HealthACE Pharma Business Intelligence

Oncology Intelligence Report

March 18, 2014 Tuesday

Today's Intelligence at a Glance

1. Medivation: Xtandi Filing in Pre-Chemo In-Line with Expectations; Approval Will Help Drive Usage Among Urologists, But Upside Unlikely to Be Significant
Barclays Capital/Huang, March 18, 2014
HealthACE Abstract *Indication: Prostate*

2. Medivation: PREVAIL Data May Not Convince All Urologists That Xtandi is Superior; Projected Utilization May Be Capped
Cowen and Company/Schmidt, March 17, 2014
HealthACE Abstract *Indication: Prostate*

3. Pharmacyclics: Reimbursementfor Imbruvica Ahead of Expectations; Street Underappreciates Costs Associated with Side Effects of Other Cancer Drugs
Deutsche Bank/Karnauskas, March 17, 2014
HealthACE Abstract *Indication: Hematologic*

4. Market Overview: Experts Expect Approval for Both Nivolumab and MK-3475 in 2014; Market Continues to Underappreciate Depth of Roche IO Pipeline
Citigroup/Baum, March 18, 2014
HealthACE Abstract *Indication: Multiple*

5. Market Overview: Synta's Ganetespib (Hsp90) in NSCLC Will Likely Fail; Consultant Sees Puma's Neratinib (HER2) Hold Some Promise
Stifel/Klein, March 16, 2014
HealthACE Abstract *Indication: Lung*

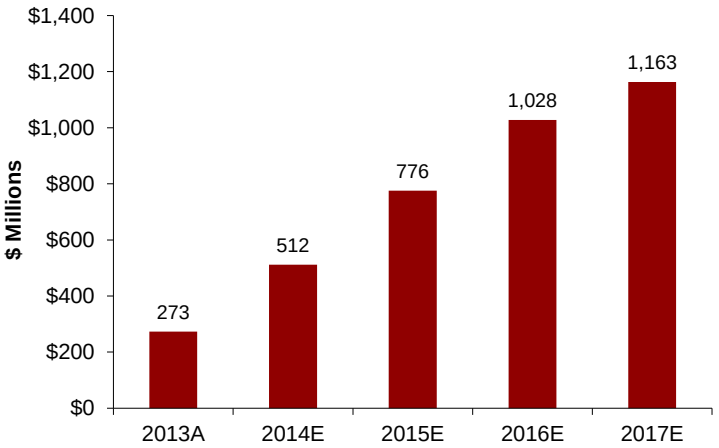
6. Novartis: May Be Pursuing a Deal to Buy Out Israel's Gamida Cell, Globes Reports
FierceBiotech/Carroll, March 18, 2014
HealthACE Abstract *Indication: Hematologic*

7. Fate Therapeutics: ProHema Phase II Trial in Hematological Malignancies Underway, Interim Data in 2H14; Initiation of Phase I ProHema Trials in Pediatric Patients in 3Q14
Cowen and Company/Simeonidis, March 18, 2014
HealthACE Abstract *Indication: Hematologic*

8. Dr. Reddy's: R&D to Remain High Due to Biologics, Oncology Injectables & EM Partnerships and Facility/Brand Acquisitions
Barclays Capital/Prasad, March 17, 2014
HealthACE Abstract *Indication: General*

Additional Analysis

Medivation - Annual Revenues Forecast



Sources: Company Reports; 5+ Brokerage Analyst Reports

Phase III Trials for Xtandi (MDV3100)

Study Name Design	Indication	Endpts	Estimated Completion Date
NCT00974311 Phase III; AFFIRM	CRPC (Patients Previously Treated With Docetaxel-Based Chemo)	1º: OS 2º: rPFS, Time to 1st SRE, PSA progression	November 2012 Has Results
NCT01212991 Phase III; PREVAIL	Prostate Cancer (Chemotherapy-Naive Patients, But Failed Androgen Deprivation Therapy)	1º: OS, PFS 2º: Time to 1st SRE, Time to intitiation of cytotoxic chemo	September 2014 Active; Not Recruiting
NCT02003924 Phase III; PROSPER	Prostate Cancer (Non-Metastatic Patients)	1º: MFS 2º: OS, Time to pain progression, 1st use of cytotoxic chemo, 1st use of new antineoplastic therapy, PSA progression	August 2017 Recruiting
NCT01949337 Phase III; w/o Abiraterone Acetate and Prednisone	CRPC (Metastatic Patients)	1º: OS 2º: Toxicity, PSA level, PFS, ORR, Tumor burden & bone activity	December 2019 Not Yet Recruiting

