Today’s Intelligence at a Glance

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   **Indication**: General
Novartis: Acquires CoStim to Gain Footing in Immuno-Oncology; Still at a Disadvantage Given Its Time-to-Market and Lesser Breadth of Its Portfolio

The acquisition of privately-owned CoStim gives Novartis a belated but potentially significant and broad footing (including anti-PD1, LAG3 and TIM3) in the paradigm shifting field of immuno-oncology (together with the previously in-licensed CART cell therapy technology). Despite today's deal, Novartis remains at a material disadvantage compared with leaders Bristol-Myers (BMY) and Roche given both its time to market and the lesser breadth of its immuno-oncology portfolio.

CoStim is a MPM-backed private biotechnology company based in Cambridge, MA close to Novartis NIBR. During our last meeting, CoStim management indicated that they anticipated taking the first of four antibodies into clinical trials during 2014. We suspect that CoStim has an anti-PD1, an anti-LAG3, and an anti-TIM3. In addition, as the name suggests, CoStim has two novel and IP-protected lead co-stimulatory targets and reagents (B7-1 and B7-2). Assuming CoStim’s anti-PD1 and LAG3 enter the clinic in 2014, their anti-LAG3 program would be only one year behind BMY. The lead investigators include Arlene Sharple, Vijay Kuchroo, Gordon Freeman, Frederic Triebel among other notables. The company has explored animal models in colorectal, renal, myeloma and mesothelioma. While the transaction terms were not disclosed, we would anticipate upfront payments of at least c.$500m with likely additional contingent payments, based on our analysis of the nature of the immunotherapy assets and average valuations for these assets. We are happy to provide further background on CoStim on request.

Source: Citigroup/Baum, February 17, 2014
Oncology Indication: Multiple
Keyword: Mergers & Acquisitions
Servier (French biotech) announced this morning (2/18) that it will collaborate with Paris-based Cellectis on UCART19, an engineered T cell with a chimeric antigen receptor for leukemia and lymphomas, as well as 5 other such programs. Servier is paying Cellectis $10 million down and up to $140 million per program in milestones in its gamble on the biotech's approach. The biotech struck the deal after reporting animal data several months ago, claiming that UCART19 "eradicated" human leukemia cells that had been transferred into mice.

Servier is gaining an early-stage entry into a field now focused on a high-stakes showdown between pharma giant Novartis (NVS) and newcomer Juno Therapeutics. NVS has been pushing hard to advance a CD19-targeting engineered T cell through the clinic after gaining rights to the program, which was first put through a small human study by University of Pennsylvania investigator Carl June. Just yesterday (2/17) Novartis said it would buy out CoStim, a Cambridge, MA-based startup focused on a PD-1 approach to immunotherapy, so it could combine it with its CAR-T therapy.

Juno Therapeutics is pursuing litigation over June's work, claiming that it controls the IP. Servier, like everyone else now focused on cancer immunotherapy, is looking to use this tech with new combination drugs.

Jean-Pierre Abastado, who heads up the Oncology Innovation Center at Servier, noted that "these original cell-based therapies will well complement Servier's innovative clinical oncology pipeline, which currently includes immunotherapeutic monoclonal antibodies, an HDAC inhibitor, kinase inhibitors, antiangiogenic and proapoptotic small molecules."

Source: FierceBiotech/Carroll, February 18, 2014
Oncology Indication: Hematologic
Keyword: Partnerships/Business Developments
GlaxoSmithKline: High-Risk But Transformational Pipeline Newsflow in 1H14; Only 10% Probability of Success for MAGE-A3

Excluding pipeline optionality GSK appears fully valued albeit well supported by a healthy cash return (2014 dividend yield 5%) and complimentary share repurchase programme. Near-term GSK offers an appealing risk-reward with potentially transformational pipeline newsflow on darapladib and MAGE-A3 in H1 2014. On a blue sky scenario these two assets could generate sales in excess of £5 bn by 2021E. However, they are extremely high risk and both we and the market assume a low probability of success (PoS).

