The Next-Wave of Immuno-Oncology
Thoughts On Combination Therapy and The Implications For Major Pharma

<table>
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<tr>
<th>US Major &amp; Specialty Pharma</th>
<th>European Pharma</th>
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<td>Richard Vosser AC</td>
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<tr>
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<th>James P Quigley</th>
<th>Diana H W Na</th>
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Our estimates reflect very little in terms of I/O combinations and any shift towards combos could represent further upside to our estimates

**BMY**: Overall, we view BMY as having one of the broadest next-gen I/O portfolio, encompassing molecules engaging different regions of the immune system. In addition to watching frontline NSCLC PD-1 data (-026 study), we expect to see clinical data from the second-generation I/O agents such as CD137, KIR and LAG-3 in 1H:16.

**MRK**: Following the updated combo data at SITC we continue to see Keytruda/Epacadostat (IDO) as one of the many promising combos in the space and in 2016 will be watching updated data in NSCLC and RCC. Beyond IDO, Merck currently has the only GITR in the clinic and we expect to see early data in 2016. While Merck may have a smaller in-house I/O portfolio, they have initiated multiple PD-1 combination trials (in collaboration) with attractive candidates such as CSF-1R (Plexxion and AMGN) and OX40 (GSK).

**Up Next**: We are expecting key PD-1/PD-L1 updates and I/O combo data in 2016. These include updates in frontline NSCLC, glioblastoma and SCHNN. For I/O combos we expect updated data from PD-1/IDO and first clinical data from novel I/O agents such as OX40, LAG3 and 41BB.
Next Generation I/O Agents: Our EU Pharma Key Takeaways

- **Roche**: Roche have multiple I/O combos in Phase I including full owned combos of atezolizumab (PD-L1) with CD-40, CSF-1R, IDO, IL-2 and OX40. We expect data for all of these combinations to be presented during 2016, which puts Roche towards the front of the pack on the development of I/O combos. Outside of the I/O combos, updated data from the atezolizumab combination with chemo in NSCLC will be presented in 2016 giving more details on the duration of response, however we believe the Phase III data in 2017, along with a comparison of this data to BMY/AZN combos with CTLA-4 is likely to be required to accurately assess the potential.

- **AZN**: Astra has a very well stocked clinical stage portfolio of I/O combo ingredients (CTLA-4, OX40, NKG2A, STAT3, CXCR2, GITR, CD73 and TLR7/8), rivaling BMY and Roche, however the development stage of Astra’s combo portfolio lags peers, with only CTLA-4 actually being in the clinic as a combo, the other agents still only being developed as monotherapies at this time. We see the key 2016 combo read-out being first OX40 monotherapy data, expected in H2 2016, with PD-L1/CTLA-4 PIII data in 2017 the first pivotal read-out.

- **Merck KGaA/PFE**: Have four other I/O products in the clinic but none in combination with avelumab in clinical development yet.
PD-1/PD-L1 Monotherapy Has Shown Compelling Activity Across Multiple Tumor Types

- Treatment with PD-1/PD-L1 results in rapid and durable objective response rates.
- Significant single agent PD-1/PD-L1 activity was observed across various tumor types (>20) and can be effective against large tumor burdens.
- According to our estimates success in just seven different tumor types should lead to the formation of ~$30bn market.

*Source: Company Reports and J.P. Morgan.*
Rationale for Combination I/O Therapies

- PD-1/ PD-L1 have the potential to transform cancer care and have shown to very effective in a subset patients across a wide range of tumor types
- Early data suggests that combination therapies may enhance the efficacy of anti-PD-1/PD-L1s and potentially transform “resistant” tumors into those which are sensitive to treatment
  - PD-1/ CTLA4 combos so far have shown deeper responses compared to PD-1/PD-L1 monotherapy alone
  - There are a wide range of additional combination opportunities being developed across the space
- KOL feedback: Deeper responses should lead to superior long-term OS rates, assuming similar durability as observed with PD-L1 monotherapy

### PD-1 Response Rates by Tumor Type

- Melanoma: 50%
- Bladder: 40%
- HNSCC: 30%
- Kidney: 20%
- Gastric: 10%
- Lung: 10%
- Breast: 10%
- Ovarian: 10%

### PD-1/ CTLA4 Combos Extend Immune Responses to a Larger Patient Population

- Lung: 60%
- Melanoma: 80%
I/O Combo Data in Melanoma and Lung Show Improvement Relative to Monotherapy

**Yervoy/Opdivo shows ~15% ORR benefit compared to PD-1 monotherapy.**

- **Melanoma:** Yervoy/Opdivo ORR in -067 was in the range of 52-63% (BRAF mutation vs wild type)
  - Superior to ~38-49% seen with Opdivo monotherapy
- **NSCLC:** Yervoy/Opdivo ORR in -012 was 48% in PD-L1+(novel dosing) compared to 30% seen with PD-1 monotherapy
- **AE profile for the combo is higher but the magnitude of benefit in a disease with poor prognosis justifies the risk/benefit profile, in our view**
- **Suggests BMY’s Yervoy will remain a core part of I/O therapies in melanoma and potentially frontline NSCLC although this will be determined by the relative benefit compared to the combination with chemo from Phase III data in 2017**

**Novel Yervoy/Opdivo dosing shows ~15-20% ORR benefit compared to PD-1 monotherapy.**

### Table: Yervoy/Opdivo vs Opdivo in Checkmate-012

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<thead>
<tr>
<th></th>
<th>Opdivo</th>
<th>Yervoy/Opdivo</th>
</tr>
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<tbody>
<tr>
<td>PD-L1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1%</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>23</td>
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</tr>
<tr>
<td>ORR</td>
<td>30%</td>
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<tr>
<td>1-year OS rate</td>
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<td>0%</td>
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<tr>
<td>Grade 3/4 AE</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td>AE treatment discontinuations</td>
<td>10%</td>
<td>10%</td>
</tr>
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</table>

