INTELLIGENT APPLICATION OF BREAST CANCER TRIALS DATA IN THE CLINIC

Summary of presentations from the prIME Oncology satellite symposium held at the European Cancer Congress 2015 in Vienna, Austria, on 25th September 2015

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Disclosure: Pierfranco Conte has received consulting fees from Roche and Novartis. He has also received fees for non-CME services from Novartis, Roche, AstraZeneca, and Celgene. Joanne Franklin has no relevant financial relationships to disclose. Sibylle Loibl has received consulting fees (for her institution) from Celgene and Amgen. She has also received fees (for her institution) for performing contracted research for Amgen, AstraZeneca, Celgene, Roche, and Pfizer. Peter Schmid has received consulting fees from Genentech. Christos Sotiriou has received consulting fees from Cepheid, Astellas, and Vertex Pharmaceuticals. Sunil Verma has received consulting fees from Pfizer, Novartis, Roche, Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, Eisai, and Eli Lilly.
Acknowledgements: Editorial assistance was provided by Ms Heather Tomlinson, prIME Oncology.
Support: This educational activity was supported by Roche and Genomic Health.
Citation: EMJ Oncol. 2015;3(2):40-48.

MEETING SUMMARY

This meeting commenced with a talk from Prof Loibl on neoadjuvant and adjuvant strategies for HER2-positive (human epidermal growth factor receptor 2-positive) early breast cancer (EBC), which featured a précis on the most pertinent, recent trial data and how these data may shape future treatment decisions in clinical practice. Prof Conte moved the discussion forward by addressing how recent studies may lead towards a new standard of care (SoC) and treatment paradigms in patients with metastatic breast cancer. Prof Schmid gave an overview of potential strategies that could be used to prevent or overcome endocrine therapy resistance in patients with hormone receptor-positive breast cancer. The session was concluded with a presentation on 'Precision Medicine for Metastatic Breast Cancer' by Prof Sotiriou, in which he highlighted the potential applications of precision medicine and some of the different approaches that have been used in metastatic breast cancer. Prof Verma, the meeting chair, opened the symposium and facilitated the discussion sessions. The contents of the presentations and discussions are summarised herein.

Neoadjuvant and Adjuvant Strategies for HER2-Positive Early Breast Cancer

Professor Sibylle Loibl

HER2-positive breast cancer is a particularly aggressive form of breast cancer that is found in approximately 20% of women diagnosed with breast cancer.[1] While patients with HER2-positive EBC have a good prognosis, challenges remain. There is a high recurrence rate despite treatment with trastuzumab, and neoadjuvant candidates have worse prognosis. Since the approval of trastuzumab, other HER2-targeted therapies have been designed and approved. Herein, the latest data on neoadjuvant and adjuvant strategies for treating patients with HER2-positive EBC will be discussed.

One evolving treatment strategy for HER2-positive EBC is dual HER2 blockade using two targeted agents. The NeoSphere trial was a four-arm study in the neoadjuvant setting evaluating whether the addition of pertuzumab, a humanised anti-HER2 monoclonal antibody, to docetaxel and trastuzumab could provide clinical benefit versus the other single-blockade cohorts. Patients receiving the double blockade plus docetaxel had a significantly higher pathological complete response (pCR) compared with trastuzumab plus docetaxel (45.8% versus 29.0%; p=0.0141); hormone receptor-positive patients derived the greatest benefit.[2] Five-year follow-up data demonstrated that patients with pCR displayed significantly better survival versus those without pCR (hazard ratio [HR]: 0.54, 95% confidence interval [CI]: 0.29–1.00). The data also suggest that there was an improvement in both progression-free survival (PFS) and disease-free survival (DFS) in the double-blockade cohort.[3] Confirmation of whether HER2 double blockade has a survival benefit is expected from the Phase III APHINITY trial,[4] which compares invasive DFS (iDFS) in patients receiving trastuzumab alone or trastuzumab plus pertuzumab for 1 year after anthracycline/taxane-based chemotherapy.