With MAGE-A3 failing to meet its first co-primary endpoint in the DERMA Phase 3 melanoma trial and the significant number of therapeutic cancer vaccine candidates which have previously failed in development, we consider a 10% probability of success appropriate. We include risk-adjusted revenues of £144 million in 2021E for NSCLC and melanoma combined.

A number of therapeutic cancer vaccine candidates have failed in development. Suggested reasons for these failures include: studying disease that is too advanced; studying tumors that are too aggressive and heterogeneous (especially melanoma), selecting patients with insufficiently strong immune systems. However low immunogenicity of TAAs, tumor adaptation and anti-immune tumor microenvironment are all reasons why immune therapy might fail anyway.

<table>
<thead>
<tr>
<th>Failed cancer vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine candidate</strong></td>
</tr>
<tr>
<td>GVAX</td>
</tr>
<tr>
<td>Canavaxin</td>
</tr>
<tr>
<td>MyVax</td>
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<tr>
<td>PANVAC-VF</td>
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<tr>
<td>PROSTVAC-VF</td>
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<tr>
<td>Melacine</td>
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<tr>
<td>Trovax</td>
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<tr>
<td>Stimuvax</td>
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Source: Barclays Capital/Purcell, February 14, 2014

Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline
Market Overview: Roche’s Gazyva Looks to Have the Edge in 1st-Line CLL, But Genmab’s Arzerra Tolerability to Maintain Niche Potential

No head-to-head data exists comparing Arzerra with Gazyva. However, the respective COMPLEMENT-1 and CLL11 trial trials in front-line CLL were conducted in broadly similar patient populations. The data confirm robust efficacy for both drugs, with a median progression free survival in excess of 20 months (27 months for Gazyva and 22 months for Arzerra). While trials of Arzerra did not include an arm directly comparing to Rituxan (Gazyva showed superiority to Rituxan), we believe both will be perceived as superior treatment options to Rituxan in this setting. However, in our view Gazyva has the edge given: (1) its proven direct superiority to Rituxan; (2) more impressive hazard ratio for PFS benefit vs. chlorambucil alone; (3) higher (improvement in) complete response rate.

One advantage for Arzerra is a lower reported rate of infusion reactions, with only 10% of patients experiencing a grade 3 or higher reaction to treatment vs. 20% of patients treated with Gazyva. This improved tolerability could make Arzerra an attractive option, particularly with community based physicians, who have more limited access to the support required for managing serious infusion reactions. However, trials suggest that infusion reactions with Gazyva are nearly all limited to the first dose and Roche believe they are likely to be manageable as more experience is gained with the drug. How this plays out in routine use is currently unknown.

At present, it seems likely that Arzerra will retain only a niche role in first-line CLL treatment. This said, as we expect CD20 based combinations to retain a significant role overall in treatment of the disease (and many patients receive multiple rounds of therapy), we believe this setting continues to represent a growth opportunity. We expect GSK to highlight Arzerra’s attractive tolerability and price point as well as practical advantages in terms of dosing (only two hospital visits are required in the first month versus four visits for Gazyva, given the need to split dosing with the latter to manage the infusion reactions).

