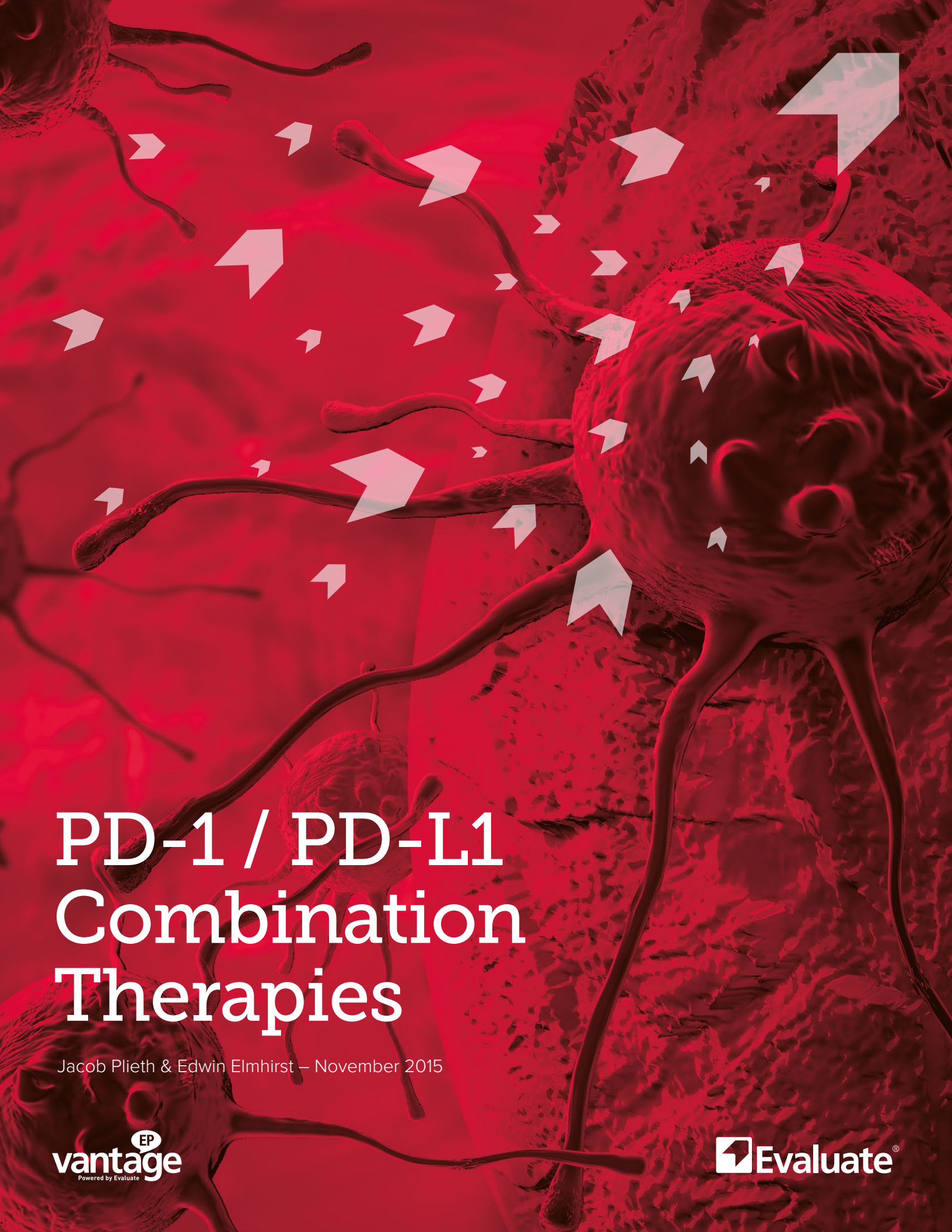

PD-1 / PD-L1 Combination Therapies

Jacob Plieth & Edwin Elmhirst – November 2015

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Foreword

Biopharma owes much of the past few years' bull run to advances in cancer – specifically to immuno-oncology approaches that harness the natural power of the immune system to combat disease. The charge has been led by antibodies against CTLA4 and PD-1, which have seen the launches of Yervoy, Opdivo and Keytruda, initially for melanoma but with additional indications now getting under way.

What does the industry do for an encore? There are several late-stage antibodies that work in identical or similar ways – tremelimumab, atezolizumab and durvalumab – and slightly further away stands an amazing array of novel immuno-oncology approaches, which target novel antigens or novel immune system checkpoints.

But most experts are now looking to combinations to build on the success of the first few immuno-oncology drugs to hit the market. This is a vital theme because, in investment terms, biopharma looks like it might at last have overheated, and as such it is desperate for another lift.

The coming 18 months could provide several. The key lies in the first clinical evidence from early trials of anti-PD-1 and anti-PD-L1 antibodies combined with novel immune system agents, as well as in combination with a barrage of old and new small-molecule and antibody drugs, chemotherapies, cancer vaccines and gene therapies.

Combining numerous new and old approaches with anti-PD-1/PD-L1 agents is logical given that the latter already look like they are becoming standard treatment in certain populations within certain tumour types. Many of the combinations will provide some of the most important inflection points for the biopharma sector.

But who is doing what, and why? This EP Vantage report identifies which approaches are being combined with which anti-PD-1/anti-PD-L1 inhibitors, explains the logic behind them, looks at the most popular oncology indications, and identifies important trends. The data comprise only clinical-stage products, and are complete as of September 18, 2015.