CRPC: Castration-Resistant Prostate Cancer
MFS: Metastasis Free Survival
OS: Overall Survival
PFS: Progression-Free Survival
PSA: Prostate Specific Antigen
SRE: Skeletal-Related Event

Source: www.clinicaltrials.gov

Back to Front Page

Medivation: Xtandi Filing in Pre-Chemo In-Line with Expectations; Approval Will Help Drive Usage Among Urologists, But Upside Unlikely to Be Significant

Medivation (MDVN) and partner Astellas announced the submission of a sNDA with the U.S. FDA for the use of Xtandi in metastatic chemotherapy-naïve castration-resistant prostate cancer (mCRPC) patients.

Based on positive results from the PREVAIL Phase III study (announced in late 2013), a filing in the U.S. by the end of 1Q14 was largely expected. Assuming acceptance of the supplemental application over the next 1-2 months, approval could come as early as late September if priority review is granted by the FDA. A supplemental application filing in the EU is expected later this year.

On Medivation's 4Q 2013 earnings call, management guided 2014 U.S. net sales for Xtandi of $500-$535mn, which was well below consensus as the midpoint only implies growth in the low single digits from the annual run rate of ~$504mn in 4Q13. We believe investors will increasingly focus on quarterly Xtandi sales given PREVAIL results have passed and most expect MDVN to receive FDA approval for the pre-chemo setting. The 2014 guidance confirms our view that there is already significant off-label use in the pre-chemo setting, particularly among oncologists. We believe an FDA approval will help drive usage among urologists, but the upside may not be as significant as the uptake of Xtandi in urology is expected to be gradual.

Source: Barclays Capital/Huang, March 18, 2014
Oncology Indication: Prostate
Keyword: FDA/Regulatory Issues

Back to Front Page

Medivation: PREVAIL Data May Not Convince All Urologists That Xtandi is Superior; Projected Utilization May Be Capped

Our Biotech team conducted a 4th survey among 32 community urologists, which indicated Xtandi's awareness and adoption have gained momentum on Zytiga since the PREVAIL data. However, Zytiga continues to hold the leading market share and questions remain on whether Xtandi can expand the pre-chemo market.

Experience with Xtandi Building, But Zytiga Still Leads in Market Share. Urologists report increasing awareness of Xtandi with 75% of doctors indicating they are now "quite knowledgeable" about the drug, an increase of 22% since our last survey. This places Xtandi essentially on par with Zytiga in terms of physician awareness. Increased familiarity has also translated into a 6% rise in the percent of their post-chemo mCRPC patients treated with Xtandi (now 16%, up from 10%), though Zytiga continues to lead in terms of market share (24%) within this subset. Greater familiarity has not resulted in much off-label use in pre-chemo mCRPC patients. Xtandi's penetration into this market was unchanged since our last survey at 7% (vs. 26% for Zytiga).

PREVAIL Data May Not Convince All Urologists That Xtandi is Superior. Our prior survey suggested positive survival data from Xtandi's PREVAIL trial might compel physicians to use significantly more Xtandi in the pre-chemo setting. It appears that news of PREVAIL is still filtering into the urology community. Four percent of surveyed physicians self-reported as "very knowledgeable" of the data, 46% were somewhat familiar, 29% were only vaguely familiar, and 21% have yet to hear about the data. After we presented physicians with the major efficacy findings of PREVAIL and Zytiga's COU-302 trial, considerably more urologists (38%) viewed Xtandi as more efficacious than Zytiga (8%). However, a majority of physicians could not pick a clear winner (38%) or viewed the drugs as having equal efficacy (17%).

Xtandi Now Expected to Take Modestly Higher Pre-Chemo Share Over Zytiga, But Projected Utilization May Be Capped. We have been concerned that some may be overestimating Xtandi's pre-chemo mCRPC opportunity, and our surveys continue to stoke such concern. For example, Xtandi's projected market share in 3 years' time (37%) is only modestly higher than Zytiga's current share (26%). In contrast, most Street models forecast far higher peak sales of Xtandi (consensus U.S. sales of nearly $2B in 2017 vs. Zytiga's <$1B run rate). With most urologists reporting that they are either already using Zytiga and/or Xtandi in pre-chemo patients (56%) or that they refer such patients to oncologists (25%) for treatment, we see limited opportunity for market growth. Moreover, physicians project that the average pre-chemo patient might be on Xtandi for just 14 months (similar to Zytiga), throwing into doubt market expansion driven by longer duration of dosing.

