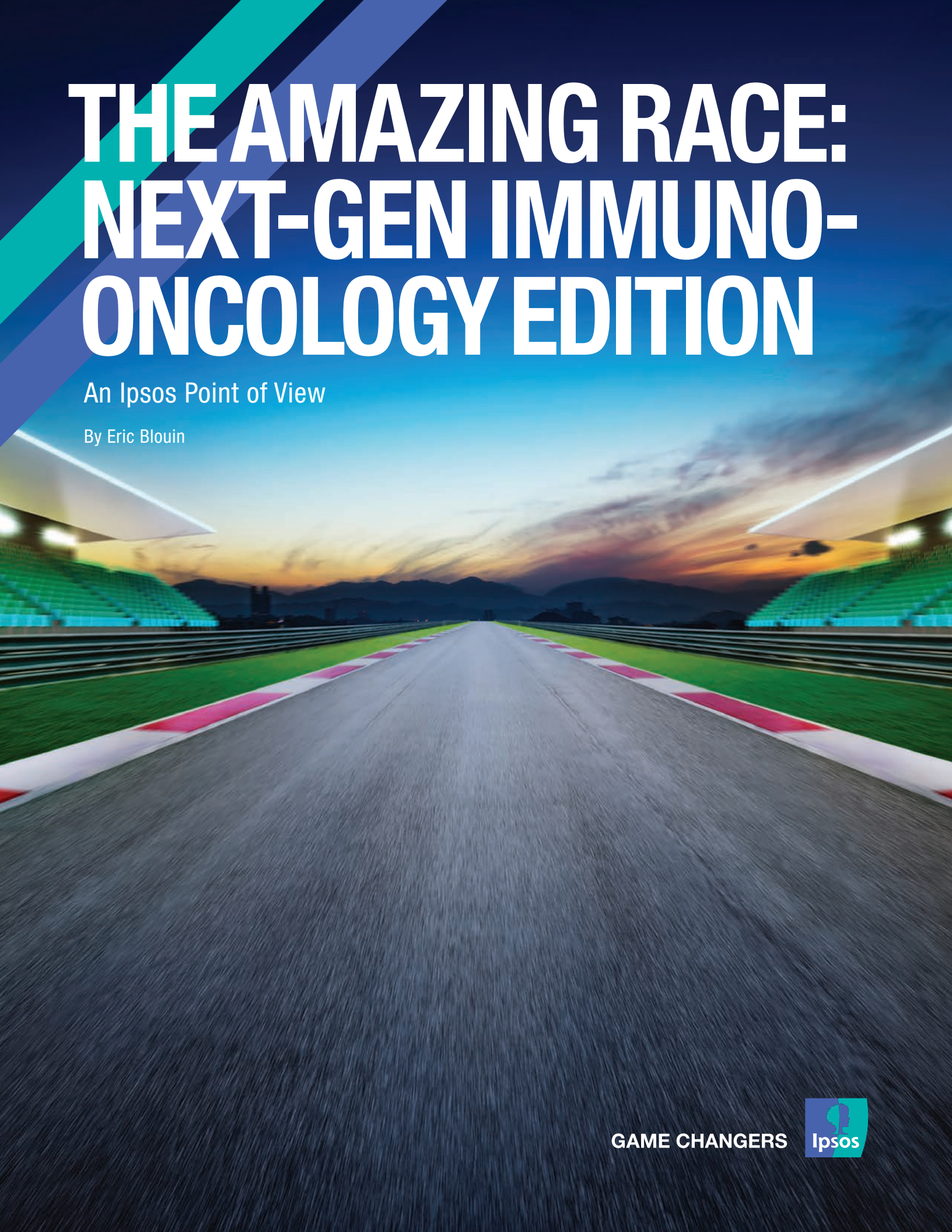
THE AMAZING RACE: NEXT-GEN IMMUNO-ONCOLOGY EDITION

An Ipsos Point of View

By Eric Blouin



GAME CHANGERS

THE AMAZING RACE: NEXT-GEN IMMUNO-ONCOLOGY EDITION

Summary

In the search for next-generation immuno-oncology agents beyond the anti-PD-(L)1s, two front-runners have finally emerged: BMS' relatlimab (anti-LAG3) and Roche/Genentech's tiragolumab (anti-TIGIT).