Report author | Jacob Plieth

Immuno-oncology plus: the combination approach

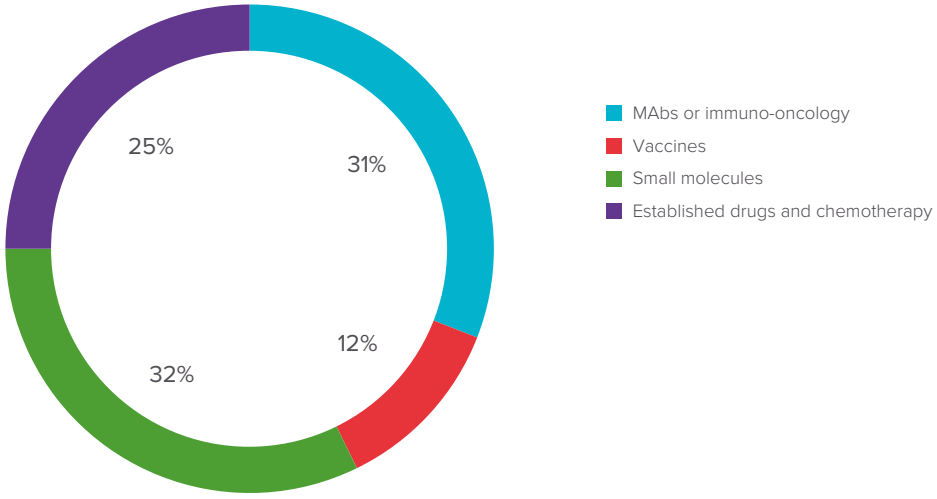
If it is abundantly clear that the discovery and initial launches of antibodies against CTLA4 and PD-1 have thrust immuno-oncology into the spotlight, it is also true that a huge effort has been made to follow this up by combining PD-1/PD-L1 agents with just about everything else.

After all, the industry cannot afford to lose the momentum that has made cancer the hottest area of drug development.

By no means all of the PD-1/PD-L1 combinations involve novel checkpoint agents; the trend now seems to be to combine all types of oncology projects – be they chemotherapies, small molecules, therapeutics vaccines or more advanced cell therapies – with antibody immunotherapies.

All anti-PD-1/PD-L1 combination studies by companion agent

Source: EvaluatePharma® September 2015

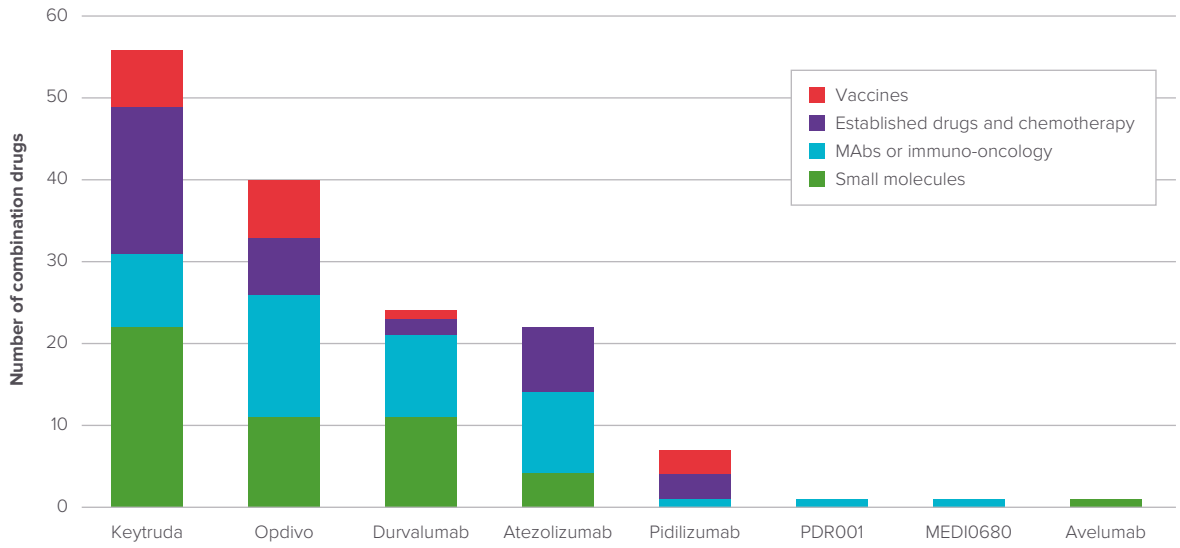


There is scientific logic behind all these approaches, though it could be argued that some biotechs are throwing less-than-promising assets into a combo just to see whether anything might be done to salvage them.

Interestingly, many of the combination approaches are not even based on collaborations; several simply involve the biotech company in question buying an approved anti-PD1 – Opdivo or Keytruda – to put into its combo clinical trial. Most others combine two experimental agents on a non-exclusive basis, with no licensing deal to speak of.

Breakdown of combination studies by anti-PD-1/PD-L1 MAb

Source: EvaluatePharma® September 2015



There are numerous reasons for combining checkpoint inhibitors with other therapies. The most obvious is that two therapies given together are more powerful than one, or alternatively that by giving low doses of two agents in concert some of the toxicity of either agent at its full monotherapy dose can be avoided.

The latter is a key aim, for instance, in combining anti-PD-1/PD-L1 therapy with CTLA4 MAbs like Yervoy or tremelibimab. There is, of course, nothing new about this type of rationale, and it has applied for decades to many other less sophisticated drugs and therapies.

PD-(L)1 combinations with MAbs or other immuno-oncology agents

The analysis reveals that Yervoy is still one of the most widely studied combo agents, appearing in 21 of Bristol-Myers Squibb's trials with its own PD-1 MAb, Opdivo. It is notable that the only other company that has both a PD-1/PD-L1 and a CTLA4 Mab in house is AstraZeneca, in durvalumab and tremelimumab respectively.

And the UK group, having come to the immuno-oncology space relatively late, has made a major effort to use combinations as a way of making up for lost ground. In clinical trials it is combining durvalumab with two in-house MAbs against Ox40, CD73 and PD-1, as well as with tremelimumab. Bristol's Opdivo combo targets comprise CD137, CXCR4, LAG3, and CTLA4, as well as KIR – as part of a deal with Innate Pharma.