Source: Cowen and Company/Schmidt, March 17, 2014
Oncology Indication: Prostate
Keyword: Market Overview

Back to Front Page

Pharmacyclics: Reimbursementfor Imbruvica Ahead of Expectations; Street Underappreciates Costs Associated with Side Effects of Other Cancer Drugs

Takeaway from our meeting with Jesse McGreivy (CMO) and Matt Outten, Head of Market Access Group.

IMS: Early in launch. Current refill rates according to IMS are low (~40%). According to the company, this is too low and that IMS is likely not capturing actual refill rates. Still early in launch, capture rates are fluctuating as well.

Type of patients using Imbruvica. Currently, there is a mix of community and KOLs that are the early adopters/prescribers of Imbruvica, with most users being large group KOLs.

Reimbursement ahead of expectations. As the company has stated previously, they overestimated the need for the free 30-day drug program. Insurers have been very fast to reimburse and majority of plans are reimbursing already for MCL & CLL, ahead of expectations. Usually, it can take up to 6 months. Most patients right now have commercial plans. The company expects patients on Medicare and Medicaid to increase over time.

Reimbursement of long durations of therapy. The company says the street underappreciates the costs associated with side effects (such as febrile neutropenia, infections, supportive care drugs) of other cancer drugs. Payers account for lack of costs associated with a drug & any reduction in hospitalizations. This is bullish, in our view, for Imbruvica's reimbursement over time and in earlier lines of therapy where duration may be quite long.

Co-pay assistance. A large group of patient is using co-pay assistant. The plan for commercial patients is more generous (patient only pays $25) vs. other plans that have a large first month deductable. The company is still taking time to get docs to understand this.

Competitive landscape. We also met with Richard Scheller (Genentech's EVP, gRED). ABT-199 combo data with Rituxan could come at the earliest at ASH'14. Roche will go to the FDA ~mid-year to try and get some of the restrictions around ABT199 in clinical trials reduced to accelerate the enrollment. The company thinks they have figured out how to dose the drug and may need to incorporate a de-bulking regimen prior to using ABT 199. From Pharmacyclics' perspective, they think it is a stretch to think docs will move to an induction regimen in CLL and that there is still not enough data to believe ABT199 will have highly effective and sustained responses.

Source: Deutsche Bank/Karnauskas, March 17, 2014
Oncology Indication: Hematologic
Keyword: Sales & Marketing

Back to Front Page

Market Overview: Experts Expect Approval for Both Nivolumab and MK-3475 in 2014; Market Continues to Underappreciate Depth of Roche IO Pipeline

This brief report summarizes key takeaways from last week's ITOC1 immunotherapy meeting, and conversations with leading immune-oncologists Holbrook Kohrt and Alexander Eggermont. Given the market potential and emergence of new treatment options, we continue to advocate our immunotherapy basket strategy.

Our speakers highlighted forthcoming data with PDL1/PD1 agents at ASCO in numerous indications, highlighting bladder cancer and NHL. Our experts expect approval for both Bristol-Myers' (BMY) nivolumab and Merck & Co.'s (MRK) MK-3475 in 2014.

Combination therapy set to dominate future treatment paradigms. PDL1 expression is emerging as important mechanism of acquired resistance to anti-CTLA4 and vice versa. Physicians described exaggerated responses to chemotherapy in patients receiving prior anti-PD1 or anti-CTLA4 therapies.

Strong anecdotal support for IDOi activity from on-going trials. The initial data from the 136 patient Phase I/II IDOi + Yervoy combo melanoma trial will be presented at ASCO; several speakers anecdotally described seeing significant rapid responses in IDOi+Yervoy treated patients. Importantly, rapid responses with Yervoy alone are unusual given its classic profile of delayed response.

Market continues to under-appreciate the depth of Roche IO pipeline. Aside from anti-PDL1 aside, Roche has a 2nd generation IL2, an anti-CSF1R and a best-in-class anti-CD40 already in clinical development with numerous other modalities (therapeutic vaccines, bispecific antibodies) set to go into clinical development.

