HealthACE Pharma Business Intelligence

Oncology Intelligence Report

February 12, 2014 Wednesday

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HealthACE Abstract *Indication: General*

Additional Analysis

Phase III Trials for Imbruvica (Ibrutinib)

Study Name Design	Indication	Endpts	Estimated Completion Date
NCT01578707 RESONATE; vs. Ofatumumab	CLL (Relapsed/Refractory)	1º: PFS 2º: OS, Hematological improvements, Improvement of diseased-related symptoms	December 2015 Ongoing
NCT01722487 RESONATE-2; vs. Chlorambucil	CLL/SLL (Patients 65 Years or Older, Treatment-Naïve)	1º: PFS 2º: OS, Hematological improvements, Improvement of diseased-related symptoms	February 2016 Recruiting
NCT01973387 CLL3002; vs. Rituximab	CLL/SLL (Relapsed or Refractory)	1º: PFS 2º: ORR, OS, Hematological improvements, Event-free survival	June 2016 Recruiting
NCT01646021 RAY; vs. Temsirolimus	MCL (Relapsed/Refractory, At Least One Prior Therapy	1º: PFS 2º: ORR, OS, 1-year survival rate, Duration of response, # of participants with adverse events	March 2017 Recruiting
NCT01886872 ALLIANCE 41202; vs. Rituximab and Bendamustine	CLL (First-Line Elderly Patients)	1º: PFS 2º: OS, TTP, DOR	March 2018 Not Yet Recruiting
NCT01611090 HELIOS; Combo with Bendamustine and Rituximab	CLL/SLL	1º: PFS 2º: # of participants with adverse events, ORR, OS, Rate of minimal residual disease-negative remissions	March 2018 Recruiting
NCT01776840 SHINE; Combo with Bendamustine and Rituximab	MCL (Newly Diagnosed)	1º: PFS 2º: OS, ORR, Minimal residual disease-negative rate, Duration of response	October 2019 Recruiting
NCT01855750 DBL3001; Combo with R-CHOP	DLBCL (Newly Diagnosed Non-Germinal Center B-Cell Subtype)	1º: Event-free survival; 2º: PFS, OS, Complete RR	June 2020 Recruiting
NCT01974440 FLR3001; Combo with Bendamustine and Rituximab or R-CHOP	iNHL (Previously Treated)	1º: Event-free survival; 2º: PFS, OS, Complete RR	August 2021 Not Yet Recruiting

CLL: Chronic Lymphocytic Leukemia
DLCBL: Diffuse Large B-cell Lymphoma
FL: Follicular Lymphoma
MCL: Mantle Cell Lymphoma
SLL: Small Lymphocytic Lymphoma
DOR: Duration of Response
PFR: Progression-Free Survival
ORR: Overall Response Rate
OS: Overall Survival
TTP: Time to Progression

Source: www.clinicaltrials.gov

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Pharmacyclics: FDA Approves Imbruvica for R/R CLL with No Black Box Warning; Approval Based on Single-Arm Trial, Not Phase III RESONATE

On February 12th, the FDA approved Imbruvica for relapsed/refractory (r/r) chronic lymphocytic leukemia (CLL). Today's approval is in-line with Street expectations and is ahead of 2/28/14 PDUFA. Our physician checks and market analysis continue to indicate Imbruvica should be a major drug. We continue to expect a strong launch and remain ahead of consensus for U.S. sales in 2014E ($312mn vs. $208mn).

No black box warning in FDA release: We view this as positive but also as in-line. Side effects highlighted in FDA press release are all highlighted in the current Imbruvica label for r/r MCL.

Difference in ORR in label vs. NEJM: The FDA press release also states that the overall response rate (ORR) with Imbruvica in r/r CLL was 58%. This does not coincide with the 71% ORR reported in the NEJM article. As per Pharmacyclics, this is due to differences in follow-up time (15.6 vs. 20.9 months). Recall ORR improves with time. Additionally, investigator assessed response in NEJM and radiologic assessment for label was different. Finally, the sample size was 48 in the label and 85 in NEJM.