The rationale here is to overcome additional checkpoints that might be utilised by the tumour, and whose presence might be contributing to lack of efficacy by a PD-1/PD-L1-directed monotherapy.

Anti-PD-1 combinations with MAbs or other immuno-oncology agents

Source: EvaluatePharma® September 2015

	Combination agent	Pharmacology class	Indication	Sponsor
Keytruda – Merck & Co				
	Cyramza	Anti-VEGF-2 MAb	Multiple tumors	Eli Lilly
	Necitumumab	Anti-EGFr MAb	NSCLC	Eli Lilly
	Epacadostat	IDO1 inhibitor	Solid tumors and NSCLC	Incyte
	MGA271	Anti-B7-H3 MAb	Melanoma	MacroGenics
	MK-4166	Anti-GITR MAb	Solid tumours	Merck
	Yervoy	Anti-CTLA4 MAb	Various	Merck
	Yervoy + entinostat	Anti-CTLA4 MAb + HDAC inhibitor	Solid tumours	NCI (NIH)
	PF-05082566	Anti-CD137 MAb	Solid tumours	Pfizer
	Ublituximab + TGR-1202	Anti-CD20 MAb + PI3K-delta inhibitor	CLL	TG Therapeutics
Opdivo – Bristol-Myers Squibb				
	ALT-803	IL-15 superagonist/ IL-15Rα-Fc fusion protein	NSCLC	Altor BioScience
	Urelumab	Anti-CD137 MAb	Advanced solid tumours, advanced B-cell NHL	Bristol-Myers Squibb
	Ulocuplumab	Anti-CXCR4 MAb	Solid tumours	Bristol-Myers Squibb
	Yervoy	Anti-CTLA-4 MAb	Various	Bristol-Myers Squibb
	With/or Yervoy, +/- azacitidine	Anti-CTLA-4 MAb / DNMT inhibitor	General blood malignancies	Bristol-Myers Squibb
	BMS-986016	Anti-LAG3 MAb	General cancer indications	Bristol-Myers Squibb
	Interleukin-21	Interleukin-21	Neoplasms	Bristol-Myers Squibb
	Lirilumab	Anti-KIR MAb	Multiple myeloma, lymphoma and solid tumors	Bristol-Myers Squibb/ Innate
	Varlilumab	Anti-CD27 MAb	NSCLC, melanoma, colorectal, ovarian, and squamous head & neck cancers	Celldex Therapeutics
	FPA008	Anti-CSF-1R MAb	NSCLC, melanoma, glioma, head & neck, pancreatic, colorectal cancers	Five Prime Therapeutics
	Epacadostat	IDO1 inhibitor	Various	Incyte
	Mogamulizumab	Anti-CCR4 MAb	Advanced or metastatic solid tumors	Kyowa Hakko Kirin
	Yervoy + sargramostim	Anti-CTLA-4 MAb + GMCSF	Melanoma	NCI
	Bavituximab	Anti-PS MAb	NSCLC	Peregrine Pharmaceuticals
	Adcetris	Anti-CD30 MAb-auristatin E conjugate	Hodgkin's and non-Hodgkin's lymphoma	Seattle Genetics
PDR001 – Novartis				
	LAG525	Anti-LAG3 MAb	Solid tumour indications	Novartis
Pidilizumab – Medivation				
	Durvalumab	Anti-PD-L1 MAb	Advanced malignancies	AstraZeneca
MEDI0680 – AstraZeneca				
	MEDI-551	Anti-CD19 MAb	Aggressive B-cell lymphomas	AstraZeneca

Neither Merck & Co nor Roche has an in-house anti-CTLA4 agent, so to achieve this mechanistic combination these groups are relying on the availability of Bristol's Yervoy to run combo studies with Keytruda – four trials in melanoma and renal and lung cancers – and atezolizumab – one study in several solid tumours – respectively.

Roche's other combos of atezolizumab with in-house immune checkpoint agents focus on CD40, CEA IL-2, an Ox40 project of its own, and CSF-1R. Merck's Keytruda, meanwhile, is in an in-house trial in combination with an anti-GITR MAb.

Anti-PD-L1 combinations with MAbs or other immuno-oncology agents

Source: EvaluatePharma® September 2015

	Combination agent	Pharmacology class	Indication	Sponsor
Atezolizumab – Roche				
	Varlilumab	Anti-CD27 MAb	Renal cell carcinoma	Celldex
	Epacadostat	IDO1 inhibitor	NSCLC	Incyte
	RO7009789	CD40 agonist	Solid cancers	Roche
	RG7813	Anti-CEA IL-2 MAb	Solid cancers	Roche
	Gazyva	Anti-CD20 MAb	Lymphoma	Roche
	NLG919	IDO inhibitor	Solid tumours	Roche
	Yervoy or interferon alfa-2b	Anti-CTLA-4 MAb	Solid tumours	Roche
	RG7888	Anti-OX40 MAb	Solid tumours	Roche
	RO5509554	Anti-CSF-1R MAb	Solid tumours	Roche
	CDX-1401	Anti-NY-ESO-1 MAb	NSCLC	Yale University
Durvalumab – AstraZeneca				
	Bavituximab	Anti-PS MAb	Solid tumours	Peregrine Pharmaceuticals
	Cyramza	Anti-VEGF-2 MAb	Solid tumours	Lilly
	IPH2201	Anti-NKG2A MAb	Solid tumours	Innate Pharma
	Mogamulizumab	Anti-CCR4 MAb	Solid tumours	Kyowa Hakko Kirin
	Epacadostat	IDO1 inhibitor	Solid tumours	Incyte
	Tremelimumab	Anti-CTLA-4 MAb	Various	AstraZeneca
	MEDI6383	OX40 agonist	Solid tumours	AstraZeneca
	MEDI9447	Anti-CD73 MAb	Solid tumours	AstraZeneca
	MEDI0680	Anti-PD-1 MAb	Advanced malignancies	AstraZeneca
	MEDI-6469	Anti-OX40 MAb	Solid tumours and B-cell lymphoma	AstraZeneca

As for small biotechs combining their novel projects with available PD-1 drugs, these include MacroGenics' anti-B7-H3 MAb and TG Therapeutics' ublituximab plus TGR-1202 – both being tested with Keytruda – and Celldex's varilumab with Opdivo, although this is part of a cost-sharing non-exclusive deal with Bristol.

