HealthACE Pharma Business Intelligence

Oncology Intelligence Report

February 26, 2014 Wednesday

## Today's Intelligence at a Glance

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*BofA Merrill Lynch,McMinn, February 25, 2014*
HealthACE Abstract *Indication: Hematologic*

**2. Ariad:** 4Q Iclusig Sales Beat Estimates Slightly; Clinical Data at ASCO to Provide Further Clarity on Future of Iclusig
*Barclays Capital/Huang, February 25, 2014*
HealthACE Abstract *Indication: Hematologic*

**3. Macrogenics:** Pipeline Expanding Faster-Than-Expected; Two Additional DART Molecules Expected to Enter Clinic for Oncology in 2015; Plans to Increase Its Manufacturing Facility in 2H14
*Leerink/Schmidt, February 24, 2014*
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**4. Agenus:** Enters Exciting Field of Checkpoint Inhibitors with Recent Acquisition of 4-Antibody; Could Become an Acquisition Target Itself
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**7. Fate Therapeutics:** Phase Ib Data of ProHema (HSCT for Hematological Malignancies) Shows Encouraging Effects on T-Cells
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*Genetic Engineering & Biotechnology News, February 26, 2014*
HealthACE Abstract *Indication: Prostate*

## *Additional Analysis*

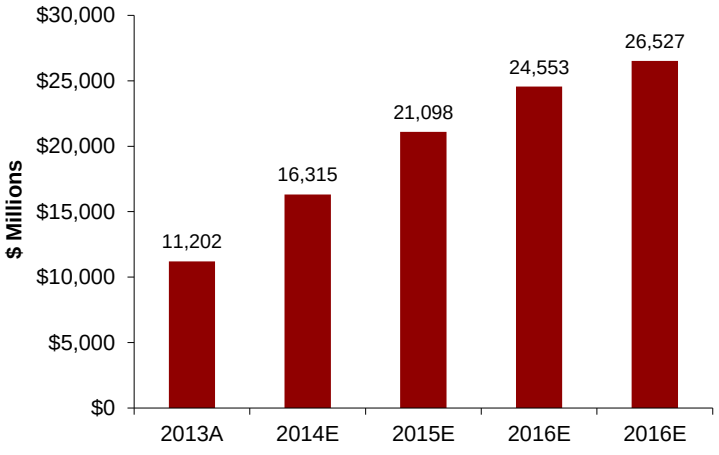
**Phase III Trials for Idelalisib (GS-1101)**

| Study Name<br>Design | Indication | Endpts | Estimated Completion Date |
|---|---|---|---|
| NCT01539512<br>With Rituximab | CLL<br>(Previously Treated) | 1º: PFS<br>2º: ORR, Disease-related biomarkers, PK, Adverse events | December 2015<br>Ongoing |
| NCT01569295<br>With Bendamustine & Rituximab | CLL<br>(Previously Treated) | 1º: PFS<br>2º: ORR, Disease-related biomarkers, PK, Adverse events | December 2016<br>Recruiting |
| NCT01659021<br>With Ofatumumab | CLL<br>(Previously Treated) | 1º: PFS<br>2º: ORR, Disease-related biomarkers, PK, Adverse events | December 2017<br>Recruiting |
| NCT01732913<br>With Rituximab | iNHL<br>(Previously Treated) | 1º: PFS<br>2º: Tumor control, Overall well-being, Safety | June 2022<br>Recruiting |
| NCT01732926<br>With Bendamustine & Rituximab | iNHL<br>(Previously Treated) | 1º: PFS<br>2º: Tumor control, Overall well-being, Safety | September 2022<br>Recruiting |

CLL: Chronic Lymphocytic Leukemia
iNHL: Indolent Non-Hodgkin Lymphoma
ORR: Overall Response Rate
PFS: Progression-Free Survival
PK: Pharmacokinetics

