Combinatorial treatment of HER2 positive breast cancer with Trastuzumab

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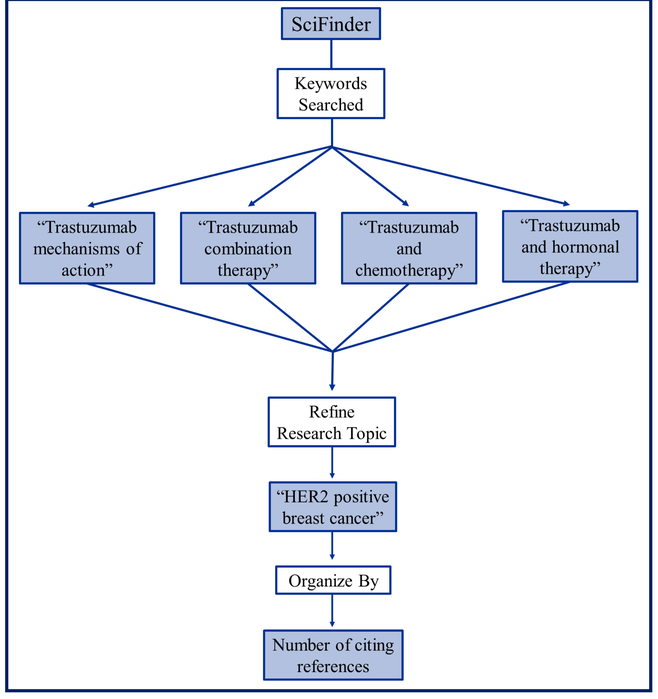
Introduction

- 1 in 8 U.S. women will develop invasive breast cancer in her life (1).
- >300,000 new cases are estimated to be diagnosed in women in 2021, killing more than 40,000 of them (1).
- Human epidermal growth factor receptor 2 (HER2) positive breast cancer is caused by an overexpression of the HER2 protein (2).
- ~ 20-25% of breast cancers show HER2 gene amplification or protein overexpression (2).
- Trastuzumab is a monoclonal antibody that selectively targets and binds with high affinity to HER2 (3).
- Trastuzumab is a leading treatment for HER2 positive breast cancer (3).
- The objective of this study is to compare the effectiveness of various trastuzumab combinations by comparing tumor size reduction and progression free survival (PFS).

Methods



Results

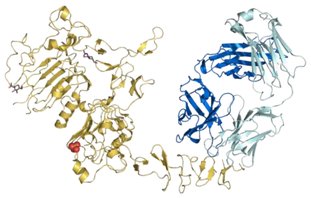


Figure 1: Structure of trastuzumab antibody binding fragment (4).

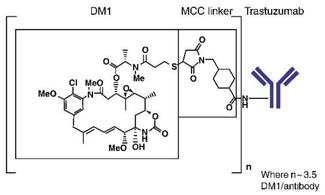


Figure 2: Structure of T-DM1 (5).

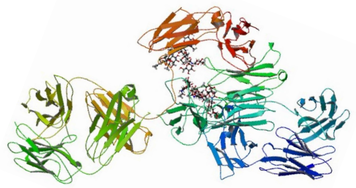


Figure 3: Structure of pertuzumab (6).

Trastuzumab in Mouse Tumor Models

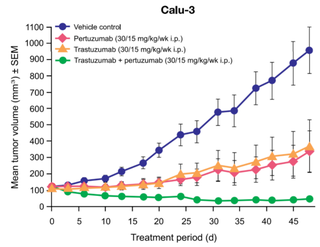


Figure 4: Calu-3 xenograft tumors treated with vehicle, pertuzumab, trastuzumab, and trastuzumab + pertuzumab. (n = 10 mice/group) (7).

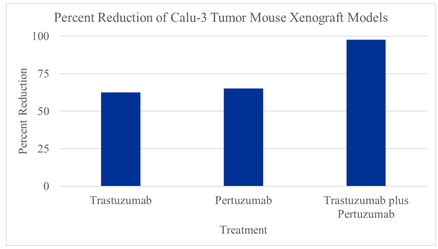


Figure 5: Reduction of Calu-3 tumor mouse xenografts treated with trastuzumab, pertuzumab, and trastuzumab + pertuzumab (7).

Trastuzumab with Chemotherapies and Hormonal Therapy

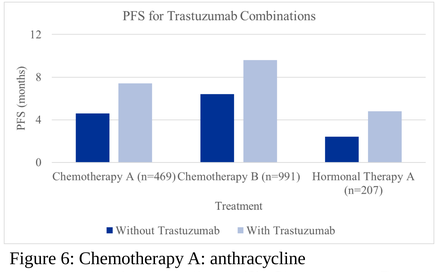


Figure 6: Chemotherapy A: anthracycline cyclophosphamide or paclitaxel (8). Chemotherapy B: oral lapatinib + oral capecitabine. The treatment with trastuzumab was an antibody conjugate, T-DM1 (9). Hormonal therapy A: oral anastrozole (10).

