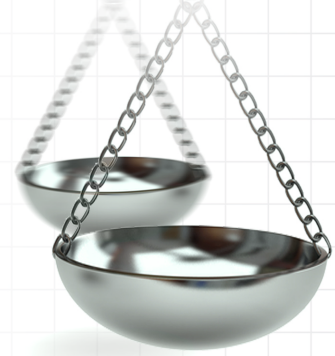
Commentary



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Combining immune checkpoint inhibitors for advanced melanoma: the key to optimizing treatment outcomes?

"The systemic nature of advanced metastatic disease renders the risk-to-benefit ratio of potential treatments much more of a hurdle..."

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With the field of melanoma oncology in desperate need of some promising data, significant strides have been made in recent years owing to the development of checkpoint inhibitor therapies. Metastatic melanoma is a formidable opponent for clinicians as incidence continues to rise in many European countries, especially among generations born up to the end of the 1940s [1]. Not only this, but metastatic disease carries a poor prognosis. 1-year survival rates range from 62%, if metastases are confined to the skin and lymph nodes (stage III), to 33% if LDH levels are elevated and distant metastases are found outside the lungs and skin (stage IV) [2]. The systemic nature of advanced metastatic disease renders the risk-to-benefit ratio of potential treatments much more of a hurdle compared with earlier disease stages. Our immune system has checkpoints in place to prevent overzealous reactions to innocuous stimuli or self-antigens, which unfortunately includes tumors, against which a powerful immune response may be well placed. Immunotherapies stimulate and take the brakes off the host immune system to enhance its antitumor attack. The promise of curing melanoma patients by simply stimulating their own natural defenses and, therefore, lowering doses, or even obviating the need of harmful drugs is enticing. Indeed, the lack of a specific histological target renders the technique a possibility for a range of tumor types. It has already proved efficacious in renal, hepatic and hematological malignancies [3]. With immune checkpoint inhibition proving to be a promising avenue and US FDA approvals following shortly after early-phase trial results, the next burning question is how these therapies can be optimized to be maximally effective in each individual patient.

Comparative effectiveness

Several trials have recently published results of the comparative effectiveness of anti-CTLA-4 and anti-PD-1 antibodies used together, compared with monotherapies [4–7]. Using an 'attack from all sides' approach is plausible owing to their varying mechanisms of action. CTLA-4 crosslinks with CD28 on T lymphocytes and inhibits T-cell proliferation and IL-2 release [8]. PD-1 is expressed by activated T cells and binds to its ligands on tumor cells to prevent immune rejection by dampening the T-cell response [9]. CTLA-4 and PD-1 blockade, therefore, awaken the host immune system to better eradicate tumors [10]. Hopes are that the efficacy of combined antitumor immunity may be greater than the sum of its parts [6].

A star is born

Early work by James Allison is heralded to be the birthplace of the CTLA-4 inhibitor [8]. Ipilimumab, a human monoclonal IgG1 antibody against CTLA-4, was the first checkpoint inhibitor licensed by the FDA in 2011 for the treatment of advanced melanoma [8]. In the first Phase III randomized controlled trial, to demonstrate its efficacy, metastatic

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melanoma patients who were assigned ipilimumab experienced a median overall survival of 10.1 months compared with 6.4 months in the control group (hazard ratio [HR]: 0.66; p = 0.003). However, the trial was not free of severe adverse events [11]. In terms of efficacy, the antibody also fared well at a higher dose of 10 mg/kg when combined with dacarbazine compared with this chemotherapeutic agent and placebo in a similar patient group [12]. The investigators estimated a 20.8% 3-year survival rate compared with 12.2% for the placebo group. Fewer ipilimumab-associated adverse events, such as enterocolitis and endocrinopathy, were reported compared with previous Phase II trials [13,14]. However, again, significantly more adverse events were reported compared with placebo and included pruritus, rash and elevated transaminases. Despite this, the durability of long-term survival in ipilimumab-treated patients with advanced melanoma has been evidenced in one Phase III study by twice as many recipients taking ipilimumab surviving to follow-up at 5 years compared with those assigned to placebo [15]. Although pooled data suggest an overall survival of 11.4 months (95% CI: 10.7–12.1 months) when taking ipilimumab, there has been evidence of a plateau in survival after 3 years, demonstrating significant effects in drug responders [16]. Moreover, early data suggest that patient factors and mutational status may not affect treatment efficacy, thus increasing the numbers of potentially eligible patients [17].