Peregrine Pharmaceuticals is testing its controversial anti-PS MAb bavituximab both in combination with Opdivo and, under a non-exclusive clinical trial collaboration, with AstraZeneca's durvalumab.

IDO inhibitors, which are not MAbs but small-molecule agents that affect T-cell activation by halting tryptophan breakdown, deserve a special mention. Incyte went to great lengths to put in place studies of its IDO project epacadostat with Keytruda, Opdivo, durvalumab and atezolizumab non-exclusively, only for Roche to strike a separate – exclusive – licensing deal covering NewLink's rival IDO agent (NewLink gets one over on Incyte – October 21, 2014).

Mechanisms

Beyond a simple amplification of response or reduction of adverse events, there is more profound mechanistic logic behind looking at combinations of checkpoint inhibitors.

These agents work by latching on to antigens that tumour cells display periodically, like PD-L1, or by hitting T-cell receptors that damp down cytotoxic activity, such as PD-1 or CTLA4.

The keyword here is "periodically". Not every tumour contains high expression levels of PD-L1, for example. This fact is thought to account for the relatively low activity of anti-PD-1/PD-L1 agents in many cancer patients, while others with the same tumour type have strong and long-lasting responses, and the search is on for biomarkers of this response (Asco – Check mate for combination promise and shortcomings – May 31, 2015).

But the key is that patients with low levels of PD-L1 expression might still benefit from checkpoint inhibition because at a later point in time, when treatment is administered, their tumours might be driven into a more antigenic state, resulting in increased expression of PD-L1 (Asco – Growing PD-1 uses fail to stem Bristol selloff – June 3, 2014).

Hence the fundamental potential provided by adding another agent, antibody, cell therapy or vaccine into the checkpoint inhibitor mix; put simply, many of these treatments can help push the tumour into a more immunogenic state, and provide checkpoint inhibitors with antigen targets to hit.

Cancer vaccines

Therapeutic cancer vaccines are a variation on this theme. These projects were once at the cutting edge of oncology development, but for a variety of reasons have a lamentable track record in the clinic. Combining them with immune checkpoint agents could offer them a new lease of life.

Cancer vaccines work by presenting single or multiple tumour antigens to the immune system, with the aim of generating new antitumour immune responses. They are a logical approach for combining with a mechanism like checkpoint inhibition, whose fundamental goal is to kickstart a natural immune system response.

Industry vaccine projects in this group include those in development by Immune Design, Heat Biologics, ISA Pharmaceuticals and Advaxis. The last company recently suffered a setback with the US FDA placing its lead asset, ADXS-HPV, on clinical hold after a patient death, though this is thought not to have any long-term effect either on the project or Advaxis's engineered listeria technology. (Advaxis stumbles on clinical hold – October 7, 2015)

Anti PD-1/PD-L1 MAb combinations with vaccines

Source: EvaluatePharma® September 2015

	Combination vaccine	Pharmacology class	Indication	Sponsor
Keytruda – Merck & Co (PD-1 MAb)				
	ADXS-PSA	Anti-PSA vaccine	Metastatic, castrate-resistant prostate cancer	Advaxis
	G100	Vaccine	Non-Hodgkin's lymphoma	Immune Design
	LV305	NY-ESO-1 cancer vaccine	Melanoma	Immune Design
	OncoTICE/Tice BCG	BCG vaccine	Bladder cancer	Merck
	MVI-816	pTVG-HP plasmid DNA vaccine	Metastatic, castrate-resistant prostate cancer	NCI (NIH)
	MVA vaccine expressing p53	Modified vaccinia virus	Solid tumours	NCI (NIH)
	6MHP	6 melanoma helper peptide vaccine	Melanoma	University of Virginia
Opdivo – Bristol-Myers Squibb (PD-1 MAb)				
	ALVAC(2)-NY-ESO-1 (M)	Cancer vaccine	Melanoma	Bristol-Myers Squibb
	DC Vaccine	Dendritic cell vaccine	Glioma	Bristol-Myers Squibb
	Viagenpumatucel-L	Cancer vaccine	NSCLC	Heat Biologics
	ISA101	HPV vaccine	Solid tumours	ISA Pharmaceuticals
	GM.CD40L	Cancer vaccine	Lung cancer	Lee Moffitt Cancer Center
	GVAX Pancreas and CRS-207	Mesothelin cancer vaccines	Pancreatic cancer	Sidney Kimmel Cancer Center
Pidilizumab – Medivation (PD-1 MAb)				
	Dendritic Cell/Myeloma Vaccines	Vaccine	Multiple myeloma	Beth Israel Deaconess Medical Center
	Provenge	T-cell vaccine	Prostate cancer	Georgia Regents University
	DC/RCC fusion vaccine	DC/RCC fusion vaccine	Renal cell carcinoma	NCI (NIH)
Durvalumab – AstraZeneca (PD-L1 MAb)				
	ADXS-HPV	HPV vaccine	HPV-associated cervical and head & neck cancers	Advaxis

Oncolytic viruses

In terms of the logic behind immune system stimulation, a similar case can be made for oncolytic virus approaches like Amgen's T-Vec and Oncolytics' Reolysin, which are now thought to have extremely limited potential as monotherapies.

