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THRIVING AS A TARGETED THERAPY IN AN IMMUNO-ONCOLOGY WORLD — LESSONS FROM THE MELANOMA, NSCLC AND RCC MARKETS

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INTRODUCTION

Few cancer therapeutics have engendered as much enthusiasm, and generated as much hype, as the new generation of cancer immunotherapy or immuno-oncology (IO) agents. Key among these IO therapies are the checkpoint inhibitors (hereafter simply referred to as IO). Since the approval of Yervoy (anti-CTLA-4) for melanoma about six years ago, IO agents have steadily altered the oncology treatment landscape and disrupted the standard of care.

IO's appeal is obvious: approvals have been driven by breakthrough clinical efficacy, manageable tolerability, and the induction of incredibly durable responses in thousands of patients with metastatic cancers. The past three years have been particularly impactful with the approval of five anti-PD-1/L1 antibodies (Opdivo, Keytruda, Tecentriq, Imfinzi and Bavencio), in 10-plus tumor types (in addition to Keytruda's approval in MSI-high patients, irrespective of tumor of origin) (See Figure 1). Unsurprisingly, substantial commercial success has followed, and in 2017, the market leaders Opdivo and Keytruda brought in blockbuster revenues of $4.9 billion and $3.8 billion, respectively. As a result, IO therapies are marching on, and our recent analysis identified 50-plus IO pivotal trials alone (See Figure 1), with peak sales moving toward an impressive ~$28 billion by 2025.[1]

This come-from-nowhere success of IO has been a tremendous boon for patients, but it also has caused substantial consternation at the R&D organizations of biotech and pharma. The success of Opdivo and Keytruda, and to an extent Tecentriq, split pharma into 'IO-haves' and 'IO-have nots,' leaving oncology-focused companies to answer several key strategic questions:

- How much investment in IO-focused R&D is required?
- Is a proprietary PD-1/L1 essential for oncology market leadership?
- Can we expeditiously join the ranks of the 'IO-haves' if we have missed the IO boat to begin with? And how?

While much has been written on these topics elsewhere[2,3], this article focuses on the equally important but somewhat less well-addressed questions regarding non-IO therapies, and their future in the oncology market. Our clients in biotech and Big Pharma continue to wrestle with defining the optimal balance between IO/non-IO agents in the pipeline and are continually grappling with optimal positioning and co-positioning (with IO) of their non-IO assets. Key among the non-IO assets are the targeted therapies (TTs), defined here as non-chemotherapy, small-molecule inhibitors, or monoclonal antibodies that are directly tumor-targeted, as compared to the immune system-targeted IO agents. Despite the understandable

1. Persistence Market Research (PMR): Global Market Study on Immuno-Oncology: Immune Checkpoint Inhibitors Segment Projected to be the Most Lucrative Segment by Therapy Type (2017)
2. Booth: What will separate the winners and the losers in the immuno-oncology R&D race?; MedCity News (2016)
3. Cavnar et al.: The immuno-oncology race: myths and emerging realities; Nature Reviews Drug Discovery (2017)

excitement about IO, it is important to remember that in 2017 alone, of the nearly 35 oncology approvals for novel agents/therapies, 20 were TTs.[4] Therefore, managing non-IO portfolios continues to be a strong strategic imperative for all oncology-focused companies.

Retrospective analyses can often provide useful insights to guide future strategy. As such, IO-impacted markets, especially those with TT competitors, represent useful case studies to answer the questions raised above. The melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC) markets have all seen substantial IO-mediated disruption of their otherwise TT-driven markets (Figure 2). Importantly, we also have 24-plus months of commercial, on-market experience in the U.S. market, post-IO entry, in each of these tumor types, providing us with a substantial 'look-back' period to inform our analysis.

Figure 1: IO and Targeted Therapies in IO-impacted tumors: Tumor types with IO approvals, and the TTs approved for the same indications are shown. Tumor types with IO approvals, and the TTs approved for the same indications are shown. The current Phase III clinical pipeline is segmented by whether the trials represent pure IO single-agent or combination trials, TT trials or IO-TT combinations, or other modalities. Data were pulled in January 2018 from TrialTrove.