Approval was based on single-arm trial: We note that approval was based on the single-arm trial and not on the phase 3 RESONATE trial which read out positively in early January. We note that RESONATE was the first randomized trial of Imbruvica. We anticipate Pharmacyclics to formally file RESONATE data shortly, which will result in a label update in H2:14. Updated label will also include survival claim for Imbruvica. RESONATE data is expected to be presented at ASCO 2014 in June.

Source: Goldman Sachs/Singh, February 12, 2014
Oncology Indication: Hematologic
Keyword: FDA/Regulatory Issues

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Seattle Genetics: 2014 Adcetris Sales Guidance Conservative, Not Fully Reflecting Future Price Increases, Improved Duration, and Off-Label Use; Focus Turns to Three Pipeline Events

Seattle Genetics (SGEN) reported Q4 Adcetris US sales of $38.5mn (5.6% Q/Q), in-line with consensus of $37mn. For 2014, SGEN guided to Adcetris sales of $155- $165mn, R&D of $245-$265mn and SG&A of $100-$110mn. Based on Q4 Adcetris run rate and recent 4% price increase, 2014 sales guidance seems conservative and does not fully reflect: (1) future price increases, (2) improved duration and (3) off-label PTCL use. We and consensus model higher at $172mn (19% Y/Y).

Catalyst #1: SGN-CD19A in r/r ALL data at ASCO. SGEN is optimizing dosing and implementing prophylactic eye drops for SGN-CD19A to minimize Grade 3 ocular toxicity. Complete response rates of >40% and lasting >4 months would be competitive.

Catalyst #2: AETHERA data in H2:14 - eyes on PFS curves. SGEN previously noted 60-70% of high-risk HL patients should relapse 12-18 months post-transplant. Thus, we should see separation of PFS curves by H2:14 (time of unblinding and >24 months since start). Separation is necessary for FDA approval of Adcetris for high-risk HL (~1K patient opportunity in US).

Catalyst #3: SGN-CD33A in r/r AML data at ASH. There are ~15K new AML cases in US and treatment options are limited. Response rates of >30% would be deemed compelling.

Exhibit 1: Q4 Actual vs. Consensus

	Q4 2013		
	Actual	Consensus	Delta
Revenues			
Adcetris	$39	$37	$1
Total revenue	$67	$59	$8
Expenses			
COGS	$4	$6	($2)
R&D	$51	$59	($9)
SG&A	$25	$24	$1
Total expenses	$83	$90	($7)
Operating income (loss)	($16)	($30)	$14
Income/Loss			
Net income (loss)	($16)	($30)	$14
Diluted GAAP EPS	($0.13)	($0.24)	$0.11

Source: Company reports, FactSet

Source: Goldman Sachs/Singh, February 11, 2014
Oncology Indication: Hematologic
Keyword: Management/Strategy/Financials

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Incyte: Jakafi and Pipeline Momentum Remains Strong; 2014 Sales Guidance of $315-335M Should Be Easily Achievable

Incyte (INCY) reported Q4 2013 earnings and provided 2014 guidance. Jakafi sales of $73MM were above our and Street consensus estimates ($68MM/$68MM), reflecting continued solid uptake, with royalties on ex-U.S. sales at $8.4MM based on ex-U.S. sales reported by partner Novartis earlier this month. SG&A expenses of $35M were meaningfully higher than our and consensus estimates, resulting in Q4 EPS of $ 0.15 vs. our and consensus' $ 0.06.

2014 Jakafi sales guidance appears to be easily achievable coming off of the Q4 2013 runrate. INCY guided for $315-335MM in sales, bracketing our $328MM and consensus' $319MM estimates. However, both R&D and SG&A guidance ranges, even with non-cash stock based compensation deducted, were still higher than both our and consensus estimates, illustrating the costs of expanding into PV and supporting multiple studies exploring Jak inhibition for solid tumors.

