TRIAL SUMMARY: Pembrolizumab shows promising results in triple-negative BCa

This study investigated the use of pembrolizumab in the treatment of triple-negative breast cancer (TNBC). Patients with recurrent or metastatic disease and programmed cell death 1 ligand 1 (PD-L1)-positive tumours were eligible for enrolment. Inclusion criteria included good performance status (Eastern Cooperative Oncology Group [ECOG] 0–1), no concurrent systemic steroid use, no active, or history of, autoimmune disease, and no active untreated brain metastases. Of the patients screened for study, 58% had PD-L1-positive tumours. A total of 32 patients participated in the trial; mean age was 51.9 years, 21.9% were African-American, 12.5% had a history of previously treated brain metastases, and 46.9% had received 3 or more prior therapies for metastatic disease, including taxanes, anthracyclines, capecitabine, platinum and eribulin. Pembrolizumab was administered at a dose of 10 mg/kg intravenously every 2 weeks and was continued as long as benefit was observed without unacceptable toxicity. Response was assessed every 8 weeks as per Response Evaluation Criteria in Solid Tumours (RECIST) criteria.

Results: In the 27 patients evaluable for response, the overall response rate (ORR) was 18.5% (3.7% complete and 14.8% partial response). Stable and progressive disease was observed in 25.9% and 44.4% of patients, respectively. At the time of final analysis, with a mean followup duration of 9.9 months, median time to response was 18 weeks (range 7–32 weeks) and median duration of response was not yet reached, considering 3 patients remained on active study treatment (range 15–40+ weeks). Median progression-free survival (PFS) was 1.9 months (95% CI, 1.7–5.4) and PFS rate at 6 months was 23.3%. Treatment-related adverse events (AEs) occurred in 56% of patients and consisted of mainly grade 1 and 2 toxicities, including arthralgia, fatigue, myalgia and nausea. Immune-related toxicities were limited to pruritus (n=3, grade 1–2), hepatitis (n=1, grade 3, not attributed to treatment effect) and hypothyroidism (n=1, grade 2). Grade 3 toxicities occurred in 12.5% of patients and included anemia, headache, aseptic meningitis and pyrexia. One patient suffered from disseminated intravascular coagulation that resulted in death.

COMMENTARY: Programmed cell death protein 1 (PD-1) is expressed mainly on T cells. The binding of PD-1 to its ligands, PD-L1 and PD-L2, inhibits T-cell activity. Tumour cells can express PD-L1 and use this pathway to escape the immune system. Pembrolizumab (MK-3475) is a humanized monoclonal IgG4 antibody directed against human cell surface receptor PD-1 that inhibits binding of both PD-L1 and PD-L2. It was recently approved in Canada and the United States for the treatment of metastatic melanoma. In this phase I clinical trial by Nanda et al, pembrolizumab demonstrated an ORR of 18.5% in heavily pretreated metastatic TNBC patients. A proportion of responses were durable, and safety and tolerability profiles were acceptable. The use of pembrolizumab for the treatment of metastatic TNBC will be investigated further in a phase II clinical trial in early 2015. Despite these promising early results, challenges remain, particularly in identifying host- and disease-related factors that predict benefit from immunotherapy.
TRIAL SUMMARY: Ibandronate performs well without capecitabine in older patients
von Minckwitz G et al, for the German Breast Group. The phase III ICE study: adjuvant ibandronate with or without capecitabine in elderly patients with moderate or high-risk early breast cancer. 2014 San Antonio Breast Cancer Symposium Abstract S3-04.

