Cross-trial comparisons with studies of neoadjuvant endocrine therapy in metastatic breast cancer are unlikely to provide further insight, but the takeaway message is based on the data discussed here that the efficacy of such treatment approaches is different in metastatic breast cancer, compared with the small effect on objective responses and pathological complete responses in neoadjuvant endocrine therapy for early breast cancer. The good news, however, is that taselisib might offer an improved therapeutic index with a more favourable toxicity profile than pan-PI3K inhibitors.

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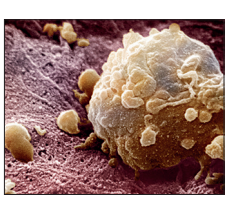
5-year results for pembrolizumab treatment of advanced melanoma

Current standard practice is to use checkpoint inhibitors for the treatment of patients with metastatic melanoma. The cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) antibody ipilimumab was the first drug that was shown to improve the survival of patients with metastatic melanoma.[1] Although the proportions of patients who achieved a response were low (only 10–20%), approximately 20% of patients achieved long-term tumour control.[2] These findings gave rise to hopes of being able to even cure patients with advanced melanoma. The KEYNOTE-006 randomised phase 3 trial, reported by Caroline Robert and colleagues[3] in *The Lancet Oncology*, has shown that the PD-1 antibody pembrolizumab is more effective than ipilimumab, with 235 (42%) of 556 patients assigned to pembrolizumab achieving an objective response versus 46 (17%) of 278 patients assigned to ipilimumab, median progression-free survival of 8·4 months versus 3·4 months, and overall survival of 32·7 months versus 15·9 months, respectively. These results for pembrolizumab are similar to those recorded for patients on nivolumab monotherapy; however, the combination of ipilimumab and nivolumab currently seems to be the most effective immunotherapy for melanoma, especially among distinct subgroups of patients with a PD-L1-negative tumour, high tumour load, or brain metastases.[4–7] Additionally, BRAF or MEK inhibition is a possible alternative for patients with *BRAF*-mutant melanoma. Hence, an individualised first-line treatment decision should be made for every patient based on their clinical situation.

The 5-year follow-up results for the KEYNOTE-006 study showed 5-year overall survival of 38·7% for pembrolizumab and 31·0% for ipilimumab, thus showing that pembrolizumab has a clear advantage over ipilimumab. However, only 23% of patients assigned to pembrolizumab remained progression free at 4 years. Today, the key question is how long patients should be treated with a PD-1 antibody. In KEYNOTE-006, 103 (19%) of 556 patients completed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2 years of pembrolizumab treatment per protocol. These were mainly patients with response, with 21 (20%) achieving a complete response, 69 (67%) achieving a partial response, and 13 (13%) with stable disease. Eight patients (8%) who were in partial remission after 2 years achieved a complete response after treatment cessation, exhibiting an ongoing immune response. Of the patients achieving a complete response, partial response, or stable disease, 16 (76%) of 21, 53 (77%) of 69, and seven (54%) of 13 were ongoing, respectively. The median time to progression was 33·3 months from the end of pembrolizumab treatment. Patients with stable disease progressed earlier than did those with complete response or partial response. The most common site of progression was the lymph nodes (n=13), followed by the liver (n=4) and lungs (n=3). However, the lymph nodes, in particular, are known to vary in size during and after immunotherapy, and it can be difficult to distinguish progression from pseudoprogression (eg, caused by a sarcoid reaction) by the use of radiological assessments alone.[8] In KEYNOTE-006, progression was confirmed by means of an excisional biopsy in only three patients. 13 patients with progressive disease received a second course of pembrolizumab as part of KEYNOTE-006. The first results for these re-treated patients indicate some effectiveness, with seven reported responders. Conclusions should, however, be drawn with caution: two patients had ongoing responses after complete resection of all progressing metastases, and, in three of the other five responding patients, progression before rechallenge and response under rechallenge was based on radiological increase and decrease of size of lymph nodes only.

At this year's American Society of Clinical Oncology Annual Meeting, a retrospective analysis was presented of 34 patients who were re-treated with a PD-1 antibody after a median treatment-free interval of approximately 1 year (range 3·5–28·6 months).[9] Only five of 34 patients responded to PD-1 antibody re-treatment, whereas almost 60% progressed. Interestingly, a response to PD-1 antibody re-treatment was seen among patients with previous remission to initial PD-1 antibody treatment (n=3), as well as among patients with previous progression (n=2). A different retrospective analysis of 185 patients who discontinued PD-1-targeted treatment without progression or treatment-limiting toxicity showed that patients in complete response at the time of treatment discontinuation were less likely to progress (14%) than patients in partial response (32%) or with stable disease (50%).[10] In this report, 19 patients were re-treated and six patients achieved a new response; however, no data on the site of progression or response were provided.

