HealthACE Pharma Business Intelligence

Oncology Intelligence Report

February 5, 2014 Wednesday

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HealthACE Abstract *Indication: Multiple*

Additional Analysis

Clinical Trials for Lambrolizumab (MK-3475)

Study Name Design	Indication	Endpts	Estimated Completion Date
NCT01866319 Phase III; Two Different Dosing Schedule; vs. Ipilimumab	Melanoma (Advanced)	1º: PFS, OS 2º: ORR	March 2016 Recruiting
NCT01905657 Phase II/III; vs. Docetaxel	NSCLC (Two Doses; Previously-Treated Participants)	1º: OS, PFS Adverse events; 2º: ORR, DOR	January 2020 Recruiting
NCT01704287 Phase II; vs. Chemo	Melanoma (Advanced)	1º: PFS, OS 2º: ORR, DOR	January 2016 Active, Not Recruiting
NCT02039674 Phase II; Combination wth Chemo or Immunotherapy	NSCLC	1º: PFS, ORR	July 2018 Recruiting
NCT01848834 Phase I	Solid Tumors (TNBC, H&N, Urothelial Tract, Gastric)	1º: Adverse events, ORR	October 2014 Recruiting
NCT01840579 Phase I	Part A: Solid Tumors Part B: NSCLC (Combo with Chemo)	1º: DLTs	April 2015 Recruiting
NCT02054806 Phase I	Solid Tumors (Advanced)	1º: Best overall response; 2º: PFS, OS, DOR	November 2015 Not Yet Recruiting
NCT01295827 Phase I	Solid Tumors (Five Parts)	1º: DLTs, Adverse events, RR, DCR	February 2016 Recruiting
NCT01953692 Phase I	Blood Cancers (MDS, HL, NHL)	1º: Adverse events, ORR	March 2016 Recruiting
NCT02007070 Phase I	NSCLC (Advanced)	1º: ORR, Adverse events; 2º: PFS, OS, Duration of response	August 2016 Not Yet Recruiting
NCT02036502 Phase I; Combination with Lenalidomide and Dexamethasone	Multiple Myeloma	1º: DLTs, Adverse events; 2º: ORR, CR, TTP, DOR, PFS, OS, Change in PD-L1 expression	March 2017 Not Yet Recruiting

CR: Complete Response
DCR: Disease Control Rate
DLTs: Dose-Limiting Toxicities
DOR: Duration of Response
NSCLC: Non-Small Cell Lung Cancer
OS: Overall Survival
ORR: Objective Response Rate
PFS: Progression-Free Survival
TTP: Time to Progression

Source: www.clinicaltrials.gov

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Merck & Co.: Establishes 3 Immuno-Oncology Collaborations with Incyte (IDO), Amgen (T-VEC) and Pfizer (Inlyta); Launch New Phase I "Signal Finding" Study of MK-3475 in 20 Different PD-L1+ Solid Tumor Types

The announcement of **three immune-oncology collaborations with Incyte (IDO), Amgen (T-VEC) and Pfizer (Inlyta, anti-CD37)** is very much as expected although notably announced ahead of competing sponsors of PD-1 mediated assets. Citi analysts expect Bristol-Myers (BMY), AstraZeneca (AZN) and Roche to announce combinations of their own in due course. The slower timelines for BMY's nivolumab+Yervoy combination provides a positive backdrop for MRK to explore MK-3475 + IDO-based therapy.

The newly-signed collaborations will all entail Phase I/II clinical studies focused on combinations of MK-3475 with:

- Incyte's investigational immunotherapy agent INCB24360, an oral indoleamine dioxygenase-1 (IDO1) inhibitor, in patients with previously-treated metastatic and recurrent non-small cell lung cancer (NSCLC), among other advanced or metastatic cancers.
- Pfizer's small molecule kinase inhibitor axitinib (Inlyta) in patients with renal cell carcinoma (RCC); as well as the combination of MK-3475 plus Pfizer's investigational immuno-oncology agent PF-05082566 (PF-2566) in multiple cancer types.
- Amgen's investigational oncolytic immunotherapy talimogene laherparepvec (T-VEC) in patients with previously untreated advanced melanoma.

The collaborations are similar to one announced by MRK in December, in which it agreed to assess the combination of MK-3475 with the GlaxoSmithKline (GSK) oral kinase inhibitor Votrient (pazopanib) in advanced renal cell carcinoma, and study other combinations of MK-3475 and other GSK drugs.

