An update on clinical oncology for the non-oncologist
Avanços em oncologia para o não oncologista
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ABSTRACT
Recent advances in the understanding of tumor driver mutations, signaling pathways that lead to tumor progression, and the better understanding of the interaction between tumor cells and the immune system are revolutionizing cancer treatment. The pace at which new treatments are approved and the prices at which they are set have made it even more difficult to offer these treatments in countries like Brazil. In this review we present for the non-oncologist these new treatments and compare their availability in Brazilian public health system and private health system with that of developed countries.

Keywords: Neoplasms/trends; Immunotherapy/trends

INTRODUCTION
Within the last few years, the field of systemic therapy in medical oncology has seen two dramatic changes. First, the advances in the understanding of genetic abnormalities led to the discovery of various tumor driver mutations with the consequent development of different targeted therapies. Second, the better understanding of interaction between tumor cells and immune system led to the now much broader field of immuno-oncology and the consequent development of immunotherapies, which is currently being tested for treatment of different cancer types. In addition to these advances, a few new traditional chemotherapies have been approved and some already well-known treatments have had their indication broadened. Our objective is to review, for non-oncologists, the most recent advances of modern systemic cancer treatment.
survival have improved. In addition, before choosing the therapies, it is necessary to test the target, which sometimes requires sophisticated and costly techniques. Considering that some targets may be present in less than 5 to 10% of the patient population, many of them need to be tested in order to find one eligible for the targeted treatment. Adding the costs of tests and the drugs, these therapies are almost prohibitive for the Brazilian Public Health System, which prevent a significant majority of our population from receiving such treatments.

Table 1 shows selected new targeted therapies made available in the last three years. Approval in Brazil has been limited, mainly due to regulatory delays, but

### Table 1. Targeted therapies

| Reference          | Tumor type (by organ) | Name of drug           | Mechanism of action | Indication                                                                 | Main results                                                                 | Availability in Brazil                                                                 |
|-------------------|-----------------------|------------------------|---------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Verma et al.(4)   | Breast                | Ado-trastuzumab emtansine (T-DM1) | Antibody-drug conjugate against Her2+ cells | Metastatic Her2+ breast cancer, after failing trastuzumab and taxane      | Improved PFS and overall survival compared with lapatinib and capecitabine   | Registered in Brazil. Not available in Brazilian Public Health System     |
| Swain et al.(5)   | Breast                | Pertuzumab             | Her2 inhibition     | Metastatic Her2+ breast cancer                                             | Improved PFS and overall survival compared with trastuzumab and taxane       | Registered in Brazil. Not available in Brazilian Public Health System     |
| Piccart et al.(6) | Breast                | Everolimus             | mTOR inhibitor      | Metastatic HR+ and Her2-breast cancer in combination with exemestane      | Improved PFS compared with second line exemestane alone                       | Registered in Brazil. Not available in Brazilian Public Health System     |
| Turner et al.(7)  | Breast                | Palbociclib            | CDK4 and CDK6 inhibitor | Metastatic HR+ and Her2-breast cancer in combination with fulvestrant   | Improved PFS compared with second line Fulvestrant alone                     | Not registered in Brazil                                                    |
| Tewari et al.(8)  | Cervix                | Bevacizumab            | VEGF inhibitor      | Metastatic cervical cancer                                                 | Improved overall survival when added to chemotherapy                          | Registered in Brazil. Not available in Brazilian Public Health System     |
| Grothey et al.(9) | Colorectal             | Regorafenib            | Multikinase inhibitor | Previously treated metastatic colorectal cancer                            | Modest improvement in overall survival compared with supportive care alone   | Not registered in Brazil                                                    |
| Fuchs et al.(10)  | Gastric               | Ramucirubin            | VEGFR2 antagonist   | Inoperable gastric or gastrointestinal junction adenocarcinoma after prior chemotherapy | Improved survival compared with placebo                                       | Not registered in Brazil                                                    |
| Demetri et al.(11)| GIST                  | Regorafenib            | Multikinase inhibitor | Metastatic GIST after standard treatment with imatinib and sunitinib      | Improved PFS compared with placebo                                           | Not registered in Brazil                                                    |
| Wu et al.(12)     | Lung                  | Afatinib               | EGFR inhibitor      | Metastatic NSCLC with EGFR exon 19 deletion or L858R EGFR mutation         | Improved PFS compared with gencitabine and cisplatin or cisplatin and pemetrexed | Not registered in Brazil                                                    |
| Sequist et al.(13)| Lung                  | Crizotinib             | ALK inhibitor, ROS1 inhibitor | Metastatic NSCLC with ALK-ENL4 fusion, or with ROS1 rearrangement          | Improved PFS compared with pemetrexed in platinum refractory disease        | Not registered in Brazil                                                    |
| Shaw et al.(14)   | Lung                  | Ceitinib               | ALK inhibitor       | Metastatic ALK-rearranged NSCLC                                            | Responses in naïve and crizotinib pretreated disease                         | Not registered in Brazil                                                    |
| Chapman et al.(15)| Melanoma              | Vemurafenib            | BRAF inhibitor      | Metastatic melanoma with BRAF V600E mutation                              | Improved overall survival and PFS compared with Dacarbazine                  | Registered in Brazil. Not available in Brazilian Public Health System     |
| Robert et al.(16) | Melanoma              | Dabrafenib             | BRAF inhibitor      | Metastatic melanoma BRAF V600E mutation                                   | Improved overall survival when combined with Trametinib, compared with Vemurafenib | Not registered in Brazil                                                    |
| Robert et al.(17) | Melanoma              | Trametinib             | MEK inhibitor       | Metastatic Melanoma with BRAF V600E or V600K mutation                    | Improved overall survival when combined with Dabrafenib, compared with Vemurafenib | Not registered in Brazil                                                    |
| Ladermann et al.(18)| Ovary             | Olaparib               | Inhibitor of poly (ADP-ribose) polymerase | BRCA mutated advanced ovarian cancer                                      | Improved PFS compared with placebo in platinum sensitive relapse              | Not registered in Brazil                                                    |
| Brose et al.(19)  | Thyroid               | Sorafenib             | Multi-kinase inhibitor | Metastatic differentiated thyroid cancer refractory to radioactive iodine | Improved PFS compared with placebo                                           | Not registered in Brazil for this indication                               |

