February 20, 2014 Thursday

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JMP Securities/King, February 20, 2014
HealthACE Abstract *Indication: Hematologic*

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Leerink/Liang, February 20, 2014
HealthACE Abstract *Indication: Hematologic*

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HealthACE Abstract *Indication: Hematologic*

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: Imbruvica Label Enjoys Wider-Than-Anticipated Coverage in CLL; Will Ultimately Become the Drug to Beat in R/R Setting

We hosted a conference call with a CLL specialist – Dr. Steven Coutre of Stanford University Medical Center – to discuss clinician reaction to the updated Imbruvica label and the impact of Imbruvica and other developing agents on the therapeutic landscape. In Dr. Coutre's view, the Imbruvica label enjoys wider than anticipated coverage in CLL and will ultimately become the drug to beat in the relapsed/refractory setting.

Imbruvica is expected to quickly supplant current agents in second-line such as Arzerra, Revlimid, and Rituxan. In Dr. Coutre's view, before Imbruvica, patients who underwent relapse were resigned to one of these agents, or in some cases a combination thereof, despite the absence of a clear rationale. Rituxan and Arzerra were described as being weak to moderately effective in second line. Revlimid effected only 'cosmetic' changes in the course of the disease without any impact to the bone marrow. In that regard, patients that may otherwise have been moved to such agents are now seen as low hanging fruit for Imbruvica.

Focusing on the label's overall response rate misses the point. Recall, the Imbruvica label cites an overall response rate of 58% composed of all partial responses, in contrast to the 71% (including two complete responders) reported in the New England Journal publication of PCYC-1102. In Dr. Coutre's opinion, this discordance is largely 'irrelevant' with respect to how Imbruvica is likely to be adopted. Physicians are more likely to focus on Imbruvica's ability to achieve at least a nodal response in virtually all CLL patients - a meaningful endpoint for second-line patients, who are more often elderly (70-75 years of age) and less amenable to aggressive treatment with chemotherapy.

Anticipating wide front-line use given positive RESONATE-2 data. In Dr. Coutre's view, Imbruvica will likely enjoy a similarly wide purview in front-line CLL if shown to be superior to chlorambucil. This view was largely based on the fact that the average CLL patient is >70 years of age at presentation with accompanying comorbidities and thus less amenable to treatment with chemotherapy. That said, while Imbruvica may see some experimental use at the fringes in combination with CD20 mAbs, broader use in younger/fit patients will be dictated by results from the ECOG and ALLIANCE studies currently underway, evaluating Imbruvica (I) plus Rituxan (R) vs. and FCR and I vs. IR vs. BR, respectively.

Shared optimism for ABT-199, but less so with Idelalisib. Looking across the development landscape, Dr. Coutre was particularly excited about ABT-199 (GCD-0199) and its potential to induce complete remissions and be used in a time limited fashion. Confident that many of the ongoing trials would ultimately identify those patients upfront at greater risk for tumor lysis syndrome, ABT-199, in his view, faces an opportunity in CLL that could rival that of Imbruvica, particularly in the front-line setting. By contrast, Idelalisib enjoys less awareness among physicians compared to Imbruvica. In his view, Idelalisib use will likely be hindered by the absence of an efficacy advantage over Imbruvica and higher risk of colitis and diarrhea. Finally, Dr. Coutre held out little hope for the other BTK and PI3K inhibitors in development, viewing them as too far down the pike and undifferentiated to have a meaningful impact on the current landscape.

Source: JMP Securities/King, February 20, 2014
Oncology Indication: Hematologic
Keyword: Market Overview

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Baxter: Rigosertib (Phase III) Fails in High-Risk MDS; Opportunity Remains for Lower-Risk MDS, Phase II Data Appears to Be Better Than Higher-Risk Setting

Yesterday (2/19), Onconova (OTNX) reported negative top-line results from its Phase III ONTIME trial of IV rigosertib in 299 higher-risk myelodysplastic syndrome (MDS) patients who previously failed or relapsed after hypomethylating agents (HMAs). While a statistically significant improvement was seen in the subset of patients who did not respond to HMAs, we believe it is appropriate for the focus to shift to the lower-risk MDS setting for which we expect an FDA-agreed trial design to be announced shortly and a Phase III could proceed relatively quickly.