Baseline serum IL10 levels may identify patients with elevated risk of immune related adverse events. Checkpoint blockers may unmask patients with latent auto-immune disorders. The predictive relevance of PDL1 as a biomarker is not absolute, and is complicated by (i) dynamic expression of the ligand (ii) presence of PD-L1 on T-cells as well as cancer cells.

Immunodiagnostics of the tumor micro-environment allow identification of patients with cold, non-inflamed tumor sites requiring activation of the innate immune system through vaccines, cytokines, or STING agonists.

Source: Citigroup/Baum, March 18, 2014
Oncology Indication: Multiple
Keyword: Market Overview

Back to Front Page

Market Overview: Synta's Ganetespib (Hsp90) in NSCLC Will Likely Fail; Consultant Sees Puma's Neratinib (HER2) Hold Some Promise

Last week we hosted a conference call with a leading medical oncologist specializing in NSCLC drug development at Memorial Sloan Kettering Cancer Center.

In-line with our views, the consultant believes that hsp90 inhibitors demonstrate no clear signal of activity, and benefits of administering these drugs would be incremental at best, going so far as to say he has completely abandoned it as a target. We note that Synta has Ganetespib, an hsp90 inhibitor, in an ongoing Phase 2b/3 trial treating NSLC patients expected to read out interim results in 2H15; we currently believe the trial will fail. Additionally, the company launched an hsp90 development platform last year, a poor use of capital in our opinion.

Alternatively, our consultant saw promise in Puma's neratinib as he believes that Her2 is a viable target for the treatment of lung cancer. He estimates that 2-3% of adenocarcinomas are Her2 positive, slightly less than ALK. We note that neratinib has shown a 33% ORR (n=2/6) in lung cancer in a Phase I combination with Torisel. We expect data from the Phase II neratinib+Torisel combination in the second half of 2014. Our consultant noted that erlotinib may prove to be more effective in targeting EGFR, though.

Lastly, our consultant believes that as molecular diagnostics become more commonplace, drugs like Exelixis' cabozantinib will be used more often for specific patient populations. Cabozantinib has shown efficacy in NSCLC, posting a 58% CBR (10% PR, 48% SD, n=60) in a randomized discontinuation trial. Cabozantinib is currently in Phase II testing for NSCLC specifically for patients with RET-fusion.

Source: Stifel/Klein, March 16, 2014
Oncology Indication: Lung
Keyword: Market Overview

Back to Front Page

Novartis: May Be Pursuing a Deal to Buy Out Israel's Gamida Cell, Globes Reports

Israel's Globes is reporting that Novartis is pursuing a deal to buy out Israel's Gamida Cell for "hundreds of millions" of dollars upfront and hundreds of millions more in milestones, adding up to a total of about $600 million. The stem cell biotech has been working on a late-stage program for boosting the concentration of stem cells derived from umbilical cord blood to implant in adult leukemia and lymphoma patients.

Reuters followed up with a story saying that two big shareholders of Gamida Cell confirmed that a buyout deal is in the works, but also noted that a Novartis spokesperson declined to comment on the news. Clal Biotechnology said that an acquisition offer had arrived March 7th, according to Reuters.

Gamida Cell had been touting plans to take the Phase II/III data on StemEx to the FDA, but was forced to announce last summer that regulators had stiff-armed the proposal, demanding a full Phase III study ahead of a decision. Teva had been engaged in a joint venture on the program, but Globes reports that the big Israeli biopharma company dropped its interest in commercializing the therapy, leaving the commercial rights to the program up for grabs if a buyer came along.

Teva is still listed as an investor, along with Amgen (AMGN), Denali Ventures and Elbit Medical Technologies, which has a big stake in the company and reportedly confirmed that the offer involves a "significant immediate payment and additional future payments totaling hundreds of millions of dollars."

Gamida Cell has been exploring a possible IPO, which could be real or could be a useful gambit in any buyout discussions.

