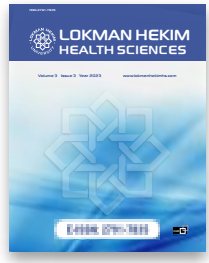
LOKMAN HEKIM HEALTH SCIENCES

DOI: 10.14744/lhhs.2023.12008
Lokman Hekim Health Sci 2023;3(3):223–229



lokmanhekimhs.com

REVIEW

# The Development, Indications, and the Safety of Monoclonal Antibodies

## *Monoklonal Antikorların Geliştirilmesi, Endikasyonları ve Güvenliliği*

**Hakkı Zafer Güney[1], Merve Mete[2], Bilgen Dölek[3], Murat Yuvakuran[4], Zehra Mantin[5]**

[1]Department of Pharmacology, Lokman Hekim University Faculty of Medicine, Ankara, Türkiye
[2]Amgen Biotechnology and Gensenta Pharma, Ankara, Türkiye
[3]Market Access, Health Policy and Corporate Affairs, Ankara, Türkiye
[4]Market Access, Health Policy, Governmental Affairs, Ankara Türkiye

**Abstract**

Monoclonal antibodies (mAbs) are described as brand-new tools used in the therapy of cancer, autoimmune and infectious diseases, transplant rejection, and some other new indications. MAbs have been shown to create some adverse events such as hypersensitivity reactions, immunological problems, cardiovascular diseases, respiratory events, proteinuria, nephrotoxicity, dermatologic events, and cytopenia. In this review, our purpose is to overview the indications and the unwanted events matched with these drugs and negotiate the developments in the development of these drugs that are able to increase the efficacy and decrease the safety problems.

Keywords: Adverse effect; Cancer molecular biology; Clinical drug studies; Drug development; Monoclonal antibody

In 1975, the reproduction of several cell lines which are able to excrete red blood cell antibodies was determined.[1] Then, the developments have let the conversion from mice to fully human.[2,3]

mAbs are new treatments for transplant refusal, autoimmune and infectious diseases, cancer, and some new indications. However, mAb practice has the ability to cause anaphylaxis, serum sickness, and the formation of related antibodies. On the other hand, there can be various adverse effects of mAbs that are described in the literature.

To build an antibody, investigators primarily identify the right antigen. For malignant cells, this is not usually simple, until now, some mAbs are found to be more effective in some malignancies than other drugs.

Various Therapies Used in the Treatment of Malignancies

There are different types of treatment strategies that are in use for the treatment of several cancer types.[4]

- Checkpoint inhibitors: Those drugs are usually realize and invade tumors.

***Cite this article as:*** *Güney HZ, Mete M, Dölek B, Yuvakuran M, Mantin Z. The Development, Indications, and the Safety of Monoclonal Antibodies. Lokman Hekim Health Sci 2023;3(3):223–229.*

**Correspondence:** Hakkı Zafer GÜNEY, M.D. Lokman Hekim Üniversitesi Tıp Fakültesi, Farmakoloji Bölümü, Ankara, Türkiye
**E-mail:** zafer.guney@lokmanhekim.edu.tr **Submitted:** 17.02.2023 **Revised:** 15.03.2023 **Accepted:** 06.06.2023

**OPEN ACCESS** This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/).

- Chimeric antigen receptor (CAR) T-cell therapy: T-cells are taken from the patient's blood, shuffles the T-cells with a virus which helps them learn how to bind to cancer cells, and afterward they are given back to the patient to kill cancer.
- Cytokines: They provoke the immune cells to attack the malignant cells.
- Immunomodulators: These drugs usually stimulate the immune system partially and cure several malignancies.
- Vaccines: Those stimulate the immune reaction. Normally, those are considered to prevent several infections. In addition, they are for several malignancies.
- Monoclonal antibodies (mAbs): Those antibodies are done by the researchers and these antibodies mimic the immune system. mAbs can be used in the treatment of malignancy because they are planned to aim the malignant cell.
- Viruses: They are generally produced in the laboratory.

### Various mAbs for the Prevention and Treatment of Malignancy

There are several mAbs that are in use for the prevention and treatment of malignancy.[5]

### Bared (Naked) mAbs

Bared mAbs work alone. They are the commonest mAbs that can be used in the treatment of malignancy. Usually bared mAbs bind to antigens on malignant cells. Bared mAbs are able to work using different methods.

