Neoadjuvant treatment in breast cancer

Subjects: Oncology

Contributor: María Rosario Chica-Parrado , Ana Godoy-Ortiz , Begoña Jiménez , Nuria Ribelles , Isabel Barragan , Emilio Alba

Neoadjuvant Chemotherapy (NAC) in Breast Cancer (BC) has proved useful for the reduction in tumor burden prior to surgery, allowing for a more extensive breast preservation and the eradication of subjacent micrometastases. However, the impact on prognosis is highly dependent on the establishment of Pathological Complete Response (pCR), in particular for Triple Negative (TN) and Hormonal Receptor negative/Human Epidermal growth factor Receptor 2 positive (HR−/HER2+) subtypes. Several pCR predictors, such as PAM50, Integrative Cluster (IntClust), mutations in PI3KCA, or the Trastuzumab Risk model (TRAR), are useful molecular tools for estimating response to treatment and are prognostic. Major evolution events during BC NAC that feature the Residual Disease (RD) are the loss of HR and HER2, which are prognostic of bad outcome, and stemness and immune depletion-related gene expression aberrations. This dynamic nature of the determinants of response to BC NAC, together with the extensive heterogeneity of BC, raises the need to discern the individual and subtype-specific determinants of resistance. Moreover, refining the current approaches for a comprehensive monitoring of tumor evolution during treatment, RD, and eventual recurrences is essential for identifying new actionable alterations and the integral best management of the disease.breast cancer; neoadjuvant chemotherapy; pathological complete response; predictive markers; residual diseasebreast cancer; neoadjuvant chemotherapy; pathological complete response; predictive markers; residual disease

breast cancer neoadjuvant chemotherapy pathological complete response predictive markers residual disease

Neoadjuvant Chemotherapy (NAC) in Breast Cancer (BC) has proved useful for the reduction in tumor burden prior to surgery, allowing for a more extensive breast preservation and the eradication of subjacent micrometastases. However, the impact on prognosis is highly dependent on the establishment of Pathological Complete Response (pCR), in particular for Triple Negative (TN) and Hormonal Receptor negative/Human Epidermal growth factor Receptor 2 positive (HR−/HER2+) subtypes. Several pCR predictors, such as PAM50, Integrative Cluster (IntClust), mutations in PI3KCA, or the Trastuzumab Risk model (TRAR), are useful molecular tools for estimating response to treatment and are prognostic. Major evolution events during BC NAC that feature the Residual Disease (RD) are the loss of HR and HER2, which are prognostic of bad outcome, and stemness and immune depletion-related gene expression aberrations. This dynamic nature of the determinants of response to BC NAC, together with the extensive heterogeneity of BC, raises the need to discern the individual and subtype-specific determinants of resistance. Moreover, refining the current approaches for a comprehensive monitoring of tumor evolution during treatment, RD, and eventual recurrences is essential for identifying new actionable alterations and the integral best management of the disease.

1. Neoadjuvant Chemotherapy in Breast Cancer Treatments

Neoadjuvant Chemotherapy (NAC) is widely used as a standard of care for early and locally advanced Breast Cancer (BC). The standard practice consists of the administration of anthracycline-based chemotherapy and subsequent treatment with a taxane, with the addition of anti-Human Epidermal Growth Factor Receptor 2 (HER2) therapy in HER2+ disease [1]. The main purposes of NAC in the clinical setting are the increase in breast preservation rate (reduction in tumor burden) and the achievement of a pathological Complete Response (pCR), which greatly influences Disease-Free Survival (DFS) and Overall Survival (OS). In addition, the implementation of NAC became a driving force in the search for new therapeutic targets and generated excellent in vivo models to investigate the sensitivity and resistance mechanisms of novel therapeutic approaches.