The assets are complementary to anti-PD-(L)1s, potentially providing increased efficacy (without incremental toxicities).

Both companies have heavily invested in broad clinical programs to expand beyond the assets' initial lead indications. There is also intense competitive R&D activity.

While relatlimab is likely to be approved first (based on having recently announced a positive pivotal trial), its lead indication (metastatic melanoma) may not initially be a significant growth driver for BMS.

In contrast, tiragolumab's lead indication, 1L mNSCLC (PD-L1 high patients) holds greater immediate commercial benefit. If its pivotal trial (SKYSCRAPPER-01) which is now underway garners positive results, tiragolumab may overshadow relatlimab despite its approval over a year earlier.

After several false starts (remember OX40 and the infamous IDO1?) and recent missteps (hello ICOS, we are looking at you!), two promising new immuno-oncology (IO) classes could soon complement the reigning champions, anti-PD(L)1s. At ASCO 2020, Roche/Genentech created buzz for **tiragolumab** (an anti-TIGIT candidate) with an update for CITYSCAPE, its phase 2 NSCLC trial. More recently, BMS upped the ante by announcing positive results for its RELATIVITY-047, a phase 2/3 trial for **relatlimab**, its anti-LAG-3 asset.

In this article, we'll analyze the strengths and weaknesses of each class, and anticipate how the race might play out and what its impact on the cancer landscape could be. Unlike most contests, this one could have more than one winner!

ANTI-LAG 3 AND RELATLIMAB

LAG-3 (lymphocyte-activation gene 3) is an immune checkpoint expressed on the surface of effector and regulatory T cells. Stimulation of LAG-3 leads to both direct and indirect inactivation of the effector T cells, inhibiting the anti-tumor response. By targeting this receptor, it is proposed that function can be restored to the effector T cells and anti-tumor response can be promoted.

The LAG-3 and PD-1 pathways are complementary, and RELATIVITY-047 was designed to evaluate **relatlimab** in combination with OPDIVO,® in previously untreated metastatic melanoma. On March 25, 2021, BMS announced that relatlimab met its primary PFS endpoint, and that no new safety signals were noted. The detailed results of RELATIVITY-047 will be presented at an upcoming medical meeting (TBD) and could form the basis of a new biologic license application (BLA) to the FDA.

With this study, BMS has also jumped ahead of other LAG-3 competitors in development (of which there are at least eight others in phase 2 development). While BMS has been somewhat tight-lipped about relatlimab's clinical development program, it's clear there are, at minimum, six other phase 2 trials underway in a range of tumors—liver, NSCLC, head & neck, colorectal, gastric, and renal—which speaks to the large potential that BMS sees in this asset.

Among BMS's key LAG-3 competitors are a couple of usual suspects: Merck/MSD and Genentech/Roche. Merck has two different compounds in phase 2: **MK-4280**, a "standard" monoclonal antibody targeting LAG-3, as well as a more novel collaboration with Immutep's **eftilagimod alpha**, an APC (antigen- presenting cell) activating soluble LAG-3 protein. The current Merck collaboration is focused on combination trials in mNSCLC and head & neck cancer, which would build upon the KEYTRUDA® franchise in these tumors.

Genentech had decided upon a different approach to LAG-3 as its lead compound: **RG6139** is a bispecific antibody which targets both PD-1 and LAG3. The first phase 2 trial is planned in esophageal squamous cell carcinoma (ESCC). Such a bispecific antibody could provide benefits to using separate anti-PD(L)1 and anti-LAG-3 drugs. MacroGenics also has a similar bispecific antibody (**tebotetimab**) in phase 2 development for head & neck and gastric cancers.

ANTI-TIGIT AND TIRAGOLUMAB

The TIGIT (T-cell Immunoglobulin and ITIM domain) pathway is an inhibitory immune checkpoint that regulates the activity of tumor-infiltrating lymphocytes (TILs), which include natural killer (NK), effector T, and regulatory T cells. Tumor activation of TIGIT receptors is believed to be another mechanism (beyond PD-1/L1) by which tumors evade immune surveillance.

