# PD-1 / PD-L1 Combination Therapies

Jacob Plieth & Edwin Elmhirst – May 2017

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# Foreword

## Sprinkling the immuno-oncology dust

When in November 2015 *EP Vantage* published its first immuno-oncology analysis we identified 215 studies of anti-PD-1/PD-L1 projects combined with other approaches, and called this an important industry theme. It is a measure of how central combos have become that today, barely 18 months on, that total has been blown out of the water.

No fewer than 765 studies involving combinations of PD-1 or PD-L1 assets are now listed on the Clinicaltrials.gov registry.

This dazzling array owes much to the transformational nature of the data seen with the first wave of anti-PD-1/PD-L1 MAbs. It also indicates how central combinations will be in extending immuno-oncology beyond just a handful of cancers, and beyond certain patient subgroups.

But the combo effort is as much about extending the reach of currently available drugs like Keytruda, Opdivo and Tecentriq as it is about making novel approaches viable by combining them with PD-1/PD-L1. On a standalone basis several of the industry's novel oncology projects have underwhelmed.

As data are generated it will therefore be vital for investors to tease out the effect of combinations beyond that of monotherapy, and it is doubtful whether the sprinkling of magic immuno-oncology dust will come to the rescue of substandard products.

This is not stopping many companies, as the hundreds of combination studies identified here show. This report aims to quantify how many trials are ongoing with which assets and in which cancer indications, as well as suggesting reasons why some of the most popular approaches are being pursued. The data are current as of 13 April 2017.

Report author | Jacob Plieth

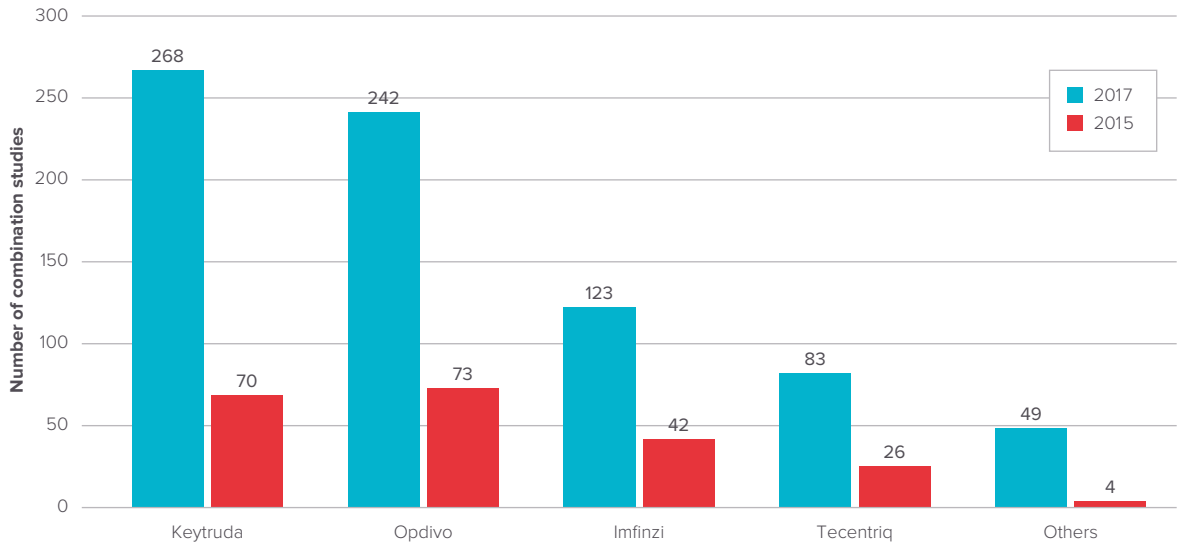
# Keytruda reigns supreme?

The surge in combo studies over the past 18 months has come across the board, but the biggest increase has been seen with Keytruda. Combinations involving Merck & Co's anti-PD-1 MAb have spiralled from 70 to 268, and the drug has overtaken Bristol-Myers Squibb's Opdivo to stand today as the most extensively combined PD-1/PD-L1 agent.

Within the Keytruda total, a remarkable 90 trials involve chemo combinations – an important emerging theme – while 88 study the drug with a small molecule. Both totals outstrip the 75 trials of straight combinations of Bristol's Opdivo plus Yervoy, which at one point looked like making CTLA4 inhibition the most important combo consideration.

**Number of Anti-PD-1/PD-L1 MAb combination studies 2015 vs. 2017**

Source: Evaluate Ltd.[a] May 2017



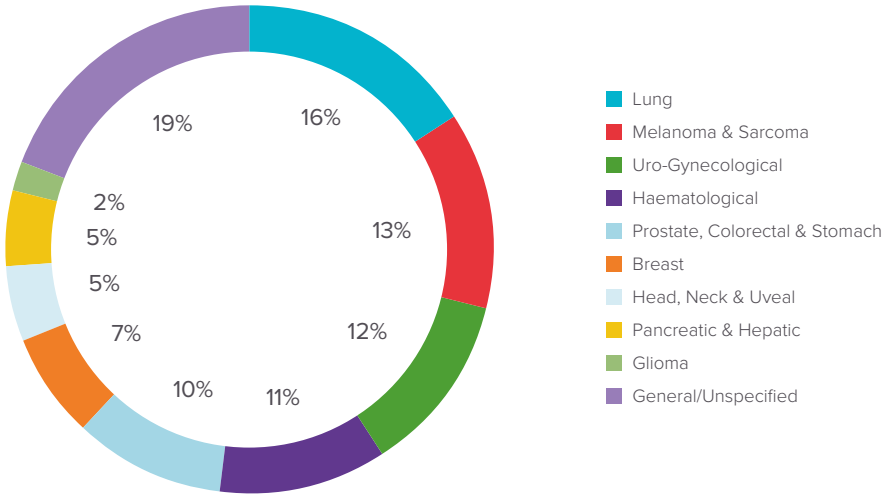

2015 data from EP Vantage PD-1 combo report (Nov. 2015)

Some immuno-oncology agents that were marginal 18 months ago have become more prominent, most notably Astrazeneca's Imfinzi and Pfizer/Merck KGaA's Bavencio. With both drugs trailing the leaders, combinations are an important way for their developers to try and make up lost ground.

Then there are entirely new entrants, such as Beigene's BGB-A317, Lilly's LY3300054 and Cytomx's CX-072, and a pair of assets in which Novartis has put its faith as it tries to catch up with the great immuno-oncology bandwagon: PDR001, an anti-PD-1 MAb, and FAZ053, an anti-PD-L1 asset. The report excludes pidilizumab, now owned by Pfizer, given that this MAb is no longer thought to act by blocking PD-1.