*Source: www.clinicaltrials.gov*

**Gilead- Annual Revenues Forecast**




Sources: Company Reports; 5+ Brokerage Analyst Reports

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**Market Overview: CLL Could Be Tough for PI3K Class with Approval of Imbruvica; PI3K/BTK Inhibitors Making the Push into Inflammatory Indications**

We are updating our comments on the novel B-cell targeted oral drug landscape following 4Q13 company business updates and feedback from an expert lymphoma physician check. Key conclusions include:

- We continue to expect JNJ/Pharmacyclics' (PCYC) first in class BTK inhibitor Imbruvica to dominate market share in CLL
- Gilead (GILD) is at least 1.5-2 years ahead of earlier stage PI3K competitors in NHL, and could pull further ahead in CLL
- Multiple companies (Infinity [INFI], PCYC, GILD) are formulating a strategy to advance BTK/PI3K inhibitors into inflammatory indications; these drug candidates could compare favorably to marketed Jak inhibitor Xeljanz, but it's too early to know how they will stack up relative to potentially better development stage Jak inhibitors
- Feedback on PD1/PDL1 is strong activity in hodgkin's lymphoma; it is hard to know whether this important new drug class will have a broader role in more common lymphomas.

GILD is seeking accelerated approval for idelalisib in indolent non-hodgkin's lymphoma (iNHL), and has a PDUFA date of Sept 11th. The FDA assigned this indication a standard review, signaling increased approval risk, which was echoed by recent expert feedback. If idelalisib receives FDA accelerated approval, filling an unmet need, it is unclear to us whether the FDA would approve INFI's similar drug candidate IPI-145 under the same regulatory pathway. INFI plans to initiate a 400- patient Phase 3 study in combination with Rituxan, which appears similar to GILD's ongoing Phase 3 program. Both companies plan on initiating treatment naïve studies this year. While INFI believes IPI-145 is a better drug than idelalisib based on its small dataset, it is unclear to us that IPI-145 will be able to differentiate itself on efficacy in the absence of running a head to head study.

With Imbruvica now approved in the US, we believe the PI3K drug class could struggle commercially, and development could be slowed as well. Experts continue to project 70% market share for Imbruvica, although we wonder if potential serious colitis warnings in a future label for idelalisib will further skew market share. Idelalisib is under FDA priority review with a PDUFA date of Aug 6th, but could be approved earlier given its breakthrough status designation. INFI's CLL Phase 3 study (IPI-145 vs. Arzerra) has been sluggish to enroll in the US, not unexpected given US Imbruvica approval in Nov 2013, and its lag behind GILD could widen unless EU enrollment picks up quickly.

PCYC announced plans to study a new BTK inhibitor in inflammatory disease. While there is no data yet available outside of oncology indications for BTK inhibitors, we believe the mechanism of action makes inflammatory indications a rational target. With very clean tolerability in the oncology setting, PCYC's BTK inhibitor could prove to be an important long term competitive threat to other oral drug classes. New data for IPI-145 in RA is expected 2H14. Additionally, INFI announced plans to advance a second PI3K inhibitor into clinical development specifically for inflammatory indications. GILD is also contemplating an inflammatory strategy, and has both idelalisib and a second gen PI3K to choose from. While INCY's pipeline priority remains oncology, given its multiple Jak inhibitor programs for inflammatory, it is reasonable to expect INCY could choose to advance its early stage PI3K inhibitor for inflammatory indications as a hedge.

**Source:** BofA Merrill Lynch,McMinn, February 25, 2014
**Oncology Indication:** Hematologic
**Keyword:** Clinical Trials/Pipeline

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## Ariad: 4Q Iclusig Sales Beat Estimates Slightly; Clinical Data at ASCO to Provide Further Clarity on Future of Iclusig

Ariad (ARIA) recorded $8.3mn in Iclusig sales with $5.4mn coming from the U.S. before the drug was pulled in the market, slightly better than our estimate of $7mn. ARIA continues to defer Iclusig sales in France ($12.9mn) until a list price is established and the deferred revenue will be recognized at once in 2H14. Since Iclusig was re-launched in the U.S. in mid-January, roughly 180 of the 305 patients in the single-patient IND program have transitioned to commercial supply. We estimate $6mn and $30mn Iclusig sales in U.S. for 1Q14 and 2014, respectively.

