MCI Daily Dose Equity Research Headlines: March 5, 2014

Oncology Equity Research Headlines

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JPMorgan/Schott, March 4, 2014
HealthACE Abstract *Indication: Lung*

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Cowen and Company/Scala, March 4, 2014
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Genetic Engineering & Biotechnology News, March 5, 2014
HealthACE Abstract *Indication: Multiple*

Additional Analysis

Selected Phase III Trials for Nivolumab

Study Name Design	Indication	Endpts	Estimated Completion Date
NCT01642004 CheckMate 017; vs. Docetaxel	NSCLC (Squamous, in Previously Treated Advanced or Metastatic Patients)	1º: ORR, OS 2º: PFS, DOOR, TTOR	August 2015 Ongoing
NCT01673867 CheckMate 057; vs. Docetaxel	NSCLC (Non-Squamous, in Previously Treated Advanced or Metastatic Patients)	1º: OS 2º: ORR, PFS, Clinical benefit in PD-L1 + vs. PD-L1-protein expression subgroups	November 2015 Ongoing
NCT01721772 CheckMate 066; vs. Dacarbazine	Melanoma (Untreated, Unresectable, or Metastatic)	1º: OS 2º: PFS, ORR, PD-L1 Expression, Quality of life	November 2015 Ongoing
NCT01721746 CheckMate 037; vs. Physician's Choice of Either Dacarbazine or Carboplatine and Paclitaxel	Melanoma (Advanced Patients That Have Pregressed Following Anti-CTLA-4 Therapy)	1º: ORR, OS 2º: PFS, PD-L1 expression, Quality of life	January 2016 Ongoing
NCT01668784 CheckMate 025; vs. Everolimus	Clear-Cell RCC (Pre-Treated Advanced or Metastatic Patients)	1º: OS 2º: PFS, ORR, DOOR, Duration of OS, Safety	February 2016 Recruiting
NCT01844505 CheckMate 067; +/- Ipilimumab	Melanoma (Unresectable or Metastatic)	1º: OS 2º: PFS, ORR, OS based on PD-L1 expression	October 2017 Recruiting
NCT02041533 CheckMate 026; vs. Chemo	NSCLC (First-Line Therapy for Stage IV or Recurrent PD-L1+)	1º: PFS 2º: ORR, OS, PFS in pts with PD-L1+ expression	January 2018 Not Yet Recruiting

DOOR: Duration of Objective Response
NSCLC: Non-Small Cell Lung Cancer
OS: Overall Survival
ORR: Objective Response Rate
PFS: Progression-Free Survival
TTOR: Time to Objective Response

Source: www.clinicaltrials.gov

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Bristol-Myers: Phase III Combo Trial of Nivolumab & Yervoy in NSCLC to Begin By End-2014; Announcement Suggests Favorable Profile and Removes Uncertainty Around Timing

Bristol-Myers (BMY) announced that the company will start a phase III trial studying the combination of nivolumab (PD-1) and Yervoy in NSCLC by the end of 2014, which we see as a clear incremental positive. This announcement suggests a more favorable profile for the combo and rules out a meaningful delay to a phase III start for the combo in lung cancer.

The next data point we expect to see for nivolumab is the single-arm phase II trial in third-line squamous NSCLC, which we expect will be top-lined in the coming months. We believe this dataset could represent the basis for the first filing of nivo given the lack of effective treatments for this patient population.

Watching ASCO for combo data in RCC and NSCLC. BMY previously announced it is moving the nivo/Yervoy combo into phase III in renal cancer based on phase I results for the combination. We expect this data will be presented at ASCO, giving a clearer picture of the incremental benefit of the combo in this tumor type. In addition, we expect to see some data from the phase I Checkmate 012 study in lung cancer, which could shed light on what the company will pursue for the combo in phase III.

Two phase III studies for nivo single-agent in 2nd-line NSCLC (one in squamous, one in non- squamous patients) are also expected to complete in the second half of this year, rounding out a steady stream of PD-1 data points over the course of 2014.

Source: JPMorgan/Schott, March 4, 2014
Oncology Indication: Lung
Keyword: Clinical Trials/Pipeline

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Novartis: Afinitor in Breast Cancer Still Expected to Be $2B; CART Technology Has Broad Application; Well-Positioned for Oncology Market's Evolution

Afinitor: Novartis (NVS) believes that $2B in sales for breast cancer is still achievable, based on use in second and third line patients and the expected duration of treatment. However, it is also possible that the franchise rolls over to NVS' portfolio of PI3Ks. Thus it appears that NVS is still confident in the sales forecast, but what products contribute to that forecast is not absolutely clear. Relative to BOLERO-2's OS endpoint, NVS says it's a wait and see. Relative to adjuvant use, NVS notes that it has not emphasized this.