Source: Company Reports and J.P. Morgan.
Combo with chemotherapy has also shown an improvement relative to monotherapy

Chemotherapy has potential to create a favorable immune environment onto which PD-L1 can build

- Chemotherapy may transiently increase inflammation around the tumour
- Chemotherapy combination with PD-L1 could extend the duration of inflammation leading to durable responses.
- Roche PD-L1 combination with chemotherapy Phase Ib data with Feb 2015 cut off shows a 63% ORR across all comers with the response similar in PD-L1 +ve and –ve tumors
- In-house data with Sept 2015 cut-off highlighted by Roche showing durability of these responses
- Potential for updated data to be presented in 2016 (AACR or ASCO) but Phase III data in 1L NSCLC not expected until 2017 and the relative benefit compared to PD-L1/CTLA-4 combos from BMY and AZN will be key.

Early data is encouraging, but duration of response awaits public confirmation

Roche Atezoliumab combo with carboplatin/nab-paclitaxel (n=16)

Source: Company Reports and J.P. Morgan.
I/O Combinations Have the Potential to Modulate Various Steps Leading to the Elimination of Cancer Cells

Source: Chen and Mellman, Immunity, 2013
The Combination I/O Likely Further Resets Landscape

- Given the impressive efficacy seen with PD-1/PD-L1s, focus is shifting to next-gen I/O molecules given their potential to extend survival benefit to a broader patient population.

- The next-gen molecules target other components of the immune system such as T cell activators, vaccines and modulators of the tumor microenvironment.

- It is still early days for I/O combos and with the list of I/O candidates rapidly expanding, it remains to be seen which combinations are likely to show the most clinical benefit.

- The preliminary data from IO combinations looks very encouraging but it is still too early to determine whether the IO market will shift to combinatorial treatment or will IO combos be positioned for second line treatment.

  - We think combos will eventually reset the competitive landscape in select tumors or niche segments of the market.
  
  - Market shouldn’t under estimate high bar that could be set by PD-1 + CTLA-4 or chemo when considering next-generation products.

- BMY and Roche have the deepest clinical portfolios (tables in the appendix).

  - ASCO 2016 could showcase the incremental IO/IO combinations for Roche and BMY.

- Our estimates reflect very little in terms of IO combinations and any shift towards combos could represent further upside to our estimates ($30bn+). Players with the best combos may gain market share and drive superior profitability.
Next-Generation I/O Assets
Immune Checkpoints and Agonists as Targets for T cell Regulation

Source: Mellman et al., Nature 2011
BMY/ Roche Appear to Have the Most Advanced In-House Clinical I/O combo Portfolio

- We expect I/O companies to study next-generation molecules both as mono and combo therapies with PD-1/PD-L1 forming the back bone for majority of the I/O combination therapies
Potential Strategies for Effective Immune-Oncology Combinations

- **Dual Checkpoint Inhibitors**
  - PD-1/PD-L1, LAG-3, TIM-3, CTLA4

- **Checkpoint Inhibitors + Costimulatory Receptor Agonists**
  - CD137/41BB, OX40, GITR, CD40, CD27

- **Checkpoint Inhibitors + Immunomodulators (Innate Immune Cells)**
  - IDO, CSF-1R, KIR

- **Checkpoint inhibitors + Other Immune System Activators**
  - Chemo, IL-2, vaccines

Source: Company Reports and J.P. Morgan.
Preliminary Immunotherapy Combination Data Continues to Appear Encouraging

<table>
<thead>
<tr>
<th>Checkpoint Inhibitors</th>
<th>Indication</th>
<th>Other Immune Modulators</th>
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- PD-1/PD-L1 in combination with different molecules shows responses in a larger patient population compared to monotherapy
- However, in order to assess the risk/benefit profile of combinations and identify optimal combination we are watching the comparative safety/efficacy data from ongoing combo trials
- In the near-term, we believe the focus is likely to be on additional updates from MRK/INCY PD-1/IDO combo and the first clinical data from 41BB, OX40 and GITR compounds
- In Europe the focus will be on the first clinical data for Roche from combos with OX-40, CSF-1R, CD40, IDO and IL-2 potentially at ASCO 2016
2015-16: Key I/O Monotherapy and Combo Data to Watch for US Pharma

**Bristol**
- Opdivo monotherapy Phase III results in frontline NSCLC in PD-L1+ patients (Checkmate-026)
- Potential updates from Yervoy/Opdivo combination in lung
- Data in other tumor types that includes glioblastoma, ovarian, NHL and head & neck
- Updates around additional I/O agents (IDO, KIR, CD27, LAG-3 and 41BB)

**Merck**
- Phase I Keytruda combination data with chemotherapy in NSCLC
- Updated I/O combo data on PD-1/IDO in melanoma, NSCLC and RCC
- Updated results from TNBC, H&N, prostate, bladder and gastric cancer among many other potential tumor types

Source: Company Reports and J.P. Morgan.
2015-16: Key I/O Monotherapy and Combo Data to Watch for EU Pharma

**Roche**
- Phase Ib atezolizumab + abraxane combo data in TNBC presented at San Antonio Breast Cancer Symposium (Dec 8-12)
- Updated Phase II (Imvigor 210) data for atezolizumab in bladder cancer at ASCO GU in Jan 2016
- Updated Phase I atezolizumab combo data with chemo in 1L NSCLC at AACR or ASCO 2016
- Phase III (OAK) atezolizumab mono vs docetaxel data in 2L NSCLC in 2016
- Phase II atezolizumab + Avastin combo data in 1L RCC in ASCO 2016- not pivotal
- Potential for Phase I combo data for atezolizumab with CD40, CSF1R, IDO, OX40, CEA-IL2v