- Several mAbs boost a person's immune response against cancer cells. Alemtuzumab is a drug that is preferred in the treatment of chronic lymphocytic leukemia. Alemtuzumab is able to bind to the CD52 antigen that is present on lymphocytes. After the attachment, the antibody is able to effect immune cells to demolish them.
- Several bared mAbs induce the immune response by targeting some crucial checkpoints.
- The rest of the bared mAbs are mostly able to attach and block antigens on cancer cells. These antigens are able to help those cancer cells develop. For instance, trastuzumab (Herceptin) acts against the HER2 protein and is used in the treatment of some cancers, for example, breast and stomach cancers. HER2 is a protein that is responsible for the development of those cells.

### Conjugated mAbs

Conjugated mAbs are used in combination with a drug or a radioactive particle. Conjugated mAbs take one of them to the malignant cells and they circulate around the body to find the right antigen and decrease the harm to normal cells.

- Radiolabeled antibodies: They have tiny radioactive corpuscules bound to themselves. The drug ibritumomab tiuxetan is a radiolabeled mAb that acts against the CD20 antigen that is present on B lymphocytes. Therapy using this antibody is called as radioimmunotherapy. The drug and radiation are delivered directly to the cells.
- Chemolabeled antibodies: They have strong drugs attached. For instance:

o Brentuximab vedotin and Ado-trastuzumab emtansine.

### Bispecific mAbs

They consist of two various parts, thus they are able to bind to two proteins concomitantly. Blinatumomab is used for the therapy of some leukemia types. This drug is able to bind to CD19 protein that is present on various leukemia and lymphoma cells. The second part of the drug is able to bind to CD3, a protein that is present on T-lymphocytes. By this mechanism of action, this drug can bind to cancer cells and immune cells, thus may force the immune system to kill the cancer cells.

## Results

### Clinical and Research Consequences

#### *The Safety of mAbs*

The side effects of some of the licensed monoclonal antibodies are listed in Table 1.[4]

### What is the Difference between Emergency Use Authorization (EUA) and FDA Approval?

To evaluate the emission of an EUA to establish promising novel treatments available does not establish FDA approval. An EUA is valid only throughout a proclaimed public health emergency is present and can change as specialists evaluate the incoming data. Several therapies that have a EUA probably have to face more rigorous demands to become FDA-approved.

To respond to COVID-19, taking into consideration that its pathophysiology is not well understood, it is necessary to evaluate the clinical data from time to time. For instance, the recent outbreak of SARS-CoV-2 variants may affect the current information on the therapeutics being developed.