This study investigated the use of ibandronate with or without capecitabine, an oral antimetabolite with demonstrated single-agent efficacy and favourable toxicity profile, in elderly patients with moderate or high-risk early breast cancer. Patients aged ≥65 years with pathologically proven node positive breast cancer or high-risk node negative breast cancer (tumour measuring ≥2 cm, of grade 2 or 3, or with negative hormone receptor status) were eligible for enrolment. Individuals with multiple comorbidities (Charlson index ≥3) were excluded from the trial. Patients were randomized to capecitabine (2000 mg/m² PO daily, day 1 to 14 q 3 weeks for 6 cycles) with ibandronate (50 mg PO daily or 6 mg IV q 4 weeks for 2 years) versus ibandronate alone. Following adjuvant capecitabine, endocrine therapy with tamoxifen or anastrozole and radiation therapy were administered when appropriate. A total of 1358 patients participated in the trial, with a mean age of 71 years. Approximately 10% of patients had comorbidities (Charlson index 2) and 15% had self-reported disabilities (Vulnerable Elders Survey [VES-13] score ≥3). Approximately 10% of tumours were locally advanced and 50% were node-positive, with roughly 80% hormone receptor positive, 20% HER2-positive and 15% triple-negative.

Results: After a median followup of 61.3 months, the primary endpoint of invasive disease-free survival (IDFS) was similar in both study arms at 3 and 5 years (85.4% and 78.8% with capecitabine and ibandronate vs 84.3% and 75.0% with ibandronate alone, respectively, p=0.7012). In subgroup analyses, no differences were seen in IDFS. In hormone receptor-negative patients (n=258), a tendency favouring the treatment arm with capecitabine was noted, however this was not statistically significant (HR 0.780, 95% CI, 0.523–1.16). OS was also similar in both groups at 3 and 5 years (95.4% and 90.1% with capecitabine and ibandronate vs 94.3% and 87.6% with ibandronate alone, respectively, p=0.3827). Treatment-related AEs occurred more frequently in capecitabine-treated patients, including skin, gastrointestinal and neurologic disorders (grade 3–4 toxicities 31.0% vs 8.7% for those on ibandronate alone).

COMMENTARY: Despite the considerable number of elderly patients among the breast cancer population, this group is underrepresented in clinical trials due to potential comorbidities and limited performance status that preclude the use of chemotherapy agents such as anthracyclines and taxanes. Recently, single-agent adjuvant bisphosphonate therapy was shown to increase distant disease-free survival (DFS) and OS in postmenopausal patients, possibly due to higher rates of therapy associated bone complications in this population. In this study by the German Breast Group, the use of adjuvant capecitabine alongside the bisphosphonate ibandronate did not improve IDFS in elderly patients with moderate- or high-risk early breast cancer. However, event rates were low and therefore longer followup might be required to observe a benefit of this drug. Approximately 25% of patients suffered bone-related complications despite the use of ibandronate, and these events were highest in the hormone-positive group treated with aromatase inhibitors. Most interestingly, the OS of this population treated with adjuvant endocrine treatment and bisphosphonate alone was very encouraging, with an OS of nearly 90% at 5 years, despite the moderate- to high-risk nature of these tumours.

Reference:

IN BRIEF
Already known:
• Elderly patients are underrepresented in breast cancer clinical trials.
• Single-agent bisphosphonate therapy increases distant disease-free survival (DFS) and overall survival (OS).

What this study showed:
• Patients over age 65 with moderate- to high-risk early breast cancer who received ibandronate alone had similar invasive DFS to those receiving capecitabine as well.
• OS at 3 and 5 years was similar between both groups.
• Grade 3 and 4 toxicities appeared in 31% of patients receiving capecitabine along with ibandronate vs 8.7% of patients receiving only ibandronate.

Next steps:
• Pursue additional study of these very encouraging results.
**TRIAL SUMMARY: Fulvestrant shows OS benefit**


The FIRST trial is a phase II open-label study that investigated the efficacy of fulvestrant compared to anastrozole in the first-line treatment of postmenopausal patients diagnosed with hormone receptor-positive (HR+) locally advanced unresectable or metastatic breast cancer. Patients (n=205) were randomized to fulvestrant (500 mg IM on day 0, 14 and 28 followed by q 28 days) versus anastrozole (1 mg PO daily). Disease and patient characteristics were well balanced in both treatment arms, with approximately 80% of patients having metastatic disease, 75% of patients having received no prior endocrine treatment and 25% having received adjuvant chemotherapy for early breast cancer.