**AZN**
- Phase II (ATLANTIC) durvalumab mono data in 3L PD-L1 positive NSCLC in 4Q15 or early 2016
- Phase II (HAWK) durvalumab mono data in 2L PD-L1 positive SCCHN in 2H16

**Merck KGaA/ PFE**
- Phase II (JAVELIN Merkel 200) avelumab mono data in Merkel cell carcinoma in 2016
- Phase I (JAVELIN Lung 101) avelumab combo data with crizotinib or PF-06463922 in NSCLC in 2016

Source: Company Reports and J.P. Morgan.
CTLA4- Cytotoxic T-Lymphocyte –Associated Antigen 4

Checkpoint Inhibitor

Source: Morgan estimates.
CTLA4 is specifically expressed on T cells and counteract the activity of T cell co-stimulatory receptor and as a result block their activation.

The inhibitors work by primarily removing this blockade and allowing the T cell co-stimulatory pathway to engage.

Currently, there are two CTLA-4 inhibitors in development:

a) with Yervoy (BMY) approved as mono- and combination therapy (PD-1) in metastatic melanoma

b) and tremelimumab, which has shown efficacy in 2L+ NSCLC in combination with PD-L1
How are we thinking about the inconsistencies between the BMY and AZN combo data in lung?

- Following the success of PD-1/CTLA4 combo is melanoma (discussed in slide 5), the focus for this combo is now squarely on NSCLC
  - In >1% PD-L1 pts: BMY’s ipi/nivo showed a 48% ORR vs. AZN’s treme/durva at 35%
  - In <1% PD-L1 pts: BMY’s ipi/nivo at 0% vs. AZN’s treme/durva at 33% ORR
  - 1-25% PD-L1 pts: treme/durva showed a 9% ORR

- Given the small patient numbers (~20pts in each cohort), we believe the difference in the responses in both PD-L1+/− patients are preliminary and may not be indicative of responses in larger pt populations

- In our view, the huge variability between the <1% and 1-25% AZN data is further suggestive of the need for larger randomized Phase III trial to clarify the differences in the efficacy profile of ipi vs treme in <1% PD-L1 patients.

- In addition, according to BMY’s PD-L1 assay 70% of all screened patients were found to have >1% PD-L1 expression and differences in assays could also result in the variability between the two studies

- Also, BMY’s combo is being tested in frontline vs. AZN which is in 2/3L patients

- Overall, we believe that given the small patient numbers and variability in line of therapy, dosing and assays it is difficult to compare the two PD-1/PD-L1 + CTLA4 combos
Next Up: Focus on CTLA-4/ PD-1 Combos in Lung

- We view frontline representing $5-10bn opportunity in NSCLC and given the preliminary data in both PD-1/PD-L1 monotherapy and PD-1/CTLA-4, It appears NSCLC will be primarily a combo market, which will be either with the CTLA-4 combos or chemo.

- Currently we see BMY leading in monotherapy and as very competitive in combo with -227 study having started at the same time as AZN’s MYSTIC trial

**Up next for PD-1/CTLA4 combos**

- **BMY:**
  - Updated -012 study results in 2016
  - Topline data from the -227 study in 2017/early 2018

- **AZN**
  - 2016- Ongoing enrollment of MYSTIC
  - 2017- Topline PFS data from MYSTIC

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<td>OS</td>
<td>Oct. 2015</td>
<td>Aug. 2018</td>
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Source: WCLC 2015. SITC 2015, Biomedtracker and JP Morgan
LAG3- Lymphocyte Activation Gene 3

Checkpoint Inhibitor

Source: Morgan estimates.
LAG-3: Lymphocyte Activation Gene 3

- Upregulated by activated and exhausted T cells
- Negative co-stimulatory receptor that suppresses T cell activation
- Expressed by regulatory T cells; promote regulatory T cell mediated immune suppression
- Binds to MHC class II molecules with high affinity on the surface of tumor-infiltrating dendritic cells (DCs) and macrophages
- LAG-3 binding to MHC class II prevents T-cell proliferation and activation

Source: Morgan estimates.
Pre-clinical: Anti-LAG-3 Induces Tumor Regression in Combination with PD-1

- Overall, PD-1/LAG-3 combo lead to a 79% reduction in tumor volume with tumor free rates of 70-80%
- Pre-clinical colon (MC38) and fibrosarcoma (Sa1N) tumors have shown to inhibit tumor effectively in combination with PD-1
- These data suggest that LAG-3 is likely to be largely used in combination with PD-1/PD-L1 inhibitors

Source: Seng-Ryong Woo et al. Cancer Res 2012;72:917-927
LAG-3: Clinical Data Expected in 2016

Currently, there are five different anti-LAG3 antibodies being developed with BMY leading both in terms of developmental timelines and depth of the program.

**BMY:** Mid-2016: We are expecting to see clinical Phase I PD-1/LAG-3 data from BMY in NSCLC and other solid tumors.

Further, we will be watching the safety profile of LAG-3 and whether it can show responses across multiple different tumor types.

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**Ongoing LAG-3 Clinical Trials**

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<tr>
<th>Company</th>
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<th>Indication</th>
<th>Phase</th>
<th>Primary Start Date</th>
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<td>LAG3+ Opdivo</td>
<td>Solid tumors</td>
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<tr>
<td>BMY</td>
<td>LAG3</td>
<td>CLL, NHL, MM</td>
<td>I</td>
<td>Feb. 2014</td>
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</table>

Source: Seng-Ryong Woo et al. Cancer Res 2012;72:917-927
IDO- Indoleamine 2,3- dioxygenase

IDO catabolizes tryptophan that is overexpressed in many different tumor types leading to tumor progression by suppressing the anti-tumor activity of CD8 T cells.

