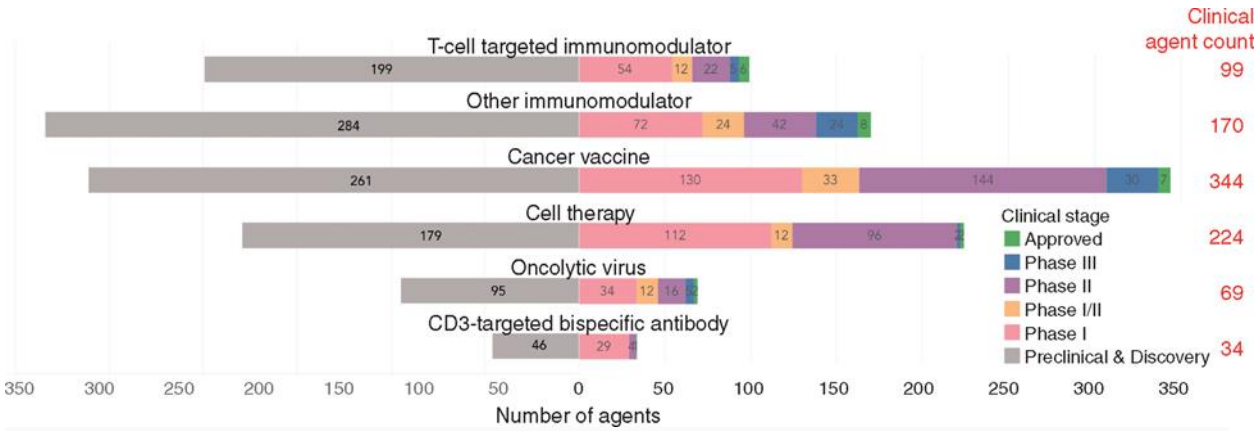
Over 50,000 cancer patients needed for IO trials, but will it make a dent?

We are in the midst of an explosion of clinical targets within the immuno-oncology field which has resulted in impactful advancements in cancer care. Since the first IO approval by BMS, over 2000 IO agents are in various stages of development. Exponential growth in the I-O space raises some significant questions: is a rationalization of clinical development needed? And will all these targets yield approvable, covered drugs that patients can get access to?

IO assets in development or approved [1]



The overview of 2004 immuno-oncology (IO) agents. Six classes of IO agents are identified on the basis of different mechanisms of actions.

Development landscape

Over half of the I-O assets modulate only 40 targets, which leads to a concern about the significant duplication of effort within the development of these therapies. The concern is increased when we understand and accept that within the drug development process, only a small percentage of assets become commercially available to patients. With 5 PD1/PD-L1 assets commercially available, it may be surprising that there are 164 additional agents targeting PD-1 or PD-L1. Over 1500 studies related to PD-1/PD-L1 are ongoing. 1105 of these are combination trials.1

Among the 164 PD-1/L1 agents 5 are approved, there are 45 in phase 1-11, and there are still 114 in preclinical/discovery. Current PD-1/L1 still have limited response rates and have not been successful in every tumor type tested. Perhaps among those still in development better outcomes can be achieved. Certainly, some of these are being developed for competitive reasons for manufacturers to have proprietary combinations.

The concentration of IO development and patient resources on a few targets, some with already approved drugs, could potentially be stalling future innovation. Rather, investing these precious resources more efficiently could help accelerate needed progress in finding cures to this deadly disease.

CAR-T therapies are the most innovative approach to cancer care and look to be curative. Following the first approvals, are 291 additional CAR-T therapies in development around the world.

1 Source: Comprehensive analysis of the clinical immuno-oncology landscape. Ann Oncol. 2017;29(1):84-91. doi:10.1093/annonc/mdx755. Ann Oncol | © The Author 2017. Published by Oxford University Press on behalf of the European Society for Medical Oncology.

