Medaysis

PD-1 / PD-L1

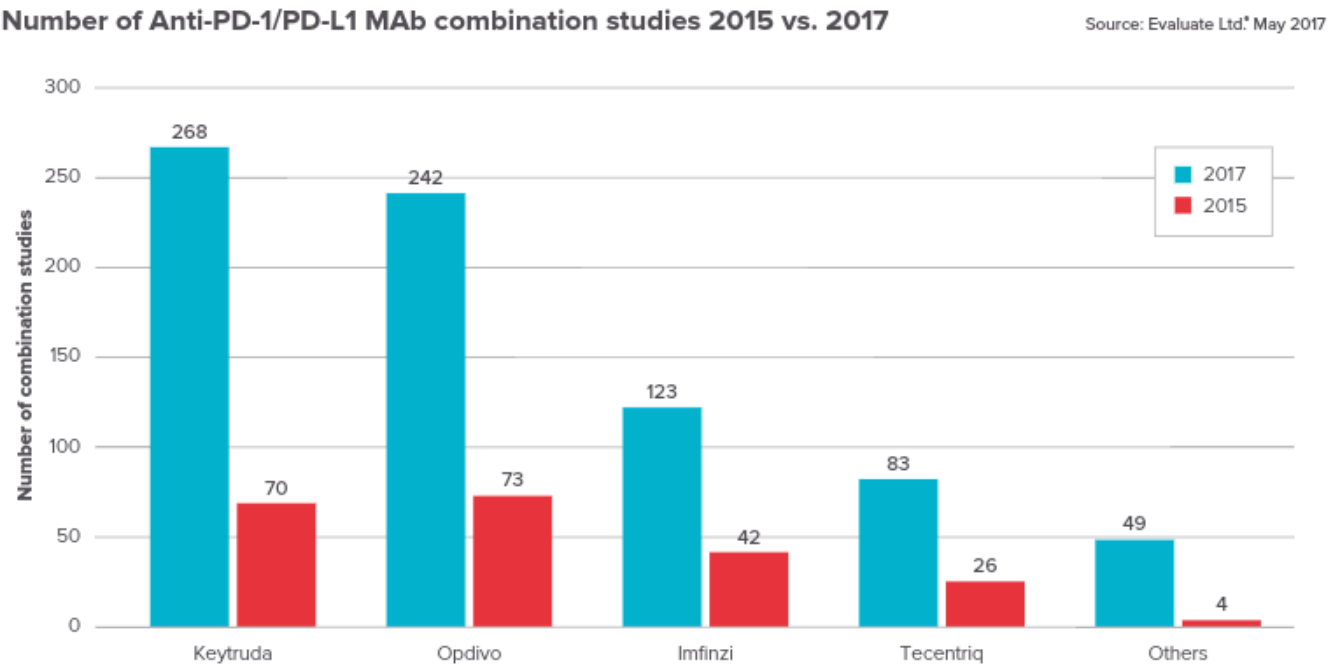
Programmed cell death ligand 1 (PD-L1) also known as CD274 or B7-H1, a member of the B7 family of cell surface ligands, involved in regulation of T cell activation and humoral immune responses. PD-1 is expressed on tumor-infiltrating lymphocytes (TIL) while PD-L1 is expressed on tumor cells including melanoma, diffused large B-cell lymphoma, lung, ovary, colon, breast, rectum and renal cell carcinomas. B7.1 is a molecule expressed on antigen presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen presenting cells can mediate down-regulation of immune responses, including inhibition of T-cell activation and cytokine production. PD-L1 binding to its transmember inhibitory receptor PD-1 provides both stimulatory and inhibitory signals in regulating T cell activation and tolerance during pregnancy, tissue allografts, autoimmune disease and malignant transformation. Therefore, blocking the PD1/PD-L1immune inhibitory checkpoints represents an attractive strategy to reinvigorate tumor-specific T cell immunity suppressed by the expression of PD-L1 in the tumor microenvironment. Detection of PD-L1 overexpression by IHC can be useful to identify tumors and support meaningful benefit for patients.