The failure in the higher-risk patient population does not necessarily predict the outcome in the lower-risk setting in part due to differences in endpoints (overall survival vs. transfusion independence). Despite controversy, we believe available data show activity for rigosertib in this population that is independent of ESA. While we are mindful of the binary nature of the lower-risk Phase III readout, we believe the more attractive commercial opportunity in the lower-risk MDS setting with an oral agent that has shown a good tolerability profile and potentially greater transferability of Phase II data based on the same endpoint (transfusion independence) makes it a worthwhile investment at current valuations.

In our opinion, rigosertib Phase II data for lower-risk MDS are better than in higher-risk MDS. Transfusion independence, which is highly likely to be primary endpoint of the Phase III in lower-risk MDS patients, has been observed compared to bone marrow response in higher-risk patients, which is of unknown significance. In the ONTARGET Phase II trial, rigosertib produced transfusion independence responses in patients who were previously transfusion-dependent. Furthermore, these responses did not appear to be correlated with the timing of erythropoietin-stimulating agent (ESA) administration (LINK). The question will be primarily whether the magnitude of the transfusion independence is robust enough and clinically meaningful. Based on the relatively large size (e.g., nearly 400) of other lower-risk MDS trials with transfusion independence as the primary endpoint, it would appear that the targeted effect size may not be especially large. We expect the company to report the design of the Phase III trial in this population imminently and would anticipate faster accrual and completion of this trial compared with ONTIME, given that overall survival is not an endpoint.

Source: Leerink/Liang, February 20, 2014
Oncology Indication: Hematologic
Keyword: Clinical Trials/Pipeline

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ImmunoGen: ADC Technology Has Not Reached Full Potential; Plans to Retain N.A. Commercial Rights in Future Partnerships to Maximize Value

Takeaways from Leerink's Global Healthcare Conference:

ImmunoGen (IMGN) does not believe antibody drug conjugate (ADC) technology has reached full potential yet. The recent partnership with CytomX Therapeutics (which specializes in antibody masking technology) is a testament to the continued advancement of the technology where more targets may be available. The masking technology could prevent therapeutic antibodies from binding to targets outside of a disease environment. In addition, IMGN's recently introduced new payloads targeting DNA synthesis could attract new partners or enable new products to be developed.

IMGN hopes to retain North American commercial rights in future partnerships to maximize value. As an overall strategy, IMGN hopes to transition to a commercial-stage company by retaining significant North American commercial rights (not necessarily worldwide rights) while continuing to invest in its own technology and pipeline.

IMGN continues to express excitement over preclinical data for IMGN289 (an EGFR- targeting ADC). Management believes IMGN289 could spare patients from skin toxicities typical of other EGFR-targeting agents. This may be due to a potentially different therapeutic window of the ADC. First clinical data for IMGN289 (in NSCLC, SCCHN, and other EGFR+ solid tumors) could potentially be available in 2H14.

Source: Leerink/Schmidt, February 19, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Oncothyreon: Initiates Third ONT-380 (Phase Ib) Combination Study in mBC; Readout from All Three Trials (Herceptin, Xeloda, & Kadcyla) Starting in 2H14

Oncothyreon (ONTY) and Array BioPharma (ARRY) announced the initiation of a Phase Ib trial of ONT-380, their oral, small molecule, HER2 inhibitor, in combination with Kadcyla, in metastatic breast cancer (mBC). This is ONT-380's third Phase Ib combo trial in mBC: the other two are testing 1) the combination of two dosing schedules of ONT-380 with Herceptin, and 2) ONT-380 combinations with Xeloda and/or Herceptin.

This will be a dose-escalation study in up to 48 patients that have been previously treated with Herceptin+taxane in the metastatic setting. The primary objective is to the find the MTD and/or the Phase II dose of ONT-380 in combination with the approved dose of Kadcyla, with safety and early evidence of anti-tumor activity as secondary objectives. There are two potential expansion arms to the study at the MTD/Phase II dose, including one in patients with brain mets.