The response to NAC is key for the assessment of outcome after surgery, which is based on the pathological examination of breast tissue and lymph nodes that are surgically removed after NAC [2][3]. This assessment can be dichotomized in pCR and Residual Disease (RD). pCR is defined as the absence of invasive cancer cells in the breast and/or axillary nodes (ypT0/Tis ypN0), while RD is defined as the non-absence of invasive cancer cells in the breast and axillary nodes. Within this frame, several types of grading and classifications of pCR and RD have been established depending on the employed pathological examination (reviewed in Penault-Llorca et al., 2016 [3]). Classifications such as Miller and Payne [4] and Residual Cancer Burden (RCB) [5] quantify the response to NAC in several grades, where one is pCR and the others correspond to a spectrum of values that reflect the extent of RD [3].

The association of sensitivity to NAC in terms of pCR achievement with better long-term outcomes has been established [6], particularly in specific BC subtypes, such as luminal B/HER2 negative (HER2−), HER2-positive (HER2+)/non-luminal, and Triple Negative (TN) BC[7].

Different studies from Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) showed that the absence of invasive tumor cells in breast and axillary lymph nodes after NAC added prognosis value when using Event-Free Survival (EFS) and OS as outcome measurements, to the sole detection of breast invasive tumor cells (EFS HR 0.44 vs. 0.6; OS HR 0.36 vs. 0.51) [8]. In general, patients that have pCR following NAC are much less likely to recur than those with RD [6][9][10][11][12]. The approximate general percentage of pCR in BC is 31%, whereas pCR achievement in BC subtypes is 12% for HR+/HER2−, 40% for TN, and 47% for HER2+ (anti-HER2 treated) subtypes [12]. The subtype-specific associations between pCR and outcome arose in three pivotal clinical trials, NeoALTTO [13], NOAH [14], and NeoSphere [15], which collectively show that pCR is a highly informative prognosis biomarker in the HER2+ subtype; those patients with HER2+ breast tumors treated with NAC and anti-HER2 treatment (Trastuzumab or Trastuzumab plus Pertuzumab) that achieved pCR had a significantly higher 6-year EFS (77% vs. 65%) and OS (86% vs. 77%) compared with those without pCR [16]. The association between pCR and long-term outcomes in the different BC subtypes has been reviewed elsewhere [6]; when pCR is documented, the risk of death was reduced by 84% in TN, 92% in HER2+, and 71% in HR+ BC. The most relevant recent clinical trials about NAC treatment with pCR as endpoint are described in Table 1. Specific recent reviews on clinical trials evaluating NAC in TN and HER2+ BC give a good account of them [17].

Given this relevant potential as a prognostic biomarker, and considering the discrete percentage of patients that achieve pCR after NAC (31%) [12], there is an urgent need to define those predictive factors that can anticipate response to NAC, and therefore, cooperate to determine the best therapeutic approach in advance.

Table 1. Summary of clinical trials based on chemotherapy**.**

Clinical Trials	Patients	Treatment	pCR (%)
I-SPY [11]	All Subtypes	NAC	HER2-enriched and Basal-like subtypes achieved the best % of pCR compared with Luminal B subtype (55% and 34% vs. 13%, respectively).
GeparDuo [18]	All Subtypes	NAC	Those tumors HR− had better response to NAC than those HR+ (22.8% vs. 6.2% of pCR)
WSG-ADAPT-TN [19]	TN	NAC	In TN, basal-like subtype, High Ki67 and low HER2 score were associated with chemosensitivity ($p = 0.015$, $p < 0.001$ and $p < 0.001$, respectively)
GeparSepto [20]	All Subtypes	NAC	TN breast cancer obtained the best ratio of pCR (48%).
NeoALTTO [21]	HER2+	NAC + (L + T)	51% with dual HER2 therapy versus 30% and 25% with T and L respectively.
CALGB 40,601 [22]	HER2+	NAC + (L + T)	51% with dual HER2 therapy versus 40% and 32% with T and L respectively.