**Table 1.** Side effects of some of the licensed monoclonal antibodies[4]

| Target | mAb | Type | FDA approval | Indications* | Selected side effects |
|---|---|---|---|---|---|
| Platelet glycoprotein IIb/IIIa | Abciximab (ReoPro; Centocor Ortho Biotech, Eli Lilly) | Chimeric antibody fragment: c7E3 Fab | 1994 | Prevention of ischemic cardiac complications of percutaneous coronary interventions and unstable angina | • Hypersensitivity and immunogenicity<br>• Increased risk of bleeding<br>• Thrombocytopenia |
| Tumor necrosis factor-α | Adalimumab (Humira; Abbott) | Fully human | 2002 | • Rheumatoid arthritis<br>•Ankylosing spondylitis<br>• Psoriasis<br>• Psoriatic arthritis<br>• Crohn's disease<br>• Ulcerative colitis | • Infusion reactions and immunogenicity<br>• Hypersensitivity reactions<br>• Immunosuppression and infections (tuberculosis)<br>• Anemia, leukopenia and thrombocytopenia<br>• Worsening heart failure<br>• Malignancy, lymphoma, and lymphoproliferative disorders<br>• Elevated liver transaminases<br>• Increased nuclear-specific antibodies |
| Tumor necrosis factor-α | Certolizumab (Cimzia; UCB) | Humanized pegylated | 2008 | Listed above | Listed above |
| | Infliximab (Remicade; Centocor Ortho Biotech) | Chimeric | 1998 | Listed above | Listed above |
| CD52 on mature B, T, and natural killer cells | Alemtuzumab (Campath; Genzyme) | Humanized | 2001 | • B cell chronic lymphocytic leukemia<br>• Graft-versus-host disease<br>•Multiple myeloma<br>•Multiple sclerosis<br>• Vasculitis<br>•Behçet's disease | • Infusion reactions<br>• Hypersensitivity and immunogenicity<br>• CRS<br>• Tumor lysis syndrome<br>• Immunosuppression and opportunistic infections<br>• Cytopenias: pancytopenia, lymphopenia and thrombocytopenia<br>• Autoimmune hemolytic anemia<br>• Thyroid disorders<br>• Cardiotoxicity |
| Interleukin-2 receptor-α on activated lymphocytes | Basiliximab (Simulect; Novartis) | Chimeric | 1998 | • Prophylaxis of renal transplant allograft rejection<br>• Severe acute hypersensitivity reactions<br>•CRS and immunogenicity<br>• Immunosuppression and infections | • Local skin reactions<br>• Warnings when combined with other immunosuppressive |
| | Daclizumab (Zenapax; Roche) | Humanized | 1997 Discontinued in Europe | Listed above | Listed above |
| Vascular endothelial growth factor | Bevacizumab (Avastin; Genentech) | Humanized | 2004 | • Metastatic colorectal cancer<br>• Non-small-cell lung carcinoma<br>• Metastatic breast carcinoma<br>• Metastatic renal carcinoma | • Infusion reactions and immunogenicity • Local complications at tumor site<br>• Arterial and venous thromboembolic events<br>• Hemorrhage<br>• Severe hypertension<br>• Cardiac failure<br>• Reversible posterior leukoencephalopathy syndrome<br>• Slower wound healing and GI perforation |
| Vascular endothelial growth factor | Ranibizumab (Lucentis; Genentech, Novartis) | Humanized (Fab fragment from bevacizumab) | 2006 | • Injected intravitreally for neovascular (wet) age-related macular degeneration<br>•Conjunctival hemorrhage<br>•Intraocular inflammation | • Increased intraocular pressure<br>• Retinal detachment<br>• Endophthalmitis |

**Table 1 (cont).** Side effects of some of the licensed monoclonal antibodies[4]

| Target | mAb | Type | FDA approval | Indications* | Selected side effects |
|---|---|---|---|---|---|
| Complement C5 | Eculizumab (Soliris; Alexion) | Humanized | 2007 | • Paroxysmal nocturnal hemoglobinuria<br>• Meningococcal and Neisseria infection | • Intravascular hemolysis |
| CD11a CD3 | Efalizumab (Raptiva; Genentech) | Humanized | 2003 | • Recently discontinued<br>• No longer licensed for chronic plaque psoriasis | • First-dose reaction complex<br>• Immunosuppression<br>• Serious opportunistic infections<br>• PML<br>• Guillain–Barré syndrome, encephalitis, meningitis<br>• Immune hemolytic anemia |
| | Immune thrombocytopenia Muromonab (Orthoclone OKT3; Ortho Biotech) | Mouse | 1986 (no European Medicines Authority authorization) | • Acute resistant allograft rejection in renal, cardiac, and hepatic transplant patients | • Severe acute infusion reactions<br>• Immunosuppression and infections<br>• Immunogenicity<br>• Cardiovascular side effects<br>• Hepatitis |

**Table 2.** Comparison of polyclonal and monoclonal antibodies[7]

| | Polyclonal antibodies | Monoclonal antibodies |
|---|---|---|
| Place of production | Obtained from various B cell clones | Obtained from a single B cell clone |
| Place of binding | Bind to multiple epitopes of all antigens that play a role in immunization | Bind to a single epitope of an antigen |
| Class of antibody | Comprises of a mixture of various antibody groups. (isotypes) | Consists of a single antigenic group |
| Antigen binding region | A mixture of antibodies that have multiple antigen binding sites. | All antibodies have the same antigen binding region. |
| Cross-reactivity | High | Low |

Hypersensitivity reactions were observed more frequently. On the other hand, adverse reactions were seen more frequently in children and in elderly patients. Close monitoring of adverse reactions is therefore necessary to prevent important medical conditions or death.