Notwithstanding that T-Vec managed to secure US approval in melanoma late last month (Adcom puts T-Vec on track to underwhelm – April 30, 2015). However, without a combo its target market will probably be narrow. Oncolytic viruses are naturally occurring, and work, at least in theory, by preferentially infecting and killing cancerous cells while being inactive inside healthy ones.

The key to their potential in combination lies in the defence mechanisms that infected tumour cells employ to evade immune response, which include upregulating PD-L1; this clearly makes additional PD-1/PD-L1 blockade a particularly apt strategy.

It has been postulated that interventions like oncolytic viruses could increase neoantigen exposure to the T-cell based immune system, acting in a manner similar to a vaccine to boost the tumour's susceptibility to immunotherapy. The Finnish biotech Oncos Therapeutics cites the "priming" effect of its ONCOS-102 project as a reason for combining it with checkpoint inhibition.

Anti-PD-1/PD-L1 MAbs combined with gene and cell therapies and other novel approaches

Source: EvaluatePharma® September 2015

	Combination vaccine	Pharmacology class	Indication	Sponsor
Keytruda – Merck (PD-1 MAb)				
	ImmunoPulse IL-12	IL-12 gene therapy	Unresectable metastatic melanoma	OncoSec Medical
	Lymphodepletion, TIL and IL-2	T-cell infusion	Melanoma	Merck
	T-Vec	Oncolytic virus	Squamous head & neck carcinoma, unresected melanoma	Amgen
Atezolizumab – Roche (PD-L1 MAb)				
	T-Vec	Oncolytic virus	Triple-neg breast cancer and colorectal cancer with liver mets	Amgen
Durvalumab – AstraZeneca (PD-L1 MAb)				
	ISIS -STAT3-2.5Rx	STAT3 inhibitor antisense	Hepatocellular carcinoma and diffuse large B-cell lymphoma	Isis Pharmaceuticals/ AstraZeneca
	CD19 - CAR T	Anti-CD19 CAR-T therapy	Non-Hodgkin's lymphoma	Juno Therapeutics
	IMCgp100 and/or temelimumab	Cell therapy	Metastatic melanoma	Immunocore

Amgen is running trials of T-Vec combos with Keytruda and Opdivo, and Oncolytics has highlighted PD-1 inhibition as a key way of unlocking the power of oncolytic viruses.

This table also includes other gene and cell therapies, the most interesting of which might be Juno's CD19-directed CAR-T project. Notwithstanding the huge promise around CAR-T therapy it is still relatively early days for this field, but combining it with an immune checkpoint agent – releasing the immune system brake, as it were – could be a way to unlocking even greater efficacy.

Another way to achieve this might be to use an appropriate gene-editing technology to "edit out" the PD-1 receptor on the CAR-T construct, and this is something being attempted by Cellectis, though this area is still years away from the clinic.

Costs and biomarkers

While the above combinations of MAbs, vaccines, gene and cell therapies are undoubtedly highly novel, one issue that must be taken into account is cost.

Opdivo and Yervoy are both expensive therapies on their own, and when they were approved in combination recently, for first-line treatment of Braf wild type melanoma, their combined cost of roughly $256,000 per patient per year did not go unnoticed (More pressure mounts on the Braf/Mek combo – October 2, 2015).

US drug costs have become an especially hot topic in recent weeks, as the practice of speciality companies routinely increasing prices of elderly drugs, and the lack of a mechanism for payers to negotiate with drug manufacturers, has prompted political interventions. It is true, however, that action on this point remains a far-off prospect.

Nevertheless, the biopharma industry is now fighting a public relations battle to prove that investing in novel R&D justifies high drug costs. While the most novel and efficacious oncology products logically lie outside the debate around speciality drug pricing, the pressure is on for the oncology combinations to show significant improvements in safety and/or efficacy over monotherapies.

The live nature of the debate around rising drug costs also feeds the push to identify cancer biomarkers, specifically to pin down in which patient populations an agent or combination is most likely to work, to avoid targeting expensive therapy at non-responding patients. For reasons outlined above PD-L1 status makes a fairly poor biomarker, and is also hard to determine with uniformity.

Speaking at a recent R&D meeting Steve Olsen, head of medical affairs at AstraZeneca's oncology group, said that almost every company was using a different PD-L1 assay, and using different cut-offs as determinants of PD-L1 positivity. This point has also repeatedly been made by sellside analysts.

But Mr Olsen reckoned that combinations might render the issue of PD-L1 positivity moot: "The question is, does it matter? Is there a way that we can unlock the immunogenic potential of a tumour so it doesn't really matter what PD-L1 is doing? Can we unlock neoantigens by combinations [of anti-PD-1/PD-L1] with other agents?"

Nevertheless, there are opposing views. Roche, for example, has invested extensively in PD-L1 assays, and at its recent R&D investor day the group's cancer immunotherapy franchise head, Daniel Chen, stated: "It is unlikely that PL-L1 will ever be in a place where it doesn't play an important marker role."

Dr Johannes Zuber, a project leader specialising in the genetics of cancer at the Boehringer Ingelheim-owned Institute for Molecular Pathology in Vienna, Austria, agrees with Mr Olsen.

"Immuno-oncology is beyond a revolution," he told EP Vantage. "Traditionally you would always see cancer as a genetic disease, but now clinicians are questioning whether it even matters which mutations you have, at least in melanoma. Perhaps as long as you have a certain number of [infiltrating] T cells it's going to work. That's a fundamental change."

Small molecules, conventional chemotherapies etc

These considerations will undoubtedly also touch parts of what seems to be the largest grouping of combinations: anti-PD-1/PD-L1 agents added to small molecules – novel as well as established drugs – and several regimens of chemo and radiotherapies.

