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New treatment strategies in the management of breast cancer

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ABSTRACT

Growing understanding of the molecular characteristics of breast cancer is raising the possibility of ultimately delivering therapies that are tailored to the tumour biology of the individual patient. Agents that are currently being evaluated in metastatic breast cancer, irrespective of specific markers such as human epidermal growth factor receptor-2 (HER2) or oestrogen receptor, include the novel microtubule inhibitor eribulin mesylate, and a monoclonal antibody directed against vascular endothelial growth factor-A, bevacizumab. Denosumab, a receptor activator of nuclear factor κB ligand (RANKL) inhibitor, has recently been demonstrated to improve bone-related metastases in patients with breast cancer, irrespective of biological phenotype. Targeted therapies directed against DNA repair mechanisms such as poly(ADP ribose) polymerase (PARP) may prove particularly useful in the treatment of triple-negative breast cancer. Turning to the adjuvant setting in patients with HER2-positive breast cancer, recent studies have shown that concomitant treatment with taxanes and trastuzumab improves survival, and data with novel anti-HER2 agents are emerging. Current adjuvant and metastatic studies are evaluating novel targeted treatments aimed at HER2 and other targets. Molecular profiling of tumours is providing and will further provide the needed answers related to therapeutic optimisation.

1. Introduction

Cancer metastasis is a complex process that consists of numerous sequential, interlinked, and selective steps with some random elements. [1] Transformation of cancer cells to a metastatic phenotype is followed by neovascularisation and invasion of the surrounding stroma, and subsequently by detachment and embolisation of clusters of tumour cells into the blood and lymph. Metastases form when these cells undergo extravasation and proliferation at remote sites, a process aided by the formation of new blood vessels and the breakdown of immune responses. [1] The outcome of each step in this process is influenced by the interaction of the metastatic cell subpopulations with homeostatic factors; each step is potentially rate-limiting in that failure of a tumour cell to complete any step effectively impedes that part of the process. Therefore, the formation of clinically relevant metastases represents the survival and growth of selected subpopulations of cells that pre-exist in primary tumours.

Advances in the diagnosis and treatment of breast cancer are raising the possibility of a personalised approach to management of this disease. However, the complexity of the proliferative and metastatic processes means that such an approach will need to consider the underlying biology of the primary

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tumour and its metastases. As discussed during this workshop, considerable research has been devoted to the identification of potential biomarkers that can be used to predict the response to therapy (see the paper by Di Leo et al. in this supplement). This article reviews recent data on the management of breast cancer, both in patients with metastatic disease irrespective of specific markers and in patients with triple-negative metastatic breast cancer or human epidermal growth factor receptor-2 (HER2)-positive tumours. New adjuvant anti-HER2 therapies are also discussed.

In view of space limitations, a subtype of breast cancer that will not be discussed here is oestrogen receptor-positive disease. There are many trials in this area investigating new combination strategies with the addition of other targeted agents, exemplified by the recently-reported data from the phase III BOLERO-2 study (via a press release in July 2011) demonstrating improved progression-free survival by adding the mammalian target of rapamycin (mTOR) inhibitor everolimus to exemestane.[2] Also, site-specific metastases will not be covered here, again due to space limitations, although there is particular enthusiasm about the evaluation of the GRN1005 agent in patients with brain metastases from breast cancer.[3]

2. Treatment of metastatic breast cancer irrespective of specific markers

Eribulin mesylate is a novel microtubule inhibitor with a mechanism of action distinct from that of the taxanes and vinca alkaloids.[4] The efficacy and safety of this agent in later stages of metastatic breast cancer have recently been evaluated in the EMBRACE study, which involved 762 patients with locally recurrent or metastatic disease.[5] All patients had been heavily pre-treated, receiving a median of four agents including an anthracycline and a taxane. Patients were randomised to receive eribulin, 1.4 mg/m^2 on days 1 and 8 of a 3-week cycle, or a treatment of their physician's choice. The primary endpoint was overall survival. The 1-year survival rates were 53.9% in eribulin-treated patients and 43.7% in patients receiving other therapies, and the median duration of overall survival was 13.1 months and 10.6 months, respectively (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.66–0.99, P = 0.041). The median progression-free survival, as assessed by independent review, was 3.7 months with eribulin and 2.3 months with other therapies (HR 0.85, 95% CI 0.70–1.03, P = 0.09).