TUMOR TYPE	IO APPROVAL?	TT APPROVAL?	CURRENT PHASE III	CLINICAL PIPELINE
Skin cancers	**Yes;** Yervoy (March 2011); Keytruda (September 2014); Opdivo (December 2014); Bavencio (Merkel cell carcinoma; March 2017)	**Yes;** Tafinlar, Mekinist, Zelboraf, Cotellic	*IO or IO-IO trials* 6	*TT trials* 1
			IO + TT trials 4	*Others* 4
Lung cancer	**Yes; NSCLC** — Opdivo (March 2015); Keytruda (October 2015); Tecentriq (October 2016)	**Yes;** Tarceva, Iressa, Gilotrif, Xalkori, Alecensa, Zykadia, Alunbrig, Cyramza	*IO or IO-IO trials* 29	*TT trials* 13
			IO + TT trials 0	*Others* 9
Kidney cancer	**Yes;** Opdivo (November 2015)	**Yes;** Sutent, Torisel, Inlyta, Votrient, Nexavar, Afinitor, Avastin, Cabometyx and Lenvima	*IO or IO-IO trials* 4	*TT trials* 3
			IO + TT trials 5	*Others* 1
Lymphoma	**Yes;** Hodgkins lymphoma only — Opdivo (May 2016); Keytruda (March 2017)	**Yes;** Adcetris, Aliqopa, Belodaq, Calquence, Gazyva, Imbruvica, Istodax, Revlimid, Rituxan, Velcade, Zevalin, Zolinza, Zydelig	*IO or IO-IO trials* 1	*TT trials* 22
			IO + TT trials 2	*Others* 6
Bladder cancer	**Yes;** Tecentriq (May 2016); Opdivo (February 2017); Imfinzi (May 2017); Bavencio (May 2017); Keytruda (May 2017)	**No**	*IO or IO-IO trials* 1	*TT trials* 22
			IO + TT trials 2	*Others* 6
Head and neck cancers	**Yes;** Keytruda August 2016; Opdivo (November 2016)	**Yes;** Erbitux	*IO or IO-IO trials* 9	*TT trials* 0
			IO + TT trials 0	*Others* 2
Colorectal cancer	**Yes;** Keytruda (May 2017) (MSI-H tumors); Opdivo (August 2017) (MSI-H or dMMR metastatic colorectal cancer)	**Yes;** Avastin, Erbitux, Cyramza, Vectibix, Stivarga, Zaltrap	*IO or IO-IO trials* 2	*TT trials* 4
			IO + TT trials 1	*Others* 4
Esophageal and stomach cancers	**Yes;** Keytruda (September 2017) (Gastric cancer)	**Yes;** Cyramza, Herceptin	*IO or IO-IO trials* 11	*TT trials* 9
			IO + TT trials 0	*Others* 1
Liver cancer	**Yes;** Opdivo (September 2017)	**Yes;** Nexavar, Stivarga	*IO or IO-IO trials* 3	*TT trials* 3
			IO + TT trials 0	*Others* 5

4. U.S. Food and Drug Administration: Novel Drug Approvals for 2017; www.fda.gov

Figure 2: Market evolution timeline in Melanoma, NSCLC and RCC: The evolution of the Melanoma (2A), NSCLC (2B) and RCC (2C) markets is shown. IO agents are in red, and targeted therapies are in green. The green background represents patient segments within these markets where IO agents are still not FDA-approved for use.

Figure 2A: Melanoma Market Evolution

		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Adjuvant Melanoma												Yervoy		
Metastatic RAF Mutant Melanoma	1L							Zelboraf		Mekinist Tafinlar	Mekinist + Tafinlar	Cotellic + Zelboraf Keytruda	Opdivo + Yervoy	
	2L+													
Metastatic Non-RAF Mutant Melanoma	1L							Yervoy				Opdivo + Yervoy Keytruda		
	2L+										Keytruda Opdivo			

Figure 2B: NSCLC Market Evolution

		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
EGFR Mutant NSCLC	1L									Tarceva Gilotrif		Iressa		
	2L+											Tagrisso		
ALK Mutant NSCLC	1L							Xalkori						Zykadia Alecensa
	2L+										Zykadia	Alecensa		Alunbrig
PD-L1 High NSCLC	1L												Keytruda	
	2L+											Keytruda		
'All-Comers' NSCLC	1L		Avastin									Portrazza		Keytruda
	2L+										Cyramza	Opdivo	Gilotrif Tecentriq	