There were minimal updates on the pipeline, with the company's multiple programs remaining on track. Two phase III registrational studies for Jakafi in mPC are to start in H1 2014; 3 additional phase II POC studies NSCLC, breast cancer, colon cancer expected to start in H1 2014. Early oncology programs, including Jak1 inhibitor ('110 and '986), IDO inhibitor ('360), and PI3K inhibitor ('093), appear to be also moving forward; the company noted that Jak1 '986 completed its phase I assessment.

INCY continues to execute commercially, with multiple market expansion opportunities for Jakafi and a progressing, deep pipeline, and we believe the higher-than-expected spend will be accepted given this potential.

Source: Wells Fargo Securities/Abrahams, February 12, 2014
Oncology Indication: Hematologic
Keyword: Management/Strategy/Financials

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GlaxoSmithKline: MAGE-A3 Phase III Data from MAGRIT Expected to Show No Benefit in Lung Cancer, But Gene Signature Positive Subgroups May Show Benefit

We believe that GSK's access to unblinded data from part of the recently concluded MAGE-A3 Phase 3 DERMA trial (melanoma) is one potential explanation for our observation of heightened optimism among GSK's MAGE-A3 senior scientists. However, we caution that any positive efficacy signal observed in the un-blinded gene-signature positive DERMA patients could result from post hoc "editing" of the gene signature, rather than confirm a real treatment benefit.

While we continue to expect that MAGRIT overall data (lung cancer) will show no benefit for the vaccine, we acknowledge that the prospects for a positive benefit in the overall NSCLC indication are likely higher than with the (failed) DERMA melanoma trial. We anticipate headline data from the MAGRIT lung cancer trial in 1Q 2014.

GSK's best hope remains gene signature subgroups, but probability still low. While we believe that the pre-defined gene signature will likely select patients with more immune-responsive cancers, we are unconvinced that GSK's AS15 adjuvated MAGE-A3 vaccine will translate into a large enough clinical benefit for reasons outlined in the following section.

Key Concerns for GSK's MAGE-A3 programme:

- **Absence of CD8+ T cell response.** Our pivotal historical concern with GSK's MAGE-A3 programme has been the lack of detectable antigen specific CD8 T cells following vaccination. There is, we note, a significant increase in monoclonal antibody and CD4+ response to vaccination. While there is an increase in monoclonal antibody levels to MAGE-A3 in response to the vaccine, historical data over the importance of a B-cell response has been underwhelming (see Canvax). Any efficacy thesis needs to be based on lymph node sequestering of CD8 cells or invoking cytotoxic CD4 cells.
- **Gene signature biasing in melanoma development**. We believe the gene signature developed in the phase II trial was based on cutaneous rather than visceral biopsies. This would bring into doubt the relevance of this gene signature as it relates to patients with non-cutaneous sites of disease recurrence. More positively, we believe that the lung gene signature was developed on the basis of mediastinal metastatic biopsies.
- **Immunosuppressive T-reg cells likely minimize the therapeutic efficacy of MAGE based vaccination.** Recent publications have highlighted the increase in antigen specific T-regs in response to MAGE A3 vaccination. We anticipate the involvement of T-regs is much reduced in the ongoing DERMA and MAGRIT programs giving the adjuvant settings being explored.
- **MAGE-A3 heterogeneity**. An important concern is the heterogeneity of MAGE A3 expression in the neoplastic cells. We are paradoxically reassured that the phase II data showed that the patients who progressed post MAGE-A3 treatment had MAGE-A3 expression with their tumor recurrence.

Potential in other cancer indications, as well as in combination. The high levels of MAGE A3 expression in other solid tumours potentially broaden the market considerably as shown in Figure 6. We note that GSK is already exploring MAGEA3 vaccine in MAGE-A3 positive bladder cancer (data expected in 2016). We also anticipate that GSK will explore the potential for additive clinical benefit or synergy by combining MAGE-A3 vaccine with other agents, including both small molecules (such as dabrafenib and trametenib) as well as IT (such as anti-PD1, and anti-ICOS).