The Phase III ExteNET trial evaluated extended adjuvant treatment of EBC with neratinib, a dual HER2 and epidermal growth factor receptor inhibitor. High-risk patients were randomised to 12 months of neratinib or placebo following 12 months of trastuzumab. A statistically significant improvement in iDFS was seen with neratinib, compared with placebo (HR: 0.67, 95% CI: 0.50–0.91; p=0.0046); patients with hormone receptor-positive disease derived greater benefit than hormone receptor-negative patients.[5]

Chemotherapy-free treatment is also being explored in EBC. The Phase I/II ADAPT umbrella trial includes a sub-trial of hormone receptor-positive/HER2-positive patients randomised to trastuzumab emtansine (T-DM1), T-DM1 plus endocrine therapy, or trastuzumab and endocrine therapy. Interim results demonstrate a significantly higher pCR rate for the T-DM1 arms, with or without endocrine treatment (40.5% and 45.8%, respectively), versus the trastuzumab-treated group (6.7%).[6] The ATEMPT study is addressing a similar question in the adjuvant setting by comparing T-DM1 versus paclitaxel plus trastuzumab versus trastuzumab monotherapy, with results being expected soon.[7]

Trial data in the neoadjuvant setting show that chemotherapy-based treatment regimens consistently produce higher rates of pCR. However, the data indicate that longer chemotherapy-free treatment consisting of trastuzumab, lapatinib, or potentially T-DM1 (pending final data), and endocrine agents produces moderate rates of pCR (Figure 1)[2,6,8-11] and may be a valid treatment option. How patients who would benefit from chemotherapy-free treatment could be selected remains to be seen – determining whether a patient's tumour(s) harbours mutations in the gene encoding PI3 kinase (*PIK3CA*) may be one approach. A retrospective study combining data from the neoadjuvant GePAR studies, the Neo-ALTTO study, and the CHERLOB study, all of which evaluated *PIK3CA* mutations as predictors of pCR, revealed a significantly lower pCR rate in patients harbouring a mutation.[12] This effect was particularly pronounced in hormone receptor-positive patients.

It may be best to consider both the HER2 and the hormone receptor status of breast cancer patients when planning their treatment. Hormone receptor-negative/HER2-positive patients should receive anthracycline, a taxane, and anti-HER2 treatment. For patients achieving pCR, an option may be to reduce the duration of anti-HER2 treatment. For hormone receptor-positive/HER2-positive patients, it may be possible to downgrade chemotherapy and start with endocrine treatment plus double HER2 blockade with or without a PI3 kinase (PI3K) inhibitor. For non-pCR patients, chemotherapy or other investigational drugs may be required.