**Anti-PD-1/PD-L1 MAb combination studies by (broad) indication (grouping)**

Source: Evaluate Ltd.® May 2017

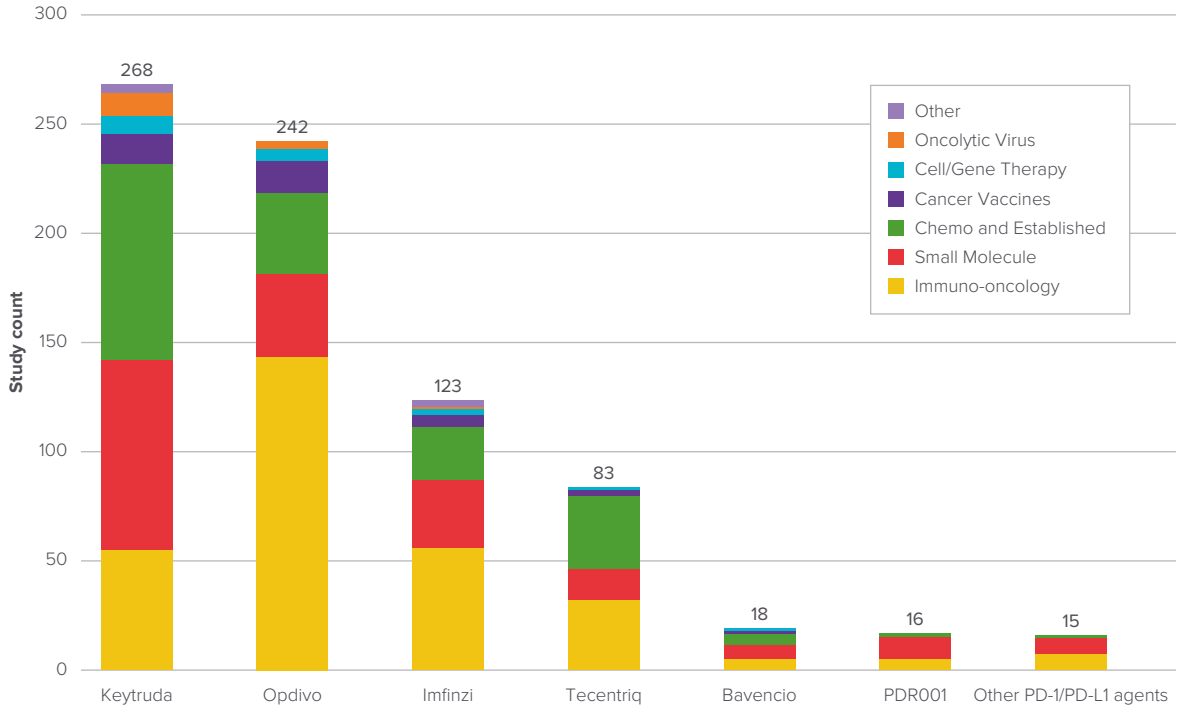



Indication-wise, it is perhaps not surprising to see major combination efforts in melanoma and NSCLC. Melanoma is the first and to date most impressive setting for immuno-oncology, and major efforts are under way to expand the reach of novel drugs beyond a subgroup of strongly responding patients.

NSCLC, meanwhile, is perhaps the biggest potential oncology market. Although with Opdivo failing in the Checkmate-026 trial, and Keytruda securing first-line US approval on the basis of Keynote-021 data, is fast becoming Merck & Co's private space (Event – Merck's daring bid for lung cancer domination, April 28, 2017). Again, however, the dominance of one player is not stopping others from fighting for a piece of the pie.

## Anti-PD-1/PD-L1 MAb study by companion agent

Source: Evaluate Ltd.® May 2017




This analysis encompasses all studies listed in Clinicaltrials.gov, excluding a handful in which the identity of the PD-1/PD-L1 agent has not been disclosed.

Broadly speaking the combo studies fall into the following groupings depending on their sponsor(s) or licensing partner(s):

1) Sole big pharma sponsor. For example trials of Keytruda plus chemo; Opdivo plus Yervoy; Imfinzi plus tremelimumab; or Tecentriq plus Avastin, where the big pharma owner of the PD-1/PD-L1 drug in question wants to extend its commercial reach.

2) Biotech sponsor under a licensing deal. For example Opdivo plus lirilumab, where a licensing deal exists between Bristol-Myers Squibb and Innate Pharma.

3) Biotech sponsor without a licensing deal. For instance the combo trial of Keytruda with Bergenbio's BGB324, where no commercial licensing deal exists; rather, the companies in question have signed an agreement under which the biotech company runs a trial for which Merck provides its anti-PD-1 drug.

4) Investigator-initiated trials, where an academic institution has decided to investigate an immuno-oncology combination, without commercial involvement from pharma or biotech.

However, rather than analysing these in depth, the aim of this report is to provide an overview of all trials, to investigate trends as to the types of combos being pursued, and to examine the broad cancer indications in which combinations are being studied.

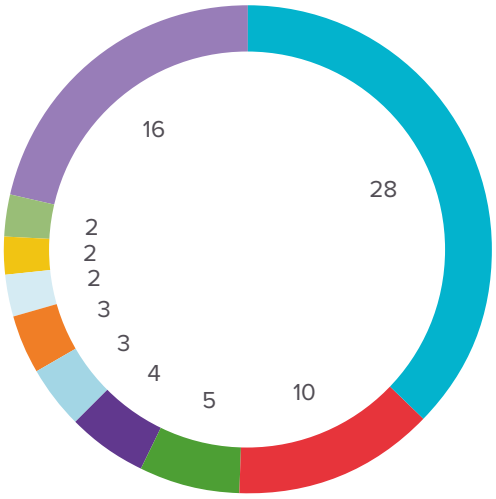
# Studies of PD-(L)1 assets combined with other MAbs or immuno-oncology agents

This is the single most prolific combo grouping, and within it the most popular combinations involve Opdivo plus Yervoy, and Imfinzi plus tremelimumab. There is an obvious reason for this: with Opdivo and Yervoy already on the market the rationale of combining PD-(L)1 with CTLA4 inhibition has been proven – though not without significant toxicity – and Bristol and Astra are the only companies boasting in-house, advanced programmes in both approaches.

The scientific rationale of hitting more than one immune checkpoint is that this increases the chances of overcoming multiple resistance pathways that the tumour might be using to evade immune system attack.

**Combinations of Opdivo + Yervoy (Bristol-Myers Squibb; 75 studies in total)**

Source: Evaluate Ltd.[a] May 2017

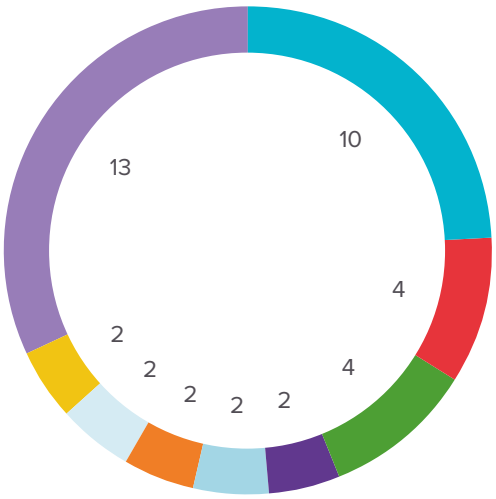



- Melanoma
- NSCLC
- Renal Cancer
- Head & Neck Cancer
- Prostate Cancer
- Mesothelioma
- Breast Cancer
- SCLC
- Uveal Melanoma
- Other – comprised of the following indications

| | Study count |
|---|---|
| AML, MDS | 1 |
| Bladder Cancer | 1 |
| Glioblastoma | 1 |
| HCC | 1 |
| Nasopharyngeal Carcinoma | 1 |
| Non-clear Cell RCC | 1 |
| Sarcoma & Endometrial Carcinoma | 1 |
| Gastric Cancer | 1 |
| Biliary Tract Cancer | 1 |
| Solid Tumours & Other | 5 |

### Combinations of Imfinzi + tremelimumab (Astrazeneca; 41 studies in total)

Source: Evaluate Ltd.® May 2017




| | Study count |
|---|---|
| Breast Cancer | 1 |
| Endometrial Cancer | 1 |
| Germ Cell Tumors | 1 |
| Glioblastoma | 1 |
| Ovarian Cancer | 1 |
| Pancreatic Cancer | 1 |
| Pleural Mesothelioma | 1 |
| Prostate Cancer | 1 |
| Pulmonary Sarcomatoid Carcinoma | 1 |
| Renal Cancer | 1 |
| MDS | 1 |
| Oesophageal Cancer | 1 |
| Multiple Myeloma | 1 |

Excluding studies that only combine Opdivo with Yervoy, or Imfinzi with tremelimumab, Opdivo again comes out on top in terms of its combinations with other MAbs or cytokines. A particularly popular approach seems to involve combinations with Bristol's in-house anti-Lag3 MAb BMS-986016 (SITC preview – bladder cancer and novel checkpoints to the rescue, November 8, 2016).