Amgen said the MK-3475/T-VEC trial is planned to begin in the fall of 2014, and will consist of two parts: A Phase Ib study assessing the safety and tolerability of T-VEC in combination with MK-3475 in patients with previously untreated, unresected, stage IIIB to IVM1a melanoma; and a Phase II study evaluating efficacy, based on the confirmed objective response rate (ORR), of T-VEC in combination with MK-3475 versus MK-3475 alone in patients with previously untreated, unresected, stage IIIB to IVM1c melanoma. The study will also evaluate the efficacy of treatment with T-VEC in combination with MK-3475 following disease progression on MK-3475 alone.

Pfizer said that under its program with Merck, it will conduct the Phase II RCC study of MK-3475 plus Inlyta: as well as a Phase I study evaluating the safety and tolerability of MK-3475 and PF-2566. PF-2566 is a fully humanized monoclonal antibody (mAb) that stimulates signaling through 4-1BB (CD-137), a protein involved in regulation of immune cell proliferation and survival.

Incyte's study with Merck will consist of a Phase I portion expected to establish a recommended dose regimen of INCB24360 and MK-3475, followed by a Phase II portion in which all patients receive MK-3475, then randomized to receive either INCB24360 or matching placebo. The study is expected to begin in the first half of 2014. Incyte said its collaboration with MRK follows preclinical studies that suggested a combination of INCB24360 and MK-3475 may lead to an enhanced anti-tumor immune response than either agent alone.

In addition, MRK said it will **launch a new Phase I "signal finding" study to evaluate the safety and efficacy of MK-3475 monotherapy in 20 different PD-L1-positive solid tumor types** that have "not responded to current therapy, for which current therapy is not appropriate, or for which no current therapy exists," according to ClinicalTrials.gov (NCT02054806). As of Feb. 3rd, the trial was not yet open for participant recruitment.

Source: Citigroup/Baum & Genetic Engineering & Biotechnology News, February 5, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Incyte: Immuno-Oncology Collaboration with Merck & Co. Validates Its IDO1 Program; Additional Partnerships Possible

This morning, Incyte (INCY) announced that it entered into a clinical collaboration agreement with Merck & Co. (MRK) to evaluate its oral indoleamine dioxygenase-1 (IDO1) inhibitor (INCB24360) and MRK's anti-PD-1 inhibitor MK-3475 in a Phase 1/2 study for the treatment of non-small cell lung cancer (NSCLC) and other advanced cancers.

We view this as an incremental positive in that it somewhat validates the IDO1 program (MRK evaluated INCY's emerging data under CDA), offset by the fact that MRK is casting a pretty wide net with collaborations also announced with Amgen and Pfizer. We believe other immuno-oncology players are also confidentially looking at '360 and wouldn't be surprised by additional clinical collaborations.

INCY and MRK will collaborate on a Phase 1/2 study in patients with previously treated metastatic and recurrent NSCLC and other advanced and metastatic cancers. The Phase 1 dose finding portion of the trial is expected to begin in 1H14. Once the regimen has been established all patients in Phase 2 will receive MK-3475 and randomized further to receive either INCB24360 or placebo. INCY will conduct the study, but it will be co-funded by both companies.

We believe INCY's IDO inhibitor is likely to be a key contributor of additional value for INCY in 2014. A combination study with Yervoy in melanoma is ongoing, and INCY is encouraged with the early data it has seen and expects to present results of the open-label dose finding run-in portion of the study at ASCO in June. INCY is confident (based on data that it has) that INCB24360 will compare favorably with historical controls with Yervoy alone (~11% ORR, 3 mos TTP).

Source: JPMorgan/Kasimov, February 5, 2014
Oncology Indication: Lung
Keyword: Partnerships/Business Developments

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Roche: Sequential and Combination Regimens Will Be Key to Growth for Its Lymphoma Franchise and Immuno-Oncology Program

Lymphoma: Roche generates c.$7bn of sales from the lymphoma drug Rituxan. Not only does it face biosimilars from 2016 in Europe, but also there are multiple new drugs threatening to disrupt the current treatment status quo. In particular J&J's ibrutinib and Gilead's idelalisib are poised to enter the market changing the treatment paradigm (initially only the $1bn CLL market) from repeated courses of Rituxan and chemotherapy to potential chronic treatment with these less-toxic pills. While new drugs are to a large extent likely to be used in combination with incumbents, at present, it is unclear exactly how the market will eventually change (this will be driven by future data) and a billion dollars here and a billion there of high margin profit contribution is at risk of erosion.