IDO inhibition removes the breaks from the tumor microenvironment and enables the immune system to recognize and eliminate tumor cells.
IDOs Are A Rational Combo Approach: Suppress Inactivation/ Death of T Cells

- IDO is broadly expressed in tumor cells, dendritic cells and macrophages and is usually associated with unfavorable prognosis
- Currently in the clinic IDOs are being tested in combination chemotherapy and immunotherapy (PD-1, CTLA-4 and vaccines) in >5 solid tumors
- Currently, five IDO’s are in development and include INCY/ MRK, NLINK/ Roche (2), BMY and PFE with Incyte having the most advanced IDO program
- Early data from INCY’s IDO looks encouraging, although differences in efficacy between the various IDOs in development remains unclear
- Given the broad expression of IDOs across a range of tumor related immune cells we will be watching for additional clinical data for PD-1/PD-L1 combos with IDO in 2016

Source: Morgan estimates.
Early PD-1+ IDO Data Appears Promising in Melanoma

Early Keytruda/Epadostat data showed an ORR of 53% (n=20) in melanoma which is comparable to 57.6% (n=314) seen with the Opdivo/Yervoy combo (-067 study).

- In addition to melanoma, the PD-1/IDO combo also showed responses across different tumor types.
- Following these encouraging updates we will be watching the durability/safety of the PD-1/IDO combo.
- Given the small patient numbers its too early to compare the benefit to monotherapy in NSCLC, RCC and TNBC.
- Importantly, safety of the combo was not concerning and was largely inline with monotherapy safety profile.
- Next up: We are watching for updated data set from Keytruda/Epadostat and other IDO inhibitors in development.

### Overall Response Rate by Tumor Type

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Melanoma (n=20)</th>
<th>RCC (n=11)</th>
<th>NSCLC (n=10)</th>
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<tbody>
<tr>
<td>Evaluable*</td>
<td>19</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>10 (53)</td>
<td>2 (25)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
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<td>DCR (CR+PR+SD)</td>
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<td>5 (26)</td>
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Source: Gangadhar, T et al., SITC 2015, JP Morgan estimates.
Are All IDO Inhibitors Made Equal?

- Preliminary data suggests that direct IDO inhibitors are superior to indirect enzymatic inhibitors
  - In the case of Newlink’s IDO indoximod (indirect inhibitor) is not as effective as IDOs from Incyte, BMY and next-gen agent from Newlink (GDC-0919) partnered with Roche
- Another potential area of differentiation for IDO is likely to be safety and we will be watching for the safety profile of BMY’s IDO and Newlink’s GDC-0919

- Next catalysts
  - **MRK/ INCY**: Phase III study with Epcadostat in combination with Keytruda is expected to start enrolling in 2016
  - **BMY** IDO is expected to enter the clinic in combination with Opdivo in 2016
  - **Roche/Newlink**: First combo data is expected in 2016
  - **AZN/ INCY**: Phase I/II study of Epcadostat in combination with durvalumab in solid tumors reporting in 1H17
CSF-1R Colony Stimulating Factor 1 Receptor

Eliminating Tumor Promoting Immune Cells in the Tumor Microenvironment
Currently, cancer immunotherapies target T-cell activation, however it is now widely recognized that immunosuppressive cells in the tumor microenvironment can also lead to the inhibition of T cells.

Tumor associated macrophages (TAMs) can be divided into two specific populations:

- M1 - that are tumor suppressive/ cytotoxic
- M2 that support tumorigenesis as they promote angiogenesis and suppress CD8 T cells

Elimination of M2 cells can potentially lead to the activation of CD8 T cells and result in the death of tumor cells.

Source: Morgan estimates.
CSF-1R: Targeting Immune Breaks in the Tumor Microenvironment

- Colony-stimulating factor 1 receptor (CSF1R) is a cell-surface receptor that binds to CSF-1 and IL-34.
  - CSF1R is important for survival of tumor associated macrophages (TAMs), and M2s implicated in immunosuppression of CD8+ T cells
  - As a result have been associated with poor prognosis
  - Anti-CSF1R antibodies should lead to the depletion of TAMs - Resulting an increase in CD8/CD4 T-cell ratio
  - As a result limiting tumor growth and progression
- CSF-1R are highly expressed in many tumor types, especially in genitourinary tumors
  - Early clinical data has shown CSF-1 dependent depletion of TAMs in solid tumors
  - Roche has initiated a Phase I study with PD-L1 in combination with CSF-1R in solid tumors including genitourinary tumors
  - Most likely to be used in combination with PD-1/PD-L1

Source: Morgan estimates.
We See Anti-CSF-1Rs Being Effective as an I/O Combo

### Companies | Compound | Targets | Tumor types | Phase
---|---|---|---|---
Bristol | FPA008 | CSF1R | NSCLC, melanoma, HNSCC, pancreatic, colorectal, malignant glioma | Phase Ia
Roche | emactuzumab | CSF1R | solid tumors | Phase I
Plexxikon | PLX3397 | CSF-1R, KIT, mutant FLT3 | melanoma and other solid tumors | Phase I/II
Lilly | IMC-CS4/LY3022855 | CSF-1R | breast, prostate and other solid tumors | Phase I

- Multiple Phase I/II PD-1/PD-L1 partnered studies are ongoing in different solid tumor indications
- We are closely watching for safety, patient selection

#### KOL Feedback & Key Controversies

Concerns on off target effects given that CSF-1R is widely expressed in all macrophages?
- Shown to target monocytes and does not appear to kill cytotoxic M1 macrophages