### Studies of Opdivo (Bristol-Myers Squibb) combined with other immuno-oncology agents*

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| Brentuximab vedotin | CD30 MAb MMAE conjugate | 6 studies in Hodgkin & non-Hodgkin lymphoma |
| BMS-986016 | Anti-Lag3 MAb | 3 studies in solid & haem tumours |
| BMS 986016 or urelumab | Anti-Lag3 MAb or anti-CD137 MAb | Glioblastoma |
| Urelumab | Anti-CD137 MAb | 3 studies in solid tumours, B-cell lymphoma & bladder cancer |
| Mogamulizumab | CCR 4 MAb | 3 studies in solid tumours |
| Varlilumab | Anti-CD27 MAb | 2 studies in solid tumours & B-cell lymphomas |
| DS-8273a | Anti-death receptor 5 MAb | 2 studies in melanoma & colorectal cancer |
| Pomalidomide +/- elotuzumab | TNFa inhibitor +/- SLAMF7 MAb | 2 studies in multiple myeloma |
| Epacadostat | IDO1 inhibitor | 2 studies in solid tumours |
| BMS-986205 | IDO1 inhibitor | Select malignancies |
| Indoximod | IDO inhibitor | Melanoma |
| ABT-399 | c-Met MAb-cytotoxic drug conjugate | Solid tumours |
| Motolimod and cetuximab | TLR 8 agonist and EGFr MAb | Head and neck cancer |
| BMS-986012 | Anti-fucosyl-GM1 MAb | SCLC |
| Glembatumumab vedotin | GPNMB MAb-auristatin E conjugate | Melanoma |

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| Combo agent | Drug class | Indication |
|---|---|---|
| BMS-986148 | Anti-mesothelin MAb-cytotoxic drug conjugate | Solid tumours |
| ALT-803 | IgG Fc MAb-IL-15 fusion protein | NSCLC |
| Cabiralizumab | CSF-1R MAb | Select malignancies |
| ABBV-085 | Anti-cancer MAb-drug conjugate | Solid tumours |
| Bevacizumab | Anti-VEGF MAb | Ovarian cancer |
| Bevacizumab and pemetrexed or erlotinib or crizotinib | VEGFr MAb and chemo agent or EGFr TK inhibitor or ALK, c-Met & Ros1 kinase inhibitor | NSCLC |
| BMS-986156 | Anti-GITR MAb | Solid tumours |
| Lirilumab | Anti-Kir MAb | MDS |
| Elotuzumab | SLAMF7 MAb | Multiple myeloma |
| Interferon-gamma | Interferon-gamma | Solid tumours |
| BMS-986179 | Anti-CD73 MAb | Solid tumours |
| BMS-986178 | Ox40 MAb | Solid tumours |
| ABBV-368 | Ox40 MAb | NSCLC/head and neck |
| Ramucirumab | Anti-VEGF receptor 2 MAb | Gastric cancer or gastroesophageal junction region (GEJ) cancer |
| Interleukin 2 | IL-2 | Renal cancer |
| Daratumumab | CD38 MAb | Solid tumours |
| Oregovomab | CA125 MAb | Epithelial cancer of ovarian, tubal or peritoneal origin |
| NKTR-214 | CD122-biased immunostimulatory cytokine | Solid tumours |
| ABBV-927 | Undisclosed immunotherapy | Solid tumours |
| JTX-2011 | Anti-Icos MAb | Solid tumours |
| Andecaliximab | MMP-9 inhibitor MAb | Gastric cancer |
| BMS-986207 | Anti-Tigit MAb | Solid tumours |
| Dinutuximab beta | Anti-GD2 MAb | Neuroblastoma |
| Nimotuzumab | Anti-EGFR MAb | NSCLC |
| ABBV-428 | Anti-CD40 MAb | Solid tumours |
| X4P-001 | CXCR 4 antagonist | Renal cancer |

Note: *antibodies or cytokines only; excludes combinations with ipilimumab.

As well as combos with other companies' assets such as Adcetris, Cyramza and ABBV-085, this list includes Bristol's own search for novel immuno-oncology agents, with in-house combos looking at additive inhibition of Ox40, CD137 and IDO. The last is included in this section because, while involving small molecules, it nevertheless targets an important immunological pathway.

Keytruda, Tecentriq and Imfinzi are themselves in numerous IO/IO combo trials including many similar approaches. Merck & Co, Astra and especially Roche have the luxury of numerous novel immuno-oncology MAbs in development in house to combine with their leading PD-(L)1-targeting drugs.

## Studies of Keytruda (Merck & Co) combined with other immuno-oncology agents*

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| Epacadostat | IDO1 inhibitor | 6 studies in solid tumours |
| Trastuzumab-DM1 | Anti-human epidermal growth factor MAb-DM1 maytansinoid conjugate | 5 studies in breast, oesophageal and gastric cancers |
| Bevacizumab | VEGFr MAb | 4 studies in glioblastoma, renal, ovarian, melanoma & NSCLC |
| Cetuximab | EGFr MAb | 3 studies in colorectal and head & neck cancers |
| Ipilimumab | CTLA4 MAb | 3 studies in melanoma, NSCLC & renal cancer |
| Interferon alfa-2b | Interferon alpha | 3 studies in melanoma and cholangiocarcinoma |
| Interleukin-2 | IL-2 | 2 studies in renal cancer & melanoma |
| MK-4166 | GITR MAb | Solid tumours |
| Indoximod | IDO inhibitor | Melanoma |
| Glembatumumab vedotin | GPNMB MAb-auristatin E conjugate | Melanoma |
| Ramucirumab | VEGFr 2 MAb | Select malignancies |
| Rituximab | Anti-CD20 MAb | Lymphoma |
| Necitumumab | EGFr MAb | NSCLC |
| Enoblituzumab | Anti-B7-H3 MAb | Select malignancies |
| GSK3174998 | Anti-OX40 MAb | Solid tumours |
| Ublituximab + TGR-1202 | Anti-CD20 MAb + PI3K-delta inhibitor | CLL |
| MK-1248 | GITR inhibitor | Solid tumours |
| PV-10 | Immunostimulant | Melanoma |
| Mirvetuximab soravtansine | Anti-FOLR1 MAb-DM4 maytansinoid conjugate | Ovarian, peritoneal, fallopian tube or endometrial cancer |
| AFM13 | Anti-CD30 & CD16A NK-cell TandAb | Hodgkin lymphoma |
| Margetuximab | Her2 MAb | Gastroesophageal junction or gastric cancer |
| IMP321 | Soluble Lag3 dimer | Melanoma |
| APX005M | Anti-CD40 MAb | Melanoma |
| AMG820 | CSF-1R MAb | Solid tumours |
| sEphB4-HSA | Ephrin B4 HSA fusion protein | Bladder cancer |
| MK-4280 | Lag3 MAb | Solid tumours |
| Demcizumab | DLL 4 MAb | Solid tumours |
| GSK3359609 | ICOS MAb | Solid tumours |
| Recombinant EphB4-HSA fusion protein | Ephrin B4 HSA fusion protein | NSCLC/head and neck |
| Resimmune/radiotherapy | Diphtheria toxin-bivalent antibody conjugate/radiotherapy | Melanoma |
| AM0010 | IL-10 | Solid tumours |
| Recombinant Interleukin-12 | IL-12 | Solid tumours |
| Interferon gamma-1b | Interferon gamma | Mycosis fungoides and Sezary syndrome |
| MK-7684 | Undisclosed | Solid tumours |
| IMM-101 | Immunomodulator | Pancreatic cancer, colorectal cancer, lung cancer, melanoma, breast cancer, sarcoma |

Note: *antibodies or cytokines only.