ARIA anticipates cash burn of $165- $175mn this year. Higher-than-expected R&D spending is attributed to ongoing trials of Iclusig, post-approval commitments, and follow-up of patients from previous trials. Based on its current cash position of $237mn, this would leave the company with a balance of $60-$70mn at year-end. We believe there is a high likelihood of capital raise by year-end unless a Japanese partnership of Iclusig brings a significant up-front payment.

Clinical data from several studies of Iclusig and ‘113 will be presented at this year’s American Society of Clinical Oncology (ASCO) meeting. The initial data from the EPIC trial may provide information on Iclusig in front-line CML. We are also interested in seeing interim results from an ongoing Phase II trial in refractory gastrointestinal stromal tumor (GIST), since this is the most likely new indication for Iclusig outside of CML.

**Source:** Barclays Capital/Huang, February 25, 2014
**Oncology Indication:** Multiple
**Keyword:** Clinical Trials/Pipeline

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**Macrogenics: Pipeline Expanding Faster-Than-Expected; Two Additional DART Molecules Expected to Enter Clinic for Oncology in 2015; Plans to Increase Its Manufacturing Facility in 2H14**

Based on a recent update with management, Macrogenics's (MGNX) pipeline is expanding faster than we had initially expected. We are adjusting our model to reflect the recently completed capital raise and the earlier than we had expected Servier license of MGD006.

**Pipeline growing faster than we had expected.** With now three proprietary INDs expected in 2015, in addition to the two INDs in 2014, we note that Macrogenics's (MGNX) pipeline is broadening much faster than we initially expected. MGNX originally guided to one IND filing per year starting in 2015. We like management's strategy since it diversifies the pipeline significantly, adds additional shots on goal, and takes advantage of MGNX's antibody discovery and development capabilities which give the company the ability and flexibility to rapidly generate and develop (or partner) antibody-based therapeutics against novel targets, which can then be optimized and manufactured in-house using the appropriate antibody technology.

**Two additional new DART molecules are expected to enter the clinic for oncology in 2015.** These new DARTs are in addition to MGD006, MGD007, and MGD010. MGNX will select these two new programs to advance from four ongoing late-preclinical programs. Only one of these four product candidates (Tx) is subject to a potential EU license by Servier, which recently exercised its licensing option for MGD006 one quarter earlier than we had expected. The targets for these two new molecules have not been disclosed yet due to competitive and IP reasons.

**MGNX to broaden MGA271 monotherapy Phase Ib program in 2H14.** In addition to three currently enrolling expansion cohorts in prostate cancer, melanoma, and B7-H3+ all-comers, MGNX will pursue other tumor types in further cohorts 2H14. The specific indications have not been determined yet but will take into consideration the expression profile of B7-H3. B7-H3 is also highly expressed on cancers of the kidney, pancreas, breast, and ovaries. MGNX expects to complete the initial three cohorts in late '14 and the additional cohorts in '15. Servier will initiate two additional tumor types this week.

**MGNX to test MGA271 combinations likely including, but not limited to, immuno-oncology (IO) combinations.** Potential combinations will take into consideration mechanistic synergies, e.g., with Tx that target the tumor vasculature where B7-H3 is expressed. Potential combos with other checkpoint inhibitors are possibilities. Combination with natural killer (NK)-cell targeted agents such as IPH/BMY's anti-KIR (lirilumab) would also make sense in our view, given that it can enhance antibody-dependent cellular cytotoxicity (ADCC), which is part of MGA271's mechanism. Combos with Tx that are approved or those that are still in development are being considered by mgmt. We like MGNX's broad and rigorous approach in Phase Ib before settling on specific development plans.