Bevacizumab is a humanised monoclonal antibody directed against vascular endothelial growth factor (VEGF)-A. Combinations of bevacizumab and chemotherapy have been shown to significantly improve progression-free survival and response rates, compared with chemotherapy alone, in patients with locally recurrent or metastatic breast cancer.[6] In a recent meta-analysis of three trials involving 2447 previously untreated patients with metastatic breast cancer receiving various anthracycline-based or taxane-based regimens, the addition of bevacizumab reduced the risk of disease progression or death by 36%, compared with chemotherapy alone.[7] Of note is that 60% of patients originally assigned to chemotherapy alone crossed over to bevacizumab treatment at the time of tumour progression, somewhat blurring the interpretation of impact of this agent on survival. Efficacy results demonstrated that there was no significant difference in median overall survival between the bevacizumab and non-bevacizumab arms (HR 0.97, 95% CI 0.86–1.08, P = 0.56), but 1-year survival rates were significantly higher in bevacizumab-treated patients (81.6% vs 76.5%, P = 0.003). In the light of the available data, there is an ongoing debate within the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) about the appropriate indications for bevacizumab.

Breast cancer patients often experience bone loss as a result of either chemotherapy or bone metastases, and hence bone-conserving therapies are attracting increasing attention in the management of breast cancer.[8] Denosumab is a human monoclonal antibody directed against receptor activator of nuclear factor κB ligand (RANKL), which is being evaluated for the treatment of bone metastases.[8] The efficacy of this agent has recently been compared with that of zoledronic acid in a randomised, double-blind study in patients with advanced breast cancer and bone metastases.[9] Denosumab significantly increased the time to first on-study skeletal-related event (SRE) by 18% compared with zoledronic acid (HR 0.82, 95% CI 0.71–0.95, P = 0.01 superiority): the median time to the first SRE was 26.4 months with zoledronic acid, and was not reached with denosumab. In addition, denosumab reduced the risk of developing multiple SREs by 23% compared with zoledronic acid (rate ratio 0.77, 95% CI 0.66–0.89, P = 0.001). The mean annual skeletal morbidity rate was also significantly lower with denosumab than with zoledronic acid (22% reduction; 0.45 vs 0.58 SREs per patient per year, respectively, P = 0.0006). Disease progression rates and overall survival did not differ significantly between the two treatments, and the overall incidence of adverse events was similar. However, zoledronic acid was associated with a higher incidence of renal toxicity than denosumab (8.5% vs 4.9%), and acute phase reactions occurring within the first 3 days after treatment were 2.7 times more common with zoledronic acid. Denosumab was approved by the FDA in November 2010 for the prevention of SREs in cancer patients with bone metastases, and the favourable EMEA decision followed in July 2011.

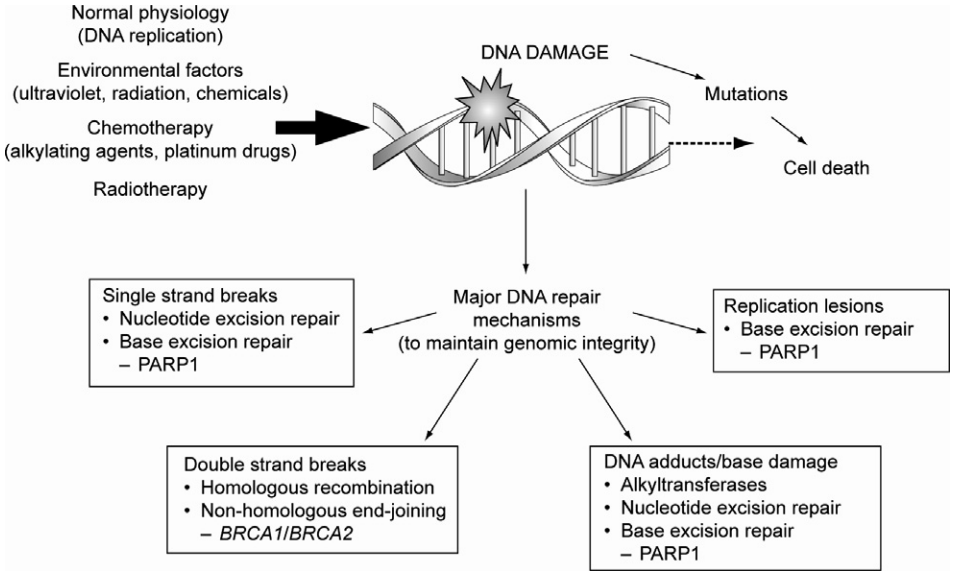

Fig. 1 – Major mechanisms of DNA damage and repair.[14] PARP, poly(ADP ribose) polymerase.