CART Technology: NVS has previously described a number of targets, including leukemias, lymphomas, and certain solid tumors. However, all targets have not been disclosed. One CART could be applicable to multiple tumors. Some patients relapse because they lose the receptor and others develop mutations. NVS would not speak to pricing for this technology.

Well-Positioned for Oncology Market's Evolution: In 5-10 years, NVS believes that chemotherapy will only be used where targeted agents are not applicable and where all other agents have failed. All patients will be next gen sequenced, with that guiding the choice of therapy. Regimens will involve 2-3 drugs, including targeted agents, immune therapies, and hormonal agents. Given these requirements, NVS believes that only a few companies will be successful in oncology.

Source: Cowen and Company/Scala, March 4, 2014
Oncology Indication: Multiple
Keyword: Management/Strategy/Financials

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Celgene: Revlimid's Potential for Non-Del(5q) MDS Underappreciated, Phase III Data in 2H14; Abraxane Still Has Much Room to Grow in Pancreatic Cancer

In conjunction with Cowen's 34th Annual Health Care conference, we hosted a dinner with Celgene's COO, Perry Karsen, and VP of IR, Patrick Flanigan.

Revlimid:

- Investor interest continues to be high in the Revlimid IP challenge by Natco, though Celgene remains confident in its many patents. A Markman hearing will be no sooner than H2:14.
- Celgene remains on track to file for a Revlimid label expansion for newly diagnosed myeloma by the end of Q1. The company is confident in EMA approval based on the strength of Revlimid's data in MM-020 with the Rd regimen, where SPMs are not an issue.
- As the first non-melphalan based front-line regimen approved in Europe, Celgene expects Rd to become the standard of care over time. While the long-term incremental revenue opportunity is significant in the EU, Celgene cautioned that time required for regulatory review and country-by-country price renegotiation means that revenue contribution from newly diagnosed myeloma in Europe will likely be modest even as late as 2017.
- In the U.S., Celgene continues to see increasing average treatment duration for Revlimid in the wake of (1) Pomalyst approval (because physicians now have an option for patients progressing on Revlimid) and (2) the MM-020 data (supporting treatment to progression).
- Revlimid's Phase III non-del(5q) MDS data are expected in H2:14. With Revlimid currently selling about $250-300MM per year in the small del(5q) MDS subpopulation, success in non-del(5q) MDS could expand the MDS opportunity to $1.2B, upside that is not in CELG's guidance. A 200-patient Phase II trial suggested activity, with a 26% rate of transfusion independence.

Abraxane:

- Celgene believes it is only in the "second inning" of Abraxane's uptake in pancreatic cancer. The company divides the market approximately into thirds: (1) patients receiving gemcitabine combinations; (2) patients receiving gemcitabine monotherapy (frailer patients); and (3) patients receiving experimental regimens. Abraxane is being taken up most rapidly in the first segment, though the company expects eventually to take some share in the second, as physicians learn how to best give the drug. There is some hint that Abraxane may even be taking share from FOLFIRINOX, though this trend is quite early and uncertain as yet.

Pipeline:

- Management continues to highlight its Acceleron partnership as a key pipeline program, with potential in beta-thalassemia, MDS, and CKD-mineral bone disorder. Data for sotatercept (ACE-011) in CKD are expected at the NKF meeting in April.
- Management noted the treatment of ibrutinib-failure CLL as a possible path to market for its Btk inhibitor, CC-292. At this year's ASH meeting, data from three early trials in rrCLL are expected: (1) CC-292 + Revlimid, (2) CC-292 + Rituxan, and (3) Revlimid + ibrutinib.

Source: Cowen and Company/Schmidt, March 4, 2014
Oncology Indication: Multiple
Keyword: Management/Strategy/Financials

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China Medical System: CMS024 Phase III Data in HCC Fails to Show Benefit; Subgroup Analysis Yields Favorable Trends

China Medical System (CMS) announced very disappointing results for its Phase 3 trial of CMS024 in hepatocellular carcinoma. In the Full Analysis Set (n=298), there is no statistically significant difference in the primary endpoint of recurrence-free survival (RFS) between the treatment and placebo groups (p=0.40). For the secondary endpoint of overall survival (OS), the difference between the two groups is also not statistically significant (p=0.58). This pretty much kills CMS024 as a major blockbuster for CMS.

The trial was a randomized, double- blind, placebo-control, multicenter study to evaluate the efficacy and safety of Tyroserleutide for injection used to treat hepatocellular carcinoma. It employed portal vein intra-abdominal chemotherapy with Fluorouracil (40ml) and Mitomycin (10mg) as a basal treatment in both treatment groups. The primary endpoint was the recurrence-free survival (RFS) and the secondary endpoint was the overall survival (OS). CMS024 Clinical Trial enrolled the first subject on 11 November 2011 and completed the enrollment of 300 subjects on 23 October 2013.