### Comparison of Gazyva to Arzerra and Rituxan

<table>
<thead>
<tr>
<th></th>
<th>Gazyva plus chlorambucil</th>
<th>Rituxan plus chlorambucil</th>
<th>Chlorambucil alone</th>
<th>Ofatumumab plus chlorambucil</th>
<th>Chlorambucil alone</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>74</td>
<td>73</td>
<td>72</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>IgVH unmutated</td>
<td>62%</td>
<td>61%</td>
<td>59%</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td>17p deleted</td>
<td>7%</td>
<td>7%</td>
<td>10%</td>
<td>5%</td>
<td>8%</td>
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<tr>
<td>11q deleted</td>
<td>16%</td>
<td>17%</td>
<td>15%</td>
<td>19%</td>
<td>11%</td>
</tr>
<tr>
<td>N=</td>
<td>333</td>
<td>330</td>
<td>118</td>
<td>221</td>
<td>226</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>78%</td>
<td>65%</td>
<td>30%</td>
<td>82%</td>
<td>69%</td>
</tr>
<tr>
<td>Complete response investigator reported</td>
<td>NR</td>
<td>7%</td>
<td>0%</td>
<td>49%</td>
<td>21%</td>
</tr>
<tr>
<td>Complete response (IRC assessed)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>14%</td>
<td>1%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>26.7</td>
<td>15.2</td>
<td></td>
<td>22.4</td>
<td>13.1</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.39 (p&lt;0.0001) vs</td>
<td></td>
<td></td>
<td>0.57 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rituxan and 0.18 vs Chl.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.66 (p=0.08)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3-5 adverse events</td>
<td>70%</td>
<td>55%</td>
<td>41%</td>
<td>50%</td>
<td>43%</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>20%</td>
<td>4%</td>
<td>n/a</td>
<td>10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33%</td>
<td>28%</td>
<td>15%</td>
<td>26%</td>
<td>14%</td>
</tr>
<tr>
<td>Infections</td>
<td>12%</td>
<td>14%</td>
<td>11%</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>MRD negative in blood at 3mths</td>
<td>87 pts (26%)</td>
<td>8 pts (2%)</td>
<td>0 pts</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MRD negative in bone marrow at 3mths</td>
<td>26 pts (8%)</td>
<td>3 pts (1%)</td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MRD negative in bone marrow or blood at 3mths</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>N/A</td>
</tr>
<tr>
<td>MRD negative in bone marrow or blood at 6mths</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>9%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Source: Deutsche Bank
### Price comparison of Azerry, Rituxan and Gazyva

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Price per dose (US$)</th>
<th>Cost per course (US$)</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gazyva</td>
<td>1000mg</td>
<td>5,160</td>
<td>41,280</td>
<td>1 cycle 100mg, 5 cycles of 1000mg</td>
</tr>
<tr>
<td>Arzerra</td>
<td>1000mg</td>
<td>4,588</td>
<td>28,911</td>
<td>6 cycles 1000mg</td>
</tr>
<tr>
<td>Rituxan</td>
<td>1000mg</td>
<td>667</td>
<td>34,517</td>
<td>1 cycle 375mg/m^2, 5 cycles 500mg/m^2</td>
</tr>
</tbody>
</table>

*Source: Deutsche Bank/Parkes, February 14, 2014*

**Oncology Indication:** Hematologic

**Keyword:** Market Overview

CD38 is a promising target for MM based on its abundant expression on MM cells; JNJ, Sanofi and Celgene are the key contenders in the CD38 race. The three companies are developing CD38 agents in-licensed from smaller antibody focused biotech companies for the treatment of MM, JNJ/Genmab developing daratumumab, Sanofi/ImmunoGen developing SAR650984 and Celgene/MorphoSys developing MOR202.

JNJ's Daratumumab is the most advanced CD38 product in clinical development:
- Phase I/II results with daratumumab monotherapy and in combination with Rev-dex have been most recently presented at the ASCO 2013 and ASH 2013 conferences, and revealed promising signs of initial efficacy as well as a relatively benign safety profile. This product is also the only one of the three to have been designated Breakthrough Therapy by the FDA.
- The first phase I results from a dose escalation study of SAR650984 monotherapy were presented at ASH 2013, while a study testing a combination of this product with Revdex is ongoing. We anticipate interim data could report out from this study at ASH 2014.
- Newsflow for MOR202 front has been rather slow since the announcement of the Celgene/MorphoSys deal in June 2013. A phase I/II study of MOR202 is ongoing, evaluating the drug in three different cohorts: as monotherapy, in combination with Rev-dex and in combination with Velcade. This study has not reported out to date, but Celgene guided that initial data could read out in 2H14 (likely at ASH).

KOLs were positively surprised with safety observations from the initial daratumumab and SAR650984 trials. Given the broad expression of the CD38 protein in blood cells and in other tissues, our consultants expected that treatment with CD38 antibodies would have resulted in some bone marrow suppression (myelotoxicity) and other side effects. However, toxicities reported to date were mainly infusion related reactions that were well managed by investigators, and few serious adverse events (SAEs) have occurred.