NSABP B-41 [23]	HER2+	NAC + (L + T)	62% with dual HER2 therapy versus 53% and 53% with T and L respectively.
CherLOB [24]	HER2+	NAC + (L + T)	TILs are associated with pCR (OR 1.03; $p < 0.001$). The PAM50 subtype with better pCR ratio was HER2-enriched (50%, $p < 0.001$).
NeoSphere [15]	HER2+	NAC + (*p* + T)	46% with dual HER2 therapy versus 29 and 24 with T and *p* respectively.
TRYPAHENA [25]	HER2+	NAC + (*p* + T)	57%–66% with dual HER2 therapy.
BERENICE[26]	HER2+	NAC + T + *p*	The highest pCR rate was in HER2-enriched PAM50 subtype (75%).
NeoPACT	TN	NAC +/− Immune checkpoint inhibitors	Ongoing
GeparNuevo	TN	NAC +/− Immune checkpoint inhibitors	Ongoing
NeoTala	TN	NAC +/− PARP inhibitors	Ongoing
GeparOla	TN	NAC +/− PARP inhibitors	Ongoing

2. Data, Model, Applications and Influences

This study applies to the area of Precision Medicine in cancer, and is particularly devoted to offer a wider and integral perspective of the molecular features related to the resistance to NAC in the management of patients affected by breast cancer. We undertake this task by agglutinating on one side the known molecular predictors of pCR and stating their comparative prediction potential to the clinicopathological classical pCR predictive factors,

and, on the other side, by analyzing the phenotype of RD from a dynamic perspective. With that strategy, we have managed to highlight the most promising pCR predictors as well as delineated the optimal approach for future identification and optimization of the molecular determinants of pCR. In addition, disentangling the transitions in subtypes and the more refined molecular alterations during NAC that define the RD phenotype provides the community with an orientated vision on possible new targets and therapeutic approaches that could help to minimize the burden of the resistance to NAC in breast cancer.

3. Future Perspectives

The incorporation of NAC to the standard of care treatment to early and locally advanced breast cancer has greatly benefited these patients in terms of survival and breast preservation. As for any other novel pharmacological approach, the implementation of NAC has been paralleled by an intense search for those factors influencing its impact on the course of the disease. In an important effort, a myriad of studies has defined different predictors of the most informative prognosis factor, pCR, and characterized the profile of residual disease. Interesting observations include gene expression signatures, some of them subtype-defining, as well as other molecular variations and clinicopathological features that are able to anticipate pCR and, in some cases, prognosis. In addition, a phenotype evolution during treatment has been revealed with a transition towards a “normal-like” phenotype, with losses of the essential breast cancer receptors, or towards the stemness or immune depleted phenotypes as characteristic of those tumors that have not been eradicated by NAC. Despite this significant progress, several concerns are yet to be addressed for an efficient implementation of NAC in terms of predicting the clinical benefit and identifying successive treatments for the residual disease. In both cases, the main pitfall is the important heterogeneity that characterizes this type of cancer; more randomized clinical trials that consider the breast cancer subtypes individually and address the intratumor heterogeneity should evaluate the determinants of pCR and the profile of residual disease. These would generate invaluable input to refine the novel cDNA “mutations tracking” approaches [27][28][29] that require knowledge of the specific predicted residual disease mutations with prognostic potential to be interrogated during the course of NAC and after surgery, and those that could be amenable as targets for ulterior treatments of the residual disease.

Moreover, some pre-clinical initiatives are also emerging to dissect the mechanisms of chemoresistance that can contribute to the identification of additional targets. In this regard, a recent study employed several systems that mimic in vivo TN BC chemoresistance, such as xenograft models, three-dimensional cultures, and primary breast cancer organoids, to identify that Lysyl oxidase (LOX) is a key inducer chemoresistance in TN BC. Indeed, higher LOX was associated with shorter survival in chemotherapy-treated TN breast cancer patients’ organoids [30].

Beyond residual disease, the field is largely lacking deterministic factors of metastasis after NAC and their inter-relation with specific profiles of the primary tumor and residual disease. Indeed, a major concern beyond the detection and prediction of residual disease is the development of distant metastatic disease, which is responsible for 90% of breast cancer-related deaths [31].

To date, a few research studies have established several candidate diagnostic biomarkers of breast cancer metastasis; however, no single predictor of metastasis after residual disease has been identified so far. Therefore, longitudinal studies with homogeneous cohorts controlled for pCR achievement would be key for identification of the impact of NAC in the development of distant metastasis, and the specific tumor evolution towards the most deleterious phenotype of this disease. Considering the current outstanding amount of high throughput generated data related to NAC response, the rational design of the future clinical trials, and the rapid transformation of the real-time non-invasive monitoring technologies, we anticipate the transition in the field towards a more patient- and evolution-specific implementation of NAC for breast cancer.