**Results:** The primary endpoint of clinical benefit rate was 72.5% with fulvestrant and 67.0% with anastrozole (p=0.386). Median time to progression (TTP) was 23.4 months with fulvestrant compared to 13.1 months with anastrozole (HR 0.66, p=0.01). Overall survival (OS), though not originally planned as an endpoint, was added to the protocol in an amendment in 2011. After a median followup of over 40 months, median OS was 54.1 months in the fulvestrant arm vs 48.4 in the anastrozole arm (HR 0.70, p=0.041). Predefined subgroup analyses, including age, specific estrogen receptor and progesterone receptor status, presence of visceral involvement, use of prior chemotherapy, presence of measurable disease and prior endocrine therapy, all favoured the fulvestrant arm.

**COMMENTARY:** Fulvestrant, a synthetic estrogen receptor antagonist, binds competitively to estrogen receptors, resulting in their deformation and subsequent decreased estrogen binding. In previous studies, fulvestrant at a dose of 250 mg was shown to be both noninferior when compared to exemestane in the second-line setting, and similar in efficacy when compared to tamoxifen in the first-line setting of HR+ metastatic breast cancer. Following these findings, the CONFIRM trial compared this lower dose to a higher dose of fulvestrant (500 mg). Both PFS and OS favoured the higher dose (HR 0.8, p= 0.006, and HR 0.81, p= 0.016, respectively).

The phase II FIRST study shows that higher-dose fulvestrant offers a statistically significant OS benefit in the first-line treatment of postmenopausal patients with HR+ metastatic breast cancer when compared to the aromatase inhibitor anastrozole. The previously reported median TTP of 23.4 months translated into a median OS of 54.1 months, which remained significant across all subgroups. A phase III trial (FALCON) comparing these same molecules is currently ongoing and has completed recruitment.

**TRIAL SUMMARY: Nab-paclitaxel vs paclitaxel in early BCa**


This phase III trial included individuals diagnosed with unilateral or bilateral primary breast cancer irrespective of their operable status, with either larger node-negative tumours (cT2-cT4a-d), clinically or pathologically node-positive smaller tumours (cT1cN1+ or pN+ on SLN), or higher-risk disease (hormone receptor-negative, Ki67 >20% or HER2-positive tumours). A total of 1204 patients were randomized, with approximately 16% having locally advanced disease (cT3-4) and 45% having clinically node-positive disease.

**Results:** Pathologic complete response (pCR) was achieved in 38% of patients treated with nanoparticle-based paclitaxel (nab-T) vs 29% with solvent-based paclitaxel (T) (p=0.001), with consistent results in all biologic subtypes. Patients with triple-negative (48.2 % vs 25.7%, p<0.001), Ki67 >20% (44.0% vs 33.1%, p=0.001) and HER2-positive breast cancers (61.8% vs 54.1%, p=0.120) had particularly higher rates of pCR. Fewer patients treated with nab-T completed treatment compared to those on T (79.0% vs 86.3%), mostly due to the occurrence of significant AEs. Higher rates of peripheral sensory neuropathies, anemia and neutropenia were noted in the nab-T arm.

**COMMENTARY:** Previous studies have reported superior efficacy and more favourable toxicity profile of nab-T compared to T for the treatment of metastatic breast cancer.1 Furthermore, in the NEO-TANGO trial, the sequence of T followed by epirubicin/cyclophosphamide (EC) demonstrated a statistically significant advantage in pCR rate.2
Finally, in the NEOSPHERE trial, the addition of pertuzumab to trastuzumab and docetaxel also significantly improved pCR rates. Based on these premises, the current study hypothesized that using nab-T (150 mg/m² weekly for 12 cycles) instead of T (80 mg/m² weekly for 12 cycles) followed by standard-dose EC with concurrent use of pertuzumab and trastuzumab in HER2-positive patients would improve pCR rates, defined as absence of residual disease in both the primary tumour bed and nodes.