## Several Adverse Effects of mAbs[6]

Depending on the monoclonal antibody used in the treatment, frequent adverse effects seen are:

- Allergy
- Adverse events caused by the immune system
- Cardiovascular adverse events
- Respiratory adverse events
- Proteinuria/Nephrotic Syndrome
- Enterotoxicity
- Dermatologic/Cutaneous AEs
- Cytopenia
- Others

In a study in Korea among 2538 patients, the rate of various adverse reactions was found to be, infection (18.2%); leucocyte abnormalities (12.1%), visual abnormalities (6.6%), and allergic reactions (4.9%).[7]

The polyclonal and monoclonal antibodies are compared in Table 2.[7]

Rituximab is able to cause progressive multifocal leukoencephalopathy and vascular endothelial growth factor antibody is able to cause reversible posterior leukoencephalopathy syndrome.

mAbs have some serious advantages, for example, high specificity that is helpful for exact action, and long half-lives that is useful for rare dosing.[8]

Other uncommon adverse events caused mAbs used are: vomiting, abdominal pain, fatigue, dysphonia, anorexia, peripheral neuropathy and leukoencephalopathy.[9–14]

## The Cytokine Storm[15,16]

Several mAbs start the discharge of several cytokines, which may cause a cytokine storm.[17,18] This is valid for muromonab,[19] alemtuzumab,[20,21] and rituximab.[22] Cancerogenic signaling in a breast cancer cell is regulated by the epidermal growth factor receptor EGFR and the members of its family. Magnification of the gene encoding HER2/neu tyrosine kinase is very important in the advancement of some human breast cancers. In the last few years, the protein is accepted as an important biomarker and target for therapy in nearly 30% of breast cancer patients.

Human epidermal growth factor receptor 2 or HER2 is a member of the human epidermal growth factor receptor

(HER/EGFR/ERBB) family. HER2/neu tyrosine kinase is able to induce the Ras-extracellular signal-regulated kinase (ERK) and the phosphatidylinositol 3-kinase (PI3K)-AKT pathways. AKT has a central oncogenic role.

ERBB2, a known proto-oncogene, is located at the long arm of human chromosome 17. Trastuzumab is able to bind to the extracellular domain of ERBB2 and inhibit the reproduction of several breast cancer cells. This drug is also able to cause the apoptosis of malignant cells. Other than inhibiting ERBB2 signaling, it might also show effects through cytotoxicity.

Cardiomyocyte proliferation needs signaling in cardiomyocytes through ERBB2-ERBB4 heterodimers and is essential for contractility. Although several of the same signaling pathways (such as Ras-ERK and PI3K-AKT) are activated in cardiomyocytes and in breast cancer cells, an increase in the ratio of BCL-Xs to BCL-XL induced by ERBB2-specific antibodies might trigger BCl-2-associated X protein (BAX) oligomerization, mitochondrial membrane depolarization, ATP depletion, and contractile dysfunction. In addition, trastuzumab cardiotoxicity is usually caused by antibody-dependent cell-mediated cytotoxicity. Trastuzumab also blocks neuregulin 1 (NRG1)-mediated activation of Src and focal adhesion kinase, and this appears to worsen left ventricular dysfunction.[23,24]

## Capillary Leak Syndrome

A leakage of fluid from capillaries into interstitial fluid that results in hypotension, edema, and multiple organs failure due to limited perfusion. In 2006, when the fully humanized mAb TGN1412 — a CD28 superagonist (CD28SA) — was first given to six healthy male volunteers, it triggered an immediate and severe cytokine storm.[25–27] The clinical, laboratory, and immunological events following rapid intravenous infusion of TGN1412 were dramatic and have been divided into four phases.[26] First, a systemic inflammatory response consisting of high levels of cytokines in the blood and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilation, and hypotension. Second, pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Third, severe blood lymphopenia and monocytopenia. Fourth, prolonged cardiovascular shock and acute respiratory distress syndrome.

Expert groups have highlighted the importance of considering the minimal anticipated biological effect level (MABEl) in deciding the initial dose of a biologic to be used in humans.[28–30] This MABEl approach selects the starting dose for a first-in-human study on the basis of the lowest dose that is found to be active in any in vitro potency assays. Based on the MABEl, the starting dose for TGN1412 should have been 20-times lower than that used in the phase I study. The MABEl approach also suggested a much lower dose than that derived from consideration of animal toxicology studies. CD28SA mAbs cause activation of TReg cells in rats[31] and have been used to treat experimental autoimmune disease.[32] In rats, lower concentrations of a CD28SA mAb induced non-specific expansion of TReg cells without causing lymphocytosis.[33] In addition, administration of a CD28SA mAb has recently been shown to cause a dramatic redistribution of T cells within 48 h, with a later phase of TReg-cell activation.[34] Selective stimulation of TReg cells is the rationale for the use of CD28-specific mAbs for the treatment of human autoimmune diseases.[35]