The following contents are cited from https://labiotech.eu/features/pd-1-pd-l1-checkpoint-inhibitors/:

Are PD-1 and PD-L1 Checkpoint Inhibitors As Good As We Thought?

Checkpoint inhibitors, especially those targeting PD-1 and PD-L1, are exploding in popularity. But how much of it is hype?

The pipelines of biotech and pharma are filling up with combination therapies for anti-PD-1 and PD-L1 antibodies. According to the Cancer Research Institute, there are now over 1,500clinical trials testing the popular checkpoint inhibitors, a dramatical increase from 215 trials in 2016. By 2025, the market for PD-1 and PD-L1 inhibitors could reach near €30Bn, a massive amount for such a young market.



Medaysis Co. Livermore, CA 94551 Tel: 510-509-3153 Toll Free: 877-524-9167 www.medaysis.com

Why have these specific drugs become so popular? Well, checkpoint inhibitors can block mechanisms that tumors use to protect themselves from being attacked by immune cells. The PD-1 receptor is an immune checkpoint on T cells that instructs them not to attack any cell carrying PD-L1. Blocking the interaction between PD-1 and PD-L1 lets T cells attack tumor cells that produce PD-L1 as a mechanism to evade the immune system.

PD-1 and PD-L1 inhibitors are not a wholly new concept. In fact, the first checkpoint inhibitor in the market, Yervoy (ipilimumab) from Bristol Myers Squibb, targeted a different immune checkpoint, called CTLA4. But concerns about strong autoimmune reactions to the drug in up to 20% of patients played in favor of the PD-1 and PD-L1 generation.

The first PD-1 inhibitor, Keytruda, had impressive effects on patients with metastatic melanoma that were unresponsive to standard therapies. And the story of how the drug curedthe cancer of former US President Jimmy Carter have driven up the hopes of many.

Major FDA Approvals of PD-1 / PD-L1 Inhibitors

Drug	Commercial name	Owner	Target	First approval date
Pembrolizumab	Keytruda	MSD	PD-1	September 2014
Nivolumab	Opdivo	BMS	PD-1	December 2014
Atezolizumab	Tecentriq	Roche	PD-L1	May 2016
Avelumab	Bevancio	EMD and Pfizer	PD-L1	March 2017
Durmalumab	Imfinzi	AstraZeneca	PD-L1	May 2017