We expect JNJ's daratumumab to be the first to market around 2018. While the most advanced MM antibody in development is Bristol/AbbVie's elotuzumab, our KOLs appear to be more excited about the CD38 class. We believe that JNJ, Sanofi and Celgene will attempt to minimize the gap with elotuzumab, likely by following Bristol/AbbVie's roadmap of starting a phase III study in relapsed MM with phase I/II results in combination with Rev-dex on hand. Assuming highly optimistic timelines for all these products, we project that daratumumab may be the first to market, with phase III trials starting in late 2014/early 2015, with potential pivotal data readout in 2017/2018 and approval in 2018 or later. We project that SAR650984 and MOR202 will follow closely, and will likely reach the market a year later. With three contenders in this class, and apparently greater independent activity than elotuzumab, Bristol's drug could suffer from a short WOO ("Window of Opportunity").

In conclusion, we anticipate that these products will impact the current treatment paradigms of MM in the 2017-2018 timeframe but that these changes bode well for Celgene for two reasons. First, KOLs (and community doctors that we surveyed) believe that antibodies will be used as an add-on to the Revlimid-dexamethasone treatment backbone, thereby extending the duration of therapy with Revlimid. Second, Celgene is the only player in this space with a portfolio of IMiD compounds and a CD38 antibody in development and is best positioned to move quickly in developing iMID-Ab combination trials and regimens.

Source: Bernstein Research/Porges, February 14, 2014
Oncology Indication: Hematologic
Keyword: Market Overview
Market Overview: MM KOL: Prior Therapy with IMiD or Proteasome Inhibitors Does Not Preclude Subsequent Therapy with Similar Modality; CV Risk with Kyprolis Minimal at Approved Dose

We hosted a discussion on Friday (2/14) with myeloma clinician and researcher, Dr. James Berenson, and share our highlights relevant to drug development across the myeloma landscape. The myeloma prevalence population continues to expand in large part due to the introduction of novel therapies, innovative combinations, and modified dosing regimens that are keeping patients alive and on therapy longer. The myeloma prevalence population is upwards of ~200,000 patients, achieving 13+ years survival, with the advent of novel therapies and novel combinations.

Prior therapy with IMiD or proteasome inhibitors does not preclude subsequent therapy with a similar modality. Challenging the dogma that ‘drug resistance equals class resistance’, Dr. Berenson made a strong case for substituting Kyprolis in true Velcade-refractory patients. Surprising results from a Phase I/II study (in press) showed that by simply replacing Velcade with Kyprolis, while holding the combination agents constant, responses could be achieved in 43% of patients, and clinical benefit in 62% of patients. Likewise for IMiD therapies, Dr. Berenson highlighted data showing Thalomid refractory patients could be resensitized to Revlimid, and vice versa (24-76%), underscoring the likely role of myeloma cell heterogeneity and that small variations among drugs of a given class can have an outsized effect on stemming the expansion resistant clones. Similar expectations were held for oral IMiD (Pomalyst) and oral PIs (Amgen’s oprozomib and Takeda’s ixazomib), opening opportunities in broader development in the refractory setting.

CV risk with Kyprolis is minimal at approved doses, less clear at higher doses. In contrast to some of the cautious KOL feedback that emerged during ASH 2013, Dr. Berenson sees little in the way CV risk is associated with Kyprolis at its approved dose of 20-27mg/m2 BIW. Rather, he has been a strong proponent for treating at higher doses of Kyprolis, currently evaluating 70mg/m2 QW in the Phase II expansion trial in R/R multiple myeloma. Extending infusion time from 30 minutes to an hour was seen as one way of reducing the risk of cardiotoxicity. That said, insufficient patients to date, in his view, have been treated with higher-dose Kyprolis to establish any correlation with CV risk, although the possibility cannot be rule out.

Minimal residual disease (MRD) is perhaps an unrealistic goal in myeloma. While many clinical thought leaders have been advocating for the use of MRD as a means of establishing superior benefit, Dr. Berenson sees limited applicability to myeloma, specifically. Unlike in CML or ALL, for example, myeloma exhibits greater heterogeneity throughout the bone marrow, making it rather difficult to reliably detect myeloma cells within the defined limit of one per million across all patients. Rather, CR and VGPR will continue to be more relevant clinical endpoints, short of patient overall survival.