Round 2

Approval for nivolumab and pembrolizumab, two anti-PD-1 antibodies, followed shortly after in 2014. These agents were recommended for patients with advanced melanoma who had already tried ipilimumab or *BRAF*-targeted therapy for those with *BRAF*V600 mutations [18]. In KEYNOTE 002, a randomized Phase II trial comparing pembrolizumab with chemotherapy in the above-described patient group, 6-month progression-free survival was demonstrated in twice as many recipients compared with the control group [19]. Further trials of combinatorial treatments with pembrolizumab are warranted.

In the first Phase III trial to demonstrate its efficacy in patients with wild-type *BRAF* who had previously received ipilimumab, sister drug nivolumab outperformed dacarbazine in overall survival (72.9 vs 42.1%), progression-free survival (5.1 vs 2.2 months) and objective response rate (40 vs 13.9%) after 1 year. Fewer grade 3 or 4 adverse events were also reported in the nivolumab group compared with dacarbazine [20]. Results such as these, among other potentially aptly named CheckMate trials, began a hype that has resulted in clinicians asking: is this the end of melanoma treatment as we know it [21]? The excitement surrounding the efficacy of new-drug-on-the-block ipilimumab appeared to be overshadowed by the performance of this novel class of anticancer drug. Comparing pembrolizumab with ipilimumab as first-line treatment for metastatic melanoma in a randomized Phase III trial demonstrated superior progression-free survival for the anti-PD1-drug (47.3, 46.4 and 26.5% for pembrolizumab 10 mg/kg every 2 weeks, or every 3 weeks, compared with ipilimumab, respectively), as well as increased overall response rate (33.7, 32.9 vs 11.9%, respectively) and superior 1-year overall survival (74.1 and 68.4 vs 58.2%, respectively) [22].

Combine, combine, combine

Although these developments have brought much hope to a tired field, there are still advances to be made in terms of treatment outcomes. Many believe combination immunotherapy to be the answer [18]. Ascierto's progressive 'combine, combine, combine' mantra welcomed in this new treatment era in 2011, at which point surgical treatment options were already being banished to the past [23]. This idea was supported by preclinical studies, which have demonstrated that combined CTLA-4 and PD-1 receptor blockade may be more effective than compromising either pathway in isolation [9,24]. However, the questions of combining which drugs, in what order, at what stage, in which patients and at what dose, remain to be elucidated.

> "...early data suggest that patient factors and mutational status may not affect treatment efficacy..."

An initial Phase I study demonstrated a manageable safety profile with concurrent nivolumab and ipilimumab administration. Half the cohort experienced an objective response, all with an 80% or greater reduction in tumor size [6]. A subsequent Phase II double-blind randomized trial found an objective response of 61% in the combined nivolumab and ipilimumab group compared with 11% in the ipilimumab monotherapy group; a complete response was demonstrated in 22 versus 0%, respectively [7]. This objective response is greater than data from nivolumab and pembrolizumab monotherapy groups; however, this could be attributed to the treatment-naive cohort in this study. Patients were stratified based on *BRAF* mutation status but similar results were recorded in both groups. By contrast, the progression-free survival (8.5 vs 2.7 months in the combination vs monotherapy groups, respectively) was much improved in patients with *BRAF* mutation-positive tumors. Grade 3 or 4 adverse events more than doubled in incidence in the combination group (54 vs 24%) but

the authors described these as 'generally manageable'. The authors anticipate favorable clinical benefit with longer follow-up as responses in many participants endured despite treatment discontinuation [7].

