**Oncology Equity Research Headlines**

1. **Roche**: MetMAb Phase III Trial in 2nd-/3rd-Line NSCLC Discontinued Early Due to Lack of Efficacy; Negative Read-Through for Ongoing 1st-Line Study
   
   **Additional Analysis**

   **Phase III Trials for MetMAb (Onartuzumab)**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Estimated Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01456325</td>
<td>Discontinued June 2016</td>
</tr>
<tr>
<td>NCT01662869</td>
<td>Recruiting December 2016</td>
</tr>
<tr>
<td>NCT02031744</td>
<td>Recruiting April 2017</td>
</tr>
<tr>
<td>NCT01887886</td>
<td>Recruiting April 2017</td>
</tr>
</tbody>
</table>

   **Indication:** Lung

2. **Market Overview**: Development Strategy for Exelixis' Cabozantinib and Mirati's MGCD-265 in NSCLC Differs from Roche's MetMAb

   **3. Medivation**: 3Q & 4Q13 Trends Overstated Current Demand; Believes Xtandi’s Main Competitor in Urology Market is Generics, Ongoing Studies Should Support Xtandi

   **4. Incyte**: Signals Generated with IDO1 and JAK Inhibitors in Solid Tumors Constitute Real Efficacy; Additional IDO1 Collaboration with Other PD1 Players Possible

   **5. Threshold**: TH-302 (Phase III): Sarcoma Data Likely in 3Q15 with Interim Look in 3Q14; Positive Pancreatic Cancer Expected in 4Q15

   **6. Halozyme**: PEG-PH20 in Pancreatic Cancer as Primary Pipeline Driver, Higher Bar for Phase II Studies with New Standard-of-Care

   **7. Epizyme**: Two Epigenetic Candidates for Hematologic Malignancies Potentially Advance to Phase II or Pivotal Trials in 2014

   **8. Pharma-Europe**: Positive for Biosimilars as EU Supports Same International Non-Proprietary Name as Branded

---

**Additional Analysis**

**Roche - Annual Pharma Sales Growth Rate (%)**

<table>
<thead>
<tr>
<th>Year</th>
<th>EPS</th>
<th>5-Yr CAGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013A</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>2014E</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>2015E</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>2016E</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>2017E</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>

**Sources:** Company Reports; 5+ Brokerage Analyst Reports
Roche: MetMAb Phase III Trial in 2\textsuperscript{nd}-/3\textsuperscript{rd}-Line NSCLC Discontinued Early Due to Lack of Efficacy; Negative Read-Through for Ongoing 1\textsuperscript{st}-Line Study

**MetMAb fails to show clinical benefit based on pre-specified interim analysis.** Roche announced this morning (3/3) that MetMAb (onartuzumab)'s Phase III trials (MetLung) in previously treated NSCLC (2\textsuperscript{nd}-/3\textsuperscript{rd}-line) was discontinued early due to the lack of clinically meaningful benefit during an interim analysis. The trial was being evaluated in combination with Tarceva vs. Tarceva monotherapy in NSCLC patients who screened positively for the MET protein (MET high).

Roche highlighted that the company is currently evaluating the implications of the MetLung data across the ongoing Phase III trials in 1\textsuperscript{st}-line NSCLC. However, we believe that today’s failure is likely to have a negative read across to these ongoing trials.

We had risk-adjusted peak sales opportunity of SFr1.0bn for the previously treated lung cancer indication. We were forecasting un-adjusted global peak sales estimates of $1.4bn (SFr1.3bn) for MetMAb in the NSCLC indication. We had applied a 70% probability of success which contributed SFr2.0 per share (1%) to our EmV. Company compiled post 3Q13 consensus was modeling MetMAb sales of SFr389m by 2017 (vs JPM of SFr168m).