The authors found that the use of nab-T followed by EC, with or without concurrent pertuzumab and trastuzumab, was associated with a significantly higher rate of pCR in the neoadjuvant treatment of breast cancer, irrespective of biological subtype, when compared to T in a similar regimen. This effect was particularly significant in triple-negative breast cancers. Peripheral sensory neuropathy was the main dose-limiting toxicity. Further followup is required to establish if this improvement in pCR will translate into a higher rate of DFS and OS.

**References:**

**IN BRIEF**

**Already known:**
• Nanoparticle-based paclitaxel (nab-T) has been shown to have better efficacy and lower toxicity than solvent-based paclitaxel (T).

**What this study showed:**
• Pathologic complete response (pCR) was achieved in 38% of patients treated with nab-T versus 29% with T.

**Next steps:**
• See if the improvement in pCR translates into better survival.

**TRIAL SUMMARY: More reasons to characterize tumours**

Knauer M et al. Survival advantage of anastrozole compared to tamoxifen for lobular breast cancer in the ABCSG-8 study. San Antonio Breast Cancer Symposium, Abstract S2-06.

This review of data from the ABCSG-8 trial aimed to investigate if gene expression profiling could better identify subgroups predictive for benefit from aromatase inhibitors (AIs) than their pathologic surrogates. Originally, the ABCSG-8 study compared adjuvant treatment with tamoxifen monotherapy vs tamoxifen for 2 years followed by anastrozole in post-menopausal patients with low- to intermediate-risk early breast cancer. Evaluable tissue samples were collected from these patients (n=1478) and were stratified as invasive lobular carcinoma (ILC) versus invasive ductal carcinoma (IDC) and, using the multigene assay PAM50, as luminal A vs luminal B tumours. Primary outcomes were DFS and OS. A benefit in OS was noted in patients with ILC (HR 0.56, 95% CI 0.34–0.92) in the tamoxifen followed by anastrozole arm.

**COMMENTARY:** Several trials have aimed to determine the optimal adjuvant endocrine therapy for post-menopausal women diagnosed with hormone positive breast cancer. The use of AIs compared to tamoxifen has demonstrated improvement in outcomes in this setting. Subsequent studies have however shown that benefit with AIs is not consistent in all pathologic subtypes. In the BIG 1-98 trial, a significant increase in DFS and OS was noted in patients with ILC, but not in those with IDC. Further studies have therefore focused on characterizing pathologic subtypes to refine the choice of adjuvant endocrine treatment. For example, analysis of the BIG 1-98 data using intrinsic subtype established by pathologic surrogate using hormone receptor status, HER2 status and Ki67 demonstrated a trend toward higher efficacy of letrozole in both luminal A and luminal B tumours, despite greater proportion of luminal A tumours among ILC patients.

The OS benefit seen in the ABCSG-8 trial presented at...
the 2014 SABCS was highly dependent on pathologic subtype. In luminal A tumours, the use of anastrozole significantly improved DFS (0.70, 95% CI 0.53–0.94) and OS (HR 0.67, 95% CI 0.47–0.95) in IDC, contrary to results reported in the BIG 1-98 trial. In luminal B tumours, a benefit of anastrozole was reported in ILC with significant increase in DFS (0.35 95% CI 0.16–0.76) and OS (0.32, 95% CI 0.12–0.85). The analysis of tissue samples from patients enrolled in ABCSG-8 supports the idea that characterization of tumours by biologic subgroups is needed to refine the selection of adjuvant endocrine treatment. Multigene assays show promise for this purpose, but further prospective trials are needed.

References
2. Metzger Filho, O et al. Relative effectiveness of letrozole alone or in sequence with tamoxifen for patients diagnosed with invasive lobular carcinoma. JCO. 2013. suppl; abstract 529.