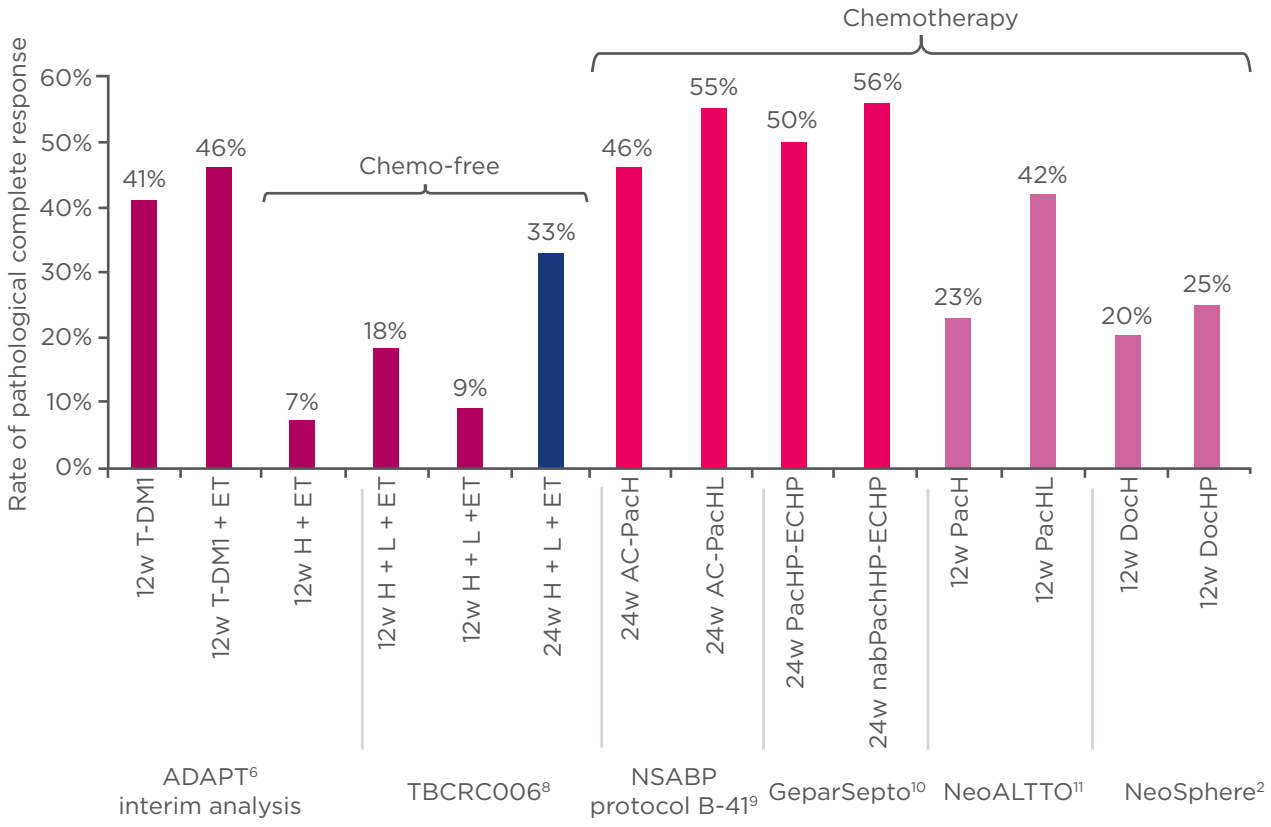

Figure 1: Rates of pathological complete response in HER2-positive early breast cancer.
A: doxorubicin; C: cyclophosphamide; Doc: docetaxel; E: epirubicin; ET: endocrine therapy; H: trastuzumab; L: lapatinib; nabPac: nab-paclitaxel; P: pertuzumab; Pac: paclitaxel; T-DM1: trastuzumab emtansine; w: weeks.

HER2-Positive Metastatic Breast Cancer: Standard of Care and What's Next

Professor Pierfranco Conte

Trastuzumab and other anti-HER2 agents have revolutionised the treatment of HER2-positive disease. However, questions remain about optimal treatment strategies in the metastatic setting. Is it feasible to target HER2 after progression on first-line treatment? What is the optimal sequence of anti-HER2 therapies? Is there a role for endocrine therapy in combination with anti-HER2 therapies?

Five trials have evaluated targeting HER2 after progression on trastuzumab.[13-17] Each trial demonstrated a significant prolongation of PFS irrespective of whether lapatinib, trastuzumab, or T-DM1 was used. Three of the trials, EMILIA,[16] EGF104900,[15] and Th3RESA,[17] also showed statistically and clinically significant improvements in overall survival (OS). Notably in both EGF104900 and Th3RESA, patients had received multiple lines of prior treatment. The survival gain observed over time is consistent with the efficacy of salvage anti-HER2 therapies.