References

1. Zaheed, M.; Wilcken, N.; Willson, M.L.; O'Connell, D.L.; Goodwin, A. Sequencing of anthracyclines and taxanes in neoadjuvant and adjuvant therapy for early breast cancer. Cochrane Database of Systematic Reviews 2019, doi:10.1002/14651858.CD012873.pub2.
2. Kasimir-Bauer, S.; Bittner, A.-K.; König, L.; Reiter, K.; Keller, T.; Kimmig, R.; Hoffmann, O. Does primary neoadjuvant systemic therapy eradicate minimal residual disease? Analysis of disseminated and circulating tumor cells before and after therapy. Breast Cancer Research 2016, 18, doi:10.1186/s13058-016-0679-3.
3. Penault-Llorca, F.; Radosevic-Robin, N. Biomarkers of residual disease after neoadjuvant therapy for breast cancer. Nature Reviews Clinical Oncology 2016, 13, 487–503, doi:10.1038/nrclinonc.2016.1.
4. Ogston, K.N.; Miller, I.D.; Payne, S.; Hutcheon, A.W.; Sarkar, T.K.; Smith, I.; Schofield, A.; Heys, S.D. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. The Breast 2003, 12, 320–327, doi:10.1016/S0960-9776(03)00106-1.
5. Symmans, W.F.; Peintinger, F.; Hatzis, C.; Rajan, R.; Kuerer, H.; Valero, V.; Assad, L.; Poniecka, A.; Hennessy, B.; Green, M.; et al. Measurement of Residual Breast Cancer Burden to Predict Survival After Neoadjuvant Chemotherapy. Journal of Clinical Oncology 2007, 25, 4414–4422, doi:10.1200/JCO.2007.10.6823.
6. Cortazar, P.; Geyer, C.E. Pathological Complete Response in Neoadjuvant Treatment of Breast Cancer. Ann Surg Oncol 2015, 22, 1441–1446, doi:10.1245/s10434-015-4404-8.
7. von Minckwitz, G.; Untch, M.; Blohmer, J.-U.; Costa, S.D.; Eidtmann, H.; Fasching, P.A.; Gerber, B.; Eiermann, W.; Hilfrich, J.; Huober, J.; et al. Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes. JCO 2012, 30, 1796–1804, doi:10.1200/JCO.2011.38.8595.