*Source:* JPMorgan/Vosser, March 3, 2014

*Oncology Indication:* Lung

*Keyword:* Clinical Trials/Pipeline
Market Overview: Development Strategy for Exelixis' Cabozantinib and Mirati's MGCD-265 in NSCLC Differs from Roche's MetMAb

Exelixis' (EXEL) and Mirati's (MRTX) development strategy in NSCLC differs from Roche's. Whereas Roche enrolled patients selected for "high-MET" expression using an immunohistochemistry-based diagnostic (~40% of NSCLC), EXEL and MRTX plan to test cabozantinib and MGCD-265, respectively, in NSCLC patients harboring certain "driver mutations" representing a much smaller patient subset.

- EXEL plans to start a Phase II/III study for Cabo in RET-fusion positive NSCLC representing 1-2% of NSCLC.
- MRTX plans to test MGCD265 in MET-mutation and Axl-fusion positive NSCLC (6-8% of NSCLC patients) with Phase I data expected in mid-2014.

Although almost all major human cancers seem to harbor some dysregulation of the MET pathway, only a minority of tumors are “addicted to MET”, explaining in our view the mixed clinical results seen thus far with Met inhibitors when studied in broader patient populations. “Met addicted” tumors are those with MET gene amplification or specific activating mutations representing only a small single-digit percentage of patients. Tumors without MET addiction including those with "high-MET" expression may rely only partly on MET signaling for invasion, growth and metastasis, according to MEDACorp KOLs we spoke to, which makes it hard to show a benefit.

Whereas the METLung discontinuation clearly raises questions regarding MET as a target in NSCLC, we note that in contrast to highly specific MetMAb, cabozantinib and MGCD-265 are multi-kinase inhibitors. In addition to MET, cabozantinib also inhibits FLT-3, VEGFR, KIT, TIE1/2, and RET. MGCD-265 inhibits MET, VEGFR and Axl. Redundancy in oncogenic signaling pathways might require inhibition of multiple kinases, which could potentially be targeted using multi-kinase inhibitors in our view.

MET inhibition with multi-kinase inhibitors may be a valid strategy in different indications. Dysregulation of the MET signaling pathway occurs in a wide range of human cancers, including the most common epithelial cancers. However we believe MET may only be an oncogenic driver in some, but not all of these cancers. Recall EXEL’s cabozantinib is already approved to treat patients with Medullary Thyroid Cancer (MTC). Interestingly 80% of patients in EXEL's EXAM trial were RET mutation positive based on a genetic analysis, suggesting cabozantinib’s multi-kinase inhibition (including RET) may be beneficial. Similarly, Pfizer's crizotinib a multi-kinase inhibitor targeting Met and ALK has been approved to treat patients with metastatic NSCLC harboring a genetic ALK fusion with a frequency of ~3% in NSCLC.

Source: Leerink Partners/Schmidt, March 3, 2014

Oncology Indication: Lung
Keyword: Market Overview
On Friday (2/28), we had the opportunity to speak with management to better understand the 2014 guidance. Key points:

[1] 4Q13 sales overstated demand by as much as $20-25m. [2] Medivation segments the market by oncology and urology, rather than post- and pre-chemo. It thinks the oncology segment is in at least the middle innings, which is why guidance is for mid-single digit q/q growth until it gets an expanded label. [3] The new label should shift the prescriber mix to urology, which would enable Xtandi to capture more pre-chemo patients sooner, and with higher market share, with longer duration and a more sticky prescribing base to drive peak sales.

Management believes the right way to think of the markets is as urology and oncology markets, rather than pre- and post-chemo markets. Oncologists are rapid adopters and comfortable writing off-label, but they are as quick to change treatments as they are to start using them. In contrast, urologists are slower to adopt new treatments than oncologists, but tend not to change easily once adopted.

Virtually of Medivation's business today is in oncology. There has been some pre-chemo use by oncologists already, but the oncology market is largely penetrated. The untapped opportunity is with urologists, who would be able to treat more patients who are younger, healthier, live longer, and remain on treatment longer.

Medivation feels strongly that Xtandi sales will not be materially impacted by urologist prescriptions until they get PREVAIL on the label. However, once the company is able to talk to the data, they believe there will be a substantial increase in demand, which is why they expect double digit growth in 4Q.