Figure 2C: RCC Market Evolution

		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Metast. RCC	1L		Sutent	Torisel		Avastin Votrient								Cabometyx
	2L+	Nexavar				Afinitor			Inlyta			Opdivo	Cabometyx Lenvima	

The melanoma and NSCLC cancer markets share several similarities, having both evolved from a genotype-dependent, segmented, pre-IO market, to one where IO is broadly approved for use in both the front-line and relapsed/refractory settings. In contrast, the RCC market pre-IO, represented a non segmented market with several approved therapies, which has seen Opdivo recently approved for previously treated RCC, alongside two other new TT entrants, Cabometyx and Lenvima (+Afinitor) (Figure 2).

IO's impact on these markets has been mixed; whereas IO therapies have become strongly preferred standards of care in their indicated melanoma and NSCLC segments, RCC represents an indication where IO and TTs both currently retain substantial market share.

This article presents a synthesis of our past work in these priority markets, identifying a list of key drivers we refer to as the 10S Drivers of Targeted Therapy Success in IO-impacted Markets (Figure 3). We believe this framework can also serve as a checklist for the evaluation of the prospects of TTs and help understand their expected competitiveness in the IO-impacted oncology markets of the future.

Figure 3: The 10S Checklist for Targeted Therapies in IO-Impacted Markets: Here, we propose 10 drivers of targeted therapy success in IO-impacted markets. The drivers encompass therapy-associated characteristics (survival, speed of response, and shrinkage), physician/patient preferences (similarity, simplicity, safety, and selection) and other strategic parameters (synergy with IO, sequencing after IO, and strategic excellence), which can help targeted therapies stay competitive in the IO-impacted oncology markets of the future.

1. Survival data: The survival benefit offered by an anti-cancer therapy is unsurprisingly the strongest driver of therapy preference, and physicians and patients are often willing to tolerate substantial toxicity in return for even modest improvement in survival outcomes. Progression-free survival (PFS) or event-free survival, which measure improvements in survival without disease progression, are currently the most common registration-enabling endpoints in oncology. However, overall survival (OS) — the simple measure of whether a new therapy makes a patient live longer — continues to be the holy grail for cancer treaters.

IO's attractiveness stems from its perceived ability to extend OS, often with only modest increases or no changes in PFS. This perception has been supported by demonstrated improvements in OS over their standard of care (SOC) comparators in NSCLC, melanoma and RCC, and driven home in the minds of treaters by the aggressive 'OS-focused' branding efforts of both Opdivo and Keytruda.[5,6]

From a TT perspective, the clearest demonstration of the importance of demonstrating an OS benefit for effectively competing with IO agents comes from the RCC market, where both the new targeted agents Cabometyx and Lenvima also have OS benefits on their label. Interestingly, each of the three approvals (Opdivo, Cabometyx and Lenvima (+Afinitor)) were based on clinical success against the same comparator, Afinitor, and demonstrated comparable OS benefits. In fact, the OS hazard ratios demonstrated by the three agents were nearly identical: Opdivo (0.73), Cabometyx (0.66) and Lenvima + Afinitor (0.67). Furthermore, the TTs also demonstrated compelling PFS benefits versus Afinitor, with PFS hazard ratios of Cabometyx (0.58) and Lenvima + Afinitor (0.37), whereas Opdivo did not demonstrate a significant PFS benefit.[7]

Physicians we speak with usually identify the comparable OS benefit, alongside the compelling PFS benefit, as strong drivers for choosing these targeted agents over Opdivo for their 2L+ RCC patients. In comparison to the RCC market, survival data comparisons between the TTs and IO agents are substantially more challenging in the melanoma and NSCLC markets, and to the detriment of the TTs.

In the NSCLC market, though IO therapies were not directly compared to their TT counterparts in the R/R setting, the absence of OS benefits with the TTs has led some treaters to view IO agents as superior choices, with some physicians preferring to use Opdivo after failure of the first-line TT despite the availability of alternate TT options. A similar dynamic was viewed in the melanoma market where both Opdivo and Keytruda's OS benefits and long-term survival rates have helped them emerge as the clear SOC, even in the RAF-mutant patients, where TTs are currently approved.