There are several trials addressing the optimal sequencing of anti-HER2 agents in this setting. The CLEOPATRA study demonstrated that docetaxel/trastuzumab plus pertuzumab was more effective than docetaxel/trastuzumab alone (PFS: 18.7 versus 12.4 months, respectively; HR: 0.69, 95% CI: 0.58–0.80).[18,19] However, the applicability of the trial data may be limited as only 10% of the trial population had failed adjuvant trastuzumab, whereas in daily practice the majority of patients have received prior adjuvant trastuzumab. Two large trials examined potential treatment regimens for patients who progress during adjuvant trastuzumab or relapse very early (within 6 months). The EMILIA study compared T-DM1 with lapatinib plus capecitabine. T-DM1 treatment resulted in significant prolongation of PFS (9.6 versus 6.4 months; HR: 0.65, 95% CI: 0.55–0.77; p<0.0001) and a significant benefit in OS (30.9 versus 25.1 months; HR: 0.68, 95% CI: 0.55-0.85; p<0.001) versus lapatinib/capecitabine.[16]

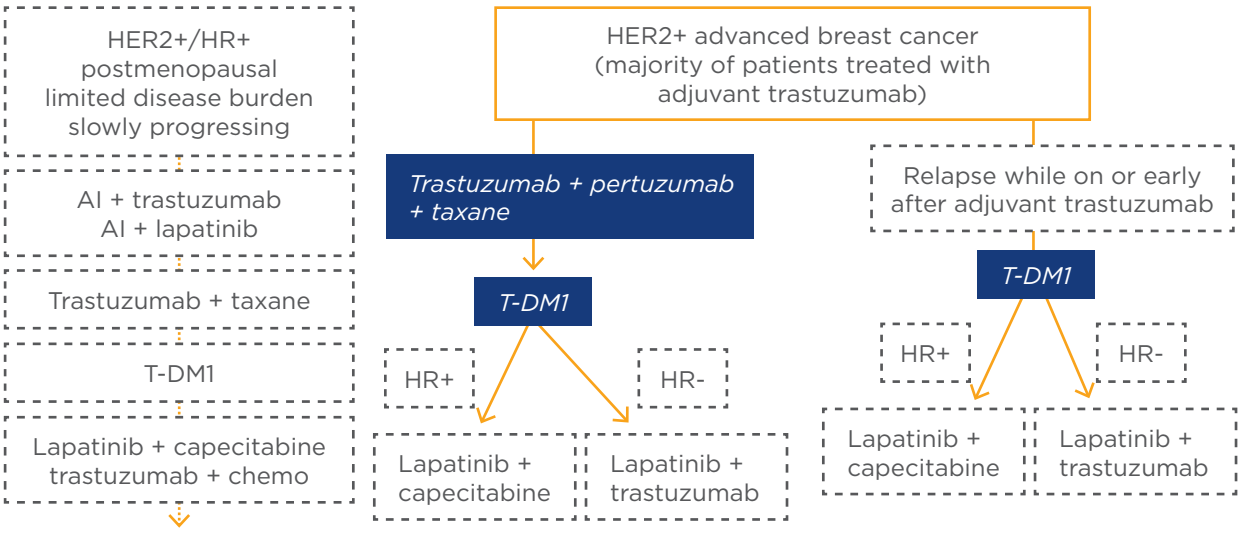

Figure 2: A new treatment algorithm for HER2-positive advanced breast cancer.
AI: aromatase inhibitor; HR: hormone receptor; T-DM1: trastuzumab emtansine.

The Th3ERSA study, which contained a more heavily pre-treated patient population, compared T-DM1 versus T-DM1 plus physician's choice treatment. T-DM1 was superior in terms of both PFS and OS.[17] It will be important to determine the efficacy of T-DM1 after the combination of trastuzumab, pertuzumab, and a taxane.

Also pertinent is whether there is any role for endocrine therapy in hormone receptor-positive/HER2-positive disease. Three relatively small randomised clinical trials, TAnDEM,[20] eLEcTRA,[21] and the trial by Johnston et al.,[22] have investigated this. Each study demonstrated that endocrine therapy alone is poorly effective, but if administered with lapatinib or trastuzumab it significantly increases response rate and PFS. Although the PFS rates are lower than those obtained using chemotherapy, adding anti-HER2 agents to endocrine therapy increases the efficacy of endocrine therapy. This is therefore an alternative option for selected patients, such as the frail and the elderly with limited tumour burden.