Management believes their main competitor in the urology market is generics and that the two ongoing head-to-head studies against Casodex (TERRAIN and STRIVE) will show Xtandi is better.

Regarding the litigation vs. Aragon, it is currently in the appeals phase. This will take a couple years to work out, and management is not sure any substantial development will come out in 2014 as the appeals just went in this month and at the moment typically has a 12-24 month cycle in California. Although they are optimistic for their chances of going through a trial, if MDVN does not succeed at the appellate level, it will likely be the end of the legal process for them. The worst case will be status quo, while the best case will be that they own ARN-509. The fraud case should proceed on a similar time scale and will add context to the claims (but not financially impactful).

Source: UBS/Roden, March 2, 2014
Oncology Indication: Prostate
Keyword: Management/Strategy/Financials
Incyte (INCY) management with the opportunity to summarize why it believes the signals generated with JAK and IDO1 inhibitors in solid tumors constitute real efficacy. We believe each mechanism could provide a foundation for treating multiple tumor types.

**IDO1 Inhibition:**

- Management takes a broader view, noting that its confidence in IDO1 inhibition is derived from multiple sources of information (IDO1 overexpression patterns, synergistic preclinical efficacy, and even the combined toxicity of IDO1+Yervoy).
- Given that INCY does not intend to develop the IDO1+Yervoy combination (in melanoma or elsewhere), the response rates generated in this trial matter only from the perspective of providing proof-of-concept for IDO inhibition and the rationale for combining IDO1 and checkpoint inhibition. Once proof-of-concept is established, what will matter going forward is whether IDO1 inhibition will show the same synergy with PD1 inhibitors. Preclinical data on the combination of ID1O and PD1 inhibition to be presented at ACR in April may therefore be just as important as the IDO1+Yervoy data at ASCO.
- Management indicated much of the details from the IDO1+Yervoy study would be revealed in an ASCO abstract that includes less than 20 patients, but that the data will be amended with more patients by the time of the meeting. The abstract will reference the toxicity of the IDO1+Yervoy combination at higher doses of drug. Since IDO1 monotherapy was clean at higher doses, the combination's toxicity is another factor supporting its biologic activity.
- Incyte continues to guide toward signing additional collaborative development arrangements with other PD1 players.
- INCY believes that the chemistry behind IDO inhibition is not trivial, and does not expect too many rapid followers to make it into the clinic (though NLNK and BMY have already announced programs).

**JAK Inhibition:**

- Management reiterated that the biomarker that defines the chosen subpopulation is on target, related to inflammation, objective, and commercially assessable. Levels for biomarker detection were established prospectively, and while INCY reported data on the best biomarker subset, the other prespecified inflammatory biomarkers also correlated with favorable outcomes on ruxolitinib in the RECAP trial.
- INCY estimates that 30-75% of all solid tumor patients might be biomarker positive at some point in their disease, this based upon a plethora of literature reports. While management's priority remains this subgroup, it is studying ruxo in colorectal cancer (CRCA) patients in both those with and without the biomarker. Management clarified that this was being done at the FDA's behest as the Agency would like to see data validating the biomarker approach in a second tumor type, and reiterated that if successful and convincing the CRCA trial could support approval.
- Management's confidence in the Phase I RECAP data (to be presented in full at ASCO) is bolstered by the design and execution of the trial (quality centers, rigorous conduct), the magnitude of the treatment benefit (HR=.047), the plausibility of the biologic hypothesis being tested, and the consistency of the data (OS, PFS, weight gain, RR). However, on this latter point, INCY noted that not all endpoints would necessarily trend in the same direction given the laws of small numbers (for example, responses in second-line pancreatic cancer are uncommon).
- Preclinical data support a possible role for Jak inhibition in B-Cell malignancies. Certain patient subsets have STAT3 activation signatures that may make them susceptible to monotherapy approaches. There is also preclinical data supporting a combination approach with receptor signally pathway inhibitors (PI3K).