3. Management of patients with triple-negative breast cancer

Gene expression profiling has identified a number of breast cancer subtypes, including luminal subtypes (hormone receptor-positive), HER2-positive subtypes, and the basal phenotype.[10] The majority of basal subtype carcinomas, although not all, are triple-negative tumours, which are negative for oestrogen and progesterone receptors and HER2.[11,12] These tumours account for approximately 11–22% of all breast cancers,[12,13] and are highly proliferative. Expression of basal cytokeratins is common, and is associated with low disease-specific survival.[11] Patients with triple-negative breast cancer are more likely to develop early distant metastases and brain metastases than those with other phenotypes.[12,13] For example, in a study of 1601 breast cancer patients, 11% of whom had triple-negative disease, the HRs for distant recurrence and death within 5 years in patients with triple-negative disease were 2.6 (95% CI 2.0–3.5, $P < 0.0001$) and 3.2 (95% CI 2.3–4.5, $P < 0.001$), respectively.[12] However, in these patients the risk of distant recurrence was highest at approximately 3 years after diagnosis, whereas in patients with other phenotypes the risk of recurrence remained constant for up to 18 years.

Triple-negative breast cancer represents a therapeutic challenge because of the lack of targeted therapies available; by definition, such tumours are unlikely to respond to treatments directed against hormone receptors or HER2. Clustering analyses of microarray RNA expression have shown that familial BRCA1-positive tumours strongly segregate with triple-negative tumours,[10] which suggests that the latter may have acquired defects in BRCA1-related DNA repair processes. DNA repair mechanisms may thus represent a potential therapeutic target in triple-negative breast cancer; inhibition of these pathways could enhance the efficacy of anthracyclines, which act by damaging DNA through inhibition of topoisomerase II alpha. One potential target is poly(ADP ribose) polymerase (PARP), which plays a key role in a number of DNA repair mechanisms. PARP is central to the repair of single-strand DNA breaks through the base excision repair pathway (Fig. 1), and is also necessary for CHFR (checkpoint protein with forkhead-associated and ring finger domains) activity and reactivation of stalled replication forks.[14] Inhibitors of PARP have been shown to be effective in killing breast and ovarian cancer cells that lack wild-type *BRCA1* or *BRCA2* genes.[15,16] An agent that was thought to be a PARP inhibitor when the trials were designed, iniparib, has been evaluated in a phase III clinical trial in patients with metastatic triple-negative breast cancer, the results of which have recently been reported as not meeting the pre-specified criteria for significance for the co-primary endpoints of overall survival and progression-free survival.[17] The data were surprising in the context of the positive randomised phase II data reported in January 2011.[18] The results of a pre-specified analysis in patients treated in the second- and third-line setting in the larger phase III trial did, however, demonstrate an improvement in overall survival and progression-free survival. A follow-up phase III trial of chemotherapy with or without iniparib is now in development. Other agents under investigation in triple-negative breast cancer include PARP inhibitors such as olaparib and ABT-888, bevacizumab and the microtubule stabiliser ixabepilone, DNA minor groove inhibitors such as brostallicin, and histone deacetylase (HDAC) inhibitors.[19,20] Although there are other targets that are also being studied (such as phosphatidylinositol 3-kinase [PI3K], epidermal growth factor receptor [EGFR],