2. Speed of response and magnitude of tumor 3. shrinkage: A second key driver of therapy choice in oncology is the ability to provide rapid palliation of cancer symptoms.

Several cancer patients present with rapidly growing, inflamed, and symptomatic tumors, with some estimates suggesting this could represent 20-25% of patients seen in the clinic. Oncology treaters in community settings often speak about the appeal of using treatments that can provide symptom relief quickly, particularly in settings like metastatic melanoma, where a substantial percentage of patients present with flaming, rapidly advancing disease.

Here, TTs have several key advantages vis-à-vis IO therapies. Firstly, targeted therapies generally have a rapid onset of disease response; in melanoma, for instance, several published reports and first-hand accounts describe symptomatic improvements that are often seen in a matter of days after treatment initiation with both Zelboraf and Tafinlar-based regimens.[8]

5. Bristol-Myers Squibb Company: OPDIVO [package insert] (2018)
6. Bristol-Myers Squibb Company: Opdivo TV Commercial, 'Longer Life' (2015)
7. Smith: RCC Advances Shake Up Drug Choices; OncologyLive - Vol. 18/No. 07 (2017)
8. Shaffer: The New Front Line in Melanoma: Immunotherapy OR Targeted Agents?; Cancer Updates, Research & Education (2016)

Secondly, targeted therapies typically also offer higher rates of tumor shrinkage, when compared to the modest response rates with IO therapies (while it is true that Opdivo + Yervoy have compelling response rates, as discussed ahead, they are often accompanied by unacceptable toxicities). The appeal of rapid and substantial tumor shrinkage from a patient's perspective cannot be underestimated as well. Physicians commonly point to the positive psychological impacts that a reduction in tumor size on a CT scan can provide. Though the durability of IO responses tends to be longer, they are generally slower, and patients benefitting from IO therapies can sometimes report an initial increase in tumor size before tumor shrinkage eventually begins.

Beyond the psychological benefit rapid tumor shrinkage can provide, there is also the very real concern that although there are now an increasing number of choices for subsequent lines of therapy in many diseases, a subset of patients will never receive their next line of therapy, particularly if they have rapid disease progression. In these patients, disease control may be the strongest driver behind therapy choice, and TTs generally have lower levels of non-responders. In RCC, for instance, the rate of primary progressive disease (no response, no stable disease) as the best response to therapy was much more common with opdivo (35%) than cabometyx (14%) or Lenvima + Afinitor (4%), supporting the choice of TTs when in search of a response.[7,9]

4. Similarity: Human beings are creatures of habit, and physicians are not immune to the status quo bias that afflicts us all. The benefits of familiarity in clinical oncology are obvious; most oncology therapies have substantial toxicities, and familiarity with a class of drugs and their associated toxicities is incredibly helpful, enabling efficient management of adverse events.

In each of the markets under consideration, physicians have had a strong legacy of experience with targeted agents, like TKIs, mTOR inhibitors, and targeted monoclonal antibodies, before the entry of IO. As such, newer targeted agents entering these markets with a similar mechanism of action and comparable characteristics to legacy standards of care are generally viewed positively. In the RCC market, for instance, the newer TKIs Cabometyx and Lenvima came to the market on the back of at least four other TKIs, which had provided physicians with a strong familiarity with the class, and the management of class-associated adverse events like nausea and skin rash. Physicians we have spoken with often point to this familiarity with the oral TKI drug class as one of the drivers behind choosing Lenvima or Cabometyx over Opdivo for their 2L+ (previously treated) RCC patients. A similar dynamic is also apparent in some melanoma and NSCLC treaters.

However, the sustainability of this advantage from a TT perspective is unclear, and as physicians get more and more comfortable with the IO agents, we expect this advantage to gradually dissipate. An additional factor chipping away at this advantage is the massive marketing blitz IO agents have unleashed, which we believe is as much about trying to overcome a familiarity disadvantage for the IO class as it is about jockeying for leadership within the class. In fact, Bristol-Myers Squibb spent more than $170 million on its immuno-oncology therapy Opdivo alone in 2016, and was the only cancer drug among Nielsen's top 20 direct-to-consumer spenders.[10] Due in part to these efforts, physicians now report the increasingly common occurrence of patients coming in with a strong awareness of IO therapies, and insisting on beginning treatment with IO agents, even if it sometimes goes against the advice of their physicians.