Anti-PD-1 MAb combinations with small molecules

Source: EvaluatePharma® September 2015

	Combination drug	Pharmacology class	Indication	Sponsor
Keytruda – Merck & Co				
	RTA 408	NRF2 activator	Melanoma	AbbVie/Reata
	BBI608	STAT3, Nanog & β-catenin pathways inhibitor	Various	Boston Biomedical
	BBI503	Cancer cell stemness kinase inhibitor	General cancer indications	Boston Biomedical
	PLX3397	FMS, c-kit, CSF-1R & Flt-3 kinase inhibitor	Melanoma and multiple other solid tumours	Daiichi Sankyo
	SD-101	TLR9 agonist	Advanced melanoma	Dynavax Technologies
	Lenvatinib	VEGFr tyrosine kinase inhibitor	Solid tumours	Eisai
	Halaven	Microtubule/tubulin inhibitor	Metastatic triple-negative breast cancer	Eisai
	Pazopanib	Multi-kinase inhibitor	Renal cell carcinoma	GlaxoSmithKline
	GSK3174998	Not disclosed	General cancer indications	GlaxoSmithKline
	ACP-196	BTK inhibitor	Various	Merck
	Mekinist + Tafinlar	MEK inhibitor/B-Raf kinase inhibitor	Melanoma	Merck
	Pomalyst	Immunomodulator	Multiple myeloma	Merck
	CC-486 and/or romidepsin	DNMT inhibitor/HDAC inhibitor	Colorectal cancer	Merck & Celgene
	Ziv-Aflibercept	VEGFr kinase inhibitor	Advanced solid tumors	NCI (NIH)
	Axitinib	VEGFr 1-3 tyrosine kinase inhibitor	Renal cancer	Pfizer
	Xalkori	ALK & c-Met kinase inhibitor	ALK-positive advanced NSCLC	Pfizer
	Entinostat	HDAC inhibitor	NSCLC or melanoma	Syndax Pharmaceuticals
	Niraparib	PARP inhibitor	Triple-negative breast and ovarian cancers	Tesaro
	Birinapant	IAP antagonist	Relapsed or refractory solid tumours	TetraLogic Pharmaceuticals
	Gilotrif	EGFR & HER2 kinase inhibitor	NSCLC	University of California/ NCI (NIH)
	Defactinib + Gemzar	FAK inhibitor + pyrimidine analogue	Pancreatic cancer	Washington University School of Medicine
Opdivo – Bristol-Myers Squibb				
	Imbruvica	BTK inhibitor	Non-Hodgkin's lymphoma	AbbVie
	RTA 408	NRF2 activator	Melanoma	AbbVie/Reata
	BBI608	STAT3, Nanog & β-catenin pathways inhibitor	Various	Boston Biomedical
	BBI503	Cancer cell stemness kinase inhibitor	General cancer indications	Boston Biomedical
	Vidaza	DNMT inhibitor	Myeloid leukaemia	Bristol-Myers Squibb
	Tafinlar	B-Raf kinase inhibitor	Metastatic melanoma	Bristol-Myers Squibb
	Mekinist	MEK inhibitor	Metastatic melanoma	Bristol-Myers Squibb
	RRx-001	Radiation sensitizer	Solid tumours	EpicentRx
	Capmatinib	c-Met kinase inhibitor	NSCLC	Incyte
	Galunisertib	TGF-beta RI kinase inhibitor	Glioblastoma, hepatocellular carcinoma and NSCLC	Lilly
	Zykadia, INC280 & EGF816	ALK, c-Met kinase & EGFR tyrosine kinase inhibitors	NSCLC	Novartis

The analysis reveals some 40 separate novel small molecules being combined with anti-PD-1/PD-L1 MAbs across 44 active clinical trials. A particularly popular combo links immunotherapy with a B-Raf and/or Mek inhibitor, of which there are three: Novartis's marketed Tafinlar and Mekinist, Roche/Exelixis's Zelboraf and cobimetinib, and AstraZeneca/Array's selumetinib.

Apart from the immunotherapy companies, trial sponsors include Clovis Oncology (its rociletinib/atezolizumab combo mirrors AstraZeneca's AZD9291/durvalumab), Mirati Therapeutics, Boston Biomedical and Tesaro.

Anti-PD-L1 combinations with small molecules

Source: EvaluatePharma® September 2015

	Combination drug	Pharmacology class	Indication	Sponsor
Atezolizumab – Roche				
	Rociletinib	EGFR inhibitor	EGFR-mutant NSCLC	Clovis Oncology
	Zelboraf	B-Raf kinase inhibitor	Malignant melanoma	Roche
	Cobimetinib + Zelboraf	MEK inhibito + B-Raf kinase inhibitor	Malignant melanoma	Roche
	Cobimetinib	MEK inhibitor	Solid tumours	Roche
Durvalumab – AstraZeneca				
	Imbruvica	BTK inhibitor	Lymphoma and solid tumours	AbbVie
	AZD9291	EGFR tyrosine kinase inhibitor	NSCLC	AstraZeneca
	Selumetinib + docetaxel	MEK inhibitor + Taxane	NSCLC	AstraZeneca
	AZD5069	CXCR2 antagonist	Squamous head & neck carcinoma	AstraZeneca
	AZD4547	FGFR tyrosine kinase inhibitor	Bladder cancer	AstraZeneca
	Tafinlar	B-Raf kinase inhibitor	Melanoma	GlaxoSmithKline
	Mekinist	MEK inhibitor	Melanoma	GlaxoSmithKline
	Mocetinostat	HDAC inhibitor	NSCLC	Mirati Therapeutics
	Cediranib	VEGFr tyrosine kinase inhibitor	Solid tumors and ovarian cancer	NCI
	Olaparib	PARP inhibitor	Solid tumors and ovarian cancer	NCI
	Motolimod	TLR8 agonist	Ovarian cancer	VentiRx Pharmaceuticals
Avelumab – Pfizer/Merck KGaA				
	Axitinib	VEGFr 1-3 tyrosine kinase inhibitor	Renal cell cancer	Pfizer

Meanwhile, many conventional chemotherapy and radiotherapy treatments also have mechanisms of action that potentiate immune function. Moreover, the basic physical removal of tumour burden by a chemotherapy can in itself provide a significant initial benefit – at least if the chemo is used at low doses, since high doses of some chemotherapies can be profoundly immunosuppressive.