## Studies of Tecentriq (Roche) combined with other immuno-oncology agents*

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| Bevacizumab | VEGFr MAb | 5 studies in renal, colorectal and other solid tumours |
| Bevacizumab + entinostat | HDAC inhibitor, anti-VEGFr MAb | Renal cancer |
| Bevacizumab + cobimetinib | Anti-VEGF MAb + Map kinase inhibitor | Colorectal cancer |
| Bevacizumab or vanucizumab | VEGFr MAb or VEGF A & ANG 2 MAb | HCC |
| Ipilimumab or interferon alfa-2b or PEG-interferon alfa-2a +/- bevacizumab or obinutuzumab | CTLA4 Mab or interferon alpha +/-VEGFr MAb or Anti-CD20 MAb | Solid tumours |
| Acetylsalicylic acid and/or bevacizumab | NSAID or VEGFr MAb | Ovarian cancer |
| MOXR0916 +/- bevacizumab | Anti-OX40 MAb +/- VEGFr MAb | Solid tumours |
| Obinutuzumab + RO6874281 +/- bevacizumab | Anti-CD20 MAb + anti-FAP Mab/IL-2 fusion protein +/- anti-VEGFr MAb | RCC |
| Obinutuzumab or tazemetostat | Anti-CD20 MAb or MLL2 EZH2 inhibitor | Lymphoma |
| Obinutuzumab +/- ibrutinib | Anti-CD20 Mab +/- Bruton TKI | Chronic lymphocytic leukemia |
| Obinutuzumab + polatuzumab vedotin | Anti-CD20 MAb + anti-CD79 MAb MMAE conjugate | Lymphoma |
| Obinutuzumab + lenalidomide | Anti-CD20 MAb+ Immunomodulator | Lymphoma |
| Bendamustine + obinutuzumab or obinutuzumab + CHOP | Chemo agent + Anti-CD20 MAb or Anti-CD20 MAb + chemo combo | Follicular lymphoma |
| MOXR0916/ RG7888 | Anti-OX40 MAb | Bladder cancer |
| Vanucizumab | VEGF & ANG2 inhibitor | Solid tumours |
| Epacadostat | IDO 1 inhibitor | NSCLC, urothelial carcinoma |
| RO7009789 | CD40 agonist | Solid tumours |
| Emactuzumab | CSF-1R MAb | Solid tumours |
| Cergutuzumab amunaleukin | CEA IL-2 MAb | Solid tumours |
| RO6958688 | Anti-CEA bispecific antibody | Solid tumours |
| Daratumumab | Anti-CD38 MAb | NSCLC |
| Lenalidomide or daratumumab +/- lenalidomide | Immunomodulator or Anti-CD38 MAb +/- Immunomodulator | Multiple myeloma |
| CDX-1401 | Anti-NY-ESO-1 MAb | NSCLC |
| Rituximab + CHOP | Anti-CD20 MAb + chemo combo | Solid tumours |
| Trastuzumab + pertuzumab or Trastuzumab emtansine or Trastuzumab emtansine or doxorubicin + cyclophosphamide or trastuzumab + pertuzumab + docetaxel | Her2 + chemo | Breast cancer |
| Trastuzumab emtansine | Her2 MAb-DM1 maytansinoid | Breast cancer |
| RG6058 | TIGIT MAb | Select malignancies |
| ALX148 | CD47 binder | Solid tumours & lymphoma |

Note: *antibodies or cytokines only.

## Combination studies of Imfinzi (Astrazeneca) with other immuno-oncology agents*

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| Bevacizumab | VEGFr MAb | 2 studies in glioblastoma breast cancer |
| Daratumumab +/- pomalidomide | Anti-CD38 MAb +/- TNFa inhibitor | Multiple myeloma |
| Daratumumab | Anti-CD38 MAb | Multiple myeloma |
| Cetuximab | Anti-EGFR MAb | Head and neck cancer |
| Efizonerimod | Ox40 agonist | Solid tumours |
| Mogamulizumab | CCR 4 MAb | Solid tumours |
| Epacadostat | IDO 1 inhibitor | Solid tumours |
| Oleclumab | Anti-CD73 MAb | Solid tumours |
| Monalizumab | CD94/NKG2A MAb | Solid tumours |
| MEDI0562 | Anti-Ox40 MAb | Solid tumours |
| IMC-CS4 | CSF-1R MAb | Solid tumours |
| Trastuzumab | HER2/ErbB-2 MAb | Breast cancer |
| MEDI5083 | Not disclosed | Solid tumours |

Note: *antibodies or cytokines only; excludes combinations with tremelimumab.

This cannot be said to have occurred to the same extent in the case of Bavencio, though the Pfizer/Merck KGaA drug has made significant progress in its own right over the past 18 months: it has reached the market in two indications, Merkel cell carcinoma and advanced metastatic bladder cancer. Still, beyond combining Bavencio with a handful of Pfizer's immuno-oncology assets the combo approach has probably yet to get fully under way clinically for Bavencio.

Meanwhile, among the earlier-stage assets Novartis and Astra are notable for combining an anti-PD-1 with an anti-PD-L1 agent, with PDR001 plus FAZ053, and MEDI0680 plus Imfinzi, respectively. It should be noted that it is still uncertain whether it is more efficacious to inhibit PD-1 or PD-L1, and a combo could give two shots on goal, though this is by no means a popular strategy. The only other player known to have both types of assets in house is Bristol, but its anti-PD-L1 MAb, BMS-936559, does not feature prominently in its plans.

For ease of comparison, studies adding a third (or more) immuno-oncology agent on top of PD-1/CTLA4 combos are split out in this analysis separately from the earlier groupings of straightforward Opdivo plus Yervoy and Imfinzi plus tremelimumab combinations.

## Studies of remaining anti-PD-1/PD-L1 agents combined with other immuno-oncology*

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| **Bavencio (Pfizer/Merck KGaA)** | | |
| Cetuximab | EGFR MAb | 2 studies in head and neck cancer |
| Utomilumab and/or PF-04518600 or PD 0360324 | Anti-CD137 MAb and/or OX40 agonist or M-CSF inhibitor | Select malignancies |
| Utomilumab + rituximab or utomilumab + azacitidine or rituximab + bendamustine | Anti-CD137 Mab + Anti-CD20 Mab or Anti-CD137 Mab + DNMT inhibitor or Anti-CD20 Mab + chemotherapy | DLBCL |
| M9241 | IL-12 antagonist | Solid tumours |
| **CX-072 (Cytomx Therapeutics)** | | |
| Ipilimumab or vemurafenib | Anti-CTLA 4 MAb or B-Raf kinase inhibitor | Solid tumours or lymphoma |
| **FAZ053 (Novartis)** | | |
| PDR001 | PD-1 | Solid tumours |
| **Durvalumab + tremelimumab (Astrazeneca)** | | |
| Ramucirumab | VEGFr-2 MAb | Gastrointestinal or thoracic malignancies |
| **LY3300054 (Lilly)** | | |
| LY3321367 | TIM-3 antibody | Solid tumours |
| **MEDI0680 (Astrazeneca)** | | |
| Durvalumab | anti-PD-L1 MAb | Select malignancies |
| **Nivolumab + ipilimumab (Bristol-Myers Squibb)** | | |
| Ipilimumab or BMS-986016 | Anti-CTLA 4 MAb or anti-Lag3 MAb | 5 studies in renal, gastric and colorectal cancers & NSCLC |
| Lirilumab | Anti-Kir MAb | 2 studies in solid and hematologic malignancies |
| Ipilimumab or bevacizumab | CTLA4 Mab or VEGFr MAb | Renal cancer |
| Plozalizumab or vedolizumab or TAK-580 | CCR 2 MAb or anti-alpha 4 beta 7 integrin MAb or pan-Raf kinase inhibitor | Melanoma |
| Rovalpituzumab tesirine | Anti DL3 ligand MAb-cytotoxic drug conjugate +/- | SCLC |
| Brentuximab vedotin | CD30 Mab MMAE conjugate | Hodgkin lymphoma |
| Blinatumomab | Anti-CD19 bispecific MAb | Lymphoblastic leukaemia |
| **PDR001 (Novartis)** | | |
| MBG453 | Tim3 MAb | Select malignancies |
| GWN323 | GITR MAb | Solid tumours and lymphoma |
| Decitabine +/- MBG453 | Chemo +/- anti-Tim 3 Mab | AML and high-risk MDS |
| Canakinumab, CJM112, trametinib or EGF816 | Anti-IL-1 beta Mab, anti-IL-17 Mab, Mek inhibitor or EGFR inhibitor | Colorectal, breast and lung cancers |
| NIS793 | Anti-TGF beta MAb | Solid tumours |
| **SAR439684 (Regeneron)** | | |
| REGN1979 | Anti-CD20 & CD3 bispecific MAb | Lymphoma |
| REGN3767 | Anti-Lag3 MAb | Select malignancies |

Note: *antibodies or cytokines only.