What are differences between biologic and small molecules CSF-1R inhibitors?
- **BMY**/ FPRX and **Roche** are developing a biologic anti-CSF-1R while Plexxion has a small molecule
- Small molecule works intracellularly and have been shown to work well in targeting mutations
- But that said antibodies tend to be more specific and can initiate ADCC upon binding leading to the depletion of M2 cells more effectively (more efficacious)
- Overall, we believe that inhibiting CSF-1R could help overcome tumor resistance and convert tumor amenable to PD-1/PD-L1 treatment

Source: Morgan estimates.
Anti-CSF-1R: Next Catalysts

- **BMY/ FPRX:** FPA008 initiated Phase Ia/b solid tumor studies both as monotherapy and in combination with PD-1 in Aug. 2015. Preliminary data from these trials may become available in 2016/2017

- **Roche:** Initiated a Phase I trial in solid tumors in Dec. 2014 and although there are no specific timelines around topline data, we expect preliminary results in 2016/17

- **Plexxikon:** The combination study with anti-CSF1R / Merck’s Keytruda began in June 2015 and we expect early data in 2017
TNF Receptor Superfamily Represent the Most Important Co-Stimulatory Molecules in I/O

- TNFR members are generally expressed on T cells, while the ligands are present on antigen presenting cells
- In general, on activation the TNFR family members lead to T cell activation, the prevention of tolerance and the development of T-cell immunity
- Given their mechanism of action, they are emerging as powerful partners of PD-1/PD-L1
- Currently, there are no front runners among the TNFR family members.
  - KOLs see OX40 and GITR as very attractive targets
- In 2016, we could potentially see early clinical data for 41BB/CD137 from BMY, OX40 from PFE and Roche, and GITR from Merck
41BB/ CD137
Co-stimulatory T-cell Agonist
Activation and Survival of CD8 T (effector) Cells

Source: Morgan estimates.
CD137/41BB:

- CD137 is an inducible co-stimulatory molecule on CD4 and CD8 T cells, Tregs, NK cells, monocytes and DCs.
- In T cells, CD137 leads to prolonged survival of T cells leading to their accumulation in tumor sites, cytokine production and functional maturation.
- Both pre-clinical/clinical models have shown reduction in tumor burdens.

Source: Morgan estimates.
Early Data in Combination with Rituxan Appears Promising in B-cell Tumors

- ORR of 38.5% in R-refractory follicular lymphoma: 2 CR (15.4%) and 3 PR (23.1%)
- Rituxan + CD137 is well tolerated in patients with relapsed or refractory B-cell NHL

Source: Morgan estimates.
41BB/ CD137: Key Differences & Controversies

- Currently **BMY** and **PFE** have 41BB/ CD137 in the clinic and are being investigated in a wide variety of solid and liquid tumors
  - Molecular/ structural studies suggest PFE’s antibody binds the 41BB ligand while BMY’s compounds binds the receptor
  - Given the differences in binding sites it remains to be seen whether the two compounds are likely to have different efficacy/ safety profile
  - Some KOLs believe that given BMY’s 41BB/ CD137 compound is likely to be more toxic (different binding sites) but also more efficacious
  - As a result BMY’s compound is being tested at low doses and we will be watching if it can be safely used at a therapeutic dose

- **Can 41BB/ CD137 extend clinical benefit in non-inflamed tumors?**
  - 41BB leads to the accumulation of T effector cells by preventing cell death rather than triggering proliferation and as a result may not be as effective in non-inflamed tumors
  - That said, they could likely result in enhancement of PD-1/PD-L1 activity in borderline inflamed tumors but majority of the responses are likely to be seen in inflamed tumors

Source: Morgan estimates.
41BB/ CD137: Next Catalysts

- **BMY**: Initiated a Phase Ib study of Urelumab in combination with Rituximab in CLL/NHL (Apr. 2014) and we expect initial data in 2016.

- **PFE**: Have multiple ongoing combination studies with 4-1BB, including 4-1BB + Keytruda, 4-1BB + Rituxan, 4-1BB + mogamulizumab. We expect data from the Phase I 41BB + Keytruda trial in advanced solid tumors to readout early 2016.
OX40

Secondary T-Cell Co-stimulatory Agonist
OX40: Dual I/O Therapeutic Target

- Increase proliferation
- Increase cytokine production
- Promote memory

CD4+ T eff

- Increase proliferation
- Increase cytokine production
- Reverse anergy

CD8+ T eff

- Deactivate suppressive function
- Eliminate Tregs

CD4+ T reg

Source: Morgan estimates.
OX40: Attractive I/O Combo Agent with PD-1/PD-L1

- Given OX40s broad expression pattern and regulation of multiple parts of the immune system
  - OX40 was highlighted as a highly combinable agent with PD-1/PD-L1 inhibitors
    - As it indirectly activates CD8 T cells via the CD4 T cells
  - OX40 was shown to synergize with PD-1 leading to tumor regression in mice
    - As a result of proliferation of CD8 T cells, increased cytokine production
    - Deactivating the suppressive activity of T regulatory cells
- Currently PFE, AZN and Roche have OX40 antibodies in the clinic
  - PFE and Roche: First clinical data are expected in 2016
  - BMY: Expected to enter the clinic in 2016
  - AZN: First data now expected in 2H:16 (murine OX40 discontinued), with MEDI6383+ durvalumab combo data in 2017
- To the extent OX40s show a manageable safety profile
  - We see the PD-1/PD-L1+ OX40 combo be used widely across different tumor types
  - Extend the benefit of I/O based therapies to a broad patient base

Source: Morgan estimates.
GITR- Glucocorticoid-Induced Tumor Necrosis Factor Receptor

Co-stimulatory T-Cell Agonist
GITR: A Specific Immune-Modulator

- GITR is widely seen as a very promising I/O target given the MOA and robust pre-clinical data.
- GITR like OX40 induces tumor cell death primarily by:
  - Enhancing CD8 T (effector) cells directly and via the activation of T helper cells.
  - Suppressing intra-tumoral T regulatory cells specifically, while preserving peripheral Tregs (unlike OX40 that targets both intra-tumoral and peripheral Tregs).

