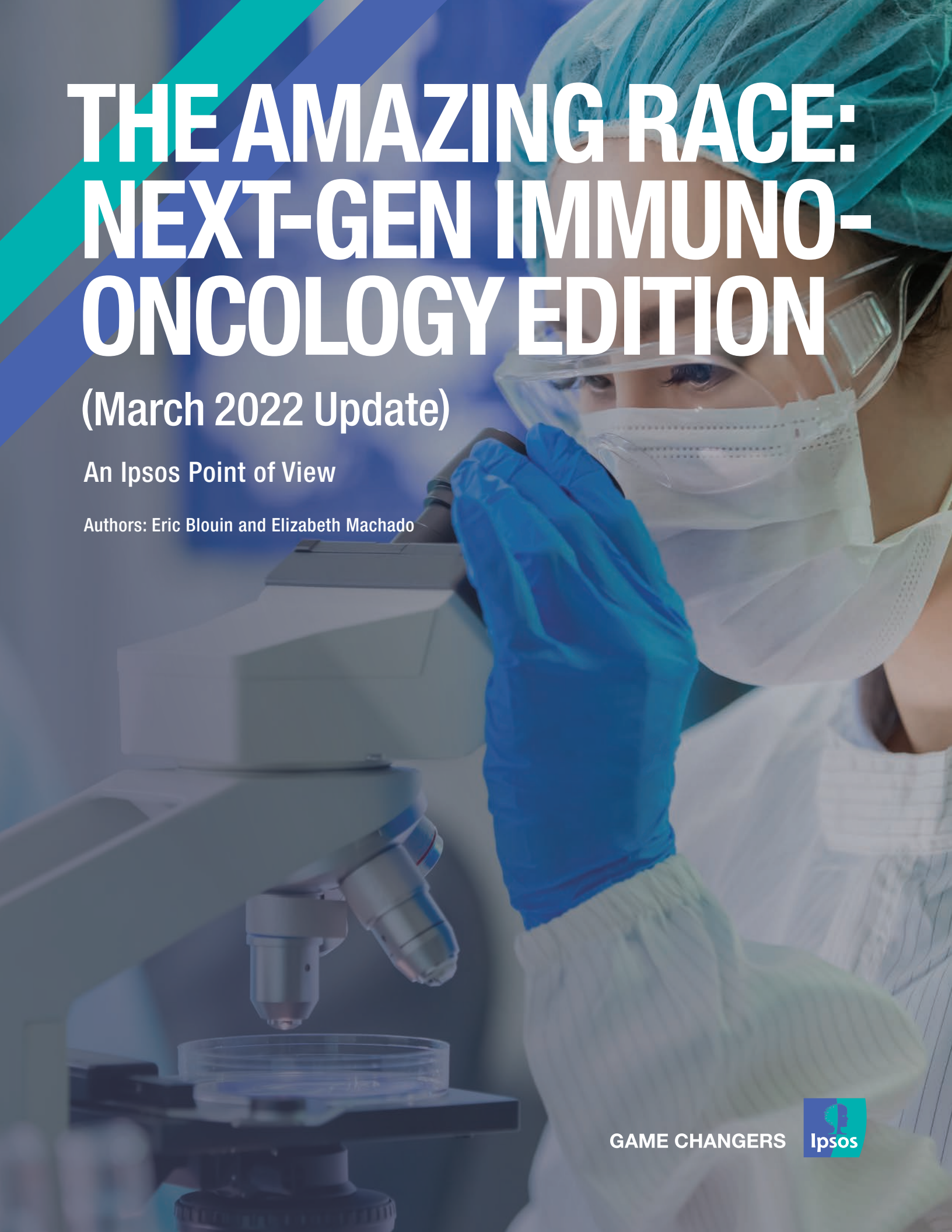

THE AMAZING RACE: NEXT-GEN IMMUNO-ONCOLOGY EDITION

(March 2022 Update)

An Ipsos Point of View

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GAME CHANGERS

Ipsos

In our previous look at next-generation checkpoint inhibitor R&D, we highlighted the two front-runners: BMS's **relatlimab** (an anti-LAG3) and Roche/Genentech's **tiragolumab** (anti-TIGIT). A whirlwind of activity has occurred over the past seven months. In this update, we'll summarize some of these key events, as well as the ones to anticipate in 2022.

TIGIT (T-cell Immunoglobulin and ITIM domain) Update

Shortly after the publication of our previous article, **GSK** announced it finalized a $2 billion deal ($625 million upfront) with **iTeos Therapeutics** to develop and commercialize its anti-TIGIT candidate, **EOS-448**. The deal adds to GSK's investment in a portfolio of novel immuno-oncology assets (anti-CD226 GSK608 and anti-PVRIG GSK562) which aims to complement its recently approved anti-PD-1, JEMPERLI.®

A week later, **Arcus Biosciences** communicated that their lead anti-TIGIT asset, **domvanalimab**, showed encouraging clinical activity in PD-L1-high-metastatic NSCLC in the first planned interim analysis of the ARC-7 trial. This news bolstered speculation about the "will they or won't they" narrative regarding Gilead's option to license domvanalimab. The chatter increased with the news a month later that Bill Grossman, Arcus's Chief Medical Officer, was leaving to join Gilead. The answer came a few months later (on November 18th) with Gilead exercising not only their option for domvanalimab, but also for three other assets (including AB308, a second anti-TIGIT molecule). With this deal, Gilead becomes a key player in the anti-TIGIT (and next-gen I-O) race.