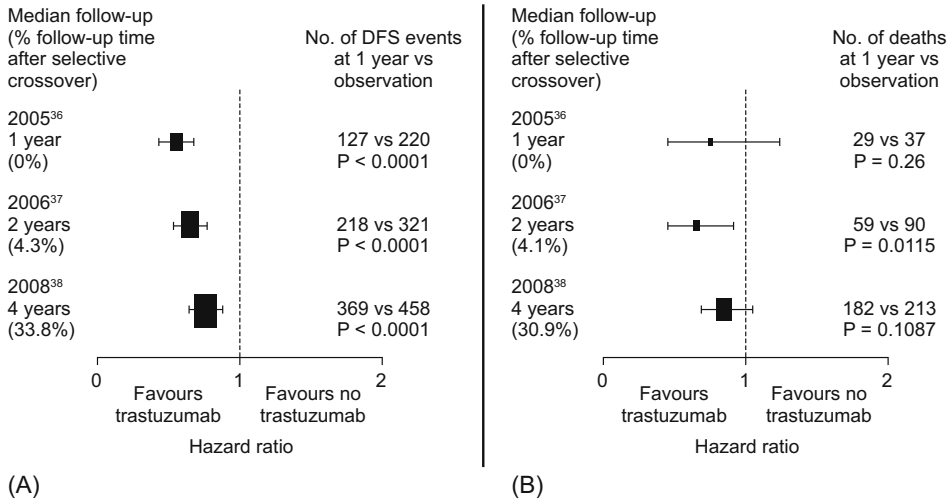

Fig. 2 – (A) Disease-free survival (DFS) and (B) overall survival at 1, 2 and 4 years in women with advanced breast cancer receiving adjuvant chemotherapy, alone or followed by trastuzumab, in the HERA study. [36–38]

fibroblast growth factor receptor [FGFR] and Notch in the setting of refractory triple-negative disease or even oestrogen receptor-positive tumours refractory to anti-oestrogens), sufficient data are not yet available to comment on efficacy. [21–24]

4. Management of HER2-positive breast cancer

Amplification or over-expression of HER2, as measured by fluorescence *in situ* hybridisation (FISH) or immunohistochemistry (IHC), occurs in approximately 15–20% of invasive breast cancers. [25,26] It is associated with decreased expression of oestrogen receptors, and hence with reduced *in vitro* and clinical sensitivity to tamoxifen and aromatase inhibitors. [27] Trastuzumab, a monoclonal antibody directed against the extracellular domain of HER2, has been shown to improve survival when used in combination with anthracyclines and taxanes in patients with advanced and adjuvant breast cancer. For example, in the recent North Central Cancer Treatment Group (NCCTG) N9831 study, concomitant treatment with paclitaxel and trastuzumab after initial anthracycline therapy improved disease-free survival, compared with sequential therapy (HR for disease recurrence 0.77, 95% CI 0.53–1.11, P = 0.02). [28] Recent guidelines recommend that HER2 status be determined in every case of primary invasive breast cancer to provide prognostic or predictive information at the time of diagnosis. [29,30] However, questions remain about the best way to identify patients who could benefit from trastuzumab. The current labelling for trastuzumab notes that both measurement of HER2 expression by IHC and measurement of gene amplification by FISH are subject to limitations, and hence the determination of HER2 status should not be based on a single assay technique. [31] Either IHC or FISH is considered appropriate for local laboratories, provided that high concordance rates (>90%) are established. [29,32] Patients with IHC 3+ or FISH-positive status should be considered for treatment; we recommend that IHC is performed when an initial FISH test is negative. [29] We also recommend that the FDA-approved criteria, rather than defining positivity by the 2007 American Society of Oncology (ASCO)/College of American Pathologists (CAP) guidelines, are used for selection of patients for adjuvant anti-HER2 therapy. [33] Other potential markers of anti-HER2 benefit that are under evaluation include *C-myc* gene and protein expression, phosphatase and tensin homolog (PTEN), insulin-like growth factor 1 receptor (IGF1R), HER3 and p95 status, although the data from Perez et al. and Reinholz et al. presented at the ASCO annual meeting in 2011 pose some doubt related to the role of PTEN or IGF1R proteins as markers of the benefit with adjuvant trastuzumab. [34,35]

4.1. Adjuvant therapy for patients with HER2-positive disease

Long-term follow-up from the HERA study, which evaluated the effect of treatment with trastuzumab after adjuvant chemotherapy, showed that the improvement in disease-free survival associated with trastuzumab was maintained for up to 4 years, whereas the initial improvement in overall survival declined during this period (Fig. 2). [36–38] The BCIRG 066 study showed that sequential therapy with anthracyclines plus cyclophosphamide followed by docetaxel and trastuzumab was fairly comparable in efficacy to combination therapy with carboplatin, docetaxel and trastuzumab (however, there was no statistical comparison between these two trastuzumab arms), although the sequential regimen was associated with a higher incidence of class 3/4 heart failure (2% vs 0.4%) and one case of leukaemia. [39]