The results of CITYSCAPE were presented at ASCO 2020 to great fanfare. A key takeaway from this trial was that the combination of **tiragolumab** & TECENTRIQ® showed significant ORR benefits vs. TECENTRIQ monotherapy 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. While slightly more toxicities were observed in the tiragolumab arm (69% vs. 47% of TECENTRIQ monotherapy patients), these were primarily grade 1-2 infusion-related reactions and rash. Occurrence of grade 3-4 adverse events were more comparable between the two groups (18% for the tiragolumab combo vs. 13% for TECENTRIQ monotherapy). With this proof-of-concept, Genentech has embarked on SKYSCRAPER, a broad phase 3 development program for the drug, with five pivotal studies initiated in 2020:

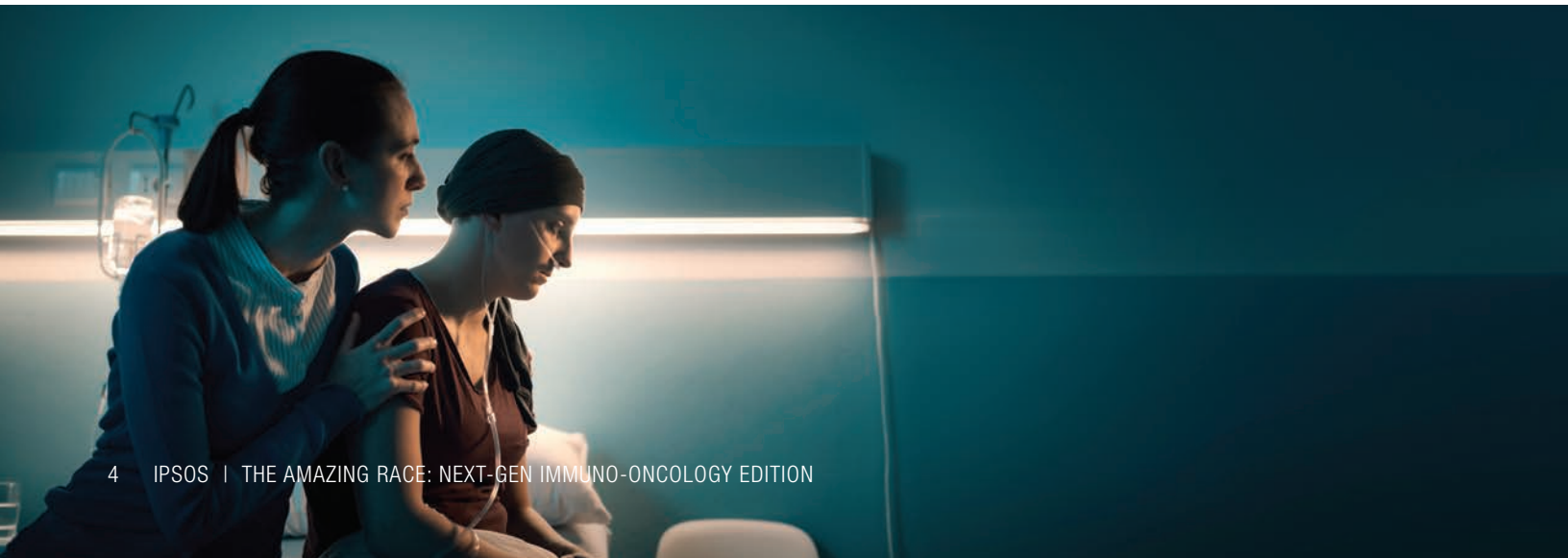
- 1L "high PD-L1" NSCLC (SKYSCRAPER-01)
- Stage III NSCLC (SKYSCRAPER-03)
- 1L SCLC (SKYSCRAPER-02)
- Esophageal squamous cell cancer (SKYSCRAPER-07 & -08)
- Multiple phase 2 studies in other tumor types (cervical, head & neck, HCC, pancreatic, breast, bladder, and hematological malignancies)

The TIGIT pipeline is also crowded, with Merck/MSD's **vibostolimab** on tiragolumab's heels. Merck has announced it would initiate a phase 3 trial in PD-L1 mNSCLC in the first half of 2021, based off the results of its phase I study presented at ESMO '20. Merck also has ongoing phase 1/2 vibostolimab studies in melanoma, called KEYMAKER. For now, Merck apparently has not invested as extensively as Roche into its TIGIT asset, but that could certainly change quickly.