Source: FierceBiotech/Carroll, March 18, 2014
Oncology Indication: Hematologic
Keyword: Mergers & Acquisitions

Back to Front Page

Fate Therapeutics: ProHema Phase II Trial in Hematological Malignancies Underway, Interim Data in 2H14; Initiation of Phase I ProHema Trials in Pediatric Patients in 3Q14

Interim look in ProHema's Phase II PUMA trial expected in 2H14. The Phase II PUMA trial of ProHema in adult patients with hematological malignancies is underway; the trial's data monitoring committee (DMC) will conduct two safety reviews in the study, after the first 6 and 12 patients have been treated with ProHema. An interim update will be provided after the 12 ProHema patient review has been completed and is anticipated in 2H14, with full data on the primary efficacy endpoint expected in mid-2015. Recall that the Phase II PUMA trial will enroll 60 patients at 10 US centers who will be randomized 2:1 to receive either ProHema plus an unmanipulated CBU or two unmanipulated CBUs. The trial is 80% powered to demonstrate with statistical significance ($p<0.05$) that 70% of ProHema patients have neutrophil engraftment before the control group's median engraftment time.

ProHema in pediatric hematological malignancies and LSDs in 2H14. In March, Fate submitted a protocol with FDA for the clinical development of ProHema in pediatric patients with hematologic malignancies. The company plans to amend its existing IND application in 2Q14, and initiate a Phase I trial in pediatric patients with hematologic malignancies in 3Q14. In addition, Fate plans to file an IND for the use of ProHema in pediatric patients with demyelinating lysosomal storage disorders (LSDs), including Hurler syndrome, Krabbe disease, and certain leukodystrophies in mid-2014, and expects to initiate a Phase I trial in this setting in 2H14.

Our view on Fate Therapeutics is based on the company’s core technology and expertise in the pharmacologic modulation of adult stem cells for the development of therapeutics for the treatment of orphan diseases. If successful in its Phase II and Phase III development, we estimate that ProHema can gain significant share in the umbilical cord blood-derived HSCT market, along with share in the bone marrow- and peripheral blood-derived markets as well. Using conservative market penetration assumptions for ProHema (16% of the overall allogeneic HSCT market), we project that it can be a $360M US/EU product in 2025, with peak US/EU sales of ~$515M in 2030. These revenue numbers do not account for the upside that exists should ProHema and follow-on products manage to demonstrate utility in rare genetic disorders for which transplantation is not currently used as the standard of care, but is being used investigationally and starting to emerge as a potential treatment option.

Source: Cowen and Company/Simeonidis, March 18, 2014
Oncology Indication: Hematologic
Keyword: Clinical Trials/Pipeline

Back to Front Page

Dr. Reddy's: R&D to Remain High Due to Biologics, Oncology Injectables & EM Partnerships and Facility/Brand Acquisitions

We met Dr. Reddy's (DRL)'s management as part of Barclays' second India healthcare trip. Takeaways were:

- FY15E could be relatively muted on a high base with lack of a blockbuster drug (>$50mn, expected in FY16E), but recent launches are to remain strong.
- India & PSAI, having undergone structural changes, should recover only gradually.

Supply chain important in US - ample levers to offset buy-side pressures include:

- Volume increase to help offset pricing pressures, as a preference for large players should be maintained.
- Smaller players expected to be more disadvantaged on pricing.
- Improving environment in US generics with relative stabilization in price erosion (vs. erratic drops earlier).
- Strategic price hikes (by US firms) are likely to contribute more to the earnings growth than volume rise in this environment.

Sustained investments into the future - R&D expenses to remain high (can go north of 10%) driven by:

- **Biologics (ahead of peers in learning curve; $50mn investments):** Management reiterated its strong focus on this segment, DRL being one of the first entrants. Management additionally highlighted that while there is no regulatory restriction on biosimilar acquisitions, there is not much added value for the company there.
- **Complex products like injectables and topicals, which should drive $/Rx:** DRL has been investing heavily in the Oncology injectable segment, highlighted in the sharp increase in the DMF filings in this therapeutic area (total of 15+ filings). The impact of this can be seen in the contribution of Oncology injectables increasing from low single-digits to c20% in 4Q13.
- **Developing capabilities and tech access in EMs through partnerships (open to product in-licensing) and facility/brand acquisitions:** Management mentioned that incremental R&D is spent in complex segments only, which in our view could have a long-gestation return period. Further, management highlighted that while long-term margin trajectory is upward, near-term volatilities could be sustained.

Source: Barclays Capital/Prasad, March 17, 2014
Oncology Indication: General
Keyword: Management/Strategy/Financials