5. Simplicity (ease) of administration: Another key driver of therapy choice that benefits ITs is the oral route of administration. Nearly all TTs in the melanoma, NSCLC, and RCC markets are oral agents, as compared to the IO therapies which currently require IV infusions. Most patients, and even some physicians, typically express a preference for oral treatments compared to IV or subcutaneously administered therapies. A preference for oral agents is especially strong when the efficacy and side effects of orally administered cancer treatments are generally similar to those of IV treatments.

Oral agents offer increased convenience, and are associated with substantially lower stress and discomfort when compared to typical IV treatments. They afford patients greater flexibility, allow patients to forgo hospital visits (saving time and travel), and are commonly associated with a greater overall quality of life. In contrast, IV infusions required for the IO agents are time consuming and interfere substantially with an individual's ability to maintain full-time employment. The impact is especially significant if individuals live outside of large urban areas and away from their doctors and infusion centers.

For instance, an RCC patient receiving Opdivo must typically receive infusions every two weeks, for at least one to two hours, in addition to a doctor's visit every four weeks. In patients where this represents a substantial burden, physicians often prefer to use an oral agent like Cabometyx instead of Opdivo, especially if the patients desire to continue their full-time employment and to minimize hospital visits. A patient on Cabometyx requires less frequent office visits every 4-6 weeks, compared to every two weeks, as would be the case with Opdivo.

7. Smith: RCC Advances Shake Up Drug Choices; OncologyLive - Vol. 18/No. 07 (2017)
9. Andtbacka et al.: Patient Selection in Melanoma: Immunotherapy vs Targeted Therapy (2017)
10. Silverman: Drug makers increased direct-to-consumer ad spending again; STATnews (2017)

It must be noted that a few physicians do express a preference for in-person IV or subcutaneous administration due to the ability to improve patient adherence and compliance. Additionally, the financial benefits associated with IV therapies due to the buy-and-bill regime can also lead some physicians (particularly those in smaller independent community practices) to prefer IV therapies, though this financial incentive is expected to rapidly dissipate with increases in bundled payments for oncology.

6. Safety: Postulating the safety profile of a TT as a driver for success against IO therapies may seem surprising. After all, one of the key reasons for IO's success has been its strong perceived tolerability profile, especially when compared to chemotherapy regimens. However, IO's overall tolerability advantages over TTs from a physician perspective are slimmer, leading physicians to rarely prefer IO agents over TTs in our experience, purely based on safety/tolerability issues. An exception may be found in the frailer patient population, where a strong preference for IO agents is observed. In RCC, for instance, physicians report a preference for using Opdivo in their older and frailer patients, whereas with fitter patients, physicians are much more tolerant of the marginal tolerability deficit of TTs and typically make treatment decisions based on other factors.

Furthermore, recent data suggest IO's tolerability benefits may have been somewhat overstated. Today, there is increasing awareness of the severe immune-related adverse events that occur in patients receiving IO therapies.[11] These toxicities mainly involve the gut, skin, endocrine glands, liver, and lung, but can potentially affect any tissue, and can manifest as severe irreversible auto-immune conditions. Here, it is worth recalling that IO's tolerability 'halo' is predominantly based on observations in contexts where single-agent IO therapies were pitted against chemotherapy regimens. It is therefore an open question as to how IO therapies will be perceived in other tumor types, and in the context of combination regimens. The Opdivo + Yervoy combination supports the contention that some concern is warranted. The combination, while highly efficacious, is highly toxic, with a potential for life-threatening, irreversible toxicities. Several physicians have strong reservations about using this combination in their patients, and the pattern of toxicities with the combination is typically not something that the average community oncologist is comfortable treating. Finally, some IO-based combinations have also run into unexpected safety challenges, and the FDA had placed several IO combination trials, attempting to replace TT regimens in multiple myeloma, on clinical holds (since lifted) based on preliminary reporting that more deaths occurred on the IO combination arm of the study.[12]

7. Selection strategy: A clear example of the benefit of a patient selection strategy in ensuring TT competitiveness is the persistence of TT usage in 1L EGFR and ALK-mutant NSCLC. Despite the march of IO in other parts of the NSCLC treatment paradigm, the 1L EGFR/ ALK-mutant patient population is yet to be disrupted by IO therapies. In fact, past pivotal IO front-line trials have excluded 1L EGFR and ALK-mutant patients and the Keytruda label for 1L usage restricts usage to patients without EGFR and ALK mutations.