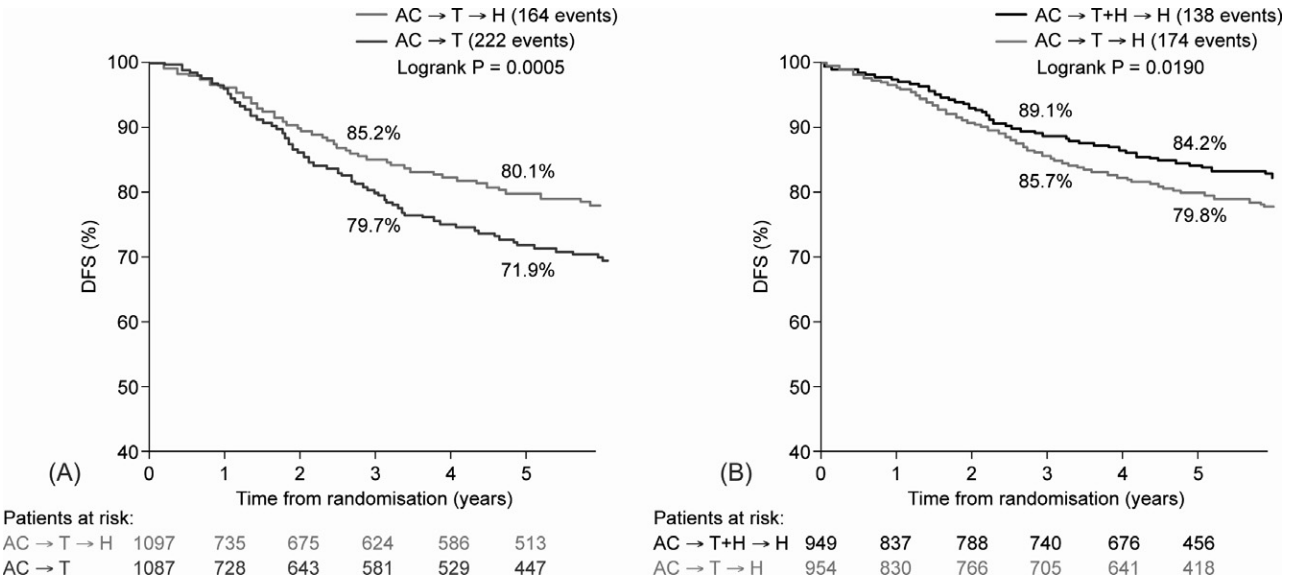

Fig. 3 – Disease-free survival (DFS) in the N9831 study after treatment with: (A) doxorubicin and cyclophosphamide followed by paclitaxel (AC → T) versus doxorubicin and cyclophosphamide, paclitaxel and trastuzumab given sequentially (AC → T → H); (B) sequential AC → T → H versus trastuzumab given concurrently with paclitaxel (AC → T + H → H). [28]

Similarly, in the N9831 study, sequential treatment with anthracycline-based therapy, taxanes and trastuzumab was associated with a significant improvement in disease-free survival, compared with anthracyclines and taxanes alone, but an additional benefit was achieved when anthracyclines were followed by taxanes plus trastuzumab, and subsequently by trastuzumab alone (Fig. 3). [28] An independent analysis of the cardiac safety data from this trial and the NSABP B31 trial showed that the incidence of symptomatic heart failure in trastuzumab-treated patients was 2.0%, compared with 0.45% in patients receiving chemotherapy alone, but complete or partial recovery occurred in 86.1% of trastuzumab-treated patients with symptomatic heart failure. [40] Other studies have reported a favourable benefit–risk ratio in patients receiving trastuzumab, with 3-year overall survival benefits of 2–5% and an incidence of fatal cardiac events of less than 0.2%. [41] On the basis of such findings, it can be recommended that trastuzumab should be added concurrently to the taxane component of adjuvant chemotherapy regimens for breast cancer; combination therapy with carboplatin, docetaxel and trastuzumab is an alternative option, although further follow-up is needed. [28]

