30-targeting chimeric IgG1 conjugated to monomethyl auristatin E (MMAE, an inhibitor of tubulin) that is approved for use in Hodgkin's lymphoma patients relapsing upon autologous hematopoietic stem cell transplantation.[10]

On February 22nd, 2013, the FDA approved a new immune conjugate for the treatment of advanced breast carcinoma, trastuzumab emtansine (T-DM1, commercialized by Genentech under the label of Kadcyla™). T-DM1 combines the ability of trastuzumab to inhibit ERBB2 signaling and activate the host immune system with the selective delivery of the maytansinoid DM1, another tubulin inhibitor, to ERBB2$^+$ cancer cells. Thus, whereas the antibody moiety of T-DM1 is degraded by lysosomes upon ERBB2 internalization, DM1 is released in the cytoplasm and exerts additional antineoplastic effects by halting cell cycle progression.[11]

The EMILIA Phase III clinical trial, which de facto drove the approval of T-DM1, enrolled a total of 991 patients affected by ERBB2$^+$ advanced or metastatic breast carcinoma that had previously been treated with trastuzumab and a microtubular inhibitor of the taxane family.[12] Patients were randomly assigned to receive either T-DM1 as a standalone intervention or lapatinib (an FDA-approved chemical inhibitor of the tyrosine kinase activity of ERBB2) plus capecitabine (the precursors of the nucleoside analog 5-fluorouracil). In this setting, the intravenous administration of T-DM1 every 21 days significantly prolonged overall survival from 25.1 months, as observed in the control arm of the study, to 30.9 months. Along similar lines, T-DM1-receiving patients exhibited a longer progression-free survival (9.6 months) than patients treated with lapatinib plus capecitabine (6.4 months), and T-DM1 was associated with a comparatively lower frequency of grade 3–4 adverse events (40.8% vs. 57%). These included thrombocytopenia (documented in 12.9% of T-DM1-receiving patients) but not severe diarrhea or palmar-plantar erythrodysestesia, both of which were

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Submitted: 03/01/2013; Accepted: 03/01/2013
Citation: Mavilio D, Galluzzi L, Lugli E. Novel multifunctional antibody approved for the treatment of breast cancer. OncoImmunology 2013; 2:e24567; http://dx.doi.org/10.4161/onci.24567

commonly observed in subjects treated with lapatinib plus capecitabine.[12]

A recent meta-analysis of clinical data demonstrates that neo-adjuvant trastuzumab not only significantly improves both disease-free and overall survival among metastatic breast carcinoma patients bearing the *ERBB2* amplification, which is observed in approximately 20% of cases and is associated with poor prognosis,[13] but also reduces the risk of relapse upon surgical removal of the primary tumor.[14] Thus, the clinical indications for T-DM1, which has specifically been approved for use in patients who previously failed combinatorial immunochemotherapeutic regimens involving trastuzumab and a taxane, may soon expand.

Several other immune conjugates are being developed for the treatment of solid and hematological malignancies,[1,2] most of which combine a tubulin inhibitor (e.g., MMAE) or an anthracyclin (e.g., doxorubicin) with mAbs targeting one out of several tumor-associated antigens.[11] Safety and efficacy data from recent clinical trials suggest that immune conjugates constitute promising tool for anticancer immunotherapy. The design of molecules that—similar to T-DM1—are able to engage the mechanisms of action of naked antibodies while specifically delivering cytotoxic agents or radioisotopes to cancer cells is expected to further increase the therapeutic potential of this approach. Future will tell not only if mAbs of this type represent a novel class of superior immunotherapeutic agents, but also whether they can be safely and efficiently combined with other immunomodulatory interventions including, but not limited to, immunogenic chemotherapeutics,[15] immunostimulatory mAbs[16] and Toll-like receptor agonists.[17,18]

References

1. Galluzzi L, Vacchelli E, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, et al. Trial Watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2012; 1:28-37; PMID:22720209; http://dx.doi.org/10.4161/onci.1.1.17938.
2. Vacchelli E, Eggermont A, Galon J, Sautès-Fridman C, Zitvogel L, Kroemer G, et al. Trial watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2013; 2:e22789; PMID:23482847; http://dx.doi.org/10.4161/onci.22789.
3. Scott AM, Wolchok JD, Old LJ. Antibody therapy of cancer. Nat Rev Cancer 2012; 12:278-87; PMID:22437872; http://dx.doi.org/10.1038/nrc3236.
4. Hubert P, Amigorena S. Antibody-dependent cell cytotoxicity in monoclonal antibody-mediated tumor immunotherapy. Oncoimmunology 2012; 1:103-5; PMID:22720225; http://dx.doi.org/10.4161/onci.1.1.17963.
5. Kute T, Stehle JR Jr., Ornelles D, Walker N, Delbono O, Vaughn JP. Understanding key assay parameters that affect measurements of trastuzumab-mediated ADCC against Her2 positive breast cancer cells. Oncoimmunology 2012; 1:810-21; PMID:23162748; http://dx.doi.org/10.4161/onci.20447.
6. Lindorfer MA, Wiestner A, Zent CS, Taylor RP. Monoclonal antibody (mAb)-based cancer therapy: Is it time to reevaluate dosing strategies? Oncoimmunology 2012; 1:959-61; PMID:23162771; http://dx.doi.org/10.4161/onci.20368.
7. Carter PJ, Senter PD. Antibody-drug conjugates for cancer therapy. Cancer J 2008; 14:154-69; PMID:18536555; http://dx.doi.org/10.1097/PPO.0b013e318172d704.
8. Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MN, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002; 20:3262-9; PMID:12149300; http://dx.doi.org/10.1200/JCO.2002.11.017.
9. Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005; 352:441-9; PMID:15689582; http://dx.doi.org/10.1056/NEJMoa041511.
10. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 2010; 363:1812-21; PMID:21047225; http://dx.doi.org/10.1056/NEJMoa1002965.
11. Adair JR, Howard PW, Hartley JA, Williams DG, Chester KA. Antibody-drug conjugates - a perfect synergy. Expert Opin Biol Ther 2012; 12:1191-206; PMID:22650648; http://dx.doi.org/10.1517/14712598.2012.693473.
12. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al.; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367:1783-91; PMID:23020162; http://dx.doi.org/10.1056/NEJMoa1209124.
13. Stern HM. Improving treatment of HER2-positive cancers: opportunities and challenges. Sci Transl Med 2012; 4(127): 127rv2; http://dx.doi.org/10.1126/scitranslmed.3001539; PMID: 22461643.
14. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev 2012; 4:CD006243; PMID:22513938.
15. Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov 2012; 11:215-33; PMID:22301798; http://dx.doi.org/10.1038/nrd3626.
16. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology 2012; 1:1223-5; PMID:23243584; http://dx.doi.org/10.4161/onci.21335.
17. Galluzzi L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial Watch: Experimental Toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:699-716; PMID:22934262; http://dx.doi.org/10.4161/onci.20696.
18. Vacchelli E, Galluzzi L, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial watch: FDA-approved Toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:894-907; PMID:23162757; http://dx.doi.org/10.4161/onci.20931.