## Cardiotoxicity

Trastuzumab (Herceptin; Genentech) is a humanized mAb directed against human ERBB2 (also known as HER2/neu) and has been used successfully in women with ERBB2-positive metastatic breast cancer.[36] However, an unexpected adverse event in women treated with trastuzumab in clinical trials was that of cardiotoxicity.[37,38] The antitumor and cytotoxic effects are linked through trastuzumab effects on mitochondrial outer membrane permeabilization (MoMp). B-cell lymphoma 2 (BCl-2) is the prototype for a family of proteins that govern MoMp, with pro-apoptotic BAX and BCl-2-associated agonist of cell death (BAD), and anti-apoptotic BCl-2 and BCl-Xl (also known as BCl2l1).

Cardiac dysfunction caused by trastuzumab is most commonly an asymptomatic decrease in the left ventricular ejection fraction that tends to be reversible. However, if cardiac failure develops, this responds well to standard medical management.[39] Cardiac dysfunction was observed in up to 4% of women treated with trastuzumab, with a higher incidence in females taking additional anthracyclines.[40] Indeed, trastuzumab causes sensitization to anthracycline-induced cardiotoxic effects:[41] when trastuzumab was given alone for breast cancer, there were no cases of heart failure and no decreases in the left ventricular ejection fraction.[42] Trastuzumab is a humanized monoclonal antibody that is able to bind to the extracellular domain of the human epidermal growth factor receptor-2.[43] Several cardiac adverse effects can occur as a result of trastuzumab treatment like: left ventricular dysfunction, acute coronary syndrome, hypertension, pericardial pathology, vasospasm and dilated cardiomyopathy.[44] Mice with cardiac-specific deletion of ERBB2 develop

age-related dilated cardiomyopathy characterized by the presence of cardiac myocytes with increased numbers of mitochondria, vacuoles, and sensitivity to anthracyclines.[45] Trastuzumab cardiotoxicity is an on-target effect due to blocking all downstream signaling from ERBB2, and causing MoMp, cytochrome c release, and caspase activation, resulting in apoptosis of cardiac muscle cells with impaired contractility and ventricular function.[46] Trastuzumab inhibits the actions of NRG1 in cardiac myocytes by multiple mechanisms,[47] preventing NRG1's potential role in the treatment of disorders of cardiac function.[48] To elucidate the mechanism of trastuzumab cardiac dysfunction, rodent, and primate models have been developed, and these may help define effects on ERBB2-positive cancer cells without causing cardiotoxicity.

## Discussion

From the beginning, we have to realize which types of risks are available for a monoclonal antibody and take necessary measures to determine and decrease the potential adverse effects. Infusion reactions can be minimized by sound preclinical and clinical practice, whereas predisposition to infection can be minimized by appropriate monitoring and selection of therapies. In the preclinical phase, the major need is for the development and validation of appropriate in vitro safety tests with biologics on human blood and tissues, and to have predictive tests for CRS on administration to humans.

## Conclusion

To ensure the safety of volunteers in clinical trials, there is the need for communication to be maintained between scientists and clinicians, pharmaceutical and biotechnology companies, and individuals involved in carrying out and regulating clinical studies. Together, these measures will help increase the safety of mAbs, which is vital for a greater use of mAb-based therapy in the treatment of human disease.

**Peer-review:** Externally peer-reviewed.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Authorship Contributions:** Concept: BD, MM, MY, ZM; Design: BD, MM, MY, ZM; Supervision: ZG; Materials: ZG; Data Collection or Processing: ZG; Analysis or Interpretation: ZG; Literature Search: BD, MM, MY, ZM; Writing: ZG; Critical Review: ZG.