BMS has pursued TIGIT with a twist. Its asset (**BMS-986207**) is being investigated (phase 1/2) as part of a "triple pathway" strategy, which would involve OPDIVO (anti-PD-1), BMS-986207 (anti-TIGIT), and Compugen's COM701 (anti-PVRIG—**P**olio **V**irus **R**eceptor-related ImmunoGlobulin domain). COM701 is a first-in-class immunotherapy targeting PVRIG, a novel immune checkpoint that is believed to be complementary and synergistic with TIGIT and PD-1 pathways.

Other players include Arcus' **domvanalimab** (which is in phase 3 development for PD-L1 positive mNSCLC in Hong Kong, in combination with its anti-PD-1 candidate zimberelimab, and in phase 2 development in the U.S., Taiwan, Korea, and Australia). Gilead already has struck a deal for zimberelimab, and has a right of first refusal for domvanalimab, hence a positive result in its phase 3 trial could trigger a further deal, as Gilead is eager to expand its oncology footprint.

Finally, BeiGene has initiated a phase 3 mNSCLC trial (NCT04746924) for **ociperlimab**, in combination with its anti-PD-1 tislelizumab. Currently, there is only one location listed (in Florida), and the trial is "not yet recruiting." Since Novartis recently secured tislelizumab rights in the U.S., EU, and Japan, it would be a logical partner should TIGIT data prove to be positive.



AND IN THE HOMESTRETCH, THE WINNER IS...?

If the data from the RELATIVITY-047 allows BMS to file for approval of relatlimab, the anti-LAG3 class would become the third IO mechanism of action approved, following in the footsteps of anti-CTLA-4 and anti-PD(L)1. This approval could come as early as H1 2022.

While RELATIVITY-047 trial compares the relatlimab/OPDIVO combo vs. OPDIVO monotherapy, it's very likely that comparisons to the OPDIVO/YERVOY® combo's efficacy will be inferred. If ORR and PFS (and ultimately OS) is at least similar to OPDIVO/YERVOY, the relatlimab/OPDIVO combo could quickly replace use of the former as its toxicity profile appears to be far better. It would also likely become an (off-label) option for BRAF+ patients who have progressed while on BRAF/MEK inhibitors (even though that wasn't the focus of RELATIVITY-047).

Despite the potential for fast uptake of the anti-LAG3 regimen in melanoma, it's important to keep in mind that metastatic/unresectable melanoma is a relatively small market, thus relatlimab's initial commercial impact to BMS's bottom line will be modest. If similar successes are reached in other tumor types, relatlimab could then potentially become an important future growth driver for BMS.

In contrast, primary completion of Genentech's SKYSCRAPPER-01 is estimated for August 2022, which theoretically could lead to an accelerated approval by the FDA in late H1 or early H2 2023. Despite being the fourth IO mechanism, the NSCLC market is far larger than that of melanoma (even if focused on high expressor of PD-L1). KEYTRUDA has claimed the PD-(L)1 throne based on of its dominance of the 1L NSCLC market, so SKYSCRAPPER-01 could have the same catalytic effect for Genentech. Whether tiragolumab can also drive use of TECENTRIQ over KEYTRUDA as the PD-(L)1 companion remains to be seen, but at the very least, KEYTRUDA (as a monotherapy or in combination with chemotherapy) would no longer be the dominant brand in lung cancer.

Genentech's aggressive investment in pivotal trials for tiragolumab could also help drive perceptions of its broad utility, as primary completion dates for SCLC (2023), esophageal (2024), and stage III NSCLC (2024) are expected in rapid succession after SKYSCRAPPER-01. This would potentially eclipse relatlimab's follow-up approvals in GI and head & neck cancer, which are likely to come after these.

As a result, even if tiragolumab is approved well after relatlimab, that doesn't mean it's lost the race…and quite possibly it may have won it! Regardless, the real winners will be patients, with new treatment options that are more effective and/or less toxic.

Contact

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Ipsos Oncology Monitor data (internal)

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