Novel targets offer attractive opportunities for drug development. Chief among these, in Dr. Berenson's view, was the Jak/Stat pathway based on both anecdotal clinical activity seen with Jakafi in patients with confirmed Jak2 mutations and preliminary lab work showing impressive anti-myeloma activity, irrespective of JAK mutation status. Although preliminary in nature, the data suggest Jakafi could be effective in myeloma at an appreciably lower dose than that approved for myelofibrosis, reducing the risk of associated anemia. That said, any potential development and use of Jakafi for myeloma would likely take place in the context of combination therapy.
MacroGenics: Broad DART Program About to Enter Clinic; Significant Support for B7-H3 as Another Checkpoint Inhibitor

The first of MacroGenics’ (MGNX) many bi-specific DARTS in development (D006) will start a phase 1 study in the hematology indication AML. Data presented at the December ASH meeting for D006 in an AML mouse model indicated higher potency vs. a CD123 antibody. Due to the near-term phase 1 start for D006 and potential for two new DARTS to enter the clinic in 2015 as a result of the recent ~ $75mn net cash raise, we are increasing our probability of approval to 20% (from 15%) for D006 and added revenue from partnered DART programs (Gilead, Servier, Boehringer and Pfizer).

Significant support for B7-H3 as another checkpoint inhibitor. We are increasing the probability of approval for MGNX’ anti-B7-H3 antibody (‘271) to 25% (from 15%) based on our review of B7-H3 literature which highlights elevated B7-H3 expression on multiple tumors (e.g. colorectal, pancreatic, gastric, non-small cell lung cancer), low expression on normal cells, a cell signaling mechanism that promotes tumor development and migration, and inhibition of T-cell immune response. B7-H3 antibodies have also shown reduced tumor progression in mouse models. ‘271 also employs the ADCC enhancement mechanism. We expect phase 1 data near YE.

Source: BofA Merrill Lynch/Byrne, February 18, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline
Pharma-Europe: Germany Considering Law that Would Force Drugmakers to Report Reduced Prices Negotiated with Insurers

Germany is considering legislation this week that would force drugmakers to report the reduced prices they negotiate with insurers, potentially pressuring prices lower elsewhere in Europe. Pharmaceutical companies would have to report rebated prices, instead of their original list prices, to databases such as IMS Health, said Ina Klaus, a Health Ministry spokeswoman in Berlin. The revised law will make it clear that the list price isn’t what’s paid in Germany, she said. German prices are influential because other countries use them as a reference. While incremental, the change would add to the pressure on drugmakers, which have faced a series of moves by European companies to keep medicine prices down in the wake of the economic crisis.

“Well, some people think it’s pure semantics, but it’s a huge difference,” Hagen Pfundner, head of Basel, Switzerland-based Roche’s German business, said at a press conference last week in Frankfurt.

The change was approved by a majority of the parliamentary health committee on Feb. 12. Parliament is scheduled to vote Feb. 20 on the proposal, which would become law by April 1. The provision is part of a law that would also scrap a plan to conduct cost-benefit analysis -- and negotiate prices -- for drugs that are already on the German market.

Drugmakers have had to negotiate rebates on new innovative medicines with German insurers for the past three years. Now instead of referring to rebates negotiated between drugmakers and insurers, the law will refer to reimbursement. The shift may seem small, but it means the talks are really about price, not discounts, Pfundner said. The change would also strip some of the flexibility in the system from drugmakers, Pfundner said. A rebate is often good for a limited time or volume and is renegotiable, he said. Not so for a price. Other countries look to Germany for reference prices for their drugs, he said, meaning that reimbursement levels in Germany have influence outside the country’s borders. Countries including Spain, France and Italy have reduced the number of drugs for which they will reimburse patients, mandated the increased use of generic medicines and lowered the amount they will pay for some products since the economic crisis.

Source: Bloomberg/Kresge, February 17, 2014
Oncology Indication: General
Keyword: Policy/Legal