# Studies of PD-(L)1 assets combined with small molecules

While the mechanistic rationale of combining immuno-oncology with immuno-oncology in many cases involves the simple desire to hit more than one immune system pathway, other approaches arguably involve more nuance.

Here the theme tends to focus on ways of making a tumour immunogenic, or "hot", so that the PD-(L)1 element of the combo has a chance to act. The key is that expression of PD-L1 by tumour cells tends to be transient, and often a second mechanism is needed to bring it about.

In the absence of additional biomarkers of response being identified – and it is clear that for various reasons PD-L1 itself is an unreliable biomarker – small molecule combinations look set to be pursued as a way of increasing PD-L1 expression. This also has an effect on line of therapy: for instance, a patient who has already undergone prior treatment is likely to have a sufficiently immunogenic tumour for PD-(L)1 therapy, but in the first-line setting a combinatorial or biomarker-driven approach will probably be needed.

As far as combinations with small molecules go Abbvie/Johnson & Johnson's Imbruvica is the most extensively combined asset with Keytruda, Opdivo and Imfinzi alike. Astra's own rival BTK inhibitor, acalabrutinib, is also being studied extensively in combinations.

**Studies of Keytruda (Merck & Co) combined with small molecules**

Source: Evaluate Ltd.[a] May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| Lenalidomide | Immunomodulator | 7 studies in haem malignancies & NSCLC |
| Acalabrutinib | BTK inhibitor | 6 studies in solid cancers |
| Lenvatinib | VEGFr TK inhibitor | 5 studies in solid tumours |
| Vorinostat | HDAC inhibitor | 4 studies in solid tumours |
| Entinostat | HDAC inhibitor | 4 studies in NSCLC, melanoma & MDS |
| Dinaciclib | CDK inhibitor | 3 studies in breast & haem malignancies |
| Trametinib +/- dabrafenib | MEK inhibitor +/- B-Raf kinase inhibitor | 3 studies in solid tumours |
| Axitinib | VEGFr 1-3 kinase inhibitor | 3 studies in renal cancer & soft tissue sarcoma |
| Ibrutinib | BTK inhibitor | 3 studies in melanoma and haem cancers |
| Abemaciclib | CDK 4 & 6 inhibitor | 2 studies in breast cancer & NSCLC |
| Eribulin | Microtubule/tubulin inhibitor | 2 studies in breast cancer |
| BL-8040 | CXCR4 antagonist | 2 studies in pancreatic and gastrointestinal cancers |
| Pomalidomide + Dexamethasone | TNFa inhibitor + corticosteroid | 2 studies in multiple myeloma |
| CMP-001 | TLR 9 agonist | 2 studies in melanoma |
| Afatinib | EGFR & Her2 dual kinase inhibitor | NSCLC |
| Amcasertib | Cancer cell stemness kinase inhibitor | Solid tumours |
| ARRY-382 | CSF1 receptor antagonist | Solid tumours |
| Azacitidine and/or romidepsin | DNMT inhibitor and/or HDAC inhibitor | Colorectal cancer |
| B-701 | FGFR 3 kinase inhibitor | Bladder cancer |
| BGB324 | Axl tyrosine kinase inhibitor | Melanoma |

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| Combo agent | Drug class | Indication |
|---|---|---|
| Binimetinib | Mek1 & 2 inhibitor | Breast cancer |
| Birinapant | IAP antagonist | Solid tumours |
| Carfilzomib + GM-CSF | ERK, Jak2, CDK inhibitor + GM-CSF | Rectal cancer |
| Crizotinib | ALK, c-Met & Ros1 kinase inhibitor | NSCLC |
| Defactinib | FAK inhibitor | Solid tumours |
| Encorafenib + binimetinib | Braf + Mek inhibitor | Melanoma |
| Enobosarm | SARM | Breast cancer |
| Enzalutamide | Androgen receptor antagonist | Prostate cancer |
| Exemestane/leuprolide | Aromatase inhibitor/Luteinising hormone-releasing hormone analogue | Breast cancer |
| G100 | TLR 4 agonist | Non-Hodgkin lymphoma |
| GR-MD-02 | Galectin-3 inhibitor | Melanoma |
| Imatinib | TYK inhibitor | Melanoma |
| IMO-2125 | TLR 9 agonist | Melanoma |
| INCB054828 | FGF inhibitor | Select malignancies |
| Itacitinib or INCB050465 | JAK-1/2 inhibitor or PI3K delta inhibitor | Solid tumours |
| letrozole + palbociclib | Aromatase inhibitor + CDK 4 & 6 inhibitor | Breast cancer |
| MK-1454 | STING agonist | Solid tumours or lymphoma |
| Napabucasin | Stat3, nanog & beta-catenin pathway inhibitor | Colorectal cancer |
| Nintedanib | Tyrosine kinase inhibitor | Solid tumours |
| Niraparib | Parp inhibitor | Breast and ovarian cancers |
| Olaparib, enzalutamide or docetaxel + prednisone | Parp inhibitor, androgen receptor antagonist or chemo | Prostate cancer |
| Pazopanib | Multi-kinase inhibitor | Renal cancer |
| PEGPH20 | Hyaluronidase | Solid tumours |
| PLX3397 | CSF-1R & FLT3 inhibitor | Solid tumours |
| Preladenant | Adenosine A2A receptor antagonist | Solid tumours |
| Ruxolitinib | Jak 1 & 2 inhibitor | Breast cancer |
| Sargramostim | GM-CSF | Biliary tract cancer |
| SCH 900353 | ERK inhibitor | Solid tumours |
| SD-101 | TLR9 agonist | Prostate cancer |
| Vemurafenib | B-Raf kinase inhibitor | Melanoma |
| Vismodegib | SMO inhibitor | Basal cell carcinoma |
| X4P-001 | CXCR 4 antagonist | Melanoma |
| XL888 | Hsp 90 inhibitor | Gastrointestinal cancer |
| Ziv-aflibercept | VEGFr kinase inhibitor | Solid tumours |

## Studies of Opdivo (Bristol-Myers Squibb) combined with small molecules

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| Ibrutinib | BTK inhibitor | 4 studies in haem malignancies, renal cancer & NSCLC |
| Dasatinib | BCR-ABL inhibitor | 2 studies in ALL & CML |
| Plinabulin | Vascular disrupting agent | 2 studies in NSCLC |
| Veliparib | Parp inhibitor | 2 studies in solid tumours & lymphoma |
| PT2385 | HIF 2 alpha inhibitor | Renal cancer |
| EGF816 or INC280 | EGFR TK inhibitor or c-Met kinase inhibitor | NSCLC |
| Ceritinib | ALK inhibitor | NSCLC |
| Galunisertib | TGFb R1 kinase inhibitor | Solid tumours, NSCLC or HCC |
| Temsirolimus or irinotecan +/- capecitabine | FKBP & mTOR inhibitor or chemo agents | Select malignancies |
| Amcasertib | Cancer cell stemness kinase inhibitor | Solid tumours |
| IPI-549 | PI3K-gamma inhibitor | Solid tumours |
| Chidamide | HDAC inhibitor | Solid tumours |
| CB-839 | Glutaminase inhibitor | Solid tumours |
| TAK-659 | Syk & FLT 3 dual inhibitor | Solid tumours |
| Sitravatinib | TKIs including RET, CHR4q12, CBL, Trk, and DDR families | Renal cancer |
| Glesatinib or sitravatinib or mocetinostat | c-Met & axl receptor tyrosine kinase inhibitor or c-Met, Eph, RET, VEGFr 1-3 kinase inhibitor or HDAC inhibitor | NSCLC |
| Avadomide | Pleiotropic pathway modifier | HCC |
| RRx-001 | Radiation sensitiser | Solid tumours or lymphoma |
| Omaveloxolone | Nrf2 activator | Melanoma |
| Valproate | GABA agonist | Glioblastoma |
| Erlotinib or crizotinib | EGFR TK inhibitor or ALK, c-Met & Ros1 kinase inhibitor | NSCLC |
| Lenalidomide + dexamethasone | Immunomodulator + chemo | Myeloma |
| CB-1158 | Arginase inhibitor | Solid tumours |
| Trametinib +/- dabrafenib | MEK +/- B-raf kinase inhibitor | Melanoma |
| Azacitidine +/- midostaurin or +/- (decitabine + cytarabine) | DNMT inhibitor +/- FLT 3 inhibitor +/- chemo | AML & MDS |

