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Adjunctive Tecentriq In PD-L1-Positive Unresectable Locally Advanced Or Metastatic Triple-Negative Breast Cancer

Keywords: Atezolizumab, Tecentriq, triple-negative breast cancer, immunotherapy, PD-L1-positive, immunohistochemistry

SUMMARY OF TECHNOLOGY

Tecentriq® (atezolizumab) is a monoclonal antibody which will bind with a protein called Programmed Cell Death –Ligand 1(PD-L1).[1] Programmed Cell Death –Ligand 1(PD-L1) is expressed on tumour cells and tumour-infiltrating immune cells, associated with apoptosis. It is a key immunoregulatory molecule which upon interacting with the receptor, PD-1, inhibits the CD8 cytotoxic immune response and the resultant antitumour immune response. Tecentriq binds to PD-L1, blocking its interactions with both PD-1 and B7-1 receptors.[2] By inhibiting PD-L1, Tecentriq may enable the activation of T cells.

Tecentriq is recommended to be used in combination with chemotherapy with Abraxane® (nanoparticle albumin-bound paclitaxel) as first line treatment for PD-L1 positive population with metastatic or unresectable locally advanced triple negative breast cancer (TNBC).[1] Abraxane is from the taxane class, which have microtubule stabilizing ability. Systemic Abraxane is used to treat metastatic cancer.[3]

Tecentriq comes in a vial of 20 ml Tecentriq (60mg/ ml) to be further diluted with 250 mls of normal saline 0.9% solution and administered via intravenous (IV) route as a 60 minutes infusion the first time and if tolerated, the next dose can be given within 30 minutes.[4]

Immune therapy is a new standard of care strategy for treatment of melanoma, lung cancer and bladder cancer among other malignancies.[5]

FDA first approved Tecentriq in May 2016 as immunotherapy for untreated or previously treated metastatic urothelial carcinoma (mUC) not eligible for cisplatin-containing

therapy, then in October 2016 for treatment of metastatic non small cell lung carcinoma.[6]

Tecentriq attained FDA approval as of March 18, 2019 for the usage as first line therapy together with chemotherapy for extensive small cell lung carcinoma.[7] Tecentriq is registered with the Malaysian National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health for the indication of metastatic non small cell lung carcinoma.[8]

Tecentriq was granted accelerated approval by FDA as an adjunctive therapy with abraxane for the treatment of PD-L1-positive unresectable locally advanced or metastatic TNBC, as tested with VENTANA PD-L1 (SP142) Assay on March 8 2019. This indication was approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.[9]

Fig 1 : Vial of Tecentriq solution (60mg/ml)

INNOVATIVENESS

Novel, completely new	
Incremental improvement of the existing technology	
New indication of an existing technology	√

DISEASE BURDEN

Breast cancer is the most common cancer among Malaysian women.[10] Triple negative breast cancer (TNBC) takes a proportion of 15% of all breast cancer, and is more common in women under the age of 50, compared to other forms of breast cancer.[11] Triple negative is defined by the lack of expression of the targetable receptors for

oestrogen, progesterone, and HER2 amplification.[1] Patients with metastatic TNBC usually present later, have rapid progression and shorter overall survival compared to other subtypes of breast cancer. Programmed Cell Death –Ligand 1 (PD-L1)-positive metastatic TNBC is a highly aggressive form of breast carcinoma with limited options.[11] Molecularly, TNBC have a higher PD-L1 expression level, which may hinder antitumour T-cell response.

CURRENT OPTIONS FOR PATIENTS

Current option is chemotherapy with platinum compounds. Chemotherapy can have serious adverse events that lead to low compliance, dose reductions, treatment delays, and treatment refusal. [12]

POTENTIAL IMPACT OF TECHNOLOGY

STUDIES INCLUDED:

A Study of Atezolizumab in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Participants With Previously Untreated Metastatic Triple-Negative Breast Cancer (IMpassion130) NCT02425891