**MGNX plans to increase its manufacturing facility in 2H14.** Management is exploring opportunities to increase manufacturing capacity and potentially be capable of having two production streams running in parallel. Management believes there are significant advantages to having in-house manufacturing capabilities as this allows decisions to be made only weeks ahead vs. having to plan one year ahead for an outsourced contract manufacturer.

**Source:** Leerink/Schmidt, February 24, 2014
**Oncology Indication:** Multiple
**Keyword:** Clinical Trials/Pipeline

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## Agenus: Enters Exciting Field of Checkpoint Inhibitors with Recent Acquisition of 4-Antibody; Could Become an Acquisition Target Itself

In our opinion, the acquisition of 4-Antibody has propelled Agenus into the ever exciting field of checkpoint inhibitors. With the addition of six lead checkpoint programs, we believe Agenus could soon find itself in the cross hairs of other Pharma/Biotech acquirers. In addition, the company's proprietary personalized platform technology encompassing cancer and infectious disease vaccines as well as the partnered QS-21 program represent significant value drivers for investors.

**The acquirer could become the acquired.** Agenus completed the acquisition of privately held 4- Antibody, bringing to the company fully human antibodies, the lead programs for which target 6 checkpoint molecules. In addition to inhibitors against well-known targets, such as PD-1 and CTLA-4, the company has molecules targeting OX40, GITR, Tim-3, and Lag-3.

**QS-21 is currently being evaluated in 21 clinical programs**, of which 4 are in Phase 3 development. If successfully commercialized, Agenus could be eligible for clinical milestone payments (from certain partners) and low-to-mid-single-digit royalties (we believe 2-4%) on sales for a period of at least 10 years from commercial launch. We calculate the risk-adjusted net present value (NPV) of the QS-21 franchise in just these three indications to be $136 MM.

- ***Melanoma:*** The ongoing DERMA Phase 3 cancer trial in Stage III B/C surgically resected melanoma has completed enrollment of 1,345 patients. Even though MAGE- A3 expression was evaluated by a companion diagnostic test developed by Abbott Molecular (ABT, Not Rated), the study missed the primary endpoint of disease free survival (DFS). Patients continue to be followed to evaluate the co-primary endpoint of DFS based on a predefined gene signature, as unanimously recommended by the Independent Data Monitoring Committee (IDMC).
- ***NSCLC:*** The MAGRIT Phase 3 trial has enrolled approximately 2,289 patients with surgically resected stage Ib, II or IIIa NSCLC with MAGE-A3 overexpression. Patients were randomized 3:1 between the MAGE-A3 vaccine, MAGE-A3 and chemotherapy and placebo. The primary endpoint is progression free survival, which we expect to be reported in 1H14.

**Source:** H.C. Wainwright & Co./Benjamin, February 24 2014
**Oncology Indication:** Multiple
**Keyword:** Clinical Trials/Pipeline

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## Sunesis: Vosaroxin (Phase III/AML) Likely to Show Positive Survival Benefit in VALOR; Awaiting for MDS Data at AACR

We are cautiously optimistic that the one-quarter push out to 3Q14 for VALOR un-blinding is due to a Vosaroxin related prolongation in survival curve tail. Given treatment standards for VALOR's active comparator full dose cytarabine arm have not changed in recent years and given VALOR is an unusually large 700+ patient AML trial, we would expect cytarabine to perform in the trial as it would in the real world. This drives our positive bias that Vosaroxin is benefitting survival and prolonging time to top-line data in 3Q14 vs. previous 2Q14.

Vosaroxin updates from the MD Anderson Investigator Sponsored Trial (IST) for Myelodysplastic Syndrome (MDS) now represent the next Sunesis catalysts, and we are positively biased for these outcomes. As a reminder, it has already been reported that MD Anderson investigators have successfully and safely been able to combine dosing of MDS patients with the highest dose of Vosaroxin at 90mg/m2 and Decitabine at 20mg/m2. We believe this may serve as a prelude to observing synergistic activity in these patients either in the AACR-2014 abstract on 3/5/14, at the AACR presentation on 4/8/14 or at ASCO in June.