- Although uncertainty is rarely a positive to share prices, current data suggests little change to the status quo. Indeed in the larger areas of Rituxan's useage (NHL) it appears that the new orals will need to be used in combination to gain maximum efficacy (and this data is not due for another 2-3 years).
- Although J&J's Ibrutinib is first to market, early data suggests Roche's ABT-199 could be best in class (of the new orals). In addition, KOLs appear to be most looking forward to combination data from ABT-199 and Roche' Gazyva in this setting. Not only does this potentially protect the lymphoma franchise through longer durations of usage, incorporation of CD-20 antibodies into multiple sequential and combination regimens and price upgrades suggest Roche is potentially in a position to significantly grow its lymphoma franchise.

Immune Checkpoint inhibitors: Roche is number 2 or 3 in a race to create an exciting new class. However, not only is there the usual clinical risk that Roche could miss out on the upside should its drug not work, the risk is that immunotherapeutics may usurp current Roche products (e.g. Avastin). Longer-term, Roche may stand to gain from combination use of products, but it is very unclear whether Roche will: A) have a competitive immunotherapeutic; B) have the portfolio most suited to combination usage. As such, until we see data from Roche late in 2014, the market may focus on the risks to Roche's franchises (potentially $6bn to Avastin, initially c.$1-2bn in lung cancer) rather than the rewards.

- We see this discussion as overly pessimistic. At present there is no evidence to suggest BMS or other companies have a more viable strategy than Roche in this field. However, there is significant evidence to suggest that on their own immunotherapeutics may not offer the full solution to all patients (eg. ~20% response rates in lung cancer), thus, both sequential and combination therapies will be needed.
- Roche's Avastin will likely remain a mainstay of treatment. Not only does the drug damage the tumor vascular development, the inhibition of VEGF may also reduce VEGF induced immunosuppression and allow for better lymphocyte trafficking to the tumor (Roche is currently conducting early combination trials of its PD-L1 with Avastin. Early data is possible in 2014).
- With the best scientisits in the industry, the best diagnostic company in-house and a wealth of products at its disposal, we believe the current winner and loser investment mentality in this field seriously underestimates Roche's ability to not only claw back BMS's (6-9 month) lead, but potentially overcome it. However, importantly we note that while investors have priced in multiple billions of outer year sales to BMS (demonstrated by its x29 PE) Roche is trading at only 15.5x with only ~$600m in PD-L1 sales carried by consensus forecasts [source: EvaluatePharma]. Risk reward, in our view, appears significantly favorable to Roche.

Source: Deutsche Bank/Race, February 5, 2014
Oncology Indication: Multiple
Keyword: Management/Strategy/Financials

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Ono Pharmaceutical: Starts Phase II Trials for Nivolumab in Esophageal Cancer; Melanoma Approval Possible By September

Q3 results were in line with expectations. Ono has started Phase 2 trials in Japan for anticancer agent nivolumab for esophageal cancer of the squamous-cell epithelium (90% of esophageal cancers in Japan are of this type, according to Gan Joho). Development is being pushed in Japan as this type of cancer particularly affects Japanese people.

We understand that the review of nivolumab for the melanoma indication, for which an NDA was filed in Japan in December, is progressing and we note the possibility that, if things go smoothly, nivolumab will be reviewed by the subcommittee in July-August and approved in September.

We also await the Phase 2 trial (Checkmate 063) results for nivolumab as a third-line treatment for non-small cell lung cancer, the top-line data for which is due to be released by March.

Source: Citigroup/Yamaguchi, February 4, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Pharmacyclics: Priority Review for Gilead's Idelalisib (CLL), Minimal Impact to Imbruvica's Launch

As detailed on its FY13 earnings call, Gilead (GILD) submitted an NDA for idelalisib in relapsed/refractory CLL on December 6, 2013, on the basis of predicted PFS benefit in Study 116 evaluating idelalisib plus rituximab versus rituximab plus placebo. A CLL PDUFA date is set for August 6th. This comes slightly ahead of idelalisib's second PDUFA date, September 11th, for indolent non-Hodgkin lymphoma (iNHL), which was granted standard review.

Although the priority review timing is slightly ahead of our expectations for idelalisib in CLL, we see minimal incremental impact to the commercial launch of Imbruvica, which has already garnered significant advantages ahead of its formal CLL PDUFA date of February 28th (e.g., current commercial availability, incorporation into NCCN guidelines, demonstrated OS benefit in the RESONATE trial). Further, we believe that as Imbruvica's commercial head-start over idelalisib draws to a close in 3Q14, patients and physicians will ultimately maintain strong preferences for the single-agent oral regimen, thus relegating idelalisib to later lines of therapy.