## Studies of Imfinzi (Astrazeneca) combined with small molecules

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| Ibrutinib | BTK inhibitor | 3 studies in NSCLC or haem cancers |
| Lenalidomide | Immunomodulator | 3 studies in lymphoma or multiple myeloma |
| Mocetinostat | HDAC inhibitor | 2 solid tumour studies |
| Osimertinib mesylate | EGFR tyrosine kinase inhibitor | 2 studies in NSCLC |
| Gefitinib | EGFR TK inhibitor | NSCLC |
| Trametinib +/- dabrafenib | MEK inhibitor +/- B-Raf kinase inhibitor | Melanoma |
| AZD6738 | ATR serine/threonine kinase inhibitor | Solid tumours |
| Olaparib | PARP inhibitor | Solid tumours |
| Olaparib and/or cediranib | PARP inhibitor and/or VEGFr kinase inhibitor | Ovarian, breast, lung, prostate and colorectal cancers |
| MEDI9197 | TLR 7/8 agonist | Solid tumours or CTCL |
| AZD5069 or nab-paclitaxel + gemcitabine | CXCR2 antagonist or chemo combo | Pancreatic cancer |
| AZD4547 or olaparib or AZD1775 or vistusertib | FGFR TK inhibitor or PARP inhibitor or Wee1 kinase inhibitor or mTORC1 & mTORC2 inhibitor | Bladder cancer |
| AZD1775 | Wee1 kinase inhibitor | Solid tumours |
| Pomalidomide | TNFa inhibitor | Multiple myeloma |
| Galunisertib | TGF beta R1 kinase inhibitor | Pancreatic cancer |
| LY2510924 | CXCR 4 antagonist | Solid tumours |
| AZD4635 | Adenosine A2A receptor antagonist | Solid tumours |
| Pexidartinib | CSF-1R & FLT 3 inhibitor | Colorectal cancer |
| Selumetinib | MAP kinase 1/2 inhibitor | NSCLC |
| Trabectedin | Cell cycle inhibitor | Soft-tissue sarcoma and ovarian carcinomas |
| Ensartinib | Alk inhibitor | NSCLC |

Elsewhere tyrosine kinase inhibitors are omnipresent, including the targeting of ERK, Jak, PI3k and others. This again shows the continued popularity of this small-molecule approach not only as monotherapy but also in combination with immuno-oncology.

Indeed, it has even been argued that some advanced kinase inhibitors are capable of boosting immune response in the tumour microenvironment (Vantage point – Life for kinase inhibitors in an immuno-oncology world, January 24, 2017).

## Studies of Tecentriq (Roche) combined with small molecules

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| Cobimetinib | Mek inhibitor | 3 studies in solid tumours |
| Cobimetinib + vemurafenib | Mapk + Braf inhibitor | 2 studies in melanoma |
| Vemurafenib +/- cobimetinib | B-Raf kinase inhibitor +/- MEK inhibitor | Melanoma |
| Alectinib or erlotinib | ALK inhibitor or EGFR TK inhibitor | NSCLC |
| Rociletinib | EMSI | NSCLC |
| CPI-444 | Adenosine A2A receptor antagonist | Select malignancies |
| Entinostat | HDAC inhibitor | Breast cancer |
| Enzalutamide | Androgen receptor antagonist | Prostate cancer |
| Etoposide/carboplatin +/- trilaciclib | Chemo +/- CDK 4 & 6 inhibitor | SCLC |
| Rucaparib | Parp 1, 2 & 3 inhibitor | Solid tumours, ovarian cancer |
| Veliparib | Parp inhibitor | Breast cancer |

## Studies of other anti-PD-1/PD-L1 agents combined with small molecules

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| **Bavencio (Pfizer/Merck KGaA)** | | |
| Axitinib | VEGFr 1-3 kinase inhibitor | 2 studies in renal cancer |
| Crizotinib or lorlatinib | ALK, c-Met & Ros1 kinase inhibitor or ALK & ROS1 kinase inhibitor | NSCLC |
| Sunitinib | Multiple tyrosine kinase inhibitor | Renal cancer |
| Entinostat | HDAC inhibitor | Ovarian cancer |
| Defactinib | FAK inhibitor | Ovarian cancer |
| **BGB-A317 (Beigene)** | | |
| Beigene-290 | Parp 1 & 2 inhibitor | Solid tumours |
| BGB-3111 | BTK inhibitor | Solid tumours |
| **Durvalumab + tremelimumab (Astrazeneca)** | | |
| Olaparib | Parp inhibitor | Ovarian cancer |
| Selumetinib | MAPK 1/2 inhibitor | Solid tumours |
| AZD5069 | CXCR2 antagonist | Head and neck cancer |
| Savolitinib (or) | c-Met kinase inhibitor | Renal cancer |
| AZD1775 (or) | Wee1 kinase inhibitor | SCLC |
| **INCSHR1210 (Jiangsu Hengrui Medicine)** | | |
| Apatinib | Anti-VEGFr kinase inhibitor | 3 studies in NSCLC, gastric and liver cancers |
| **JS001 (Shanghai Junshi Biosciences)** | | |
| Axitinib | VEGFr 1 & 3 kinase inhibitor | Kidney cancer and melanoma |
| **LY3300054 (Lilly)** | | |
| Ramucirumab or abemaciclib or merestinib | VEGFr 2 MAb or CDK 4 & 6 inhibitor or c-Met kinase inhibitor | Solid tumours |
| **Nivolumab + ipilimumab (Bristol-Myers Squibb)** | | |
| Citarinostat | HDAC 6 inhibitor | 2 studies in melanoma & NSCLC |
| Entinostat | HDAC inhibitor | Solid tumours |
| Emurafenib + cobimetinib | BRAF inhibitor + Mek inhibitor | Melanoma |
| Binimetinib + encorafenib | Mek1/2 inhibitor + BRAF inhibitor | Melanoma |
| Cabozantinib | Multiple tyrosine kinase inhibitor | Urothelial cancer and other genitourinary |
| Sunitinib or pazopanib | Multi-kinase inhibitor | Renal cancer |
| Cobimetinib | MEK inhibitor | Solid tumours |
| **PDR001 (Novartis)** | | |
| WNT974 | Porcupine inhibitor | Solid tumours |
| FGF401 | FGFR4 inhibitor | HCC |
| PBF 509 | Adenosine A2A receptor antagonist | NSCLC |
| LXH254 | Pan-RAF inhibitor | Solid tumours |
| Regorafenib | Multi-kinase inhibitor | Colorectal cancer |
| Sorafenib | Multi-kinase inhibitor | HCC |
| LCL101 +/- everolimus or panobinostat | SMAC mimetic +/- mTor or HDAC inhibitor | Colorectal/lung/breast cancers |
| Dabrafenib + trametinib | BRAF inhibitor + MEK inhibitor | Melanoma |
| Capmatinib | c-Met kinase inhibitor | HCC |
| BLZ945 | CSF 1 receptor antagonist | Solid tumours |

Also popular are combinations with HDAC inhibitors, which are postulated to have an epigenetic mode of action, as well as PD-(L)1 agents given on top of established Braf/Mek inhibitors such as Novartis's Tafinlar and Mekinist, or Roche/Exelixis's Zelboraf and Cotellic.

# Studies of PD-(L)1 assets combined with traditional chemo or radiotherapy

One of the most important immuno-oncology themes to emerge over the past year or so concerns the potential importance of combinations of anti-PD-(L)1 drugs with simple chemo or radiotherapy.

This was initially pioneered by Roche, which made chemo the backbone of numerous studies of Tecentriq in NSCLC that it initiated, and was thought by some to have been the result of the Swiss group having little else in-house to use to move Tecentriq into the front-line setting (Roche powers up for first-line lung duel, February 2, 2017).

However, there was also a clear scientific rationale, in that chemotherapy can potentiate immune function, as well as releasing cancer cells as the tumour is attacked. This is speculated by some to result in something akin to a vaccine effect, yielding antigens for the immune system to act against.