Larkin *et al.*'s comparative Phase III multicenter trial took things up a gear by randomizing treatment-naive participants with advanced melanoma to receive nivolimumab or ipilimumab alone or nivolimumab combined with ipilimumab [5]. The study was powered to compare progression-free and overall survival for the combination treatment compared with ipilimumab alone and for ipilimumab alone versus nivolumab alone. In the combination group, following four doses of both drugs, participants entered a maintenance phase of receiving nivolumab alone. Progression-free survival at 12 months follow-up was 6.9 months (95% CI: 4.3–9.5) in the nivolumab group, 11.5 months (95% CI: 8.9–16.7) in the nivolumab-plus-ipilimumab group and 2.9 months (95% CI: 2.8–3.4) in the ipilimumab group [5]. A similar pattern of response between the study arms was demonstrated in objective response rates (43.7% for nivolumab and 19% for ipilimumab) with a rate of 57.6% in the combination group, which is higher than in previous studies of PD-1 blockade monotherapy [20]. Reductions in tumor burden, although impressive (51.9, 34.5 and 5.9% from baseline for the combination, nivolumab and ipilimumab groups, respectively), could not match the 80% reduction demonstrated in the Phase I study investigating nivolumab plus ipilimumab [6]. These results were independent of metastasis stage and *BRAF* mutation status. However, the authors suggest that negative PD-L1 tumor expression could one day be used as a biomarker to stratify patients who may benefit from combination therapy, as this patient subgroup experienced superior progression-free survival. Further work to validate this biomarker is certainly warranted to save nonresponders from the toxic adverse events associated with combination therapy if they would respond just as well to a PD-1 blocker alone. The authors are eagerly awaiting results to indicate whether these promising data will be translated into overall survival benefit: the best immunotherapy end point. Previous Phase I data suggest a survival rate of 79% at 2 years with patients taking nivolumab plus ipilimumab [25].

Health versus safety

Despite these promising results, 95.5% of patients assigned to the combination treatment reported adverse events, mainly diarrhea (44.1%), fatigue (35.1%) and pruritus (33.2%), with hepatotoxicity an additional concern. This rate was greater than either nivolumab (82.1%) or ipilimumab (86.2%) alone. In total, 55% of patients in the mixed arm reported grade 3 or 4 adverse events, compared with 16.3 and 27.3%, respectively, in the nivolumab and ipilimumab groups. Over twice the number of participants in the nivolumab plus ipilimumab group compared with either monotherapy group discontinued the study drug. Immune modulatory agents settled most events and there were no treatment-attributable deaths [5]. These data are in-line with previous reports [7].

Future optimization

These drugs have proved themselves to be useful tools in the melanoma-defeating arsenal but the questions of how best to utilize them remain unanswered. Subtle changes in dosage or timing of administration may prove to make a relatively substantial difference in survival. The Phase II CheckMate-064 study investigated sequential drug administration by comparing nivolumab followed by ipilimumab with ipilimumab followed by nivolumab in patients with advanced melanoma. Patients in the nivolumab–ipilimumab group were found to have a better response rate (41.2 vs 20%), a reduced rate of progression (38.2 vs 60%) but also a higher incidence of severe adverse events. It was concluded that, in this trial, sequential therapy had no advantage over concurrent therapy; however, with an altered study design, future efforts may be warranted [4]. Immunotherapies are also currently being combined with chemotherapy, radiotherapy and electrochemotherapy. Clinical trials in the pipeline are combining nivolumab with different immunomodulating antibodies, such as those that bind inhibiting receptors, such as LAG-3 (NCT01968109). Combinations of ipilimumab and pembrolizumab with the oncolytic virus, T-VEC, are also being investigated (NCT01740297).

Checkmate or stalemate?

This newly born field has recently exploded with numerous trials ranging from early translational-stage studies to currently ongoing late-phase clinical trials. Nivolumab has proven its efficacy and enhanced safety profile over ipilimumab and can be recommended more highly. Moreover, the combination of the two drugs has been found to be even greater than the sum of the monotherapies in isolation in many studies in all measured parameters. So what are we waiting for? Safety concerns revolve around the high incidence of adverse effects, which also increase in number and severity when the two agents are combined. Investigators have described these as manageable, and no compromised durability of response has been seen, but it is hard to ignore a third of study participants withdrawing due to

adverse events [5]. In terms of further optimizing these checkpoint inhibitor regimens, researchers must return to the drawing board. Therefore, these data represent the start of a new chapter, not the neat conclusion some may have hoped for. Although still suboptimal, this combined immunotherapy approach will likely benefit research into other solid and hematological cancers. In terms of melanoma treatment, these data, although preliminary, could result in a paradigm shift in terms of gold standard treatment for this aggressive and difficult to treat disease. The field awaits key data demonstrating overall survival benefit and longer term follow-up data to assess whether combination immunotherapy treatments, involving anti-PD1-agents or otherwise, warrant integration into first-line treatment regimens.

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Disclosure

S Freeston is a former employee of Future Science Group (2011–2013) in the Editorial Department, and worked on the *Journal of Comparative Effectiveness Research*. This article was peer-reviewed in a double-blind manner, and the decision to publish based solely on this process.

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