We remain confident in management's ability to execute on the launch of Imbruvica, and continue to believe that Imbruvica will achieve blockbuster status, and go on to become the largest selling drug in hematologic malignancy. We forecast initial Imbruvica FY14 sales of $327.7MM, approaching $600MM by 2015 and growing to $5.9bn by 2022.

Source: JMP Securities/King, February 4, 2014
Oncology Indication: Hematologic
Keyword: FDA/Regulatory Issues

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Ariad: Re-Launches Iclusig with a Smaller Field Force; Has Potential to Slowly Gain Share in Earlier Lines of Therapy for CML, Approach $500M in U.S. Sales By 2018

Ariad is re-launching with a slimmed down field force roughly half the size of the previous sales force of 65. The company indicated there were a total of 370 requests for drug under the IND process of which they shipped drug to 305. As of January 16th, the company began converting those patients to commercial drug. Importantly, many treated patients are still finishing doses from the IND process, suggesting to us that the true sales ramp for the re-launch begins this month. Ariad also indicated that for competitive reasons they are not reporting sales to IMS and are only using one specialty pharmacy compared to nearly 10 in 2013.

Our analysis of IMS weekly script data shows that under 25% of Iclusig patients switched to either Bosulif, Tasigna, or other treatments following Iclusig suspension. We see this as indicative of the lack of consensus options to replace Iclusig and view this positively for the positioning of Iclusig as a viable late-line therapy. As patients finish their January doses of CML drug, we expect to see a decrease in scripts as patients switch back to Iclusig and will look to this metric to gauge re-adoption of Iclusig.

We believe Iclusig has the potential to slowly gain share in earlier lines of therapy for CML, and approach $500M in U.S. sales by 2018. For chronic phase patients, management suggested therapy duration of 3-4 years is reasonable, which is higher than our average estimate of 18 months, suggesting potential upside to our estimates. Given 1300 U.S. patients that fail two or more TKIs each year (including 315i patients) at a net annual price of ~$113k and 3.5 year duration of therapy, we arrive at greater than $500M annual US market opportunity with significant upside potential based on penetration into the 2600 annual incidence of 2nd line patients. We note that ~30% of patients on Gleevec fail after three months of therapy, so we believe that there is upside potential to the size of the second line population.

Though Iclusig's approval is for third-line and T315i mutants, we note that approximately 25% of the patients on commercial drug in 2013 were second-line patients, and that approximately 20% of the patients on IND access were second line patients. We view this as supporting our 31% estimate of 2014 second line patients. This segment of Iclusig usage is important because duration of therapy increases substantially in earlier lines of therapy and could exceed 10 years. Management believes that they have room to be more aggressive on increasing price, but that they are reluctant to pursue greater increases in order to preserve the opportunity in the second line, pending further data and a label expansion.

We reduce our 4Q13 Iclusig ex-US revenue estimate to $7.3M from $11.3M to recognize that sales from certain countries will require deferred revenue recognition. This is due to the ongoing price negotiations, for example in France. Management indicated France and Italy should contribute to EU sales by 2H14.

The low dose Iclusig trial is on track to start in 2H14 with data by year-end 2015. The intention of the trial is to determine if Iclusig could maintain its efficacy at a lower dose while improving tolerability. If so, it could facilitate usage in earlier lines of therapy. We see the analysis of the PACE trial presented at ASH that showed a 40% decrease in CV events for each 15mg decrease in dose as a framework from which to work from for this trial. We note that in that trial, 96% of complete cytogenic response patients who had their dose reduced maintained the CCR through dose reduction.

GIST remains another area of potential upside for Iclusig. Management expects FDA to soon lift the clinical hold on the current study in GIST. Given the trial has already enrolled 43 of 50 targeting patients and most continue to receive drug, the trial should not take long to complete, and will now incorporate dose reductions. Investigators showed promising data from 1 patient in January that showed shrinkage of progressive lesions in a patient who had progressed on 4 previous therapies.

Source: Stifel/Sendek, February 5, 2014
Oncology Indication: Hematologic
Keyword: Management/Strategy/Financials

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Myriad Genetics: Private Payor May Not Follow CMS Price Cut; myRisk Gaining Momentum; Acquisition of Crescendo to Diversifies Business

Myriad Genetics (MYGN) reported solid F2Q14 results, aided by continued publicity tailwinds ($15- 20M) and early myRisk uptake (~$12M), while also announcing the formal acquisition of Crescendo Bioscience for $270M.