What's next for ONTY? 1) Initiation (by Merck KGaA) of Phase III START2 trial of tecemotide in NSCLC, 1Q14; 2) Initial data readouts from three Phase Ib combination trials of ONT-380 in mBC, starting in 2H14; 3) Data from a Phase II trial of tecemotide in Japan, late 2014; and 4) Full data from the Phase III INSPIRE trial of tecemotide in Asian patients, 2015.

Why we like ONTY: The tecemotide/ONT-10 M&A argument and ONT-380's potential in breast cancer. We expect tecemotide to succeed in the Phase III START2 trial, and in our view, the fact that Oncothyreon, in addition to the tecemotide royalty that it would be owed, owns 100% rights to follow-on vaccine ONT-10, which could be licensed to another big pharma and compete head-to-head, makes an acquisition by partner Merck KGaA likely. We also believe other pharmas would also have interest, both for the tecemotide royalty and access to ONT-10. Furthermore, the M&A argument only relies on the therapeutic vaccine part of the Oncothyreon story and does not account for ONT-380, the oral, selective HER2 inhibitor licensed recently from Array and in development for breast cancer, which we view as a very promising, albeit early, agent that has potential to penetrate the blood brain barrier and address the significant issue of brain metastases in metastatic breast cancer.

Source: Cowen and Company/Simeonidis, February 20, 2014
Oncology Indication: Breast
Keyword: Clinical Trials/Pipeline

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Curis: FDA Discussions on CUDC-427 Phase I Study Still Ongoing; CUDC-907 (Lymphoma & MM) Dose-Escalation Phase to Conclude in Mid-2014

Takeaways from Leerink's Global Healthcare Conference:

Discussions with FDA relating to lifting partial clinical hold on CUDC-427 study are ongoing. Curis (CRIS) has submitted a data package to the FDA that is currently being reviewed. A new clinical protocol with a risk-mitigation strategy will be in place in the event the partial clinical hold gets lifted. Discussions with the FDA encompass all 58 patients treated by both Genentech and Curis. CRIS remains keenly interested in evaluating CUDC-427's potential in ovarian cancer and lymphoma. This is based on the 2 CRs observed in the Genentech study in ovarian cancer and MALT lymphoma.

CUDC-907 dose-escalation phase to conclude in mid-2014. CUDC-907 is CRIS' dual PI3K and HDAC inhibitor. CRIS plans to initiate enrollment in expansion cohorts in patients with select malignancies in the second half of 2014. In addition to the ongoing Phase I clinical study in advanced lymphomas and multiple myeloma, CRIS is conducting preclinical studies with CUDC-907 in solid tumor models and expects to initiate additional studies using CUDC-907 in combination with other anti-cancer agents in patients with solid tumors around the end of 2014.

CRIS management optimistic about increasing Erivedge sales in EU. Management noted that, based on Roche comments that sales in Europe have begun to take hold. Recall that EU approval was not obtained until mid-13. Management also noted that Roche has recently initiated a Phase Ib/II study of Erivedge in relapsed/refractory AML and relapsed/refractory high risk MDS.

Source: Leerink/Schmidt, February 19, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Roche: May Share Avastin Trial Data in Brain Cancer to Address Conflicting Results on Quality of Life

Roche and a group of outside investigators may share raw data from conflicting trials of Avastin to help determine whether the $7 billion-a-year treatment really helps patients with deadly brain cancer.

The data is from two trials that both found the drug didn't help patients with glioblastoma to live longer, but differed on a more subjective measure: quality of life. In results published yesterday (2/18) in the New England Journal of Medicine, researchers who led a Roche-sponsored trial said Avastin improved or maintained quality of life and brain function. An independent study dubbed RTOG 0825 said Avastin patients were worse off on both counts.

The outcome may help determine how broadly Avastin is used for glioblastoma. The difference between the studies is "neither trivial nor academic," Howard Fine, deputy director of the New York University Cancer Institute, wrote in an editorial published with the results. If Avastin improves patients' quality of life and brain function, "then a strong argument can be made for its use as part of the initial treatment of glioblastoma, regardless of its effect on survival."