Subgroup analysis yields a bit of hope but we are not optimistic. According to the clinical design, Interactive Voice/Web Response System (IVRS/IWRS) was employed in the randomization process, stratified by tumor invasion (yes/no, branches of portal vein involved by the tumor) and number of tumors (single/multiple) to ensure the balance at baseline. Statistical Analysis Plan (SAP) also pre-specified the subgroup analysis based on these two factors. The subgroup analysis on subjects with no tumor invasion (n=149) reveals that there are favorable trends for the treatment group compared to the placebo group in both RFS and OS. In this subgroup, the relapse rate was notably reduced in the treatment group compared to the placebo group (p=0.37) with the improvement in OS even more notable (p=0.08).

Since the subgroup of patients with tumor invasion is pre-specified, the subgroup analysis is legitimate and should not be regarded as pure data-mining. It is reasonable to expect tumor invasion to interfere with CMS024 treatment. However, we do caution that another costly trial, not a financial burden for CMS, will need to be carried out and the commercial opportunity will be much more limited and delayed significantly. In addition, it has been quite common for large trials not to replicate results from small trials with few patient samples.

Source: JPMorgan/Wu, March 5, 2014
Oncology Indication: Liver
Keyword: Clinical Trials/Pipeline

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Puma Biotech: Neratinib (Phase III): Positive Results Expected from Adjuvant Trial; Data in Other Indications Expected in 1Q15; Key Concern is Its Toxicity Profile

Positive results expected from the adjuvant neratinib trial, which we estimate has the greatest market opportunity as duration of treatment would likely be 12 months. The Phase III trial compares 1-year of either neratinib or placebo after 1-year of Herceptin has already been administered. We estimate an interim data release at the 3-year mark in 1H14. We note that the HERA trial, which examined adjuvant Herceptin for 1 year vs. 2 years, showed a non-statistically significant trend favoring 2 years of Herceptin treatment at 3 years, but that trend vanished when the full data was released at 5 years. We see positive results at 3-years as a de-risking event, though not an assurance of 5-year success. Nonetheless, we anticipate positive results and estimate $937M of adjuvant neratinib sales in 2020.

We see the clearest path to approval for neratinib coming from the late-line combination with Tesorlimus in metastatic breast cancer, which has shown 44% PR and 48% CBR (n=27) in interim releases from the Phase II study. We expect mature data from the full 34 patient cohort in 2H14, with the results informing the design of a Phase III study before the end of 2014. We also see a pathway to registration through the brain metastases studies, currently in Phase II in combination with Xeloda against single agent neratinib. Neratinib has shown a clear clinical signal with Xeloda with a 64% ORR and mPFS of 40.3 weeks in second-line metastatic breast cancer. We expect data from that trial in 1H14.

In neoadjuvant breast cancer, neratinib graduated from the I-SPY 2 trial by demonstrating a Bayesian probability of superiority compared to Herceptin, though we believe positive results from the FB7 trial using the combination of neratinib + Herceptin are necessary for approval. We expect positive data from both trials to in 1H14 with initiation of the Phase III I-SPY3 trial in 4Q14.

In NSCLC with Her2 mutations, we estimate an ORR of 44% alone and 47% in combination with Torisel from researchers at Dana Farber studying neratinib. We expect data from this non-placebo controlled Phase II trial in 2H14. In solid tumors, PBYI is studying neratinib in a “basket” trial for multiple types of tumor. We expect expansion of an initial indication in 1Q14 with data in 1Q15 in either colon, pancreatic, or bladder cancer.

We see the biggest concern for neratinib not being from its efficacy, which we believe investigators have clearly demonstrated in myriad trials, but rather its toxicity profile. Recent trials with mandatory prophylaxis have had 3% grade 3/4 diarrhea with 10-20% lower grade diarrhea, which is a significant reduction from the ~30% of grade 3/4 diarhea seen in earlier trials. We estimate that as larger trials require the use of prophylaxis, the toxicity profile will continue to improve.

Source: Stifel/Sendek, March 3, 2014
Oncology Indication: Breast
Keyword: Clinical Trials/Pipeline

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Ziopharm: Completely De-Emphasizes Small Molecule Programs and Seeks to Out-License Them; Clinical Proof-of-Concept for Novel Gene-Rx Oncology Platform Possible in 2014

Early data from the lead inducible-IL-12 adenovirus (Ad-RTS-IL-12) Phase II studies in metastatic melanoma and breast cancer is expected in 4Q14. Additionally, Ziopharm expects to file multiple INDs through 2015. While we remain fundamentally optimistic for future developments in immunotherapies for oncology and "synthetic biology," we also view Ziopharm's programs as having limited clinical validation, particularly within the context of past pipeline challenges.