Clinical Impact

IMpassion130 is a phase 3 clinical trial involving 902 participants from 246 sites in 41 countries.[13] It was a double blinded randomized 1:1 study evaluating the efficacy, safety and pharmacokinetics of Tecentriq and Abraxane (ARM A) compared with placebo in combination with Abraxane (ARM B) in patients with locally advanced TNBC who have not received prior systemic therapy or targeted therapy for metastatic TNBC. Patients in ARM A received atezolizumab (840 mg), while ARM B patients received placebo intravenous infusions on days 1 and 15 of every 28-day cycle. Both groups had paclitaxel protein-bound (100 mg/m2) administered via intravenous infusion on days 1, 8, and 15 of every 28-day cycle. They were given a target of at least 6 cycles, until unacceptable toxicity or disease progression. Patients in ARM A showed a better median progression free survival of 7.4 months compared to patients in ARM B (4.8 months). (HR=0.60, 95% CI: 0.48,0.77, p<0.0001).[14]

Tecentriq with Abraxane prolonged progression free survival among patients with metastatic TNBC in both the intention to treat population and the PD-L1-positive subgroup. [13]

Cost

Tecentriq is quoted to cost $ 13,400 per month.[15] Since it cannot be used as a single immunotherapy agent, the cost of Abraxane have to be factored in the cost. Abraxane is not listed in the blue book but was quoted for a self funded patient in Malaysia for RM1422.70 per vial of 100mg Abraxane. [16]

Organisational – Patients need to be tested for the PD-L1 amino chain using a reliable immunohistochemical assay.

Societal/ethical- No major societal or ethical issue is expected with introduction of brolucizumab.

Safety – Some of the most common side effects of Tecentriq are nausea, peripheral neuropathy, low blood counts, and fatigue. As an immunotherapy, Tecentriq has systemic immune related adverse effects, including myositis, nephritis, pneumonitis (3.1%), colitis (1.1%), endocrinopathies, pancreatitis (0.5%), hepatitis (0.3%), neuropathies (0.2%) , myocarditis and myasthenic syndrome (<0.1%). The mechanism of immune related adverse events are still not clear. Although they mostly can be well controlled with withholding immune checkpoint inhibitor drugs or discontinuation and administering glucocorticoids as supportive treatment, safety and patient tolerability are still a concern. [12] Roche had communicated that there were reports of 51 serious and 14 non-serious cases of immune related myositis and nephritis, as was highlighted by NPRA.[17, 18]

Tecentriq has the best safety profile in general when compared with the five immune checkpoint inhibitor drugs.[12]

FDA issued caution that Tecentriq when used as a single agent therapy in metastatic urothelial cancer caused decreased survival. Thus they revised patient selection for use of Tecentriq treatment in patients with locally advanced or metastatic urothelial carcinoma to have a requirement of an FDA-appoved test. The indication is now for patients who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 as determined by the FDA-appoved test, or are not eligible for any platinum-containing therapy regardless of PD-L1 status.[19]

In conclusion, adjunctive Tecentriq has been approved to be used for a new indication of treatment of PD-L1-positive unresectable locally advanced or metastatic TNBC, and can be considered under the Medicines under Special Authorisation Forms on special case basis, but have to be on continued surveillance for clinical benefits other than progression free survival and also weighed against the severity of immune related adverse effects.

EVIDENCE

Published Papers:

1. Schmid P, Adams S, Rugo HS et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer, NEJM. 2018; 378:2108-2121

2. Emens LA, Lois S, Rugo HS, et al: IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, phase III study of atezolizumab + nab-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer. 2018 San Antonio Breast Cancer Symposium. Abstract GS1-04.

3. Balar AV, Galsky MD, Rosenberg JE et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single –arm, multicenter, phase 2 trial. The Lancet. 2017; 389(10064): 67-76 NCT02108652

4. Fehrenbacher L, Spira A, Ballinger M et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicenter, open-label, phase 2 randomised controlled trial. The Lancet. 2016;387(10030):1837-1846 NCT01903993

5. Bordoni R, Ciardiello F, Pawel J et al. Patient-reported outcomes in OAK: A Phase III study of Atezolizumab versus Docetaxel in Advanced Non-small-cell lung cancer. Clinical Lung Cancer. 2018;19(5) 441-449.e4

REFERENCES

1. Media release by Roche. IMpassion130 Study. Available at https://www.roche.com/media/releases/med-cor-2018-07-02.htm Accessed 20 Feb 2019.