As a result, we expect GITR agonists are unlikely to lead to widespread loss of immune tolerance and immune-related adverse events.

GITR: Functions Synergistically With PD-1

GITR is expressed on many immune cells and is often upregulated upon activation

<table>
<thead>
<tr>
<th>Cell type</th>
<th>GITR expression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Naïve</td>
</tr>
<tr>
<td>Regulatory T cells</td>
<td>High</td>
</tr>
<tr>
<td>T cells (CD4/CD8)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>NK cells</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Intermediate/low</td>
</tr>
<tr>
<td>Basophils</td>
<td>Intermediate/low</td>
</tr>
<tr>
<td>Monocytes/macrophages</td>
<td>Low</td>
</tr>
</tbody>
</table>

- Pre-clinical combination of anti-GITR and Keytruda appears to be effective in inducing cell death
- Differentiation is likely to arise from the epitopes each of the GITR antibodies target
- Given the robust pre-clinical data, dosing may have to optimized to establish a manageable safety profile
- Finally, like other members of the TNFSR family, it is likely to work effectively when partnered with a PD-1/ PD-L1

Source: Schaer et al., Curr Opin Immunol. 2012, Merck Company Reports, JP Morgan
GITR: Next Catalysts

- Currently, **Merck** has the only GITR (MK-4166) in the clinic. Phase I study in combination with Keytruda in multiple tumor types was initiated in 2014 and early data is expected in 2016
- **BMY** and **PFE** also have pre-clinical GITR molecules, expected to enter the clinic in 2016
KIR- Killer-Cell Immunoglobulin-like Receptor

Priming Natural Killer (NK) Cells to Eradicate Tumor Cells
KIRs Interactions Block NK Cell Functionality in Tumor Cell Elimination

NK cells are lymphocytes that can recognize and kill tumor cells (in which the MHC class I molecule has been altered).

Some tumors escape immune surveillance by increasing the expression of the HLA (MHC-I) molecules on their surface.

They can eliminate cancer cells using a variety of mechanisms and can be combined with diverse array of agents to promote cell death.

- KIR/HLA class I ligand is key to immune tolerance.
- The interaction between HLA and KIR prevents NK cells from killing/eradicating tumor cells.
- As a result KIR blockade should prime NK cells to identify and eliminate tumor cells.
Lirilumab (KIR3): Early Promising Data in AML and MM

Phase I Dose Escalation Study in Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Dose</th>
<th>N*</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mg/kg</td>
<td>16</td>
<td>2.3</td>
<td>12.6</td>
</tr>
<tr>
<td>1-3 mg/kg</td>
<td>16</td>
<td>9.5</td>
<td>20.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td>0.515</td>
<td>0.490</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.075</td>
<td>0.076</td>
</tr>
</tbody>
</table>

- Preliminary data from AML patients in complete remission showed OS of the range of 12.6-20 months across different dose levels
- Early data suggests that patients on lirilumab maintenance therapy compare favorably to patients on SOC
- Overall lirilumab (KIR3) appeared tolerable and showed a clear PK/PD relationship with MTD not being reached

Phase I Dose Escalation Study in Multiple Myeloma

<table>
<thead>
<tr>
<th>Overall best response</th>
<th>Total</th>
<th>Dose lirilumab - LEN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.2mg/kg - 10mg</td>
</tr>
<tr>
<td>VGPR</td>
<td>2 (13.3%)</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>3 (20%)</td>
<td>1</td>
</tr>
<tr>
<td>MR/SD</td>
<td>7 (46.7%)</td>
<td>3</td>
</tr>
</tbody>
</table>

- Early data in MM patients treated with lirilumab in combination with lenalidomide (LEN) showed ORR of 33.3%
- Most AE’s were grade 1 and were largely related to infusion of the drug

Source: Vey et al., Blood Sep. 21.
**KIR: Key Questions & Controversies**

- **Innate in collaboration with BMY** has the most advanced and comprehensive program, with six ongoing Phase I and II trials in solid and hematological tumors.


- **Is anti-KIR sufficient to activate NK cells?**
  - According to KOL feedback, anti-KIR may not be sufficient to activate NK cells and may have to be used in combination with activating agents such as IL-13.

- **What are the differences between anti-KIR and NKG2A?**
  - Lirilumab only blocks KIR-HLA-C interactions in half the NK cells (those expressing KIR2D receptors).
  - On the other hand, NK2A (Innate/ AZN) is an inhibitory receptor expressed in both NK and CD8 T cells and as a result the antibody can lead to the activation of both NK and T cells, and may not need additional activating agents.
  - Given the slightly different MOA, we will be watching the safety/ efficacy and combinability of the two compounds.

---

**Company** | **Single agents/ Combination** | **Indication** | **Phase**
--- | --- | --- | ---
BMY/ Innate | Rituxan + lirilumab | R/R CLL | II
| nivolumab +lirilumab+ 5-azacytidine | MDS | II
| nivolumab +lirilumab | Solid Tumors | I
| Elotuzumab + Lirilumab/ Urelumab | Multiple Myeloma | I

**Company** | **Single agents/ Combination** | **Indication** | **Phase**
--- | --- | --- | ---
AZN/ Innate | NKG2A | Head & Neck | I/II
| NKG2A | Ovarian cancer | I/II
| NKG2A+ Imbruvica | R/R CLL | I/II
| NK2A+ durvalumab (PD-L1) | Solid tumors | II

Source: Morgan estimates.
Key Questions and Controversies

Source: Morgan estimates.
Will Combination I/O Therapies Lead to Remissions and Treatment Discontinuations?