Newer therapeutic targets are also being looked at in the metastatic setting. Mutation of *PIK3CA*[23] is an emerging tumour marker and there are agents available for PI3K-mutated tumours. The mTOR inhibitor everolimus can be used to abrogate signalling through the PI3K–Akt–mTOR pathway. The BOLERO-1 and BOLERO-3 trials investigated the addition of everolimus to trastuzumab/paclitaxel in first-line therapy (BOLERO-1) and to trastuzumab/vinorelbine in second-line therapy (BOLERO-3). No statistically significant improvement was seen in BOLERO-1,[24] but the combination of everolimus with trastuzumab/vinorelbine in BOLERO-3 resulted in a significant improvement in median PFS (everolimus: 7 months, placebo: 5.78 months; HR: 0.78, 95% CI: 0.65–0.95; p=0.0067), although this gain was small.[25] The data are more powerful if patients are stratified according to PI3K pathway activation. Slamon et al.[26] performed a subanalysis of BOLERO-1 and BOLERO-3 in patients with an activated PI3K pathway (44% of the overall population). In this subpopulation, the addition of everolimus was quite effective, with a 33% reduction in the risk of progression (combined population: placebo versus everolimus, HR: 0.67, 95% CI: 0.48–0.93). While this does not constitute sufficient evidence to be practice-changing, the data suggest that combining mTOR/PI3K inhibitors with HER2-targeting agents may be a valid strategy in PI3K-mutated tumours.

A survey of trials in the metastatic setting would not be complete without mentioning the MARIANNE trial. This study compared T-DM1 ± pertuzumab versus trastuzumab plus docetaxel/paclitaxel with the SoC. The primary endpoint was non-inferiority and, assuming this was reached, the co-primary endpoint was superiority of the T-DM1 cohorts. While non-inferiority was demonstrated for T-DM1 ± pertuzumab versus SoC, neither arm proved to be superior to the SoC.[27]

In summary, the following treatment strategies may be recommended at the current time (Figure 2):

- For the majority of patients with HER2-positive metastatic breast cancer, standard first-line therapy should be a taxane plus trastuzumab plus pertuzumab
- For certain carefully selected patients with hormone receptor-positive/HER2-positive disease, specifically indolent with a limited tumour burden, the first-line treatment may be an aromatase inhibitor (AI) plus either lapatinib or trastuzumab
- T-DM1 may:
  - Provide an option for patients who progress while on, or very shortly after, adjuvant trastuzumab
  - Be considered the standard second-line treatment
  - Be an alternative option to taxane plus trastuzumab

Hormone Receptor-Positive Breast Cancer: Preventing and Overcoming Endocrine Therapy Resistance

Professor Peter Schmid

Endocrine resistance remains problematic in oestrogen receptor (OR)-positive, metastatic breast cancer. Resistance can be clinically categorised as either *de novo* resistance, which occurs early in the first 2 years of disease, or acquired resistance, which occurs at later disease stages. Strategies with the aim of reducing the risk of resistance are a current goal in the management of HER2-positive breast cancer. There are two main mechanisms of endocrine resistance: altered OR signalling and altered alterative signalling, e.g. through other growth factor receptors.[28] Agents that target either of these altered pathways may have utility in overcoming resistance. The OR ligand-binding domain, for example, is susceptible to mutations that lead to constitutive receptor activation and, consequently, resistance.[29] Using a selective OR degrader that downregulates the receptor, e.g. fulvestrant, may surmount this resistance.[30]

Historically, AIs have been used as first-line hormonal therapy in post-menopausal women with metastatic breast cancer, but poor PFS remains an issue. Fulvestrant may present a feasible alternative. The FIRST study compared high-dose fulvestrant (500 mg) with anastrozole in the first-line setting in a population in which 75% of patients were endocrine-therapy-naïve with *de novo* metastatic disease. The fulvestrant arm showed an advantage in terms of time to progression (HR: 0.66, 95% CI: 0.47–0.92; p=0.01) and a benefit in OS (HR: 0.70, 95% CI: 0.50–0.98; p=0.041).[31] The ongoing Phase III FALCON study should confirm these data.[32,33]