Source: Drugs.com

LABIOTECH.eu

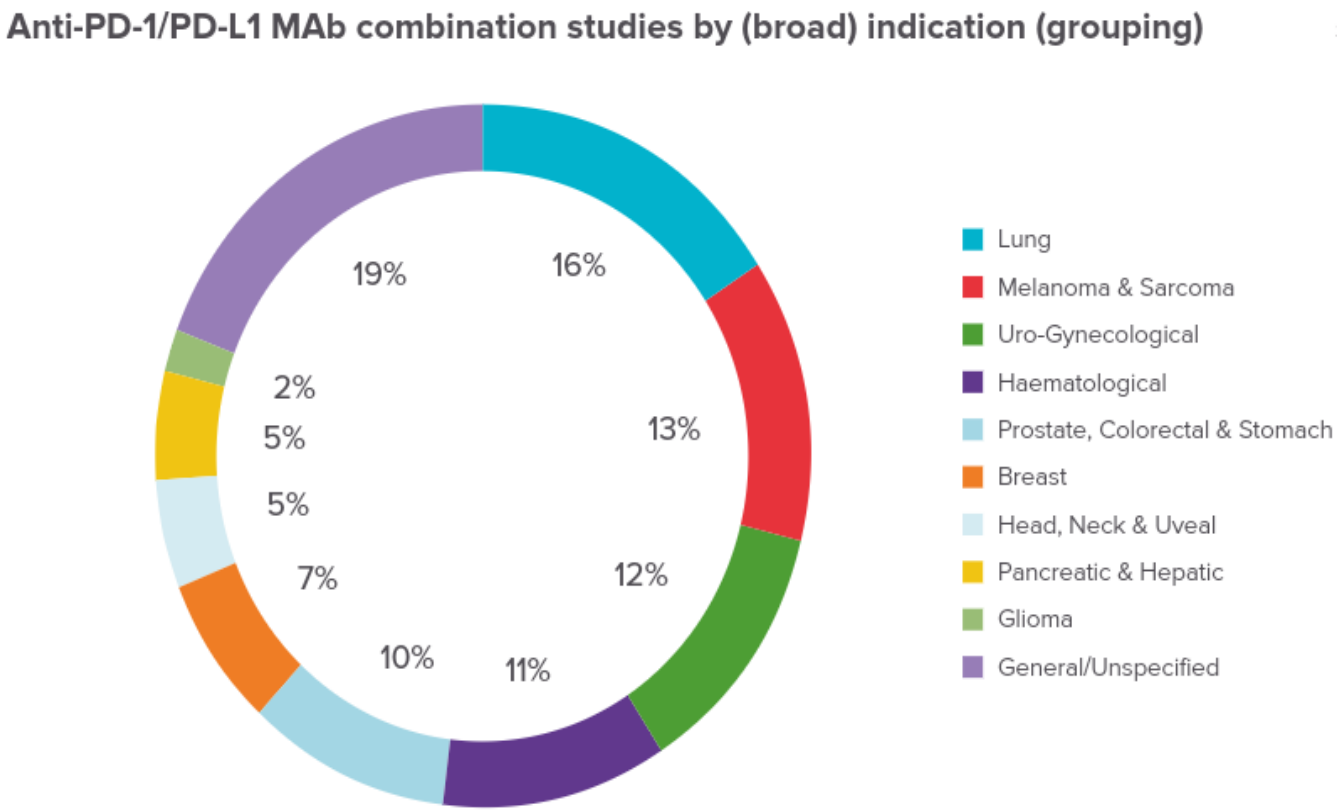
But after the initial excitement, unexpected side effects and some big clinical failures started to bring us back to reality. Checkpoint inhibitors do work, but only in a small percentage of patients. It is not yet known exactly why, though doctors have noticed that the drugs seem to work especially well for patients whose cancer cells have a higher number of mutations.

Biotech and pharma now seem convinced that the solution lies in combining checkpoint inhibitors with other cancer treatments. Everyone's giving it a try, hoping that their own therapies will improve the safety and efficacy of the successful PD-1 and PD-L1 inhibitors.

But many of them might just be jumping in blindly. "*Rational combination of clinical strategies should be based on strong biological principles, and we have a lot of clinical trials being done now that may not have that rationale,*" Masoud Tavazoie, CEO of the immuno-oncology biotech Rgenix, told me. "*Over the next two to three years we're gonna start to see the real winners. And the losers, which are likely based on poor combinations.*"

One strategy to find rational combinations is testing patients for specific biomarkers. For example, before administering Keytruda, doctors need to test whether the patient's tumor presents a minimum level of the PD-L1 immune checkpoint. Although this strategy reduces the number of patients that can get the drug, it drives the success rate up. BMS recently failed a big clinical trial in non-small cell lung cancer that recruited patients with very

low PD-L1 expression. As a result, its checkpoint inhibitor, Opdivo, fell behind Keytruda in the non-small cell lung cancer market.



"*We need to do better at identifying predictive biomarkers for who is most likely to respond to these drugs, not only to save people from potential toxicity, but also because these drugs are very expensive,*" says Justin Gainor, Doctor at the Massachusetts General Hospital.

Bearing in mind that the cost of a checkpoint inhibitor therapy is around $150,000 per year, imagine having to double to that figure. It seems that all these companies erratically testing combinations are confident that there will always be someone willing to pay. But given the huge competition in the cancer market, ignoring this aspect might doom many a not-so-carefully planned combination.

Checkpoint inhibitors are definitely bringing new hope to patients that used to have no alternative after chemo failed. But we shouldn't let hype and huge market projections blind the decisions that will help scientists continue improving the technology and making it accessible to more and more patients. The same goes for any other popular cancer immunotherapy, such as CAR-T cells, which have impressive results but carry price tags of $400,000.