Is chemotherapy still an option in the treatment of melanoma?

Before the recent developments in targeted [1–4] and immune therapies [5–7], the standard systemic treatment of metastatic melanoma was limited to chemotherapy, and in selected patients interleukin-2. These standards had not changed for over a decade, and dacarbazine was the reference systemic therapy against which others were compared, despite having never been compared with best supportive care in a randomised study. More toxic multidrug chemotherapy-based combinations have been trialled leading to improved response rates without improving overall survival (OS) compared with single-agent dacarbazine [8].

In the last 5 years, four classes of systemic therapies have significantly improved OS compared with single-agent dacarbazine [1, 4, 9, 10] (Table 1). Ipilimumab was the first systemic therapy proven to improve OS in patients with metastatic melanoma, both in combination with dacarbazine chemotherapy [9] and as monotherapy [5]. The response rate for single-agent ipilimumab is similar to that observed with chemotherapy (10%–15%), yet responses are more durable as 20% of patients survive beyond 5 years [11]. Recently, the anti-PD1 agents nivolumab and/or pembrolizumab have been approved for use in metastatic melanoma in the first-line setting in the United States, Australia and several countries within Europe. This approval is based on phase III studies that demonstrated an improved response rate [6, 7], progression-free survival (PFS) [6, 7] and overall survival [6] compared with ipilimumab. Similarly, the combination of ipilimumab and nivolumab improved response rate and PFS compared with ipilimumab, yet with higher toxicity than nivolumab alone [7]. Concurrently, but separately from immunotherapies, targeted therapies were developed for the 40% of patients with BRAF-mutation-positive metastatic melanoma. Initial trials demonstrated an improved response rate, PFS and OS of single-agent BRAF inhibitors (vemurafenib or dabrafenib) compared with dacarbazine [1, 2]. Later, the combination of a BRAF and MEK inhibitor was shown to improve the OS compared with single-agent BRAF inhibition [3, 12, 13].

In this issue of *Annals of Oncology*, Hersh and colleagues [14] report the results from the phase III randomised study of nab-paclitaxel compared with dacarbazine in 529 chemotherapy-naive patients with metastatic melanoma. Nab-paclitaxel significantly improved the PFS [median: 4.8 versus 2.5 months, hazard (HR) = 0.792, \( P = 0.044 \)], the primary end point of the study; however, there was no improvement in the OS (median 12.6 versus 10.5 months, HR = 0.897, \( P = 0.271 \)), a secondary end point. There was a non-statistically significant difference in response rate (15% versus 11%, \( P = 0.239 \)). The PFS benefit of nab-paclitaxel over dacarbazine was seen across most subgroups including disease stage, LDH and BRAF mutation status, although the trial excluded patients with an LDH >2 times the upper limit of normal. Nab-paclitaxel was associated with higher rates and grades of neutropenia and peripheral neuropathy, while dacarbazine was associated with higher rates of thrombocytopenia. No quality-of-life data were collected as part of the study, and given the lack of improvement in OS, it is difficult to argue for the use of nab-paclitaxel over dacarbazine based on the PFS improvement alone. However, as the authors suggest, the lack of improvement in OS may be attributable to post study therapy, although post study therapies proven to improve OS appeared well matched between the two arms.

The study reported by Hersh et al. was conceived before the success of the immune checkpoint inhibitors and targeted therapies. Recruitment commenced in April 2009, 8–11 months before the start of the phase I trials of dabrafenib combined with trametinib [15] and nivolumab combined with ipilimumab [16], and 32 months before the start of the phase I trial of pembrolizumab [17]. Nab-Paclitaxel appears to have a response rate comparable with combination chemotherapy regimens such as carboplatin/paclitaxel [18]; however, because of the rapid change in the treatment landscape, the role of chemotherapy in general, and nab-paclitaxel in particular, is uncertain. For almost all patients, chemotherapy would only be considered in the second or subsequent lines of therapy. The typical patient considered for chemotherapy treatment would be one who had failed or was intolerant to ipilimumab and an anti-PD1 agent, as well as the BRAF/MEK inhibitor combination if they had BRAF-mutation-positive melanoma. In such heavily pre-treated patients, the benefit of chemotherapy may be attenuated and/or toxicities more debilitating. Furthermore, recently published

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<th>Table 1. Clinical trials of systemic therapies with improved OS compared with single-agent dacarbazine</th>
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<td>Agent</td>
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<tr>
<td>Ipiilimumab [9]</td>
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<tr>
<td>Vemurafenib [1]</td>
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<td>Trametinib [4]</td>
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<td>Nivolumab [10]</td>
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\( ^{a} \)Ipilimumab given in combination with dacarbazine.  
\( ^{b} \)Limited to patients with BRAF\(^{V600}\) mutant melanoma.  
\( ^{c} \)Limited BRAF wild-type patients.
data suggest that chemotherapy worsens quality of life when administered beyond the first line and near death, particularly in patients with a good performance status [19]. Thus, caution is required in selecting patients for chemotherapy in later lines of therapy.

It has been suggested that chemotherapy remains an appropriate first-line treatment option for BRAF wild-type patients in whom checkpoint inhibitors are contraindicated, most commonly because of a history of autoimmune disease. Clinical trials of such agents excluded patients with a significant history of autoimmunity based on the concern of exacerbating such conditions. Recently, retrospective data have been presented to suggest that ipilimumab can be safely used in patients with a history of autoimmunity including inflammatory bowel disease and rheumatoid arthritis, suggesting that the fraction of patients for whom checkpoint inhibitor treatment is contraindicated may be smaller than initially predicted [20]. Data on the safety of the newer, better tolerated, anti-PD1 agents in those with pre-existing autoimmune conditions would assist in determining the true proportion of melanoma patients for whom a checkpoint inhibitor is not an option.

Given the changing treatment landscape in metastatic melanoma, the role of chemotherapy may be in combinations with targeted or immunotherapeutic agents. In a phase I study of the MEK inhibitor trametinib and cremophor–paclitaxel, RECIST responses were seen in 6 of 15 melanoma patients, with a further 6 minor responses. This level of activity is beyond what would be expected with either agent alone [21]. A subsequent study is in planning combining nab-paclitaxel with trametinib (NCT02300935). There is increasing evidence that anti-PD1 agents are more active in patients whose tumours show evidence of a pre-existing T-cell activation, i.e. baseline tumour-infiltrating lymphocytes (TILs) and tumour PDL1 expression [22]. As a result of this, there is much interest in determining whether TILS can be induced in tumours without them, for example with chemotherapy, in an attempt to trigger a response to anti-PD1 therapies. Because of its activity as a single agent, and lack of requirement for steroid co-administration, nab-paclitaxel may be a good candidate to explore in such combinations. It remains to be determined whether chemotherapy offers more than the plethora of other strategies under investigation, e.g. combined immunotherapies or combined immune and targeted therapies and there is an urgent need for preclinical models that enable robust comparisons between various combination strategies. Furthermore, there is a need to segregate the ‘non-inflamed’ tumours into subgroups that may benefit from one combination strategy over another.

Despite the advances in melanoma management, chemotherapy remains a treatment option for a decreasing subset of patients with metastatic melanoma. Based on the results of the study by Hersh et al., nab-paclitaxel is another chemotherapeutic to consider in the armamentarium against melanoma, although the lack of OS or quality-of-life data, means it is another chemotherapy that has failed to knock dacarbazine off its crumbling perch.

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disclosure
The authors have declared no conflicts of interest.

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