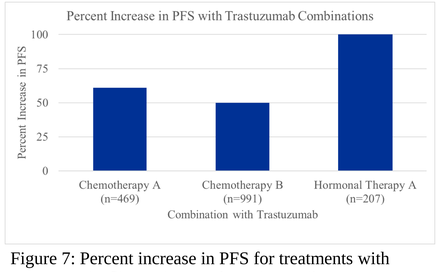


Figure 7: Percent increase in PFS for treatments with trastuzumab. Chemotherapy A: anthracycline cyclophosphamide or paclitaxel (8). Chemotherapy B: oral lapatinib + oral capecitabine. The treatment with trastuzumab was an antibody conjugate, T-DM1 (9). Hormonal therapy A: oral anastrozole (10).

Trastuzumab with Pertuzumab, Chemotherapy, and Hormonal Therapy

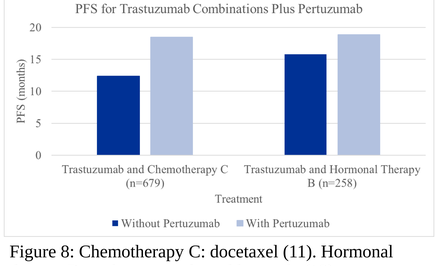


Figure 8: Chemotherapy C: docetaxel (11). Hormonal therapy B: oral anastrozole and letrozole (12).

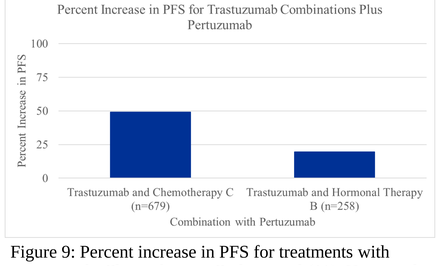


Figure 9: Percent increase in PFS for treatments with pertuzumab. Chemotherapy C: docetaxel (11). Hormonal therapy B: oral anastrozole and letrozole (12).

Discussion/Conclusion

- Trastuzumab with pertuzumab enhanced the percent size reduction in tumor mouse xenografts from 62-65% to 97%.
- Trastuzumab increased the progression-free survival in combination with:
  - Chemotherapy (61%)
  - Anti-body drug conjugate (50%)
  - Hormonal therapy (100%)
  - Pertuzumab (19.6-49.2%)
- Increased signal inhibition with combinatorial treatment with hormonal therapy and pertuzumab.
- The versatility of trastuzumab allows it to be used in various applications that can suit a variety of patients with different needs.

References

1. U.S. Breast Cancer Statistics. https://www.breastcancer.org/symptoms/understand _bc/statistics (accessed Feb10, 2021)
2. Fiszman, G. L.; Jasnis, M. A. *Int. J. Breast Cancer.* **2011**. *2011*, 352182.
3. Jones, A. *Ann. Oncol.* **2003.** *14* (12), 1697–1704.
4. Trastuzumab. https://en.wikipedia.org/wiki/Trastuzumab (accessed Feb 25, 2021)
5. Poon, K. A.; Flagella, K.; Beyer, J.; Tibbitts, J.; Kaur, S.; Saad, O.; Yi, J.-H.; Girish, S.; Dybdal, N.; Reynolds, T. *Toxicol. Appl. Pharmacol.* **2013**. *273* (2), 298-313.
6. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. https://go.drugbank.com/drugs/DB06366 (accessed Feb 25, 2021)
7. Scheuer, W.; Friess, T.; Burtscher, H.; Bossenmaier, B.; Endl, J.; Hasmann, M. *Cancer Res.* **2009**. *69* (24), 9330-9336.
8. Slamon, D. J.; Leyland-Jones, B.; Shak, S.; Fuchs, H.; Paton, V.; Bajamonde, A.; Fleming, T.; Eiermann, W.; Wolter, J.; Pegram, M.; Baselga, J.; Norton, L. *N. Engl. J. Med.* **2001**. *344*, 783-792
9. Verma, S.; Miles, D.; Gianni, L.; Krop, I. E.; Welslau, M.; Baselga, J.; Pegram, M.; Oh, D. Y.; Diéras, V.; Guardino, E.; Fang, L.; Lu, M. W.; Olsen, S.; Blackwell, K.; the EMILIA Study Group. *N. Engl. J. Med.* **2012**. *367*, 1783-1791.
10. Kaufman, B.; Mackey, J. R.; Clemens, M. R.; Bapsy, P. P.; Vaid, A.; Wardley, A.; Tjulandin, S.; Jahn, M.; Lehle, M.; Feyereislova, A.; Révil, C.; Jones, A. *J. Clin. Oncol.* **2009**. *27* (33), 5529-5537.
11. Baselga, J.; Cortes, J.; Kim, S-B.; Im, S-A.; Hegg, R.; Im, Y-H.; Roman, L.; Pedrini, J. L.; Pienkowski, T.; Knott, A.; Clark, E.; Benyunes, M. C.; Ross, G.; Swain, S. M. *N. Engl. J. Med.* **2012**. *366*, 109-119.
12. Rimawi, M.; Ferrero, J.; de la Haba-Rodriguez, J.; Poole, C.; De Placido, S.; Osborne, C. K.; Hegg, R.; Easton, V.; Wohlfarth, C.; Arpino, G.; The PERTAIN Study Group. *J. Clin. Oncol.* **2018**. *36* (28), 2826-2835.

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