2. Constantinidou A, Aliferis C, Trafalis DT. Targeting Programmed Cell Death-1 (PD-1) and Ligand (PD-L1):A new era in cancer active immunotherapy. Pharmacology &Therapeutics 2018; 194: 84-106

3. Abraxane and advanced (metastatic) breast cancer. Available at https://www.abraxane.com/mbc/abraxane-and-advanced-breast-cancer/ Accessed 20 July 2019

4. Tecentriq Product Leaflet. Annex 1. Summary of Product Characterics.

5. Sanchez K, Page D, McArthur HL. Immunotherapy in breast cancer: An overview of modern checkpoint blockade strategies and vaccines. Curr Probl Cancer 2016;40:151-162

6. Tecentriq (Atezolizumab) Receives New Indication for First-Line Treatment of Locally Advanced or Metastatic Urothelial Carcinoma. Available at http://www.ahdbonline.com/issues/2018/april-2018-vol-11-ninth-annual-payers-guide/2549-tecentriq-atezolizumab-receives-new-indication-for-first-line-treatment-of-locally-advanced-or-metastatic-urothelial-carcinoma Accessed 20 July 2019

7. American Cancer Society. FDA Approves Tecentriq (Atezolizumab) for Small Cell Lung Cancer. Available at https://www.cancer.org/latest-news/fda-approves-tecentriq-atezolizumab-for-small-cell-lung-cancer.html Accessed 15 August 2019.

8. MIMS. Tecentriq. Available at http://www.mims.com/malaysia/drug/info/tecentriq?type%20full Accessed 15 August 2019

9. US Food & Drug Administration. Drug Approvals. FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer. Available at https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-locally-advanced-or-metastatic-triple-negative Accessed 15 August 2019.

10. Dahlui M, Ramli S, Bulgiba AM. Breast Cancer Prevention and Control Programs in Malaysia. Asian Pacific J Cancer Prev 2011;12:1-4

11. Tan GH, TAib NA, Choo WY et al. Clinical characteristics of triple negative breast cancer: Experience in an Asian Developing Country. Asian Pacific J Cancer Prev 2009;10:395-398

12. Xu C, Chen YP, Du XJ et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ 2018;363:k4226

13. Schmid P, Adams S, Rugo HS et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer, NEJM. 2018; 378:2108-2121

14. National Cancer Institute. Atezolizumab Approved for Some Patients with Triple-Negative Breast Cancer. Available at https://www.cancer.gov/news-events/cancer-currents-blog/2019/atezolizumab-triple-negative-breast-cancer-fda-approval Accessed on 27 May 2019.

15. Federal News Network. FDA approves 1st immunotherapy drug to treat breast cancer**.** Available at: https://federalnewsnetwork.com/business-news/2019/03/fda-approves-1st-immunotherapy-drug-to-treat-breast-cancer/ Accessed on 27 May 2019

16. Verbal conversation with Malaysia National Institute of Cancer pharmacist, Pn Suhaida Bt Baharudin in Jan 2019.

17. NPRA: Tecentriq® (atezolizumab): Risk of nephritis. Available at https://www.npra.gov.my/index.php/en/health-professionals/recent-updates/79-english/safety-alerts-main/safety-alert-2018/1775-tecentriq-atezolizumab-risk-of-nephritis Accessed 20 July 2019

18. NPRA: TECENTRIQ® (atezolizumab): A new important identified risk – immune-related myositis. https://www.npra.gov.my/index.php/en/health-professionals/recent-updates/414-english/safety-alerts-main/safety-alerts-2019/2108-tecentriq-atezolizumab-a-new-important-identified-risk-immune-related-myositis.html Accessed 20 July 2019

19. US Food & Drug Administration. Drug Approvals. FDA limits the use of Tecentriq and Keytruda for some urothelial cancer patients. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-limits-use-tecentriq-and-keytruda-some-urothelial-cancer-patients Accessed 20 August 2019

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