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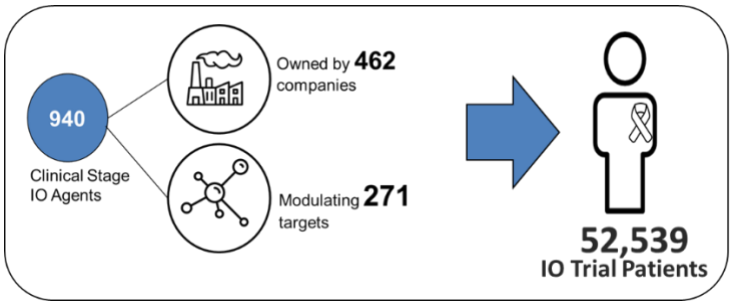
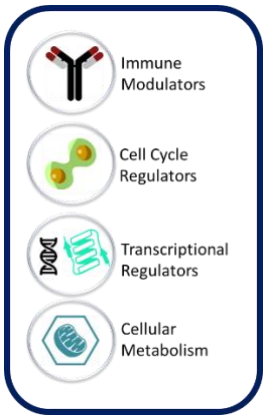
According to the Anna-Maria Kellen Clinical Accelerator of the Cancer Research Institute (CRI), "The concentration of IO development and patient resources on a few targets, some with already approved drugs, could potentially be stalling future innovation. Rather, investing these precious resources more efficiently could help accelerate needed progress in finding cures to this deadly disease."

The 1105 PD-1/PD-L1 trials are seeking 52,539 patients to enroll. Many patients could be excluded based on inclusion criteria limiting prior therapy exposure. However, many of these patients may be relegated to the standard of care comparison arm. Many of these patients may be entering trials that are seeking to answer duplicative questions, limiting innovation.



Recruiting over 50,000 patients into clinical trials may not be entirely feasible. According to Greg Simon, President of the Biden Cancer Initiative, access to clinical trials is a critical issue to address in cancer care. Clearly the issue is not a lack of trials, but rather awareness of the trials and ability to enroll. Mr. Simon spoke recently at the IO360 conference about the need to improve communication to patients and community oncologists about the availability of trials and the need to help patients enroll and stay in trials. According to Mr. Simon, this may mean support for transportation and childcare so that patients can go to clinic appointments, and it certainly means more transparency in clinical trial enrollment information that patients can understand.

IO development is aggregating along a few pathways. At ASH 2017, four predominant classes dominated: immune modulators, cell cycle regulators, transcriptional regulators, and cellular metabolism. multiple target molecules and mechanisms of approach were presented, especially within immune modulators and cell cycle regulators. Within classes or across, it likely will require a multi-pronged approach using multiple mechanisms of action and attacking multiple targets to combat cancer's ability to evade the immune response.



Access to innovation

The next question will be access for IO therapy. Will the healthcare marketplace, government and commercial payers, have the funds to enable access to new life saving innovation? The US expenditure on healthcare already exceeds any other country in terms of percent of GDP. How will this same bucket of funds be able to cover all the new innovative therapies, especially when they may be used in combination?

Already we are seeing a change in the oncology access environment with restrictions and prior authorizations that were not in existence prior to recent growth in available I-O therapies in diseases with high unmet need and EU authorities not commissioning some products at all. We have 5 PD-1/L1s now that compete across different tumor types. As the tumor trial data expands and new PD-1/L1s come to market we may see a first in oncology as something akin to commodity pricing starts to take

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effect where payers have even more power to push prices down and add restrictions. A new model will have to evolve to enable patients to take regimens consisting of multiple of the new mechanisms.

Novartis is the first company to potentially change the game with an innovative pricing model for Kymriah®. Kymriah® is a drug within the CAR-T class of therapy. This nearly $500,000 drug is given out free to patients with treatment centers only billing CMS for patients who demonstrate drug response within the first month. However, on the commercial side payers are still evaluating this new therapy option and limiting access with case by case evaluation and contracting with centers required.

Will payers, providers, and manufacturers be able to work together to find solutions that enable the breadth of clinical development and financial incentives to ensure I-O? innovation occurs and reaches patients? Time will tell.

For more information on Herspiegel Consulting's oncology commercial expertise, please contact:
Beth Schurman
Beth@Herspiegel.com

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