CDK4/6 inhibitors are another treatment option. CDK4/6 proteins are involved in regulating the cell cycle, and inhibiting their signalling should slow down the cell cycle and potentially overcome endocrine resistance. The Phase II PALOMA-1 trial compared letrozole ± the CDK4/6 inhibitor palbociclib in all-comers as well as a subpopulation of patients with cyclin D1 amplification or loss of p16. Overall results clearly demonstrated that the combination of letrozole and palbociclib was substantially better than letrozole alone; no added benefit was seen in the selected patients.[34] Data from the Phase III PALOMA-2 trial (comparing palbociclib and letrozole with letrozole alone) should confirm whether CDK4/6 inhibitors may be good candidates for first-line therapy.[35]

A third potential first-line therapy is the addition of bevacizumab to AIs. The current evidence base is conflicting. The CALBG 40503 trial, which investigated letrozole versus letrozole plus bevacizumab, reported a significant improvement in PFS,[36] while the LEA trial, comparing letrozole/fulvestrant versus letrozole/fulvestrant plus bevacizumab, showed a marginal albeit not statistically significant improvement.[37] Further investigation is required to clarify if there is a role for bevacizumab.

Adding molecularly targeted agents to endocrine therapy is also being investigated in the second line. Two trials have explored whether mTOR inhibitors can prevent/reverse endocrine resistance. BOLERO-2 compared exemestane alone with a combination of exemestane plus everolimus, with clear superiority achieved in the combination arm (HR: 0.38, 95% CI: 0.31–0.48).[38,39] In contrast, no change in PFS was observed in the HORIZION trial (letrozole ± temsirolimus).[40] Along with the differences in choice of AI and mTOR inhibitor, the conflicting data may also reflect the different study populations: 84% of patients in BOLERO-2 had prior endocrine response, whereas 57% of patients in HORIZION had received no prior endocrine therapy. These data may indicate that endocrine pathways must first be activated

(via prior endocrine therapy) in order for mTOR inhibitors to be effective.

This leads to the question of how to best select patients who will benefit from mTOR inhibitors. In BOLERO-2, the everolimus-related PFS benefit was maintained in patients regardless of *PIK3CA* gene alterations, although a subanalysis suggested that patients with ≤1 genetic alteration derive greater PFS benefit with everolimus.[41] Luminal B versus luminal A cancers also appear more sensitive to PI3K inhibitors.[42]

PI3K inhibitors and CDK4/6 inhibitors are also being investigated in the metastatic setting. The FERGI study looked at the addition of the pan-PI3K inhibitor pictilisib to fulvestrant; only a marginal improvement in PFS was observed.[43] The ongoing BELLE-2 trial,[44] which investigates the addition of the pan-PI3K inhibitor buparlisib to fulvestrant in patients who have received prior AI, may provide further clarity. As in the first line, CDK4/6 inhibitors also have activity in the metastatic setting. PALOMA-3 compared palbociclib plus fulvestrant versus placebo plus fulvestrant in patients with hormone receptor-positive/HER2-positive metastatic breast cancer and revealed a statistically significant improvement in PFS in the combination arm (9.2 versus 3.8 months; HR: 0.422, 95% CI: 0.32–0.56; p<0.001).[45]

In conclusion, when determining strategies for overcoming resistance it may be necessary to consider endocrine sensitivity (possibly by using biomarker testing), the time and type of resistance (primary versus secondary), and intrinsic subtype (luminal A or B) before the optimal treatment plan is developed.

Precision Medicine for Metastatic Breast Cancer

Professor Christos Sotiriou

The National Institutes of Health define precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[46] This approach allows for the identification of 'driver' mutations specific to breast cancer, determination of genomic alterations that cause secondary resistance and DNA repair defects that may be therapeutic targets, and elucidation of immune escape mechanisms. Herein, several examples of how precision medicine has been used in breast cancer are discussed.

