# A Better Combination?

New research asks if an alternative dosing schedule can produce the same effects with fewer side effects.

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By Cody R. Barnett, MRA Director of Communications

Four years ago, the FDA approved the first ever immunotherapy combination therapy of ipilimumab (Yervoy) and nivolumab (Opdivo) for advanced melanoma. The combination brings together the power of ipilimumab — a CTLA-4 inhibitor — with nivolumab — a PD-1 inhibitor — to create complementary and synergistic effects. The approval was hailed as a breakthrough and represented another way in which melanoma was leading the field of oncology forward.

To help us better understand and contextualize the impact of the ipilimumab + nivolumab combination — and the clinical trial results that move this work forward — we spoke with MRA grantee Caroline Robert, MD, PhD. Robert serves as the head of the dermatology unit at Gustave Roussy and co-director of the Melanoma Research Unit at INSERM 981 Paris-Sud University.

“The ipilimumab + nivolumab combination appeared as the most effective treatment option even if the trial only directly compared the combination to ipilimumab monotherapy,” Robert said. “That said, the trends consistently show a slightly higher level of efficacy and persisting responses with the tradeoff of higher toxicities.”

Checkmate 067: More Effective, but at What Cost?

Then in October, 2017 — two years after the approval of the combination — three-year overall survival (OS) data for 945 patients with advanced melanoma who were treated with ipilimumab, nivolumab, or the combination of ipilimumab + nivolumab were reported

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|---|---|---|
| Ipilimumab | 34% | 28% |
| Nivolumab | 52% | 21% |
| Ipilimumab + Nivolumab | 58% | 59% |

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The results were interesting for two reasons. First, the study proved what many clinicians already believed: that nivolumab alone or in combination with ipilimumab was more effective than single-agent ipilimumab. Second, while not designed specifically to study this, the ipilimumab + nivolumab combo was slightly more effective than single-agent nivolumab at the cost of dramatically higher rates of serious or life-threatening side effects — what researchers call Grade 3 or 4 Adverse Events.

“All patients need to be fully informed of the potential benefits and risks when making a treatment decision,” said Robert. “Understanding the frequency of adverse events is an important part of that discussion.”

Robert added that in some circumstances, the available data does point to one treatment over another: “Recent results suggest that the ipilimumab + nivolumab combination is the most effective treatment for patients with asymptomatic brain metastases.”

Checkmate 511: Can the Combo be Optimized to Reduce Side Effects While Preserving Efficacy?

Next, researchers wanted to know if they could optimize the combination in a way that would allow more people to benefit from the combo’s increase in efficacy while making it more tolerable. One way that researchers hoped to do this was by adopting an alternative dosing regimen, and results from the first study testing this hypothesis were published in March, 2019.

The Checkmate 511 study, led by a team of researchers from Europe, including Robert, randomly assigned 360 patients to receive either the standard, FDA-approved dose of nivolumab 1 mg/kg + ipilimumab 3 mg/kg or an experimental dose of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. Both groups received their respective dose on the same schedule — once every three weeks for four doses. Investigators then compared the rates of treatment-related adverse events between the two groups and found that the alternative dosing regimen had a much lower rate of serious side effects (33.9% versus 48.3%). After median follow up of 12 months, the efficacy — or how well it worked — between the two dosing regimens were largely the same.

The results of this study “confirmed the lower adverse event rate and although reassuring, are not totally convincing in terms of equivalence,” said Robert.

Not So Fast: The Limits of the Study Design

When interpreting the results of any study, it is important to look at what the researchers set out to answer. This is what is called the Primary Endpoint. The primary endpoint for Checkmate 511 was to evaluate the rate of treatment-related Adverse Events. In addition to this, the trial has several Secondary Endpoints — which are like ‘bonus’ findings — meaning that while the data are suggestive they are not definitive.

So, while Checkmate 511 demonstrates an improved safety profile for the ‘low-dose ipilimumab’ dosing regimen, it offers no definitive conclusions on the comparative effectiveness between it and the FDA-approved dosing regimen. A new clinical trial, that is powered and randomized specifically to answer that question, is needed to answer this once and for all.

“I think physicians will offer this low-dose regimen to [medically] fragile patients or to those who are afraid of adverse events,” said Robert. “It is likely that younger patients, those more willing to accept the increased risk of adverse events, and patients with brain metastases will continue to receive the standard dose until know more about the efficacy equivalence.”

Checkmate 511 is an important step forward for patients who want the benefits of combination immunotherapy while minimizing side effects. Studies such as this provide critical evidence and insight to clinicians so they can adapt treatments for specific patients.

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