In conclusion, the long-term follow-up results from the KEYNOTE-006 study show the potential of pembrolizumab for long-term tumour control. Nonetheless, most patients will subsequently progress. Although patients can respond to re-treatment, the effectiveness of a second course of pembrolizumab seems to be lower. Clinical trials are urgently needed to assess the best duration of pembrolizumab treatment for melanoma. Current data suggest that patients who achieve complete remission under PD-1 antibody treatment have a good chance of remaining relapse-free.

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I am the principal investigator of several clinical trials sponsored by Bristol-Myers Squibb (BMS), Novartis, Roche, Immunocore, 4SC, BioNTech, and Philogen, but was not involved in the trial discussed. I have taken part in advisory boards for Merck Sharp & Dohme (MSD) and Pierre Fabre and have received speaker honoraria from BMS, MSD, Novartis, Roche, Sanofi, and Pfizer.

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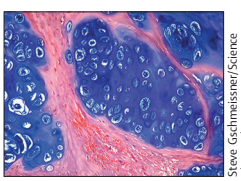
Fusion gene-oriented precision medicine in soft tissue sarcoma

Collection of clinical data and development of drugs for rare cancers is difficult because of the small numbers of patients who have the disease. Soft tissue sarcoma is one such rare cancer, which comprises more than 50 histological subtypes.[1] Doxorubicin has been the gold standard drug over the past 30 years because it is the most effective and first choice drug for soft tissue sarcomas in general. The combination of ifosfamide and doxorubicin is the next standard treatment owing to its high toxicity. Gronchi and colleagues[2] introduced a histotype-tailored chemotherapy regimen in the ISG-STS 1001 study to account for probable differences in the efficacy of the standard chemotherapy according to the different histological subtype. Patients were randomly assigned to standard chemotherapy (with epirubicin) versus trabectedin for the treatment of high-grade myxoid liposarcoma, gemcitabine plus dacarbazine for leiomyosarcoma, high-dose ifosfamide for synovial sarcoma, etoposide plus ifosfamide for malignant peripheral nerve sheath tumour, and gemcitabine plus docetaxel for undifferentiated pleomorphic sarcoma. However, none of the histotype-tailored regimens were more efficacious than the standard chemotherapy regimen. Through the development of the first molecular targeted drug in this niche field, pazopanib became the first approved molecular targeted drug for non-adipocytic soft tissue sarcoma, after publication of the results of a randomised, double-blind, placebo-controlled phase 3 trial (PALLETTE).[3] Although oral pazopanib resulted in significant efficacy in progression-free survival compared with placebo, it is more commonly used as a second-line treatment following previous chemotherapy (such as doxorubicin).

Extraskeletal myxoid chondrosarcoma is an extremely rare subtype of soft tissue sarcoma, characterised by middle-age onset, and very slow but steady growth. The typical scenario is that the gradually spreading disease deteriorates patient's prime of life over a long period of time. At the molecular level, this disease is characterised by the fusion of the genes EWSR1–NR4A3 or TAF15–NR4A3. Stacchiotti and colleagues[4] reported the effectiveness of doxorubicin for extraskeletal myxoid chondrosarcoma in a retrospective study in 2013. The results showed partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) in four patients, stable disease in three patients, and progressive disease in three patients, with a median progression free-survival of 8 months (range 2–10). These results differed from those of previous reports, which showed poor responses of extraskeletal myxoid chondrosarcoma to chemotherapy.[5] The authors explained that this discrepancy might be due to the distinct diagnostic criteria of extraskeletal myxoid chondrosarcoma restricted to positive NR3A4 translocation. Following this analysis, they used sunitinib for the treatment of patients with progressive metastatic extraskeletal myxoid chondrosarcoma. The results were partial response in six cases, stable disease in two cases, and progressive disease in two cases.[6] The median progression-free survival was not reached at the median follow-up of 8·5 months (range 2–28). Notably, patients with a EWSR1–NR4A3 fusion gene were significantly more responsive than those with the TAF15–NR4A3 fusion gene. On the basis of these results, a prospective, multicentre, single-arm, phase 2 trial of pazopanib was done.

In *The Lancet Oncology*, Silvia Stacchiotti and colleagues7 report the results of this phase 2 trial. A total of 23 eligible patients were recruited during approximately 2·5 years, despite the extreme rarity of this disease, and received oral pazopanib (800 mg/day). Four patients had a partial response, 16 patients had stable disease, and two cases patients had progressive disease; radiographically detectable tumour shrinkage was measured in 12 patients. The median progression-free survival was 19 months (95% CI 11–27) with a median follow-up of 27 months (IQR 18–30). A significant difference in progression-free survival



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