**Source:** Leerink/Kozul, February 26, 2014
**Oncology Indication:** Hematologic
**Keyword:** Clinical Trials/Pipeline

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## Acceleron: ACE-536 Will Likely Advance into Phase III for MDS and Beta-Thalassemia, While Celgene's Sotatercept Will Develop for CKD

Takeaways from meeting with the Acceleron management team. Overall, we continue to believe the company is making rapid progress advancing the pipeline and view Acceleron as a promising early-stage biotechnology company with a novel platform. While the company's programs are still in the validation stage, we expect proof of concept phase 2 data in β-Thalassemia and MDS at EHA in June 2014 and CKD data in April 2014 to continue to drive interest.

**Keys Differences Between ACE-536 and Sotatercept:** The primary difference between these drugs is that ACE-536 is a pure red cell agent while sotatercept is a potent inhibitor of Activin A which results in bone activity in addition to red blood cell activity. Thus, in our view, ACE-536 will probably get advanced to phase 3 for MDS and Beta-Thalassemia while sotatercept will be developed for CKD. The bone activity of sotatercept is not required in Beta-Thalassemia or MDS making CKD a more likely candidate for this indication.

**Beta-Thalassemia Update:** We are favorably inclined with the ACE-536 efficacy in Beta-Thalassemia as a 1.5 g/dL increase in Hb was observed at the 0.6 mg/kg dose and dose escalation is ongoing at 0.8 mg/kg and may go to 1.0mg/kg. In our view, the efficacy bar is a 2.0 g/dL Hb increase as most patients receive 2 transfusion units and we believe Acceleron is on track to achieve this. One key question that remains is whether the drug will have activity in more serve transfusion dependent patients (50% of patients) in addition to transfusion independent patients. 25-50% of transfusion dependent patients produce no beta- globin, the underlying cause of the thalassemia, and management noted that these patients would not likely be candidates for therapy based on the ACE-536 mechanism.

**Sotatercept in CKD:** Celgene will present sotatercept phase 2a data at the NKF 2014 Spring Clinical Meeting April 23rd. In addition to increasing red blood cell formation to address anemia, sotatercept corrected electrolyte imbalances which resulted in positive effects on bone formation and a decrease in calcification of vasculature, a cardiovascular risk factor. We believe this could potentially differentiate the drug in Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), a condition affecting many of the 500k ESRD patients in the US. Celgene is currently enrolling the dose finding part 1 of the ph2b study (n=60) in ESRD patients switched from ESAs and part 2 (n=230) will be an active controlled study to test efficacy.

**Dalantercept Update:** In Q1:14, Acceleron will begin the randomized part of the phase 2 study in RCC of dalantercept + axitinib vs. axitinib with PFS as the primary endpoint. Acceleron also plans to study dalantercept in HCC in combination with sorafenib in a phase 2 study which will begin enrollment in Q2:14, and noted that the drugs are tolerated in combination. We do not include dalantercept in our model currently, but note that the compound is wholly owned by Acceleron and has shown promising activity synergistic with oral TKIs as the drug works downstream from VEGF.

**Source:** Citigroup/Werber, February 25, 2014
**Oncology Indication:** Hematologic
**Keyword:** Clinical Trials/Pipeline

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## Fate Therapeutics: Phase Ib Data of ProHema (HSCT for Hematological Malignancies) Shows Encouraging Effects on T-Cells

Fate announced new data from the completed ProHema-01 trial, a Phase Ib clinical study of ProHema in patients undergoing HSCT for hematological malignancies. The data announced today show that treatment with ProHema led to a doubling in the percentage of naïve and early memory T-cell fraction within the CD8+ T-cell compartment compared with patients who did not receive ProHema.