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*Note: Continuation of Table 1 follows.*
Certainly influenced by costs as well. The table describes the main indications, the targets for each drug and the most important outcomes reported in clinical trials.

Some targeted therapies that have been approved and made available in the private health system in Brazil for several years still have limited access in the Brazilian Public Health System. Some examples are trastuzumab for metastatic Her2+ breast cancer; erlotinib and gefitinib for epidermal growth factor receptor (EGFR) mutated metastatic lung cancer; cetuximab and panitumumab for RAS-wild type metastatic colorectal cancer, in addition to several treatments used in hematological malignancies, which are not the focus of this report. Some other targeted treatments have been available for several years in North America and/or Europe, but they are still not registered in Brazil. Examples are aflibercept for colorectal cancer, pazopanib and trabectedine for soft tissue sarcomas, and axitinib for renal cell carcinoma.

**IMMUNOTHERAPY**

Human immune system has been known for quite some time for recognizing tumor antigens and mounting an immune response, although the actual explanation for the variability in tumor control by the immune system remains elusive. Cancer cells are capable of evading the immune surveillance by suppressing tumor-directed immunity through mechanisms described over the last two decades.(24) It occurs by inhibiting helper and cytotoxic T cells while stimulating regulatory T cells instead. Inhibitory mechanisms determined by cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed death 1 (PD1) and its ligand programmed death ligand 1 (PD-L1) can currently be targeted and inhibited by new immunotherapies, which lead to unblocking the immune response. This will ultimately unleash an immune attack on cancer cells. Anti-CTLA-4 antibodies as well as PD1 and PD-L1 inhibitors are already approved and used to treat a limited number of tumor types (melanoma and lung cancer), and promising preliminary results indicate potential future use in a large variety of cancers.

Table 2 outlines the new immunotherapies, its approved indications, mechanism of action and main results in clinical trials.

The successful combination of two immunotherapies was already reported. Combined nivolumab and ipilimumab had better results than either drug alone to treat metastatic melanoma.(32,33) Both nivolumab and pembrolizumab, as well as other anti-PD1, anti PD-L1 and combinations with anti-CTLA-4, are under test for a variety of tumors, with some extraordinary preliminary results. Positive results with these immunotherapies have been reported in kidney, bladder, pancreatic, metastatic colorectal cancer related to Lynch syndrome, gastroesophageal cancer and glioblastoma, among others. Of note, although, is that for most diseases exist a clear correlation of benefit with the higher expression of PD-L1 on tumor cells,(34,35) and there is still no standardized evaluation for the expression of PD1 or PD-L1. An unique aspect related to immunotherapies is sometimes the significant delayed response, which has been reported both with anti-CTLA-4 as well as anti-PD1 inhibitors.(36,37) This highlights the need for careful consideration before deeming these drugs ineffective, and it has led to the establishment of a different set of response criteria, known as immune-related response criteria (irRC).(38) Immune related adverse events derive from the activation of autoimmune-mediated diseases in the skin, gastrointestinal tract, liver and endocrine system. The most clinically relevant adverse
event is diarrhea, which may have late onset and be life threatening if not rapidly and properly treated.