Ziopharm has completely de-emphasized the small molecule programs and seeks to out-license them for further development. The only remaining ongoing program, to our knowledge, is the Phase III study of palifosfamide in small-cell lung cancer (MATISSE) which had enrollment halted at 188 patients following the PICASSO3 sarcoma results. An interim for overall survival for MATISSE is now projected for 2H14 (we had previously estimated 1H14).

Broader potential from novel platform. While it makes sense that Ziopharm's gene-therapy constructs for local delivery are less toxic than systemic IL-12, we're not convinced it offers any advantages over local delivery of IL-12. The addition of a layer of technical complication through regulation by adenoviral or adenoviral + dendritic cell carriers, which are almost certainly no easier to manufacture in a GMP manner than IL-12 itself, and then another layer through the use of a small-molecule regulator (veledimex), with its own ADME properties to manage, seems fraught with execution risk. In other words, can delivering IL-12 through a drug-inducible viral vector really be more controllable vs. simply injecting IL-12 locally? That said, particularly with an indication in a difficult-to-access location, like brain cancer, taking an oral activator to produce IL-12 likely has advantages over direct injections. Also, it is possible Ziopharm's constructs provide more sustained expression of IL-12, and the ability to express multiple genes, possibly using independent promoters and/or integrating feedback loops could prove useful and possibly achieve ends otherwise unachievable. These possible advantages in the clinic drive our inclusion of a pipeline/platform value for Ziopharm.

Source: Piper Jaffray/Duncan, March 4, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Synta: Long-Time CEO Resigned; Hopes to Name Replacement within Six Months; Management Change Could Move Company Forward in a New Direction

Synta (SNTA) announced several executive management changes yesterday. Most notably, Dr. Safi Bahcall resigned as CEO, President and Board member. In our view, the timing is very much unexpected. A national search firm has been retained, and while there is no sense of urgency, SNTA hopes that a new CEO might be named within six months.

Other changes include a newly formed Executive Committee of the Board, led by Mr. Gollust and including other key Board members, will serve as a "the principal executive body" for the company. In addition, the news also coincides with the naming of Dr. Paul Friedman, MD to the Board of Directors. Dr. Friedman is a well-known name in biotech: he was most recently CEO of Incyte (INCY) from 2001 until 2014, and in addition to still serving as a Board Director at there, he is also a Director at Auxilium Pharmaceuticals (AUXL), Durata Pharmaceuticals (DRTX), and two private companies. Thus, overall, we see him as a strong addition.

Given the near-term commercial prospects for ganetespib (Phase III) and excitement around the new Hsp-90 drug conjugate (HDC) platform, we're not surprised by the management change. Also, given a view that Dr. Bahcall was not universally embraced by the Street, we think this allows SNTA to move forward in a fresh new direction.

Source: MLV & Co/Suvannavejh, March 4, 2014
Oncology Indication: Lung
Keyword: Management/Strategy/Financials

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Santen: Enters Deal with TRACON for Development and Commercialization of Anti-Endoglin Antibodies (Cancer/Ophthalmology)

TRACON Pharmaceuticals and Santen Pharmaceutical have entered into an exclusive agreement for the development and global commercialization of TRACON's anti-endoglin antibodies, including TRC105, in ophthalmology. Santen will make a $10 million upfront payment and certain milestone payments to TRACON in the development phase, and will pay commercialization milestones and tiered royalties on global sales of the product. Santen will fund 100% of all global development, and commercialization activities, including the initiation of IND-enabling studies. TRACON will continue ongoing Phase II development of TRC105 in a number of oncology indications, and will retain global rights on applications of its anti-endoglin antibody portfolio outside of ophthalmology.

According to TRACON, preclinical and clinical data from its ongoing development of TRC105 in combination with anti-VEGF products in oncology indicate inhibiting both the endoglin and VEGF pathways has the potential to show advantages over inhibiting VEGF alone in the treatment of conditions such as wet age-related macular degeneration.

"The experience TRACON has gained in the development of TRC105 in oncology, by combining TRC105 with bevacizumab and other inhibitors of the VEGF pathway, reinforces our belief that development of TRC105 in serious angiogenesis-driven eye diseases is an outstanding product development opportunity," said Charles Theuer, M.D., Ph.D., president and CEO of TRACON.

"TRC105 is an antibody that inhibits a novel target, endoglin, a key mediator of resistance to VEGF inhibitor treatment in angiogenesis-driven diseases," said Akira Kurokawa, president and CEO of Santen.

The TRC105 oncology development program includes two ongoing randomized Phase IIb studies with bevacizumab in renal cell carcinoma and glioblastoma, and combination studies with axitinib in renal cell carcinoma, with pazopanib in advanced soft tissue sarcoma and with sorafenib in hepatocellular carcinoma.

Source: Genetic Engineering & Biotechnology News, March 5, 2014
Oncology Indication: Multiple
Keyword: Partnerships/Business Developments