Immunotherapy is revolutionising the outcomes for patients with advanced melanoma, and ipilimumab was the first drug in living memory to show a survival benefit in a randomised trial (1). Progress in adjuvant therapy for high-risk patients has lagged behind, and until recently high-dose interferon (HDI) was the only drug to show a survival benefit, though there remains a lack of consensus on the benefits of this treatment (2). This has now changed. A recent study from the European Organisation for the Research and Treatment of Cancer (EORTC) that randomised patients with fully resected stage III cutaneous melanoma to ipilimumab 10mg/kg or placebo reported a clear survival benefit at five years of 11% (65% vs 54%, HR 0.72; 95% CI, 0.58 to 0.88; P = 0.001) (3). Toxicity was significant, with 54% of patients experiencing grade 3-5 adverse events including 42% immune-related adverse events (irAE) and 1% treatment-related deaths. Adjuvant ipilimumab was approved in the US in October 2014 based on the primary endpoint of progression-free-survival, but has yet to be submitted for approval in the EU. There remains significant concern about the toxicity of this regimen when almost 50% of patients will have been cured by surgery.

The publication of the quality of life (QOL) data from the EORTC study would seem at first sight to bring some reassurance about tolerability of adjuvant ipilimumab (4). The authors report that health-related QOL, as measured by the EORTC QLQ-C30, was similar between groups, with no clinically relevant differences in global health status scores (defined by the authors as a difference of at least 10 points) observed during or after induction. Clinically relevant deterioration for some symptoms was observed at week 10, but after induction treatment was completed, no clinically relevant differences remained. How can this be for a treatment that was discontinued by half of all patients due to drug-related AEs, when the median number of treatments received was four (i.e. 12 weeks duration), and when only 42% of patients had one or more maintenance treatments?

The timing of the assessments may have contributed to the results. Each assessment related only to the preceding 7 days. The last assessment during the induction phase was at week 10, when the 4th treatment was given, and there were no further questionnaires until week 24. However the median time to onset of grade 2-5 IrAEs ranged from 4-12 weeks, and the median time to resolution was 4-8 weeks. Therefore, the QOL questionnaires may not have picked up all patients with symptoms. Furthermore, the consistently lower completion rates in the ipilimumab-treated patients (92% vs 80% at week 10) is a particular concern. Although the authors found no evidence that this was related to dropout due to side-effects, given that both toxicity and attrition were far higher in the
treated patients, one could deduce that the smaller proportion of patients who remained on treatment and completed the QOL questionnaires were systematically different to their counterparts in the placebo group, and so one is no longer comparing like with like.

It is also unclear if it is appropriate to determine that only differences of 10 points or more in QOL scores are clinically significant in today’s treatment setting. This determination was set two decades ago, long before the QOL impact of immune-related adverse events could be taken into account, and it raises the question of whether a new instrument is needed to reliably capture the QOL of patients treated with immune therapy. Fatigue and insomnia were not specifically identified in the original report as they are not immune-related adverse events, but these were two of the three symptoms that showed a significant deterioration in the symptom-specific scores. Insomnia is an unexpected toxicity, rarely reported in clinical trials, and almost certainly related to use of corticosteroids to manage toxicity. This highlights the importance of reporting all toxicity experienced, rather than focusing on specific items of special interest related to the mechanism of action of a drug. Chronic low grade fatigue is likely to have a much more significant impact on QOL than a transient, asymptomatic grade 3 rise in hepatic transaminases. Finally even if we accept the precise 10-point difference as the threshold of clinical significance, there is the difficulty that at 10 weeks the 95% CIs around the mean global health score show that the data are compatible with there being a 10+ point difference in QOL between the treated and placebo groups. This raises further concern about a conclusion of there being little impairment in the ipilimumab patients’ QOL despite grade 3-4 investigator-reported AEs.

It is interesting to note that the QOL conclusions are very different to the results of the of the ECOG 1697 Study of 4 weeks induction with adjuvant interferon alfa-2b. This also reported a high rate (58%) of treatment-related grade 3 or higher toxicity in patients receiving IFN and significantly worse quality of life in the treatment group. While direct comparison is difficult as the toxicity profile of HDI is not the same as for ipilimumab, and QOL was not assessed in the same way, many clinicians with experience of both treatments will be surprised by the different outcomes.

Where to from here? There are three main questions that are being addressed in clinical trials, many of which have completed accrual (Table 1). These are whether the lower dose of ipilimumab (3mg/kg, the licensed dose in advanced disease) will have a similar benefit to the higher dose tested in the EORTC study but with less toxicity; how do adjuvant ipilimumab and adjuvant HDI compare; and whether the newer PD-1 checkpoint inhibitors are active as adjuvant therapy. Most of these studies will report in the next two to three years.
Conclusions

Adjuvant ipilimumab has demonstrated a clear survival benefit and the investigators are to be congratulated for having assessed QOL in this study. However, there remain significant concerns about the tolerability of this regimen, and how best to assess it. We would urge caution in interpreting these QOL data in an overly positive way.

Table 1
Ongoing and completed adjuvant immunotherapy trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG1609</td>
<td>Ipilimumab 10mg/kg vs Ipilimumab 3mg/kg vs High-dose IFNalpha-2b</td>
<td>Completed accrual</td>
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<tr>
<td>SWOG S1404</td>
<td>Ipilimumab 10mg/kg vs Pembrolizumab 2mg/kg vs High-dose IFN alpha-2b</td>
<td>Recruiting</td>
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<tr>
<td>Checkmate 238</td>
<td>Ipilimumab 10mg/kg vs Nivolumab 3mg/kg</td>
<td>Completed accrual</td>
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<tr>
<td>Keynote 054</td>
<td>Pembrolizumab 2mg/kg vs Placebo</td>
<td>Completed accrual</td>
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<tr>
<td>Checkmate 915</td>
<td>Ipilimumab 10 mg/kg vs Ipilimumab 1mg/kg every 6 weeks + Nivolumab 240mg every 2 weeks vs Nivolumab 480mg every 3 weeks</td>
<td>Recruiting</td>
</tr>
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References