The approach is not without controversy, since chemo is typically thought of as being immunosuppressive, whereas checkpoint blockers clearly need the tumour to be immunogenic to work. This problem of immunosuppression could be overcome by using only a low dose of chemo or radiotherapy.

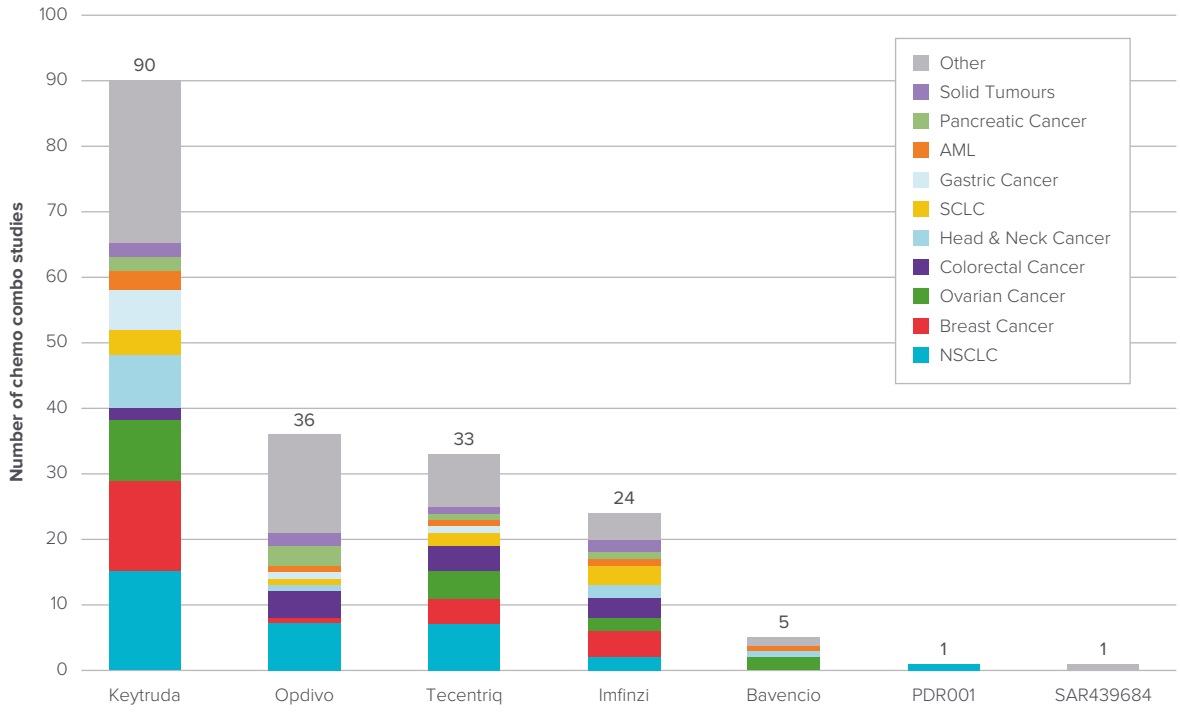
Another obvious advantage of using chemo as the backbone of a PD-(L)1 combo is the relatively low additional price, in contrast to the ramp-up in drug cost that an approach combining various MAbs will likely entail.

While the chemo effort was initially led by Roche, it is Merck with Keytruda that has powered into the lead in terms of trials initiated, with 90 chemo-combo studies under way in a variety of tumour types. And recently Merck got regulatory backing for a Keytruda plus chemo approach in first-line treatment of NSCLC, even though its data showed progression-free but not overall survival (Merck cements its lung cancer lead, May 11, 2017).

NSCLC leads the way in Keytruda plus chemo studies, as well as in those involving Tecentriq and Opdivo, but breast, ovarian and colorectal cancers – and even some haematological malignancies – also have a significant presence.

## Breakdown of anti-PD-1/PD-L1 MAb chemo combos by indication

Source: Evaluate Ltd.[a] May 2017




This listing includes Roche's Tecentriq studies that also comprise Avastin, since these are fundamentally based on the chemo approach, and thus fit better in the chemo-combo category than under IO/IO.

# Studies of PD-(L)1 assets combined with other approaches

Away from the limelight of the major combination groupings in this report, one of the most striking observations is the sharp increase over the past 18 months of PD-(L)1 combinations involving cancer vaccines and oncolytic viruses.

Neither approach has made waves on its own: cancer vaccine monotherapy is thought to result in little beyond the stimulation of low-affinity T cells that escaped negative selection in the body's development, and thus are probably ill-equipped to target tumour-associated antigens that the body does not necessarily regard as non-self – as numerous industry failures have shown.

Oncolytic viruses, meanwhile, have registered one commercial success, with the approval of Amgen's Imlygic, though this has hardly set the market alight. Combinations could provide both with a bigger role, as long as the additive effect is greater than that of either monotherapy – or indeed the anti-PD-(L)1 agent – alone.

**Studies of anti-PD-1/PD-L1 agents combined with cancer vaccines**

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| **Bavencio (Pfizer/Merck KGaA)** | | |
| Ad-CEA vaccine + bevacizumab | Anti-CEA vaccine + anti-VEGFr Mab | Colorectal cancer |
| **Imfinzi (Astrazeneca)** | | |
| Axalimogene filolisbac | HPV vaccine | Cervical cancer, head and neck cancer |
| Vigil | Cancer vaccine | Breast cancer |
| TPIV 200 | FRa vaccine | Ovarian cancer |
| PVX-410 + Hiltonol | Cancer vaccine + TLR 3 agonist | Breast cancer |
| DC/AML Fusion Cell Vaccine | Dendritic cell vaccine | AML |
| PVX-410 +/- lenalidomide | Vaccine +/- immunomodulator | Multiple myeloma |
| **Keytruda (Merck & Co)** | | |
| LTX-315 | Cancer vaccine | Solid tumours |
| LV305 | Cancer vaccine | Melanoma, NSCLC, ovarian cancer and sarcoma |
| Intravesical BCG therapy | Mycobacterium bovis | Bladder cancer |
| ADXS-PSA | PSA vaccine | Prostate cancer |
| p53MVA | Cancer vaccine | Solid tumours |
| pTVG-HP plasmid DNA vaccine | pTVG-HP plasmid DNA vaccine | Prostate cancer |
| 6MHP | 6 melanoma helper vaccine | Melanoma |
| Vigil | Cancer vaccine | Melanoma |
| GVAX pancreatic | GM-CSF secreting cell vaccine | Pancreatic cancer |
| GVAX | Cancer vaccine | Colorectal cancer |
| DNX-2401 | Cancer vaccine | Glioblastoma or gliosarcoma |
| DPX-Survivac vaccine | Cancer vaccine | Ovarian, fallopian tube or primary peritoneal cancer |
| Dendritic cell therapy + cryosurgery + Prevnar 13 | Cell therapy + cryosurgery + pneumococcal vaccine | Non-Hodgkin lymphoma |
| mDC3/8 | Dendritic cell vaccine | Melanoma |

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| Combo agent | Drug class | Indication |
|---|---|---|
| **Opdivo (Bristol-Myers Squibb)** | | |
| NY-ESO-1 + gp100:280-288 | Cancer vaccine | Melanoma |
| NY-ESO-1 + gp100:280-288 or ipilimumab | Cancer vaccine | Melanoma |
| CRS-207 + GVAX Pancreas | Anti-mesothelin vaccine + GM-CSF secreting cell vaccine | Pancreatic adenocarcinoma |
| ISA101 | HPV vaccine | Solid tumours |
| Viagenpumatucel-L | Cancer vaccine | NSCLC |
| Dendritic Cell Vaccine | Cancer vaccine | Brain cancer |
| Vigil | Cancer vaccine | NSCLC |
| WT1 Vaccine | WT 1 vaccine | Ovarian Cancer |
| TG4010 | MUC 1 & IL-12 vaccine | NSCLC |
| CV-301 | Cancer vaccine | NSCLC |
| PD-L1/IDO peptide vaccine | Cancer vaccine | Melanoma |
| DCVax-L | Cancer vaccine | Glioblastoma |
| NEO-PV-01 | Vaccine | Melanoma, lung or bladder cancer |
| CimaVax-EGF Vaccine | EGFr vaccine | NSCLC |
| Attenuated measles virus | Sodium Iodid Simporter Measles Virus | NSCLC |
| Prostvac +/-ipilimumab | PMSA vaccine +/- CTLA4 | Prostate cancer |
| **Tecentriq (Roche)** | | |
| CMB305 | Cancer vaccine | Sarcoma expressing NY-ESO-1 |
| Vigil | Cancer vaccine | Gynaecological cancers |
| Sipuleucel-T | Anti-prostatic acid phosphatase vaccine | Prostate cancer |