- PD-1+ CTLA4 combos have extended the benefit to a larger patient population
  - In general these responses tend to be deeper responses compared to monotherapy (higher CRs),
  - Deeper responses seem to be correlated with long-term outcomes but it remains to be seen if these responses translate into survival benefit/ remissions compared to monotherapy

- Currently the standard duration of treatment with I/O therapies is not well established
  - KOLs believe that 33-50% with clinical benefit could discontinue treatment, while the rest together (including patients achieving SD) would likely have to be chronically treated
  - That said, we expect I/O combos to deepen responses resulting in a higher % of patients eligible for treatment discontinuation/ maintenance on PD-1/PD-L1 monotherapy

- Further, we expect treatment discontinuations to depend on tumor types

Source: Company reports
Will Combination I/O Therapies Dominate Frontline Therapies?

<table>
<thead>
<tr>
<th>Combo Dominate 1L</th>
<th>Monotherapy Dominate 1L</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The magnitude of benefit with combos relative to PD-1/PD-L1 monotherapy is &gt;20%</td>
<td>- Toxicity profile is high and difficult to manage for combos</td>
</tr>
<tr>
<td>- I/O combos result in remissions and treatment discontinuations</td>
<td>- Community doctors comfortable using monotherapy</td>
</tr>
<tr>
<td>- Optimal dosing leads to a safety profile comparable to monotherapy</td>
<td>- As a result combos will be used in patients that fail PD-1/PD-L1 monotherapy</td>
</tr>
</tbody>
</table>

- Overall we think the choice between I/O combo vs. monotherapy will depend on the relative clinical benefit seen with each of the therapies in different tumor types

- Ultimately we believe that the development of predictive biomarkers will help select a patient population likely to benefit the most for a given I/O, which in the LT should lead to I/O combos dominating treatment paradigms

Source: Morgan estimates.
Will Simultaneous Administration of I/O Combos Have Better Outcomes to a Serial Approach?

- Generally simultaneous treatment is likely to be more effective given the high degree of cross-regulation between the MDSCS (non CD8/CD4 T immune cells) and CD8 T cells.

- However, if PD-1 or IO agents are used together with non-I/O therapies such as chemo/radiation, sequential treatment may lead to better outcomes.
  - Priming first with chemo/radiation can cause inflammation (infiltration of TILs), potentially leading to robust outcomes with PD-1/PD-L1 therapy.

- Overall, given the dynamic expression pattern of many of the I/O targets, there is unlikely to be going to a uniform mode of treatment for the various I/O combos in development.

- Ultimately, the choice will depend on whether the agents being used target interconnected immune pathways or independently regulate the immune system.
What Role are Biomarkers Likely to Play for I/O Combos?

*Given the large number of I/O combos being investigated in overlapping tumor types standardized assays assessing immune profile of tumors need to be developed*

*Most cancers have an underlying genetic basis leading functional deficits in specific immune cells and pathways*

*Tumor profile will help identify these dysfunctional immune pathways and as a result help determine appropriate combos for a given tumor type*

*To the extent biomarkers/ immune ratios assessed are non-adaptive and the tests are standardized tumor profiling will play an important role in determining treatment with I/O combos*
Should Patients be Treated Immune Based Therapies Beyond Progression?

Data on Opdivo beyond first RECIST-defined progression in patients with mRCC.

After first RECIST-defined progression, some patients continuing Opdivo treatment experienced subsequent tumor shrinkage and extended survival.

Given that I/O agents produce antitumor effects by inducing cancer specific immune cell responses, the resulting clinical responses may show an initial increase in tumor burden.

As a result until imaging techniques can reliably differentiate between tumor vs immune cells, a subset of patients could potentially benefit by continuing treatment beyond progression.

### Differences in Overall Survival in 2L RCC in Patients Treated to Progression vs. Beyond Progression

<table>
<thead>
<tr>
<th>Patients treated beyond progression (n = 36)</th>
<th>Patients not treated beyond progression (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate, % (95% CI)</strong></td>
<td><strong>Time to objective response, months</strong></td>
</tr>
<tr>
<td>13.9 (4.7–29.5)</td>
<td>Median (min, max)</td>
</tr>
<tr>
<td></td>
<td>4.2 (1.4, 6.9)</td>
</tr>
<tr>
<td></td>
<td>2.6 (1.2, 5.6)</td>
</tr>
</tbody>
</table>

Source: BMY reports, ESMO 2015 and JP Morgan
Immuno-Oncology 101
The interplay between the host immune system and the developing tumor

- **Elimination Phase**: The immune system protects the host against tumor formation by selectively destroying the more immunogenic cancer cells.

- **Equilibrium Phase**: The immune system prevents tumor cell outgrowth while “sculpting” the immunogenicity of the tumor.

Source: Holtzhausen, A et al., Frontiers in Immunology, Company Reports and J.P. Morgan.
The Immune system consists of a large network of cells that include macrophages, dendritic cells (DCs), myeloid derived suppressor cells (MDSCs), natural killer cells (NK) and different types of T cells. These cells identify and eliminate disease causing foreign agents in a coordinated fashion (co-stimulation). In addition to eliminating disease, co-regulation/co-suppression between immune cells also prevents unwarranted eradication of normal cells (autoimmunity). These inhibitory mechanisms to limit attack on self have also been implicated in tolerating cancer cells resulting in tumor progression.