MYGN reported revenues of $204M, +37%, coming in significantly above consensus ($175M) and JPMe ($169M), as celebrity tailwinds had more of a positive impact than expected (guidance was for $7-9M) and myRisk had solid early uptake, with revenues of $11.5M or ~6% of total. Management noted that the celebrity tailwind wore off in December and no further impact is expected. BRACAnalysis in total grew 28% (or 17% for the core business removing ~$12.5M for the Angelina Jolie effect), while total Oncology grew 12% to $102M and Women's Health grew 90% to $95M. BART revenues were again strong as well, coming in at $25M, and now almost all BRCA tests now have a corresponding BART test. Elsewhere in the portfolio, COLARIS/COLARIS AP grew 29% and the company continues to expect Medicare reimbursement for Prolaris by the end of FY14.

Regarding competitive dynamics, management acknowledged modest share loss in the quarter, on top of the <3% share loss in F1Q, primarily in the genetics portion of the oncology business, which is now 15% of revenues. We expect larger players, including Quest and LabCorp – both entrants in the market late in 2013, to have more of an impact on market share in F2H14. Management also discussed the recent CMS pricing cut, noting that the company has had conversations with private payors compromising ~75% of revenues and have not seen any change in ASP, suggesting that private payors may not follow the CMS cut, although it remains to be seen whether they will go down this path in the future. The company did note that the CMS cut will result in a 40% reduction to pricing, but only for 9% of revenues (~$13M impact for the year).

myRisk gaining momentum. In the first full quarter of sales, myRisk contributed an impressive $11.5M in revenues. MYGN is currently expanding the access launch and believes the ease of use when ordering (no longer have to prioritize what genes to test), as well as the improving turnaround time (approximately two weeks based on process improvements) will continue to drive strong uptake. The company is in the process of collecting clinical utility data from early users, publishing clinical validation data, and performing pharmacoeconomic studies to further support payor conversations. We note that currently myRisk is reimbursed under BRCA codes, so the CMS pricing cut will also impact this ASP. Management continues to expect to fully convert the hereditary market to myRisk by the summer of 2015.

Crescendo Bioscience acquired for $270M. Crescendo develops diagnostic tests for patients with autoimmune disorders. The first product, Vectra DA, was launched in late 2010 and is used to determine the level of disease activity in patients with rheumatoid arthritis (RA) and subsequently, assesses patient response to interventions (i.e. severity of disease, is patient on the right therapy, what is effect of co-morbidities, is patient at risk for bone erosion, is patient in remission, chances of a flare up, etc.). We expect follow on tests to cover other autoimmune disorders, such as lupus and juvenile arthritis (JA).

Source: JPMorgan/Peterson, February 4, 2014
Oncology Indication: Multiple
Keyword: Management/Strategy/Financials

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Genomic Health: 4Q13 Revenue In-Line with Strong Growth in Prostate and International Growth; Increases Urology Field Team and Accelerated Investments to Drive Adoption

Genomic Health (GHDX) reported 4Q13 results in line with expectations for revenue and well below for EPS. The company saw traction in key growth products and international markets, although continued investments have deteriorated leverage in the near-term. Management also guided below our estimates on the top-line and for a loss in 2014, as it plans to invest further in new products and growing markets.

Revenues of $68.8M were in-line with consensus, primarily driven by strong growth in prostate and international (+49% y/y). Validating the uptake in new markets, GHDX delivered 22,720 tests in 4Q13 (+21% y/y). Looking ahead, management guided for FY14 sales of $278-286M and for 98,000-102,500 Oncotype DX tests.

Highlighting the commercial progress in international markets specifically, management noted that the company has established breast cancer coverage for an additional 7.5M individuals through contracts with payors in the Czech Republic, Mexico and Peru, bringing total OUS coverage to +115M lives. Oncotype DX also received NICE's exclusive recommendation as the only multi-gene breast cancer test to guide chemotherapy decisions, which should serve as a driver for adoption with payors in Western Europe.

Turning to other products, management noted that >500 physicians and 80% of targeted urology accounts ordered Oncotype DX Prostate tests with >50% of physicians ordering tests for multiple patients. Domestically, GHDX also received notice of allowance from the US Patent Office for patent claims related to the Oncotype DX Prostate cancer test algorithm.

GHDX posted 4Q13 EPS of $0.30, missing expectations, in part due to continued investments in sales and marketing for the Oncotype DX Prostate test and in OUS markets. Given the large prostate cancer opportunity and encouraging uptake, management has increased the urology field team and accelerated investments to drive adoption.

Source: JPMorgan/Peterson, February 4, 2014
Oncology Indication: Multiple
Keyword: Management/Strategy/Financials