8. Cortazar, P.; Zhang, L.; Untch, M.; Mehta, K.; Costantino, J.P.; Wolmark, N.; Bonnefoi, H.; Cameron, D.; Gianni, L.; Valagussa, P.; et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. The Lancet 2014, 384, 164–172, doi:10.1016/S0140-6736(13)62422-8.
9. Goorts, B.; van Nijnatten, T.J.A.; de Munck, L.; Moossdorff, M.; Heuts, E.M.; de Boer, M.; Lobbes, M.B.I.; Smidt, M.L. Clinical tumor stage is the most important predictor of pathological complete response rate after neoadjuvant chemotherapy in breast cancer patients. Breast Cancer Research and Treatment 2017, 163, 83–91, doi:10.1007/s10549-017-4155-2.
10. Bownes, R.J.; Turnbull, A.K.; Martinez-Perez, C.; Cameron, D.A.; Sims, A.H.; Oikonomidou, O. On-treatment biomarkers can improve prediction of response to neoadjuvant chemotherapy in breast cancer. Breast Cancer Res 2019, 21, 73, doi:10.1186/s13058-019-1159-3.
11. Esserman, L.J.; Berry, D.A.; DeMichele, A.; Carey, L.; Davis, S.E.; Buxton, M.; Hudis, C.; Gray, J.W.; Perou, C.; Yau, C.; et al. Pathologic Complete Response Predicts Recurrence-Free Survival More Effectively by Cancer Subset: Results From the I-SPY 1 TRIAL—CALGB 150007/150012, ACRIN 6657. J Clin Oncol 2012, 30, 3242–3249, doi:10.1200/JCO.2011.39.2779.
12. Spring, L.; Greenup, R.; Niemierko, A.; Schapira, L.; Haddad, S.; Jimenez, R.; Coopey, S.; Taghian, A.; Hughes, K.S.; Isakoff, S.J.; et al. Pathologic Complete Response After Neoadjuvant Chemotherapy and Long-Term Outcomes Among Young Women With Breast Cancer. Journal of the National Comprehensive Cancer Network 2017, 15, 1216–1223, doi:10.6004/jnccn.2017.0158.
13. Huober, J.; Holmes, E.; Baselga, J.; de Azambuja, E.; Untch, M.; Fumagalli, D.; Sarp, S.; Lang, I.; Smith, I.; Boyle, F.; et al. Survival outcomes of the NeoALTTO study (BIG 1–06): updated results of a randomised multicenter phase III neoadjuvant clinical trial in patients with HER2-positive primary breast cancer. European Journal of Cancer 2019, 118, 169–177, doi:10.1016/j.ejca.2019.04.038.
14. Gianni, L.; Eiermann, W.; Semiglazov, V.; Manikhas, A.; Lluch, A.; Tjulandin, S.; Zambetti, M.; Vazquez, F.; Byakhow, M.; Lichinitser, M.; et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. 2010, 375, 8.
15. Gianni, L.; Pienkowski, T.; Im, Y.-H.; Roman, L.; Tseng, L.-M.; Liu, M.-C.; Lluch, A.; Staroslawska, E.; de la Haba-Rodriguez, J.; Im, S.-A.; et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. The Lancet Oncology 2012, 13, 25–32, doi:10.1016/S1470-2045(11)70336-9.

16. von Minckwitz, G. Neoadjuvant chemotherapy in breast cancer—insights from the German experience. Breast Cancer 2012, 19, 282–288, doi:10.1007/s12282-012-0393-7.
17. Diana, A.; Carlino, F.; Franzese, E.; Oikonomidou, O.; Criscitiello, C.; De Vita, F.; Ciardiello, F.; Orditura, M. Early Triple Negative Breast Cancer: Conventional Treatment and Emerging Therapeutic Landscapes. Cancers 2020, 12, 819, doi:10.3390/cancers12040819.
18. von Minckwitz, G.; Raab, G.; Caputo, A.; Schütte, M.; Hilfrich, J.; Blohmer, J.U.; Gerber, B.; Costa, S.D.; Merkle, E.; Eidtmann, H.; et al. Doxorubicin With Cyclophosphamide Followed by Docetaxel Every 21 Days Compared With Doxorubicin and Docetaxel Every 14 Days As Preoperative Treatment in Operable Breast Cancer: The GEPARDUO Study of the German Breast Group. JCO 2005, 23, 2676–2685, doi:10.1200/JCO.2005.05.078.
19. Gluz, O.; Kolberg-Liedtke, C.; Prat, A.; Christgen, M.; Gebauer, D.; Kates, R.; Paré, L.; Grischke, E.; Forstbauer, H.; Braun, M.; et al. Efficacy of deescalated chemotherapy according to PAM50 subtypes, immune and proliferation genes in triple-negative early breast cancer: Primary translational analysis of the WSG-ADAPT-TN trial. Int. J. Cancer 2020, 146, 262–271, doi:10.1002/ijc.32488.
20. Untch, M.; Möbus, V.; Kuhn, W.; Muck, B.R.; Thomssen, C.; Bauerfeind, I.; Harbeck, N.; Werner, C.; Lebeau, A.; Schneeweiss, A.; et al. Intensive Dose-Dense Compared With Conventionally Scheduled Preoperative Chemotherapy for High-Risk Primary Breast Cancer. Journal of Clinical Oncology 2009, doi:10.1200/JCO.2008.20.3133.
21. Baselga, J.; Bradbury, I.; Eidtmann, H.; Di Cosimo, S.; de Azambuja, E.; Aura, C.; Gómez, H.; Dinh, P.; Fauria, K.; Van Dooren, V.; et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet 2012, 379, 633–640, doi:10.1016/S0140-6736(11)61847-3.
22. Carey, L.A.; Berry, D.A.; Cirrincione, C.T.; Barry, W.T.; Pitcher, B.N.; Harris, L.N.; Ollila, D.W.; Krop, I.E.; Henry, N.L.; Weckstein, D.J.; et al. Molecular Heterogeneity and Response to Neoadjuvant Human Epidermal Growth Factor Receptor 2 Targeting in CALGB 40601, a Randomized Phase III Trial of Paclitaxel Plus Trastuzumab With or Without Lapatinib. JCO 2016, 34, 542–549, doi:10.1200/JCO.2015.62.1268.
23. Robidoux, A.; Tang, G.; Rastogi, P.; Geyer, C.E.; Azar, C.A.; Atkins, J.N.; Fehrenbacher, L.; Bear, H.D.; Baez-Diaz, L.; Sarwar, S.; et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. The Lancet Oncology 2013, 14, 1183–1192, doi:10.1016/S1470-2045(13)70411-X.
24. Dieci, M.V.; Prat, A.; Tagliafico, E.; Paré, L.; Ficarra, G.; Bisagni, G.; Piacentini, F.; Generali, D.G.; Conte, P.; Guarneri, V. Integrated evaluation of PAM50 subtypes and immune modulation of pCR in HER2-positive breast cancer patients treated with chemotherapy and HER2-targeted agents in the CherLOB trial. Annals of Oncology 2016, 27, 1867–1873, doi:10.1093/annonc/mdw262.