**Conflict of Interest:** None declared.

**Financial Disclosure:** The authors declared that this study received no financial support.

## References

1. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 1975;256(5517):495–7. [CrossRef]
2. Dubel S, editor. Handbook of Therapeutic Antibodies. Weinhem:Wiley;2007. [CrossRef]
3. Lonberg N. Human antibodies from transgenic animals. Nat Biotechnol 2005;23(9):1117–25. [CrossRef]
4. American Society of Clinical Oncology (ASCO). Understanding immunotherapy. Accessed at: https://www.cancer.net/navigating-cancer-care/how-cancertreated/immunotherapy-and-vaccines/understanding-immunotherapy Accessed Dec 19, 2019.
5. Weiner GJ. Building better monoclonal antibody-based therapeutics. Nat Rev Cancer 2015;15(6):361–70. [CrossRef]
6. Wolska-Washer A, Robak T. Safety and tolerability of antibody-drug conjugates in cancer. Drug Saf 2019;42(2):295–314. [CrossRef]
7. Lakshmi Deppthi Gedela. Monoclonal antibodies. https://www.slideshare.net/LAKSHMIDEEPTHIGEDELA/monoclonal-antibodies-198366965 Accessed Oct 9, 2023.
8. Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and pharmacological classification. Nat Rev Drug Discov 2008;7(1):21–39. [CrossRef]
9. Guan M, Zhou YP, Sun JL, Chen SC. Adverse events of monoclonal antibodies used for cancer therapy. Biomed Res Int 2015;2015:428169. [CrossRef]
10. Sim DW, Park KH, Park HJ, Son YW, Lee SC, Park JW, et al. Clinical characteristics of adverse events associated with therapeutic monoclonal antibodies in Korea. Pharmacoepidemiol Drug Saf 2016;25(11):1279–86. [CrossRef]
11. Du XL, Xia R, Burau K, Liu CC. Cardiac risk associated with the receipt of anthracycline and trastuzumab in a large nationwide cohort of older women with breast cancer, 1998-2005. Med Oncol 2011;28 Suppl 1:S80–90. [CrossRef]
12. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350(23):2335–42. [CrossRef]
13. Garcia JA, Hudes GR, Choueiri TK, Stadler WM, Wood LS, Gurtler J, et al. A phase 2, single-arm study of ramucirumab in patients with metastatic renal cell carcinoma with disease progression on or intolerance to tyrosine kinase inhibitor therapy. Cancer 2014;120(11):1647–55. [CrossRef]
14. Wang W, Zhao LR, Lin XQ, Feng F. Reversible posterior leukoencephalopathy syndrome induced by bevacizumab plus chemotherapy in colorectal cancer. World J Gastroenterol 2014;20(21):6691–7. [CrossRef]
15. Conti P, Pregliasco FE, Calvisi V, Caraffa Al, Gallenga CE, Kritas SK, et al. Monoclonal antibody therapy in COVID-19. J Biol Regul Homeost Agents 2021;35(2):423–7.
16. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 2010;9(4):325–38. [CrossRef]
17. Clark IA. The advent of the cytokine storm. Immunol Cell Biol