4.2. *Future treatment strategies*

A number of promising treatment strategies are currently being evaluated in clinical trials, including combinations of anti-HER2 therapies with agents directed against other targets, such as mTOR and PI3K inhibitors. For example, the ALTTO study is investigating the benefits of combination or sequential treatment with trastuzumab and the dual tyrosine kinase inhibitor lapatinib. [42] This trial will involve approximately 8400 patients from 44 countries worldwide. Other trials, such as GEPARQuinto and NeoALTTO, are investigating the use of lapatinib as neoadjuvant therapy in HER2-positive patients. In the NeoALTTO study, women with HER2-positive primary breast cancer were given neoadjuvant treatment with lapatinib plus paclitaxel, trastuzumab plus paclitaxel or concomitant lapatinib and trastuzumab plus paclitaxel. The initial results indicate that dual blockade of the HER2 pathway is a valid concept: [43] the pathological complete response (pCR) rate was significantly higher with the combination of lapatinib plus trastuzumab compared with either trastuzumab or lapatinib alone (51.3% vs 29.5% vs 24.7%, respectively, $P < 0.01$ for both), and the corresponding clinical response rates at 6 weeks and at surgery (18 weeks) were also higher in the combination arm. The other small molecule anti-HER2 agent in phase II and III trials is neratinib, although diarrhoea is a particularly challenging adverse effect of this agent. [44]

Another novel therapy is pertuzumab, which inhibits the dimerisation of HER2 with other epidermal growth factor receptors. [45] This agent is currently being evaluated in a number of studies, including CLEOPATRA (in metastatic disease), NEOSPHERE (as neoadjuvant therapy), TRYPHAENA (as a component of adjuvant therapy regimens in patients with newly diagnosed disease), and MARIANNE (as first-line therapy in patients with metastatic breast cancer). The results of the NEOSPHERE study in patients with HER2-positive metastatic breast cancer whose disease had progressed on prior trastuzumab therapy were reported at the San Antonio Breast Cancer Symposium in December 2010. They showed a significantly higher pCR with neoadjuvant docetaxel plus

trastuzumab plus pertuzumab than with docetaxel plus trastuzumab (P = 0.014), which was significantly higher than trastuzumab plus pertuzumab (P = 0.031).[46] Once again, the data suggest that further studies of dual blockade of the HER2 pathway are justified. Top-line results of CLEOPATRA became known via a press release in July 2011, stating that pertuzumab added to the benefit of docetaxel plus trastuzumab in patients receiving first-line therapy for advanced HER2-positive breast cancer; further data are expected later this year.

Other trials are evaluating trastuzumab emtansine (T-DM1), a novel therapy consisting of trastuzumab linked to the microtubule inhibitor maytansine (DM1).[47] In a recent randomised phase II open-label study involving 137 patients with HER2-positive recurrent locally advanced or metastatic breast cancer, an objective response rate of 47.8% (95% CI 35.4–60.3) was achieved after a median of eight cycles of T-DM1, compared with 41.4% (95% CI 30.2–53.8) with trastuzumab plus docetaxel.[48] Recent data suggest that this agent showed an improved progression-free survival compared with docetaxel plus trastuzumab in this study. T-DM1 was associated with a markedly lower incidence of grade 3–4 adverse events (37% vs 75%), and no increased risk of cardiotoxicity, compared with trastuzumab plus docetaxel. T-DM1 is also being evaluated in the phase III recently activated MARIANNE study for patients eligible to receive first-line therapy for HER2-positive advanced disease. This trial compares taxane plus trastuzumab versus T-DM1 plus placebo versus T-DM1 plus pertuzumab.

5. Conclusions

Growing understanding of the molecular characterisation of breast cancer is highlighting potential new therapies and strategies by which existing treatments can be optimised in terms of improving their therapeutic ratio.[49–51] These developments raise the possibility of ultimately delivering therapies that are tailored to the tumour characteristics of the individual patient.

6. Conflict of interest statement

Dr Perez has received research grants for her studies at Mayo Clinic from Genentech, Roche, Glaxo, sanofi oncology and Novartis, and also the Breast Cancer Research Foundation and the 26.2 with Donna Foundation.

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