We see very limited near term competition given GSK's competitive lead time with MAGE A3. In addition, the immune related adverse events associated with PD1 mediated therapies likely preclude use in lower risk adjuvant patients, in contrast to the placebo like profile of MAGE-A3. The terminal value of the MAGE-A3 (assuming positive data) is significant given the almost insurmountable barriers in generating a generic vaccine.

Source: Citigroup/Baum, February 11, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Market Overview: Utility of Multiple Cancer Vaccines Set to Be Validated in Next 3 Years

Cancer vaccines have thus far failed to demonstrate efficacy compared with checkpoints, bi-specific antibodies or cell based therapies. We anticipate that patient selection strategies, superior antigens and combination based approaches will translate into the approval and widespread adoption of a broad range of therapeutic cancer vaccines.

Both GSK and Merck Serono are exploring their peptide vaccines based on patient selection after initial disappointing data in an unselected patient population. While we remain cautious on Merck Serono's Stimuvax Phase 3 outcome, we maintain a modicum of optimism for the prospect for GSK's MAGE-A3 in gene signature positive lung cancer and melanoma, despite the apparent absence of antigen specific CD8 T cells. We do not anticipate gene signature data to be made public until late 2014/ early 2015.

Recent Aduro data very encouraging proof-of-concept for cancer vaccines. Recent positive phase II vaccine data phase II from Aduro and Celldex indicate that we are close to establish proof of concept for systemically administered therapeutic cancer vaccines. Aduro's randomized, controlled, multi-center study phase II 93 patient phase II trial showed a statistically significant survival benefit in patients receiving the combination of GVAX Pancreas and CRS-207 cancer vaccines (Arm A) compared to GVAX Pancreas vaccine alone (Arm B). The median overall survival of the patients receiving the combination was 6.1 months compared to 3.9 months for those receiving GVAX monotherapy (HR=0.54, one-sided p=0.011). One-year survival probability for patients in Arm A was 24% compared with 12% for patients in Arm B. We see similar encouraging approaches for therapeutic cancer vaccines from the likes of Inovio and Immatics (albeit with very different technologies), both partnered with Roche.

We remain most excited by the potential for the combination of vaccines with checkpoint inhibitors, such as PD1 antagonists to optimize the activity of the innate immune system. We anticipate Roche to begin combination vaccine trials with their anti-PDL1 as early as 2014.

Source: Citigroup/Baum, February 11, 2014
Oncology Indication: Multiple
Keyword: Market Overview

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OncoGenex: Custirsen SYNERGY Trial (Phase III/mCRPC) Reached Required Number of Events for Final Analysis, OS Results By Mid-2014

OncoGenex (OGXI) announced that the Phase III SYNERGY trial of custirsen in the metastatic castrate-resistant prostate cancer (mCRPC) setting has reached its required number of events for final analysis, and final survival results are expected by mid- 2014.

This study enrolled 1,022 male subjects at 148 centers in North America, Europe, Israel and South Korea. Subjects were randomized to custirsen in combination with docetaxel and prednisone or docetaxel and prednisone. Custirsen was administered weekly at 640 mg following three loading doses and docetaxel and prednisone were administered as 3-week cycles. We believe that with a potential 500 events, the study would be more than 90% powered to detect a hazard value of 0.8 ($p<=0.04$). OGXI is not disclosing the number of events or threshold for potential success for the interim or final analyses.

We continue to anticipate that the final survival results of the SYNERGY trial, expected by mid-2014, will be positive. Phase II data from a study of custirsen in combination with front-line docetaxel chemotherapy versus docetaxel alone showed an improvement in unadjusted hazard ratio of 0.61, $p=0.06$.