OTHER NEW SYSTEMIC TREATMENTS

In addition to the new targeted therapies and immunotherapies, few other new treatments (with various mechanisms of action) with significant clinical impact have emerged and been approved for clinical use in recent years.

Table 3 describes new systemic treatments, its indications, mechanisms of action and main results in clinical trials.

Table 3. Other new cancer therapies

| Reference          | Tumor type (by organ) | Name of drug | Mechanism of action | Indication | Main results | Availability in Brazil                        |
|--------------------|-----------------------|--------------|---------------------|------------|--------------|---------------------------------------------|
| Ryan et al.        | Prostate              | Abiraterone  | Blocks cytochrome P450 17 alpha-hydroxilase reducing androgen production | Metastatic castration resistant prostate cancer | Improvement in overall survival compared with prednisone | Registered in Brazil. Not available in the Brazilian Public Health System |
| Beer et al.        | Prostate              | Enzalutamide | Androgen receptor blocker and androgen receptor signal inhibitor | Metastatic Castration resistant prostate cancer | Improvement in overall survival compared with placebo | Registered in Brazil for castration and chemotherapy refractory disease. Not available in Brazilian Public Health System |
| Sweeney et al.     | Prostate              | Docetaxel    | Interferes with mitotic spindle | Upfront treatment of castration sensitive metastatic prostate cancer | Improvement in overall survival when added to castration, compared with castration alone | Registered in Brazil. Available in the Brazilian Public Health System |
| Parker et al.      | Prostate              | Rad 223 dichloride | Alpha emitter that targets bone metastases | Metastatic (to the bones) castration resistant prostate cancer | Improved overall survival compared with placebo | Registered in Brazil. Not available in the Brazilian Public Health System |
| Cortes et al.      | Breast                | Eribulin mesilate | Microtubule inhibitor | Previously treated metastatic breast cancer | Improved overall survival compared with treatment of physicians choice | Registered in Brazil. Not available in the Brazilian Public Health System |

CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; PD1: programmed death 1; BRAF: proto-oncogene B-Raf; NSCLC: non small cell lung cancer.

There is currently a very vivid discussion around the world about the significant costs associated with new cancer therapy in general, and specifically about anti-cancer drugs. Immunotherapies, which seem to be on their way to become indicated for a large proportion of cancer patients, and some of the newer targeted therapies can cost hundreds of thousands of dollars per patient annually. (45) Cost is certainly a significant limiting factor for these drugs becomes available in Brazil.

Some good cancer treatments are still under registration process in Brazil, highlighting the gap between what is practice here in comparison with developed countries. No less important is the significant
between what is registered and used in the private health system and what is available and used in the Brazilian public health system. Unless pricing of drugs becomes more reasonable in the near future, and unless health technology evaluation for the public health system starts to be dictated by well-established standards and pre-specified cost-effectiveness limits, new cancer therapies will be ever more limited in developing countries like Brazil, and as a consequence the difference between what is practiced internationally and in our country will widen significantly.

REFERENCES

1. National Cancer Institute. National Human Genome Research Institute. The cancer genome atlas [Internet]. Bethesda: NCT [cited 2015 Sep 12]. Available from: http://cancergenome.nih.gov/publications

2. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57-70. Review.

3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74. Review.

4. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéses V, Guarino E, Fang L, Lu MW, Olsen S, Blackwell K, EMILO Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91. Erratum in: N Engl J Med. 2013;368(25):2442.

5. Swain SM, Baselga J, Kim SB, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, Huang H, et al. Trastuzumab in oestrogen receptor-positive breast cancer. N Engl J Med. 2015;372(8):724-34.

6. Piccart M, Hortobágyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015;372(19):1783-91. Erratum in: N Engl J Med. 2013;368(25):2442.

7. Turner NC, Ro J, André F, Loi S, Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéses V, Guarino E, Fang L, Lu MW, Olsen S, Blackwell K, EMILO Study Group. Trastuzumab emtansine for HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-34.

8. Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370(8):734-43.

9. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cordonnier C, Caputo L, Wagner A, Laurent D; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.