The first mutational landscape of metastatic breast cancer was recently published.[47] Retrospective analysis of biopsy sample data from the SAFIR01 and MOSCATO studies determined that, while metastatic tumours harboured mutations common to primary tumours (e.g. mutations in the genes encoding p53 and PI3K), they also displayed a high frequency of gene mutations that are rare in primary tumours (e.g. mutated *ESR1*, *TSC1*, and *TSC2*). In another recent study by Juric et al.,[48] the genomic evolution of a tumour in a patient with metastatic breast cancer with an activating *PIK3CA* mutation was studied. The patient had responded to the PI3Kα inhibitor BYL719, but eventually developed resistance. Post-mortem, metastatic lesions were analysed and compared with pre-treatment tumour tissue and it was determined that there was a convergent loss of *PTEN* in the tumour and this likely led to PI3Kα inhibitor resistance.

Precision medicine can also be used to identify DNA repair defects. This was highlighted in a recent publication by Alexandrov et al.[49] analysing 4,938,362 mutations from 7,042 tumours. More than 20 distinct mutational signatures were identified; 5 of these were found in breast cancer and 3 of them are involved in DNA repair, including 1 corresponding to *BRCA1/2* deficiency. Such information can be used to drive forward new targets for research and development. Sequencing technologies can be used to identify neoantigens (responsible for priming the immune response) or elucidate the presence of tumour-infiltrating lymphocytes (TILs); both are potential readouts for tumour growth/progression and TILs may have utility as surrogate markers for the efficacy of checkpoint inhibitors. These techniques may also be used to analyse genetic polymorphisms associated with immune effects, and this information could be exploited to produce immunotherapeutics.

There are clearly challenges with these technologies, one of which is how to define a driver mutation and determine if it has significant diagnostic, prognostic, or therapeutic implications in subsets of cancer patients for specific therapies. In breast cancer, the identification of these driver mutations has not met with total success. For example, the presence of *PIK3CA* mutations does not necessarily predict response to PI3K inhibitors or mTOR inhibitors. Similarly, it was anticipated

that cyclin D1 amplification or p16 loss may be good surrogate markers to predict response to palbociclib, but the trial data have disproven this. It seems that a single-gene alteration does not automatically mean a patient will respond to a drug.

A better approach may be to think beyond a single gene, and evaluate signal pathway activation and tumour dependency. Assessing multiple genomic alterations in conjunction with functional studies should also be considered. This was highlighted in the BOLERO-2 trial, which demonstrated that patients who have multiple alterations in their breast cancers do not benefit from the exemestane and everolimus combination, whereas if they have ≤1 mutation they derive great benefit.[41] Similar evidence in support of considering multiple genomic alterations comes from the *HER2* gene, which can harbour numerous mutations. One study demonstrated that there are mutations that activate the signalling pathways and other mutations that are non-pathway activating within *HER2*. There are also mutations that confer different drug responses; for example, the L755S mutation results in lapatinib resistance, while the D769H mutation does not. It would be ideal to determine which phenotype is associated with individual mutations in order to facilitate optimal treatment strategies.[50]

Tumour heterogeneity and evolution is another challenge to precision medicine. It has been demonstrated that geographical heterogeneity exists even within a tumour, with different areas containing different mutations.[51] For metastatic disease, the tumour evolves as a consequence of internal and external pressures, prior treatment, and different driver mutations which may be acquired and be sub-clonal. The result is a lesion very different from a primary tumour and consequently the metastatic tumour should be analysed when making treatment decisions.

In conclusion, when planning therapy it is important to remember that there is currently a lack of strong functional evidence to differentiate between driver and non-driver mutations. It may be necessary to look beyond one single gene and to also consider pathway activation, host interactions, the microenvironment, the immune system, and the significant problem of substantial intra-tumour and inter-lesion heterogeneity.

Please **click here** to see a webcast of the live meeting.

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