There were several other TIGIT updates in November and December 2021:

- Compugen declared that its anti-PVRIG COM701, combined with BMS's OPDIVO® and anti-TIGIT **BMS986**, was safe and tolerable in an initial interim safety update of its phase ½ trial for a number of solid tumors.
- Mereo Bio also communicated interim results form its phase 1b/2 ACTIVATE trial, which is assessing **etigilimab** with OPDIVO.®
- To complement its existing partnership with BeiGene on **tislelizumab** (an anti-PD-1), Novartis announced that it had signed a global (excluding China) commercial rights option for BeiGene's anti-TIGIT **ociperlimab** for USD 300 million upfront, with a further USD 700 million if the option is exercised by 2023.

Arguably, the biggest splash in TIGIT news came from the updated results of the Roche/Genentech's CITYSCAPE trial for **tiragolumab**. As you may recall, the first update was presented at ASCO 2020 and showed that the combination of tiragolumab and TECENTRIQ® provided significant ORR benefits vs. Tecentriq alone in previously untreated metastatic NSCLC patients with a high level of PD-L1 expression (PD-L1 TPS ≥ 50%)—66% vs. 24%, respectively. The study's other co-primary PFS endpoint was also met, with a 70% risk reduction in the high PD-L1 group. Would these initial results hold with a larger number of patients enrolled and more mature data?

The answer is "yes," as the update presented at ESMO I-O showed a 71% risk reduction in risk of death or disease-worsening in the PD-L1-high subgroup, with ORR of 69% vs. 24%. What somewhat marred the promising new data was that there were two reported patient deaths in the tiragolumab/TECENTRIQ® arm vs. none in those receiving TECENTRIQ® alone (the significance of which is still under evaluation).

LAG-3 (lymphocyte-activation gene 3) Update

We noted in our earlier paper that BMS's **relatlimab** led the anti-LAG3 race (which, in turn, leads the "next-gen" I-O race). To follow on its March 25th, 2021 announcement that relatlimab met its primary PFS endpoint in its initial pivotal phase ⅔ trial (RELATIVITY-047), more detailed results were disclosed at the ASCO 2021 Annual Meeting in June. This was followed a few months later with an announcement that relatlimab's BLA had been accepted for Priority Review, setting its **PDUFA date for March 19, 2022.**

Assuming there are no surprises, relatlimab will become the third checkpoint inhibitor class approved; with BMS being the only company to have received approvals for agents in all three (i.e., YERVOY®/anti-CTLA-4, OPDIVO®/anti-PD-1, and relatlimab/anti-LAG3).

Compared to the frenzy of activity seen with the anti-TIGITs, there was relatively little LAG3 news beyond relatlimab and Immutep's **eftilagimod alpha** (*"efti"*). Immutep is a small biotech company based in Australia, with operations in France, Germany, and the US. Its lead candidate, *efti*, is a soluble LAG3Ig fusion protein. Rather than being an antagonist like relatlimab, *efti* is an agonist which aims to boost antigen- presenting cell (APC) activation. Immutep has partnered with Merck, Pfizer, EMD-Serono, and GSK for a number of tumors, and it still holds most global rights for metastatic breast cancer.

In November, the phase 2b AIPAC study, which evaluated *efti* in combination with paclitaxel in HER2-/HR+ metastatic breast cancer, was described "*…as showing improved overall survival (OS), and as supporting its further phase III development.*" While the intent-to-treat population saw a non-significant 2.9 month increase in overall survival (OS) vs. single-agent paclitaxel, predefined patient sub-population analysis demonstrated some significant survival benefits. While these results are encouraging, it remains to be seen if they can be replicated in a larger phase 3 study necessary for regulatory submission.

The Road Ahead

Barring any surprises, relatlimab should receive FDA approval by its March 19th PDUFA. However, BMS will still face several challenges and will need to overcome them to ensure commercial success of relatlimab:

- While relatlimab's tolerability profile appears to be superior to OPDIVO®/YERVOY®, it is still inferior to OPDIVO® monotherapy, which may lead oncologists to select young/fit/healthy patients (similar to what is done with OPDIVO®/YERVOY®).
- Overall Survival (OS) data has not matured, and BMS has not yet provided details regarding Overall Response Rate or Durability of Response.
- The lack of head-to-head comparison with OPDIVO®/YERVOY® (as well as the above-mentioned OS data) might also relegate initial use to those who either progress or are intolerant to OPDIVO®/YERVOY® (despite its first-line indication).

All eyes will also be on Genentech's expected presentation of SKYSCRAPPER-01 results (in Q3), tiragolumab's pivotal phase III study in first-line mNSCLC. Should results not live up to CITYSCAPE and/or further safety signals be uncovered, the recent frenzy of activity surrounding the TIGITs might come to an abrupt halt (case in point: IDO1 inhibitors).

Watch this space for more updates on this fascinating and amazing race!

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