In general, most treaters, as well as payers and providers, have an extremely favorable view of companion diagnostic-enabled TTs that are preferentially active in biomarker-defined populations. TTs, particularly when they are targeting so-called oncogenic drivers and tested in patients who are positive for that specific oncogenic driver, typically have very high response rates. They also often provide more straightforward opportunities to target mechanisms of resistance, offering opportunities to create well-defined treatment sequences (e.g., patients with the T790M mutation, a common mechanism of resistance to first- and second-generation EGFR inhibitors, almost invariably respond to the third-generation EGFR inhibitor AZD9291 / osimertinib (Tagrisso)).[13] Consequently, TTs may be able to carve out niche areas, wherein they may be able to demonstrate compelling activity and set up a sequencing narrative that can serve to limit IO impact.

The limitations of a patient selection / market segmentation strategy approach for TTs are also obvious. As discussed before, despite the availability of a similar patient selection strategy (BRAF mutation) and high response rates, IO therapies have substantially disrupted the BRAF-mutant melanoma market. In fact, nivolumab (Opdivo) and pembrolizumab (Keytruda), are both approved for first-line treatment of melanoma patients regardless of BRAF mutation status. The approval based on clear clinical efficacy for the IO agents in these mutant melanoma populations is contrasted with NSCLC, where IO data in EGFR/ ALK-mutant patients has been weak. This suggests that patient selection strategies may only provide a moat against IO impacts if they prove to enrich IO non-responders.

Finally, the excitement for companion diagnostic-enabled therapies rapidly dissipates if clear efficacy benefits have not been conclusively demonstrated versus those seen with untargeted agents. A clear illustration of this dynamic is in R/R EGFR/ ALK-mutant NSCLC. Here, some physicians actually prefer IO therapies over available second-line TTs, despite no clear guideline support or the availability of clinical data supporting preferential IO use. A recent survey found that

11. Postow et al.: Immune-Related Adverse Events Associated with Immune Checkpoint Blockade; NEJM (2018)
12. Pagliarulo: FDA cautiously lifts holds on combo studies of checkpoint inhibitors; BioPharma Dive (2017)
13. Ricciuti et al. Osimertinib in patients with advanced epidermal growth factor receptor T790M mutation-positive non-small cell lung cancer: rationale, evidence and place in therapy; Ther Adv Med Oncol. (2017)

when the choice is whether to prescribe patients experimental, targeted drugs based on genetic markers driving their tumors or recommend immunotherapies, doctors are often going with the latter.[14] One of the key reasons identified was that NGS test results can take weeks to come back to the doctor, while treatment with an unselected agent can begin immediately.

8. Synergy with IO: It is important to remember that despite the substantial impact that IO agents have had so far, only a small minority of patients derive durable benefit from IO, especially outside the high response rates seen in melanoma.

The development of IO combinations represents the obvious next step in clinical development for these therapies, with the potential to increase the number of patients who can derive meaningful and durable benefits. IO combinations have focused on three approaches — IO-IO combinations typified by the Opdivo + Yervoy combination, approved in melanoma; IO-Chemo combinations typified by the Keytruda + platinum + Alimta combination, approved in 1L NSCLC; and IO-TT combinations, which have yet to see an approval in the clinic.

The appeal of the IO-TT combinations is based on expectations of increased response rates with fewer toxicity concerns than those seen with the IO-IO combinations such as Opdivo + Yervoy or the IO-chemo combinations such as Keytruda + Chemo. With both these combinations the substantial tolerability challenges have served to diminish some of the efficacy-driven excitement these approvals have engendered. In each of our priority markets, initial IO entry has been followed by an attempt to expand the label by evaluating combination between the IO agent and approved TTs.

But the experience with these combination has so far been decidedly mixed; promising early data in melanoma and RCC on the one hand, whereas IO combination development in NSCLC has been limited by a high incidence of treatment-related toxicities.[15] Importantly, the combination potential appears to be strongly influenced by compound-specific parameters, suggesting the potential for substantially varied outcomes for different targeted agents in combination with the same/similar IO partner. Case in point is the development of a pembrolizumab combination with pazopanib (Votrient) was discontinued based on high incidence of liver toxicities in early-stage trials, while a pembrolizumab combination with axitinib (Inlyta) was safe and efficacious, and has consequently advanced into Phase III development, alongside three other IO-TT combinations[16,17] (also see Figure 1).