10. Fuchs CS, Tomasek J, Yang CJ, Dumitru F, Passalicq R, Goswami C, Safran H, dos Santos LV, Argile G, Ferry DR, Melichar B, Paliwal C, Popov S, Alberti J, Wyrzykowski A, Cividino E, Crompton M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2015;381(9863):303-12.

11. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gschwendt L, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Baldalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Baurer S, Nguyen BV, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.

12. Wu YL, Zhou C, Feng J, Lu S, Huang Y, Li W, et al. Afinitor versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LU-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213-22.

13. Sequist LV, Yang JC, Yamamoto N, O’Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327-34.

14. Shaw AT, Kim DW, Nakagawa K, Seto T, Créot L, Ahn MJ, et al. Crizotinib versus chemotherapy in advancedALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-94.

15. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon B, Salgia R, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014;371(21):1963-71.

16. Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014;370(13):1189-97.

17. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Longin P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O’Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolok K, Li J, Li, Nelson B, Hou J, Lee R, Raftery KT, McArthur GA; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(28):2507-16.

18. Robert C, Karaszewska B, Schachtler J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30-9.

19. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed aerous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet. 2014;15(8):852-61. Erratum in: Lancet Oncol. 2015;16(4):e158.

20. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Barthold L, de la Fouchardière C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Peña C, Molinar I, Schlumberger MJ; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319-28.

21. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372(7):621-30.

22. Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose M, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31(29):3639-46. Erratum in: J Clin Oncol. 2014;32(17):1864.

23. Wells SA Jr, Robinson BG, Gagel RF, D’Angelico SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Improved overall survival with ipilimumab in previously untreated melanoma. N Engl J Med. 2011;364(26):2507-16.

24. Hodi FS, O’Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23. Erratum in: N Engl J Med. 2010;363(13):1290.

25. Robert C, Thomas L, Bondarenko I, O’Day S, Weber J, Garbe C, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who have progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375-84.
29. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlini MS, McNeil C, Lotem M, Larkin J, Loigian P, Neyns B, Blank CU, Hamid O, Mateus C, Shapiro-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A; KEYNOTE-006 Investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-32.

30. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;372(2):123-35.

31. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Mainwaring P, Marisbach H, Miller K, Nkwong SB, Prabhu F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424-33.

32. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2016;375(3):2128-28.

33. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23-34.

34. Grosso J, Horak CE, Inzunza D, Cardona DM, Simon JS, Gupta AK, et al. Association of tumor PD-L1 expression and immune biomarkers with clinical activity in patients (pts) with advanced solid tumors treated with nivolumab (antiPD-1; BMS-936558; ONO-4538) [abstract]. J Clin Oncol. 2013;31(Suppl abstract 3016).

35. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Chodacki A, Wiechno P, Logue J, Seke M, Widmark A, Johannessen DC, Hoskin P, Bottomley D, James ND, Solberg A, Syndikus I, Kliment J, Wedel S, Boehmer S, Dall’Oglio M, Franzén L, Coleman R, Vogelzang NJ, O’Byrne TT, Staudacher K, Garcia-Vargas J, Shan M, Bruland DS, Sartor O; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):737-46.

36. James ND, Sydes MR, Mason MD, Clarke NW, Dearlaney DP, Spears MR, Docietaxel and/or zoledronic acid for hormone-naive prostate cancer: First overall survival results from STAMPEDE [abstract]. J Clin Oncol. 2015;33(Suppl abstract 5001).

37. Parker C, Nilsson S, Heinrich D, Helle SI, Sørensen JM, Fosså SD, Chodacki A, Wiechno P, Logue J, Seke M, Widmark A, Johannessen DC, Hoskin P, Bottomley D, James ND, Solberg A, Syndikus I, Kliment J, Wedel S, Boehmer S, Dall’Oglio M, Franzén L, Coleman R, Vogelzang NJ, O’Byrne TT, Staudacher K, Garcia-Vargas J, Shan M, Bruland DS, Sartor O; ALSYMPCA Investigators. Alfa emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-23.

38. Cortes J, O’Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Didras V, Delozier T, Vladimirov V, Cardoso F, Koh H, Bougnoux P, Dutschke CE, Seegobin S, Mir D, Meneses N, Wanders J, Twelves C; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician’s Choice Versus E7389) investigators. Erlinib monotherapy versus treatment of physician’s choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377(9769):914-23.

39. Durkee BY, Qian Y, Pollom EL, King MT, Dudley AS, Shaffer JL, et al. Cost-Effectiveness of Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2016;34(9):902-9.