Our view is that OGXI's enterprise value of about $50M, undervalues the potential opportunity with three partner-funded Phase III trials, and its wholly owned '427 program in a broad, but relatively inexpensive program across bladder (with overall survival results from the Borealis-1 trial reading out in H2:14), prostate, lung and pancreatic cancers. We do not include potential revenues from apatorsen ('427) in our valuation at this time.

Source: Wedbush Securities/Wade, February 11, 2014
Oncology Indication: Prostate
Keyword: Clinical Trials/Pipeline

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Immunomedics: Clivatuzumab Phase III Pancreatic Cancer Trial On-Track; Plans to Market Clivatuzumab Independently in the U.S. and Partner for Ex-U.S.

Immunomedics has initiated the pivotal Phase III clinical trial of clivatuzumab in pancreatic cancer patients who have failed at least two rounds of therapies. As of today (2/11), there are three surviving patients from the completed Phase I clinical trial, one for 17 months and two for 11 months, all significantly longer than the expects survival time for this patient population. Immunomedics had announced target enrollment of 440 patients and expects to complete patient enrollment in calendar 1H15, with top-line data to be reported in 2016.

Recently approved front-line therapies for pancreatic cancer have increased the number of eligible patients for the clivatuzumab trial, and enrollment for the Phase I study was faster than the management had expected. Therefore, we believe the need for an efficacious third-line therapy is real. Immunomedics plans to market the drug independently in the U.S. and to partner for ex-U.S. territories. We believe the company should be able to target the limited number of patients and that it has sufficient manufacturing capacity to support the commercialization. We project the clivatuzumab program to be Immunomedics' major value driver.

Immunomedics plans to fund clinical development with BD revenues. The company ended the quarter with cash of approximately $26.8MM, and management foresees potential near-term partnerships for IMMU-130 and IMMU-132, both of which are antibody-drug conjugates for the treatment of solid cancers in Phase II clinical trials, to be the source of additional capital to fund the ongoing clinical development. Immunomedics expects to provide updates from the Phase II clinical trials in calendar 2H14. However, to be conservative, we model an equity raise in the coming quarters.

Source: Cowen and Company/Nash, February 11, 2014
Oncology Indication: Pancreatic
Keyword: Management/Strategy/Financials

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Ambit Biosciences: Quizartinib (AML) Maintenance Opportunity Could Come into Focus Earlier-Than-Expected; Phase III Design Provides Significant Optionality

Quizartinib Phase 3 on-track, but a few incremental nuggets. First patient dosing in March, with top-line data still late 2015; consistent with our base case which assumes 2016 launch. Two additional points:

- **Maintenance opportunity perhaps more near-term?** The Phase 3 relapsed/refractory trial includes the option for patients bridged-to-transplant to continue on quizartinib maintenance therapy post-transplant. We are encouraged that the FDA has blessed this design and note that data from a 12-patient Phase 1 maintenance study is possible at ASCO in early-June. Bottom-line, we now think the maintenance opportunity (estimated $300-$500M US market) could come into focus a bit sooner than anticipated (we don't model meaningful maintenance use until 2018).
- **Phase 3 design provides significant optionality.** Recall, an interim Phase 3 look is built-in at 50% of events, expected late-summer/early-fall 2015. This trial is 90% powered to show a ~2-month OS improvement (six vs. four months; HR=0.65); however, just under an additional month of benefit (e.g., 6.7 months for quizartinib arm), all things equal, would trigger early stoppage for efficacy. With the inclusion of quizartinib maintenance post-transplant, we do not think this potential should be overlooked. On the flip-side, should the interim signal a less pronounced OS trend (e.g. HR=0.7), the trial can be up-sized by 150 patients to improve statistical powering.

Earlier-stage pipeline coming into focus. AC410 (JAK2 inhibitor) chronic tox study planned for 2014, followed by proof-of-concept work early 2015. Also, AC708 (CSF1R inhibitor) IND-filing anticipated end-of-Q214.

Source: Baird/Raymond, February 12, 2014
Oncology Indication: Hematologic
Keyword: Clinical Trials/Pipeline