## Studies of anti-PD-1/PD-L1 agents combined with oncolytic viruses

Source: Evaluate Ltd.® May 2017

| Combo agent | Indication | Project Partner |
|---|---|---|
| **Imfinzi (Astrazeneca)** | | |
| ONCOS-102 | Ovarian cancer or colorectal cancer | Targovax |
| **Keytruda (Merck & Co)** | | |
| ONCOS-102 + cyclophosphamide | Melanoma | Targovax |
| Coxsackievirus A21 | Melanoma | Viralytics |
| Coxsackievirus A21 | NSCLC | Viralytics |
| Coxsackievirus A22 | Solid tumours | Viralytics |
| Pelareorep | Pancreatic cancer | Oncolytics Biotech |
| Ad-MAGEA3/MG1-MAGEA3 | NSCLC | Turnstone Biologics |
| Talimogene laherparepvec | Head and neck cancer | Amgen |
| Talimogene laherparepvec | Melanoma | Amgen |
| Talimogene laherparepvec | Melanoma | NCI |
| Talimogene laherparepvec | Sarcoma | Amgen |
| HSV-tk-expressing adenovirus | NSCLC | Merck & Co |
| **Opdivo (Bristol-Myers Squibb)** | | |
| Talimogene laherparepvec | Non-melanoma skin cancers | NCI |
| Pexa-Vec | HCC | Transgene |
| Enadenotucirev | Colorectal cancer, bladder carcinoma, head and neck | Psioxus Therapeutics |

Both vaccines and oncolytic viruses could result in upregulation of immune system checkpoints, exposing targets for anti-PD-(L)1 MAbs. Where activity of either approach has been stymied by upregulation of an immune checkpoint, combination with PD-(L)1 blockade could release a brake on the immune system.

Oncolytic viruses in particular are thought to 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, providing a "priming" effect for immunotherapy.

### Studies of anti-PD-1/PD-L1 agents combined with cell or gene therapies

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| **Bavencio (Pfizer/Merck KGaA)** | | |
| MCPyV TAg-specific autologous CD8+ T cells | T-cell therapy | Merkel cell carcinoma |
| **Imfinzi (Astrazeneca)** | | |
| IMCgp100 +/- tremelimumab | eTCR cell therapy | Melanoma |
| JCAR014 | CAR-T cell therapy | Non-Hodgkin lymphoma |
| **Keytruda (Merck & Co)** | | |
| TIL therapy | TIL therapy | Digestive tract, urothelial, breast, or ovarian/ endometrial cancers |
| TIL therapy | TIL therapy | Melanoma |
| TIL therapy | TIL therapy | Melanoma |
| TIL therapy | TIL therapy | Gastrointestinal cancer |
| iC9-GD2 T Cells | CAR-T cell therapy | Neuroblastoma |
| E7 TCR T cells | eTCR cell therapy | HPV-associated cancers |
| pIL-12 | IL-12 gene therapy | Melanoma |
| ISF35 | CD40 gene therapy | Melanoma |
| **Opdivo (Bristol-Myers Squibb)** | | |
| NY-ESO-1 TCR PBMC + DC vaccine | eTCR cell therapy + NY-ESO-1-pulsed vaccine | Solid tumours |
| TILs + urelumab | TIL therapy + anti-CD137 MAb | Melanoma |
| HPV Specific T Cells | T-cell therapy | HPV-associated cancers |
| HPV Specific T Cells | T-cell therapy | Non-Hodgkin lymphoma |
| NK immunotherapies | NK cell therapy | Solid tumours |
| **Tecentriq (Roche)** | | |
| Axicabtagene ciloleucel | CAR-T cell therapy | Diffuse large B-cell lymphoma |

There has also been an uptick in combo trials involving cell therapies, with Keytruda, Opdivo, Imfinzi, Bavencio and Tecentriq being studied with CAR-T, engineered T-cell receptor therapeutics and tumour-infiltrating lymphocytes.

This approach is based mainly on the idea that removing the immune system brake can boost the activity of a cell therapy – an effect that can be achieved either by editing out PD-L1 on the T cells (an approach still in its infancy) or by combining with an anti-PD-(L)1 MAb, a simpler strategy.

There has been one notable case report of striking tumour regression and CAR-T cell expansion after PD-1 blockade in a lymphoma patient who had initially not responded to CAR-T alone, and this will undoubtedly have fuelled enthusiasm.

Finally, PD-(L)1 therapy could be synergistic with other approaches, though for now these are limited to two studies each with antisense, an antiviral and Imprime PGG, Biothera's Beta-D glucan.

### Studies of anti-PD-1/PD-L1 agents combined with other approaches

Source: Evaluate Ltd.® May 2017

| Combo agent | Drug class | Indication |
|---|---|---|
| **Imfinzi (Astrazeneca)** | | |
| AZD9150 | STAT3 antisense | Pancreatic, NSCLC and colorectal cancers |
| AZD9150 (or tremelimumab) | STAT3 antisense | Solid tumours |
| Poly ICLC (+/- tremelimumab) | Antiviral | Select malignancies |
| **Keytruda (Merck & Co)** | | |
| Poly-ICLC | Antiviral | Colon cancer |
| Imprime PGG | Beta-D glucan | NSCLC |
| Imprime PGG | Beta-D glucan | Breast cancer |

# The future?

Given the speed with which immuno-oncology combination studies have proliferated, and the transformational, blockbuster potential of the anti-PD-(L)1 class, there is little to suggest a slowdown in this field.

However, the focus will increasingly turn from throwing everything into a combination and seeing what sticks to generating real data. The Asco meeting this year will serve as a platform for the IDO plus PD-(L)1 approach, for instance, and this has already featured extensively at scientific meetings such as Esmo last year.

Other novel immune checkpoint blockers, however, have moved through development more slowly than had been thought possible a couple of years ago: targets like Ox40, Tim3, Lag3, Icos and GITR still have much to prove, despite some highly promising preclinical studies.

It will also be interesting to watch the progress of the PD-(L)1 plus CTLA4 combination. Given how much toxicity Yervoy adds into the mix, its continued relevance can be questioned. Meanwhile, 2017/18 will be a key time for Astrazeneca, which could show for the first time whether Imfinzi plus tremelimumab has potential in first-line NSCLC: readout of its Mystic study, due mid-year, is one of the most important events for investors focusing on this field. The fact that so far tremelimumab has not yielded astonishingly good monotherapy data could be dampening enthusiasm.

Faced with the twin assaults of Yervoy toxicity and an inability of other CTLA4 inhibitors to match Yervoy's efficacy, the coming years could see an increasing effort to eliminate CTLA4 inhibition from combinations and replace it with something that is at least as efficacious but safer.

On the other hand, combinations with chemotherapy could grow in popularity, based on Merck & Co's success in securing a front-line NSCLC label on the back of its Keynote-021 trial, and on the obvious pricing advantages. It is surprising that Bavencio and the more recent entrants into the PD-(L)1 field are not already being studied more extensively with chemo and/or radiotherapies.

That said, investors and biotech companies are likely to remain most interested in the discovery and development of novel immuno-oncology agents. And it will be vital to generate more evidence to back the idea of synergy; until then the addition of PD-(L)1 to everything will seem like the optimistic sprinkling of fairy dust in the hope of making a mediocre pharmacological approach stronger. Ultimately, it will all come down to hard data.

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