Radiotherapy is thought in some cases to prevent cancer cells from evading an immune response via several mechanisms. This is largely through the increase of tumour-specific antigens for presentation that is occasioned by radiation-induced cell death, leading to tumour cells becoming increasingly susceptible to lysis by cytotoxic T cells.

Reduction of tumour burden by radiotherapy can also reduce the presence of antigens that contributed to T-cell tolerance.

Anti-PD-1 combinations with established drugs/chemotherapy

Source: EvaluatePharma® September 2015

	Combination drug	Pharmacology class	Indication	Sponsor
Keytruda – Merck & Co				
	Vidaza	DNA methyltransferase inhibitor	NSCLC	Celgene
	Alimta	Thymidylate synthase inhibitor	NSCLC	Eli Lilly
	Gemzar	Pyrimidine analogue	Urothelial carcinoma, NSCLC	Merck
	Metronomic cyclophosphamide	Alkylating agent	Sarcoma	Merck
	Paclitaxel/carboplatin/ Tarceva/Iressa/Avastin	Various	NSCLC, ovarian cancer, glioma	Merck
	Pomalyst	Immunomodulator	Multiple myeloma	Merck
	Cisplatin + 5-FU	Platinum compound + pyrimidine analogue	Stomach cancer	Merck
	Pemetrexed + cisplatin	Thymidylate synthase inhibitor	NSCLC	Merck
	Rituxan	Anti-CD20 MAb	Lymphoma	Merck
	Intron A	Interferon alpha	Melanoma	Merck
	PEGIntron	Interferon alpha	Melanoma	Merck
	Pegylated Interferon Alfa-2b	Interferon Alpha	Renal cell carcinoma	Merck
	Vidaza	DNA methyltransferase inhibitor	Colorectal cancer	Merck
	Revlimid + dexameth-asone	Immunomodulator + corticosteroid	Multiple myeloma	Merck/Celgene
	Zolinza + tamoxifen	HDAC inhibitor + eestrogen antagonist	Breast cancer	University of California
	Rituxan, prednisone, cyclophosphamide, doxorubicin + vincristine	Anti-CD20, corticosteroid + chemo	Large B-cell lymphoma	University of Washington/NCI
	Gemzar/Abraxane/ irinotecan	Chemo	Solid tumours	Western Regional Medical Center
	Herceptin/Kadcyla/ Erbitux	Anti-HER2 MAb/anti-EGFR MAb	Solid tumours	Western Regional Medical Center
Opdivo – Bristol-Myers Squibb				
	Avastin	Anti-VEGF MAb	NSCLC	Bristol-Myers Squibb
	Sprycel	Tyrosine kinase inhibitor	Chronic myeloid leukemia	Bristol-Myers Squibb
	Sutent/Votrient	Multi-kinase inhibitor	Renal cell carcinoma	Bristol-Myers Squibb
	Gemzar/Alimta/ Herceptin/Tarceva + various chemos	Various	NSCLC	Bristol-Myers Squibb
	Abraxane	Taxane/vasodilator	HER-2 negative metastatic breast cancer, pancreatic cancer and NSCLC	Celgene
	Temodar	Alkylating agent	Glioblastoma, gliosarcoma	NCI
	Votrient	Multi-kinase inhibitor	Melanoma	Pfizer
Pidilizumab – Medivation				
	Revlimid	Immunomodulator	Multiple myeloma	Curetech
	Rituximab	Anti-CD20 MAb	Relapsed follicular lymphoma	Curetech
	Folfox	Platinum compound	Colorectal cancer	Medivation

While this last category of combinations is significant in terms of numbers of clinical trials, it is novel agents, such as immuno-oncology plus immuno-oncology, that will be of more interest to the market.

Indeed, a recent panel of key opinion leaders convened by Cowen agreed that additional checkpoint inhibitors were the most promising add-on to PD-1/PD-L1/CTLA4 therapy. The experts viewed Bristol and Roche as the two companies with the strongest portfolios outside the already marketed checkpoint mechanisms – a surprising opinion given AstraZeneca's concerted effort in this field.

Anti-PD-L1 combinations with established drugs/chemotherapy

Source: EvaluatePharma® September 2015

	Combination drug	Pharmacology class	Indication	Sponsor
Atezolizumab – Roche				
	Carboplatin + paclitaxel	Platinum compound + taxane	NSCLC	Roche
	Carboplatin	Platinum compound	NSCLC	Roche
	Abraxane	Taxane	Breast cancer	Roche
	Avastin	Anti-VEGF MAb	Various	Roche
	Tarceva	EGFr tyrosine kinase inhibitor	NSCLC	Roche
	Revlimid	Immunomodulator	Multiple myeloma	Roche
	Gemzar + cisplatin	Pyrimidine analogue + platinum compound	NSCLC	Roche
	Azacitidine	DNMT inhibitor	Myelodysplastic syndrome	Roche
Durvalumab – AstraZeneca				
	Iressa	EGFr tyrosine kinase inhibitor	NSCLC	AstraZeneca
	Abraxane + doxorubicin/ cyclophosphamide	Taxane + alkylating agent/ anthracycline	Breast cancer	Yale University

Speaking to EP Vantage earlier this year AstraZeneca's Steve Olsen admitted that his group was behind the first movers Bristol Myers-Squibb, Merck & Co and Roche.

But he insisted: "Where we believe we can win is with the combination approach. We are combining with our own portfolio, we are combining with external partners, we are combining immuno-oncology with immuno-oncology, and immuno-oncology with small molecules."