9. Sequencing pre/post-IO: While combinability with IO is obviously most desirable, data supporting sequencing before or after IO therapy are also likely to become more valuable in the oncology treatment landscape of the future. In the absence of such data, physicians will likely be driven to make treatment sequencing decisions based on other less-desirable factors.

Importantly, scientific bases for treatment sequencing before or after IO agents may exist. For example, preclinical work suggests that BRAF/ MEK induction therapy administered over several weeks to a month alters the tumor microenvironment, making a 'cold' tumor 'hot', and supporting a TT approach in first-line melanoma, before exposure to immunotherapy.[18] Interestingly, a randomized Phase III trial is testing exactly this hypothesis in the clinic by pitting dabrafenib + trametinib followed by ipilimumab + nivolumab (at progression) vs. ipilimumab + nivolumab followed by dabrafenib + trametinib (at progression), in patients with advanced BRAF-mutant melanoma.[19] We view this trial and others like it as a potential win-win for the sponsor(s). While Novartis stands to benefit significantly if the trial supports the usage of the TTs prior to the IOs, the reverse outcome would still provide important data supporting the usage of the Novartis TT combination post-1L IO challenge. The competing Roche products will not have such supporting data and could therefore be viewed as inferior in comparison. We believe it is a matter of time before other similar pivotal trials supporting the clarification of optimal sequencing paradigms will be initiated in other tumor types, and if appropriately designed, may provide individual TTs valuable competitive advantages in the oncology landscape of the future.

10. Strategic excellence: We believe strategic excellence is a final key driver of future success. We define strategic excellence to encompass all supporting activities that enable the creation of an effective go-to-market strategy and flawless on-market execution. The key here in competing with IO therapies in the short term, and co-existing in the medium-to-long term, is always a clear understanding and successful articulation of your therapy's value proposition to all relevant stakeholders of commercial success, and a highlighting of key differentiating elements. We strongly believe our 10S framework can provide a useful starting point for such activities.

14. Ray: Oncologists Often Favor Immunotherapy Over NGS-Guided Targeted Drugs, Survey Finds; genomeweb (2017)
15. Ahn et al. EGFR TKI combination with immunotherapy in non-small cell lung cancer; Expert Opin Drug Saf. (2017)
16. Furlow: Pembrolizumab Plus Pazopanib Is Not Safe for Patients With RCC; cancernetwork (2017)
17. Kuznar: Pembrolizumab Plus Axitinib Active in Frontline RCC; OncologyLive (2018)
18. Hu-Lieskovan et al.: Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAFV600E melanoma; Sci Transl Med. (2015)
19. clinicaltrials.gov: NCT02224781, Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients With Stage III-IV BRAFV600 Melanoma

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Interestingly, both Cabometyx and Lenvima (+Afinitor), which represent particularly relevant case studies for TT 'co-existence', have placed strong branding emphasis on the '10S' elements that offer clear differentiation from their IO competitor, Opdivo. Cabometyx's "charge forward with the power of 3" tagline highlights its demonstration of significant improvement across three endpoints, OS, PFS and ORR, and serves to articulate its critical differentiation from Opdivo (which demonstrated a pure OS benefit).[20] Similarly, Lenvima + Afinitor has focused on 'Response,' an articulation of its superior response rate to Opdivo.[21]

Obviously, nothing can replace good, old-fashioned commercial launch excellence as a key facilitator of optimal initial positioning. Nevertheless, a continuous evolution of brand strategies will be essential to compete and co-exist in the markets of the future.

CONCLUDING REMARKS

Immunotherapies have and continue to lead to transformative change in oncology treatment paradigms. However, as discussed in this report, we expect TTs to continue to be important players in the treatment paradigm, based on the substantial value they provide from both a physician and patient perspective. Our report therefore supports continued investments in TT portfolios, in particular if the new TTs can successfully deliver on the 10S drivers outlined in our framework.

20. Cabometyx (cabozantinib) Official Site For Physicians (2016)
21. Lenvima (lenvatinib) Official Site For Physicians (2016)