Source: Cowen and Company/Schmidt, March 3, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline
Threshold: TH-302 (Phase III): Sarcoma Data Likely in 3Q15 with Interim Look in 3Q14; Positive Pancreatic Cancer Expected in 4Q15

We recently met with Threshold (THLD) management to review progress with TH-302 including the timelines for their two most advanced clinical programs, TH-302 plus gemcitabine in pancreatic cancer and TH-302 plus doxorubicin in sarcoma. Both of these combinations are in pivotal Phase III trials under SPAs from the FDA.

Sarcoma pivotal TH-302 data likely in 3Q15 with interim look in 3Q14. This study is scheduled for a data safety monitoring board review in mid-2014 following an interim analysis after 235 events. The study completed enrollment of 620 patients on December 28, 2013 after expanding the enrollment over this past summer. The interim analysis is designed for an early stoppage of the trial if investigators find an approximate 45% improvement in overall survival (p< 0.0023, HR < 0.69), or as part of a futility analysis. We view this interim look as a high bar and therefore we assume the trial continues after the interim analysis with final analysis in 3Q15, following the predefined 434 events. The trial is powered to detect a 33% improvement in OS, but a 21% improvement (HR < 0.825, P< 0.048) should be sufficient for approval. Numerically, this means that if the control arm produces a 12 month OS as historical data suggests, the TH-302 arm would need to produce a 14.5 month OS to meet its OS endpoint. We expect this trial to meet its primary endpoint based on the 21.5m OS survival benefit from in the Phase Ib trial, though we note that that trial had only a single arm. We are enthusiastic about the prospects for this trial and the validity of the 21.5month from the single arm trial because the Phase 3 has an identical design including TH-302 maintenance doses, with no maintenance in the control arm.

We expect positive data for TH-302 in pancreatic cancer in 4Q15. We expect the front-line metastatic pancreatic cancer Phase III trial to complete enrollment at the end of 2014 and have data available at the end of 2015. The majority of the patients are enrolling at sites in the U.S. We note that the OS benefit for the Phase III dose of TH-302 in the Phase IIb trial was 2.8 months, which compares favorably Abraxane’s 1.8 month benefit. The trial included a crossover for patients who progressed on Gemcitabine alone, which lowered the median OS delta to 2.3 months, though we believe the 2.8 month OS benefit excluding the crossover patients is a more accurate reflection of the drug’s efficacy. We believe there is a significant market opportunity for TH-302 as docs have been critical of the high price and low OS benefit of the doublet of Abraxane and Gemcitabine, most recently in a letter to the New England Journal of Medicine. We view the pancreatic cancer opportunity as the major value driver for Threshold and the primary component of our $536M sales estimate in 2018.

Abraxane combo study set to start soon. According to Clinicaltrials.gov, there is now an open Phase I “triplet” study of TH-302 plus Gemcitabine plus Abraxane pancreatic cancer trial. The trial aims to enroll 48 patients and is a single arm study. We expect the triplet to show greater anti-tumor activity than either doublet alone. We expect the first patient to enroll soon and catalyze subsequent randomized studies to potentially improve upon the doublet OS benefits.

We expect updated data at ASCO for TH-302 in other indications, possibly multiple myeloma, glioblastoma, and RCC. We are particularly enthusiastic about the multiple myeloma opportunity as the prior data in heavily pretreated patients (median 6 prior therapies) showed a 38% response rate. Management suggested next steps include single agent registration studies and also combination studies with either imidis or proteasome inhibitors in earlier stage patients. In glioblastoma, TH-302 showed a 21% response rate in combination with Avastin in Avastin-refractory patients.

We expect a third TH-302 registration study to start in 1Q14. Management did not reveal which indication but we assume a major solid tumor indication such as melanoma or NSCLC.

Source: Stifel/Sendek, February 28, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline
Halozyme: PEG-PH20 in Pancreatic Cancer as Primary Pipeline Driver, Higher Bar for Phase II Studies with New Standard-of-Care

**PEG-PH20 in oncology is primary pipeline driver:** Based on Phase Ib data of PEGPH20 in pancreatic cancer, two Phase II studies were initiated (one is investigator-sponsored) to examine PEG-PH20 in combination with gemcitabine/Abraxane, or FOLFIRINOX. While the Phase Ib study showed encouraging response rates and progression-free survival data, it remains to be seen how this will translate into overall survival. Further, we believe the bar is now set higher in the Phase II studies given that PEG-PH20 is being combined with more than just gemcitabine and will be compared to the new standard-of-care, Abraxane/gemcitabine combination. Lastly, Halozyme plans to start a new study in 4Q that will test PEG-PH20 in an undisclosed cancer indication.