- Tumor tolerization can result from suppression by different immune cells including T cells and cells in the tumor and the microenvironment.
- Immune suppression can also be caused by inhibitory signals from the tumor.
Immune Tolerance: Multiple Barriers to Tumor Elimination

- Regulatory immune cells
  - T reg cells
  - MDSCs

- Immunosuppressive cytokines
  - IL-6, IL-10, TGF-β, VEGF

- T-cell inhibitory receptors
  - CTLA-4, PD-1, LAG-3, etc.

**Solution:**

- Adoptive transfer of T cells optimized/engineered ex vivo

- Systemic blockade of suppressive cytokines or inhibitory receptors/ligands (‘‘immune checkpoints’’)

Source: Company Reports and J.P. Morgan.
Modulating Different Parts of the Immune System to Eliminate Tumor Cells

DCs play a key role in tumor immuno-surveillance:
- Priming CD8+ T cells to eliminate tumors
- Also promote Treg generation and activation within tumors

Macrophages are phagocytic cells that form a part of the innate immune system. Depending on the stage of the tumor:

NK cells are part of immuno-surveillance machinery that can distinguish between malignant and healthy cells.

Cytotoxic T cells are important for killing cancerous or virally infected cells, and CD8-positive suppressor T cells restrain certain types of immune responses.
Differences Between Inflamed and Non-Inflamed Tumors

- Converting T-cell poor tumors to an inflamed immuno-phenotypes remains one of the key challenges of the field
- Vaccines and adoptive T-cell based therapies in combination with I/O molecules could play a role in directing T cells to the tumor site and potentially convert T cell-poor tumors to T-cell inflamed tumors
Appendix
## I/O Molecules In Development

<table>
<thead>
<tr>
<th>Checkpoint Inhibitors</th>
<th>PD-1</th>
<th>PD-L1</th>
<th>LAG-3</th>
<th>TIM-3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opdivo</strong> (BMS)</td>
<td></td>
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<tr>
<td><strong>durvalumab</strong> (AZN)</td>
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<tr>
<td><strong>BMS 986016</strong> (BMS)</td>
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<tr>
<td><strong>anti-TIM-3</strong> (BMS)</td>
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<tr>
<td><strong>Keytruda</strong> (MRK)</td>
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<tr>
<td><strong>atezolizumab</strong> (Roche)</td>
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<tr>
<td><strong>anti-LAG3</strong> (TSRO/ AnaptysBio)</td>
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<tr>
<td><strong>anti-TIM3</strong> (TSRO/ AnaptysBio)</td>
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<tr>
<td><strong>Pidilizumab</strong> (MDVN/ CureTech)</td>
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<tr>
<td><strong>Avelumab</strong> (PFE/ Merck KGaA)</td>
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<tr>
<td><strong>IMP701</strong> (Prima BioMed)</td>
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<tr>
<td><strong>anti-TIM3</strong> (AGEN)</td>
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<tr>
<td><strong>MEDI0680</strong> (AZN)</td>
<td></td>
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<tr>
<td><strong>regin2810</strong> (REGN)</td>
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<tr>
<td><strong>PD-1</strong> (AGEN)</td>
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<tr>
<td><strong>LAG3</strong> (AGEN/ INCY)</td>
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</tr>
<tr>
<td><strong>LAG3</strong> (MRK)</td>
<td></td>
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</tr>
</tbody>
</table>

Source: Morgan estimates.
## I/O Molecules In Development

### Co-stimulatory Agents

<table>
<thead>
<tr>
<th>CD137/41BB</th>
<th>OX40</th>
<th>CD27</th>
<th>GITR</th>
<th>CD40</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-05082566 (PFE/ MOR)</td>
<td>MEDI-0562 (AZN)</td>
<td>Varilumab (CLDX/ BMY)</td>
<td>MK-4166 (MRK)</td>
<td>SEA-CD40 (SGEN)</td>
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<tr>
<td>Urelumab (BMY)</td>
<td>MEDI-6383 (AZN)</td>
<td></td>
<td>GITR (BMY)</td>
<td>CD40 (Roche)</td>
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<td></td>
<td>RG7888 (Roche)</td>
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<td>GITR (PFE)</td>
<td></td>
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<tr>
<td></td>
<td>OX40 (Agonox)</td>
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<td>FPA154 (FPRX)</td>
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<tr>
<td></td>
<td>OX40 (GSK)</td>
<td></td>
<td>anti-GITR (TGTX)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OX40 (AGEN)</td>
<td></td>
<td>anti-GITR (AGEN/ INCY)</td>
<td></td>
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</table>

Source: Morgan estimates.
# I/O Molecules In Development

## Immunomodulators

<table>
<thead>
<tr>
<th></th>
<th>CTLA4</th>
<th>KIR</th>
<th>IDO</th>
<th>IL-2</th>
<th>IL-21</th>
<th>CSF1R</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
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## Approved

- JNJ40346527 (JNJ)
- IMA942 (Roche)

## Phase III

- FPA008 (BMY/FPRX)
- LY3022855 (LLY)
- AMG820 (AMGN)
- ARRY382 (ARRY/ CELG)

Source: Morgan estimates.
Compelling Data in Additional Tumor Types Could Transform the I/O Market Significantly over $30bn

- PD-1/PD-L1s have shown remarkable efficacy across more than 20 different tumor types
- According to our estimates success in just seven different tumor types should lead to the formation of ~$30bn market
- In addition our estimates are not taking into consideration I/O combinations and revenue from other I/O agents in development.
- Furthermore, in tumors with better SOC, I/O combinations are more likely to significant clinical benefit over the SOC.

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<th>Indication</th>
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<td>Myelodysplastic Syndrome</td>
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Source: Company Reports and J.P. Morgan
Note: MRK’s Keytruda was only approved in >50% PD-L1+ NSCLC patients
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*Percentage of investment banking clients in each rating category.

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