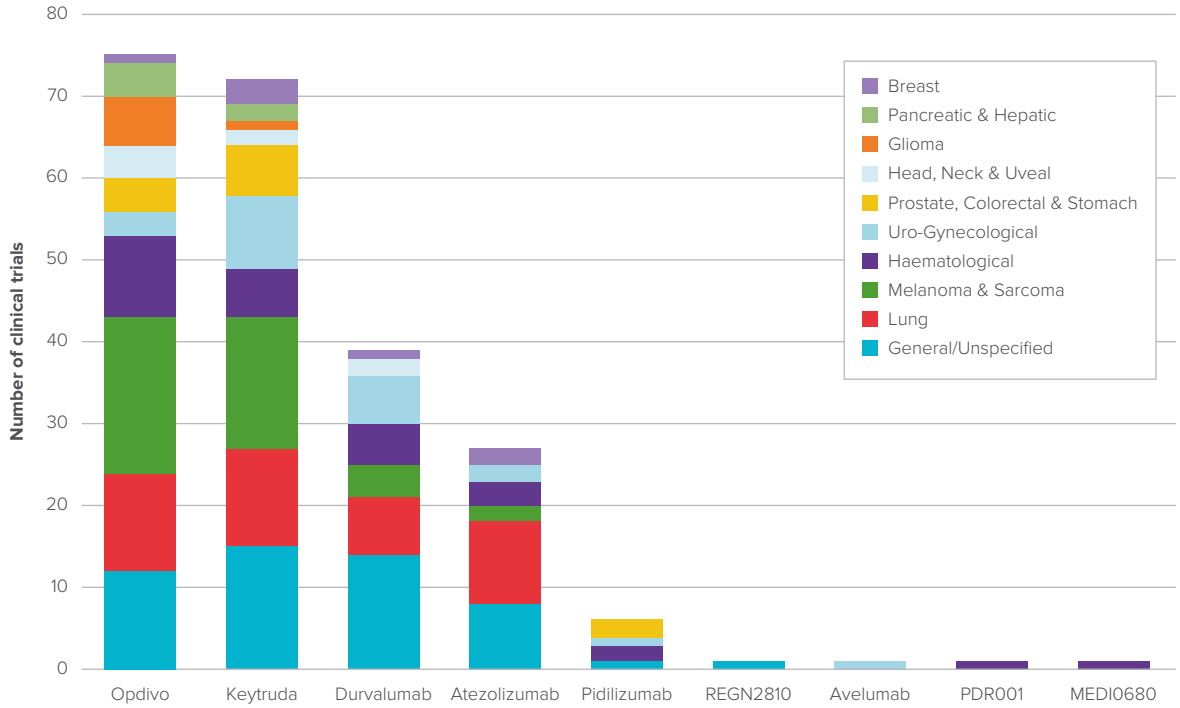
Popular indications

Across all the clinical-stage combinations of anti-PD-1/PD-L1 projects it is perhaps not surprising that the most popular indications have been the ones that have led to the first monotherapy approvals: melanoma and non-small cell lung cancer.

It is interesting to see haematological malignancies also featuring strongly, comprising lymphomas and myeloma (ASH – A way in for anti-PD-1 therapy in haematology – December 6, 2014). The upcoming ASH meeting in December will undoubtedly provide further insights.

Cancer indications in immuno-oncology combinations, split by anti-PD-1/PD-L1 agent

Source: EvaluatePharma® September 2015



Experts in the Cowen panel cited mechanisms targeting Ox40 (Roche and Astra), IDO (Incyte, Newlink and partners) and CD137 (Pfizer) as the most promising add-ons to immuno-oncology. Targeting Ox40 had previously been highlighted as an important upcoming immuno-oncology approach by Jefferies, and the most advanced agent, Astra's MEDI-6469, should yield data from its durvalumab combo next year.

Confidence in the IDO approach has recently been supported by data at the European Cancer Congress showing durable responses for epacadostat in combination with Yervoy in melanoma, and the non-exclusive tie-up between Incyte and Merck & Co has just been expanded.

It seems that one problem companies might face is not having too few combinatorial possibilities, but too many, something that in the opinion of Ross Stewart, principal scientist in AstraZeneca's translational medicine oncology group, means that coming relatively late to this field might not be so bad.

"There's still unmet need there," he told EP Vantage. "There's a 20-30% response rate across a range of cancers [with monotherapies], but that leaves 70% or 80% of patients still not benefiting. Combinations of different agents, together with a greater understanding of what is driving response, provide an awful lot of opportunity for us to continue."

The Institute for Molecular Pathology's Dr Zuber says the opportunity is bigger than ever before, highlighting the still disappointing results in some cancers, even those that are highly mutated.

But this means threats as well as possibilities. "How do we model these things before we launch a clinical trial?" he asks.

"It's very hard to build a hypothesis; in the past we had one new agent at a time, perhaps in five years. Now we have 20 new agents in parallel. How are you going to prioritise them for clinical trials? Is it all going to be, say, a three-patient phase I and then if you don't see a major effect you drop [the project]?"

But how are scientists and doctors to deal with all these combinations? "It's reached a level where we have to be very careful. Many small molecules have a very clear effect on the T cell," says Dr Zuber.

In the old days when two drugs were combined the worst that could happen was a complete lack of added value. This is no longer the case in a situation where combinations involving immuno-oncology agents risk producing a deleterious effect.

Nevertheless, nothing can now stop the progress of combinatorial approaches. And increasing awareness of the two key findings – the lack of immunogenicity of certain tumours and the presence of additional blocking checkpoints – will continue to drive investment in this area.

Much more work will be needed to understand the basic science, and it could be that companies have to rethink the way clinical trials are conducted. If many of the current combinatorial approaches look like throwing things together and hoping for the best this will not be sustainable over time and, as the various studies start generating data, the understanding of mechanistic interactions will improve.

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