Fate announced new data from the completed ProHema-01 trial, a Phase Ib clinical study of ProHema evaluating its effect of pharmacologic modulation on CD8+ T cells and immune reconstitution in adult patients undergoing hematopoietic stem cell transplantation for hematological malignancies. The company is currently optimizing the ProHema manufacturing process and expects to resume enrollment in the Phase II ProHema-03 trial in 1H14, with full data expected in mid-2015.

According to the data, the 12 patients who received ProHema and a unit of un-manipulated cord blood showed a two-fold increase in the percentage of naïve and early memory T cell fraction within the CD8+ T cell compartment compared with the 9 patients who did not receive ProHema but two units of un-manipulated cord blood. In addition, the functional properties of CD8+ T cells were also significantly improved. Details of the study were recently published in Blood Cancer Journal. On the safety side, viral reactivation was observed in 17% of the ProHema subjects (2/12) with no cases of CMV disease (vs. 36-56%, as reported in the literature), and no cases of Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorders (PTLD) were observed vs. up to 16% reported in the literature.

What’s next? 1) Resumption of enrollment in Phase II ProHema-03 trial, 1H14; 2) Initiation of Phase Ib trial of ProHema in pediatric patients, mid-2014; 3) Initiation of Phase I trial of ProHema in lysosomal storage disorders, 2H14; 4) IND submission for Wnt7a, YE14; 5) Full data from Phase II ProHema-03 trial, mid-2015; and 6) Initiation of Wnt7a Phase I program, 2015.

**Source:** Cowen and Company/Simeonidis, February 26, 2014
**Oncology Indication:** Hematologic
**Keyword:** Clinical Trials/Pipeline

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**Bayer: Bid for Algeta Successful; Xofigo is Expected to Generate Over €1B in Annual Sales If It Receives Approval in Further Indications**

Bayer said today (2/26) it will proceed with plans to buy Algeta over the next few weeks after its NOK 16.2 billion (~$2.6 billion) bid for shares in the Norwegian biotech surpassed expectations.

Following completion of the deal, Bayer would have sole control of Xofigo, which last year was launched in the U.S. following FDA approval, and also won European Commission approval. A Bayer takeover of Algeta will free the pharma giant from having to pay its partner a share of profits and royalties under their up-to-€560 million ($767.8 million) collaboration deal inked in 2009, through which they teamed up to develop Xofigo, an alpha particle emitting radiopharmaceutical delivered once a month via injection. At the time, the companies announced that Algeta had an option for up to 50% co-promotion with Bayer in the United States under a profit-share arrangement.

"We are absolutely convinced of the potential of this drug and the underlying technology to provide patients with innovative treatment options," Bayer CEO Marijn Dekkers said.

Xofigo is indicated for men with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease. FDA approved Xofigo in June under its priority-review program, allowing decisions up to six months faster on new drugs that appear to provide safe and effective treatment when no other satisfactory treatment exists, or offer a significant improvement over existing treatments.

Algeta is also attractive to Bayer because of its pipeline of radiation therapy candidates. Algeta specializes in developing anticancer therapeutics based on alpha particle emitting radionuclides, whose short range (typically less than 0.1 mm) and high linear energy transfer enables them to be used in molecular targeted radiation of tumors. When selectively delivered to tumor tissue, the alpha particles kill the tumor cells, leaving surrounding normal tissues unharmed.

"This transaction will strengthen our oncology business and support our efforts to provide patients with innovative treatment options. We plan to work together with the Algeta team to leverage the full value of this business," said Olivier Brandicourt, CEO of Bayer HealthCare.

Bayer said Xofigo is expected to generate at least €1 billion (about $1.4 billion) in annual sales “if it receives marketing authorization in further indications.” Xofigo is one of five recently-launched treatments Bayer says have combined total peak sales potential of more than €5.5 billion per year.

**Source:** Genetic Engineering & Biotechnology News, February 26, 2014
**Oncology Indication:** Prostate
**Keyword:** Mergers & Acquisitions