If Avastin actually damages brain function, there's no argument for its wide use, especially since it wasn't shown to help patients live longer in the trials, he wrote. "The first question is, is the outcome different just because they used different statistical methodologies?" Fine said. He wasn't involved in either study published today, though he has led previous research on Avastin in brain cancer. "You can apply different statistical tests and get very different statistical answers."

Roche is open to sharing its trial data and is already in talks with researchers from the RTOG study as well as other parties, spokesman Daniel Grotzky said.

The accelerated approval for Avastin in glioblastoma required the Swiss company to file trial data showing a clinical benefit for patients by the end of 2015. Roche is discussing the results of the latest studies with the FDA.

Source: Bloomberg/Kresge, February 19, 2014
Oncology Indication: Brain
Keyword: Clinical Trials/Pipeline

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Verastem: Scientific Rationale Supports Targeting FAK Inhibition in Multiple Cancer Settings; Considering VS-6063 in B-ALL as First Priority

We reached out to management following last week's Nature Immunology paper that showed the dependence of focal adhesion kinase (FAK) on cancer cell survival and proliferation in B-cell acute lymphoblastic leukemia (B-ALL), and that FAK inhibition led to B-ALL pre-cancer cell death by apoptosis. We had the opportunity to speak with CMO Joanna Horobin and Biomarker Head David Weaver (a former Harvard/Dana Farber professor) to connect the dots on the implications of these findings to clinical development options for Verastem's 3 wholly-owned FAK inhibitors in the clinic. Overall we think the body of evidence supporting FAK inhibition is getting hard to ignore, and expect several avenues of value creation to emerge for Verastem's FAK franchise.

Scientific rationale hard to ignore. The B-ALL paper (Joshi et al) shows that in Ikaros-mutated B cells (a marker of poor prognosis in B-ALL), FAK is required for stromal adhesion, a critical step in leukemic transformation. FAK inhibitor VS-6062 inhibits the adhesion, and pre-leukemic B cells die. In our view, these data create strong support for the use of FAK inhibitors in hematologic malignancies, and complements a significant and growing amount of literature supporting FAK's role in solid tumors. In heme-onc, Verastem is now considering potential clinical trial protocols for VS-6063 in B-ALL as a first priority, while exploring other hem/onc settings in which the rationale supports development.

Source: UBS/Roden, February 20, 2014
Oncology Indication: Hematologic
Keyword: Clinical Trials/Pipeline

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In Research: Study Shows That Genetically-Modified T-Cells Can Induce Complete Remission in Advanced B-ALL

Investigators at Memorial Sloan Kettering Cancer Center (MSKCC) have been pioneering the use of genetically modified T cells to fight cancer. to underscore the potential of this technology, which they have used to help start up the high-profile Juno Therapeutics, new human data has produced another round of jaw-dropping outcomes from a small but influential study.

MSKCC investigators say that in a study with 16 patients, their modified T cells produced complete remission in 88% of patients with advanced adult B cell lymphoblastic leukemia (B-ALL). Only 30% of patients in the control arm responded to salvage chemotherapy.

"These extraordinary results demonstrate that cell therapy is a powerful treatment for patients who have exhausted all conventional therapies," said Michel Sadelain, director of the Center for Cell Engineering at MSKCC and one of the study's senior authors. "Our initial findings have held up in a larger cohort of patients, and we are already looking at new clinical studies to advance this novel therapeutic approach in fighting cancer."

The big idea, which is being pursued by warring camps behind Juno as well as the rival Novartis (NVS), is that you can re-engineer a patient's T cells with chimeric antigen receptors (CAR) to go after cancer cells; in this case cancer cells that express CD19 on the surface. For NVS, it's a straight pathway to combination immunotherapies that hold blockbuster potential in revolutionizing the way cancer is treated.

Additional studies to determine whether cell therapy can be applied to other types of cancer are already underway, and studies to test whether B-ALL patients would benefit from receiving targeted immunotherapy as frontline treatment are being planned.

Source: FierceBiotech/Carroll, February 20, 2014
Oncology Indication: Hematologic
Keyword: Discovery & Reserach