25. Schneeweiss, A.; Chia, S.; Hickish, T.; Harvey, V.; Eniu, A.; Hegg, R.; Tausch, C.; Seo, J.H.; Tsai, Y.-F.; Ratnayake, J.; et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals of Oncology 2013, 24, 2278–2284, doi:10.1093/annonc/mdt182.
26. Swain, S.M.; Ewer, M.S.; Viale, G.; Delaloge, S.; Ferrero, J.-M.; Verrill, M.; Colomer, R.; Vieira, C.; Werner, T.L.; Douthwaite, H.; et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Annals of Oncology 2018, 29, 646–653, doi:10.1093/annonc/mdx773.
27. De Mattos-Arruda, L. Liquid biopsy for HER2-positive breast cancer brain metastasis: the role of the cerebrospinal fluid. ESMO Open 2017, 2, e000270, doi:10.1136/esmoopen-2017-000270.
28. Garcia-Murillas, I.; Chopra, N.; Comino-Méndez, I.; Beaney, M.; Tovey, H.; Cutts, R.J.; Swift, C.; Kriplani, D.; Afentakis, M.; Hrebien, S.; et al. Assessment of Molecular Relapse Detection in Early-Stage Breast Cancer. JAMA Oncol 2019, 5, 1473, doi:10.1001/jamaoncol.2019.1838.
29. Saatci, O.; Kaymak, A.; Raza, U.; Ersan, P.G.; Akbulut, O.; Banister, C.E.; Sikirzhytski, V.; Tokat, U.M.; Aykut, G.; Ansari, S.A.; et al. Targeting lysyl oxidase (LOX) overcomes chemotherapy resistance in triple negative breast cancer. Nat Commun 2020, 11, 2416, doi:10.1038/s41467-020-16199-4.
30. Robinson, D.R.; Wu, Y.-M.; Lonigro, R.J.; Vats, P.; Cobain, E.; Everett, J.; Cao, X.; Rabban, E.; Kumar-Sinha, C.; Raymond, V.; et al. Integrative clinical genomics of metastatic cancer. Nature 2017, 548, 297–303, doi:10.1038/nature23306.
31. Lesurf, R.; Griffith, O.L.; Griffith, M.; Hundal, J.; Trani, L.; Watson, M.A.; Aft, R.; Ellis, M.J.; Ota, D.; Suman, V.J.; et al. Genomic characterization of HER2-positive breast cancer and response to neoadjuvant trastuzumab and chemotherapy—results from the ACOSOG Z1041 (Alliance) trial. Ann Oncol 2017, 28, 1070–1077, doi:10.1093/annonc/mdx048.