2007;85(4):271–3. [CrossRef]
18. Wing M. Monoclonal antibody first dose cytokine release syndromes-mechanisms and prediction. J Immunotoxicol 2008;5(1):11–5. [CrossRef]
19. Plevy S, Salzberg B, Van Assche G, Regueiro M, Hommes D, Sandborn W, et al. A phase I study of visilizumab, a humanized anti-CD3 monoclonal antibody, in severe steroid-refractory ulcerative colitis. Gastroenterology 2007;133(5):1414–22. [CrossRef]
20. Wing MG, Waldmann H, Isaacs J, Compston DA, Hale G. Ex-vivo whole blood cultures for predicting cytokine-release syndrome: dependence on target antigen and antibody isotype. Ther Immunol 1995;2(4):183–90.
21. Wing MG, Moreau T, Greenwood J, Smith RM, Hale G, Isaacs J, et al. Mechanism of first-dose cytokine-release syndrome by CAMPATH 1-H: involvement of CD16 (FcgammaRIII) and CD11a/CD18 (LFA-1) on NK cells. J Clin Invest 1996;98(12):2819–26. [CrossRef]
22. Winkler U, Jensen M, Manzke O, Schulz H, Diehl V, Engert A. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). Blood 1999;94(7):2217–24. [CrossRef]
23. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer 2007;7(5):332–44. [CrossRef]
24. Chen MH, Kerkelä R, Force T. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. Circulation 2008;118(1):84–95. [CrossRef]
25. Ransohoff RM. Natalizumab for multiple sclerosis. N Engl J Med 2007;356(25):2622–9. [CrossRef]
26. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med 2006;355(10):1018–28. [CrossRef]
27. Kenter MJ, Cohen AF. Establishing risk of human experimentation with drugs: lessons from TGN1412. Lancet 2006;368(9544):1387–91. [CrossRef]
28. UK Government National Web Archives. Report of a UK Expert Group commenting on safety of Phase I studies in the light of the TGN1412 cytokine storm. Available at: https://webarchive.nationalarchives.gov.uk/ukgwa/20130105090249/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063117 Accessed Oct 9, 2023.
29. Association of the British Pharmaceutical Industry (ABPI). Early Stage Clinical Trial Taskforce — Joint ABPI/BIA Report. Available at: http://www.abpi.org.uk/ information/pdfs/BIAABPI_taskforce2.pdf Accessed Oct 9, 2023.
30. Muller PY, Milton M, Lloyd P, Sims J, Brennan FR. The minimum anticipated biological effect level (MABEL) for selection of first human dose in clinical trials with monoclonal antibodies. Curr Opin Biotechnol 2009;20(6):722–9. [CrossRef]
31. Beyersdorf N, Hanke T, Kerkau T, Hünig T. Superagonistic anti-CD28 antibodies: potent activators of regulatory T cells for the therapy of autoimmune diseases. Ann Rheum Dis 2005;64 Suppl 4(Suppl 4):iv91–5. [CrossRef]
32. Beyersdorf N, Gaupp S, Balbach K, Schmidt J, Toyka KV, Lin CH, et al. Selective targeting of regulatory T cells with CD28 superagonists allows effective therapy of experimental autoimmune encephalomyelitis. J Exp Med 2005;202(3):445–55. [CrossRef]
33. Hünig T, Dennehy K. CD28 superagonists: mode of action and therapeutic potential. Immunol Lett 2005;100(1):21–8. [CrossRef]
34. Müller N, van den Brandt J, Odoardi F, Tischner D, Herath J, Flügel A, et al. A CD28 superagonistic antibody elicits 2 functionally distinct waves of T cell activation in rats. J Clin Invest 2008;118(4):1405–16. [CrossRef]
35. Hünig T. Manipulation of regulatory T-cell number and function with CD28-specific monoclonal antibodies. Adv Immunol 2007;95:111–48. [CrossRef]
36. Hudis CA. Trastuzumab--mechanism of action and use in clinical practice. N Engl J Med 2007;357(1):39–51. [CrossRef]
37. Hsu JY, Mao YC, Liu PY, Lai KL. Pharmacology and adverse events of emergency-use authorized medication in moderate to severe COVID-19. Pharmaceuticals (Basel) 2021;14(10):955.
38. Guglin M, Cutro R, Mishkin JD. Trastuzumab-induced cardiomyopathy. J Card Fail 2008;14(5):437–44. [CrossRef]
39. Klein PM, Dybdal N. Trastuzumab and cardiac dysfunction: update on preclinical studies. Semin Oncol 2003;30(5 Suppl 16):49–53. [CrossRef]
40. Perez EA. Cardiac toxicity of ErbB2-targeted therapies: what do we know? Clin Breast Cancer 2008;8 Suppl 3:S114–20. [CrossRef]
41. Chien KR. Herceptin and the heart--a molecular modifier of cardiac failure. N Engl J Med 2006;354(8):789–90. [CrossRef]
42. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, et al.; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354(8):809–20. [CrossRef]
43. Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, et al. Cancer therapy-related cardiac dysfunction and heart failure: part 1: definitions, pathophysiology, risk factors, and ımaging. Circ Heart Fail 2016;9(1):e002661. [CrossRef]
44. Nemeth BT, Varga ZV, Wu WJ, Pacher P. Trastuzumab cardiotoxicity: from clinical trials to experimental studies. Br J Pharmacol 2017;174(21):3727–48. [CrossRef]
45. Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 2002;8(5):459–65. [CrossRef]
46. Kuramochi Y, Guo X, Sawyer DB. Neuregulin activates erbB2-dependent src/FAK signaling and cytoskeletal remodeling in isolated adult rat cardiac myocytes. J Mol Cell Cardiol 2006;41(2):228–35. [CrossRef]
47. Grazette LP, Boecker W, Matsui T, Semigran M, Force TL, Hajjar RJ, et al. Inhibition of ErbB2 causes mitochondrial dysfunction in cardiomyocytes: implications for herceptin-induced cardiomyopathy. J Am Coll Cardiol 2004;44(11):2231–8. [CrossRef]
48. Lemmens K, Doggen K, Keulenaer GW. Neuregulin-1 and its potential role in the control of cardiac function. Heart Fail Monit 2008;5(4):119–24.