**Diabetes program is progressing; we see more commercial risk than clinical risk:** HALO plans to provide top-line data from the CONSISTENT-1 trial over the next several months followed by detailed results at an upcoming medical meeting, likely the American Diabetes Association (ADA) meeting in June. We continue to believe that Hylenex plus analog insulin will provide some benefit over analog insulin alone. However, the question is how much commercial opportunity it provides given the extra cost.

Revenues for the fourth-quarter came in at $12.5mn, in-line with our estimate of $12.2mn. HALO reported $33,000 in royalties from Baxter and Roche.

_Source_: Barclays Capital/Huang, February 27, 2014
_Oncology Indication_: Pancreatic
_Keyword_: Clinical Trials/Pipeline
Epizyme: Two Epigenetic Candidates for Hematologic Malignancies Potentially Advance to Phase II or Pivotal Trials in 2014

On the 4Q:13 earnings call, Epizyme (EPZM) provided financial guidance for 2014 with cash burn estimated at $80M and YE:14 cash of $170M following a recent capital raise. The company also provided an incremental update on clinical development and potential milestones for the two epigenetic candidates EPZ-5676 (DOT1L inhibitor) and EPZ-6438 (EZH2 inhibitor). Both programs are expected to have detailed Phase I data and advance to Phase II or pivotal trials in 2014. Following initial clinical proof-of-concept data for EPZ-5676 in difficult to treat MLL-r acute leukemias, rapid progress in DOT1L and EZH2 inhibitors and GSK partnership advancing to candidate selections show a high level of interest in targeted epigenetics for cancer drug development.

Following initial proof-of-concept EPZ-5676 data in MLL-r after dosing modification, management expected timely enrollment for the expansion cohorts in both MLL-r and MLL-PTD patients. Data from dose escalation and expansion cohorts are expected in 2H14. Assuming positive readout, management plans to meet with the FDA to discuss the potential registration trial. Data from EPZ-6438 Phase I dose escalation studies in hematologic and solid tumors are also expected in 2H14 and Phase II trials in non-Hodgkins lymphoma (NHL) and synovial sarcomas will be initiated in 2014 upon completion of Phase I trials.

In 4Q:13, EPZM earned $25M from Celgene for showing initial proof-of-concept data for EPZ-5676, and $6M from Eisai for Phase I initiation for EPZ-6438. Following the recent $4M milestone received from GSK for initial selection of the three HMT candidates, EPZM announced the second selection of the HMT candidate, earning an additional $2M in milestones. EPZM could also gain a $10M milestone for initiating a Phase II trial for EPZ-6438 in 2014.

Source: Leerink/Liang, February 28, 2014
Oncology Indication: Hematologic
Keyword: Clinical Trials/Pipeline
Pharma-Europe: Positive for Biosimilars as EU Supports Same International Non-Proprietary Name as Branded

According to a recently published development, EU members have agreed that the biosimilars should have the same international non-proprietary name (INN) as their reference biological. We note that a key controversy for the biosimilars is around the name and having same INN would help them get greater market share once they get approved. We continue to see these developments would help Amgen’s biosimilar biz as it could help them get higher share in the EU.

Amgen is developing biosimilars and 3 of them (Humira, Avastin & Herceptin) are already in clinics. We expect biosimilars to generate ~$3B peak sales for the company by 2025 and at 50% probability. Data from all three programs are expected in 2015. In total Amgen is targeting 6 biosimilars which in total represent ~$40B+ branded market opportunity WW.

Source: Deutsche Bank/Karnauskas, February 28, 2014
Oncology Indication: General
Keyword: Policy/Legal