HealthACE Pharma Business Intelligence

Oncology Intelligence Report

February 10, 2014 Wednesday

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Additional Analysis

Ongoing Prostate Cancer 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
NCT01547299 Phase II	Prostate Cancer (Neoadjuvant Therapy for Patients Undergoing Prostatectomy)	1º: Pathological Complete RR; 2º: Effect on PSA, testosterone, & DHT, Rate of positive surgical margins, PD, Safety	August 2013 Active; Not Recruiting
NCT01650194 Phase II; Combo with Abiraterone Acetate & Prednisone	CRPC (Bone Metastatic)	1º: Adverse events; 2º: Effect on PSA, testosterone, & DHT, PFS, ORR, Bone scan	June 2014 Recruiting
NCT01664923 Phase II; vs. Bicalutamide	Prostate Cancer	1º: PFS 2º: Time to PSA progression, PSA response, Time to radiographic progression, Safety	July 2014 Recruiting
NCT01288911 Phase II; vs. Bicalutamide	Prostatic Neoplasms (Patients Who Have Progressed While on Luteinizing Hormone Receptor Hormone Agonist/Antagonist or After Receiving a Bilateral Orchiectomy)	1º: PFS 2º: PSA response, Time to PSA progression, Safety	November 2014 Recruiting
NCT01302041 Phase II	Prostate Cancer (Never Have Hormone Therapy)	1º: PSA level 2º: PD, PK, PSA dynamics & kinetics, Safety	December 2015 Active; Not Recruiting
NCT01534052 Phase II	Prostate Cancer (To Assess Safety of Continued Administration of MDV3100	1º: Long-term safety	December 2022 Recruiting

CRPC: Castration-Resistant Prostate Cancer
DHT: Dihydrotestosterone
MFS: Metastasis Free Survival
OS: Overall Survival
PD: Pharmacodynamic
PFS: Progression-Free Survival
PK: Pharmacokinetic
PSA: Prostate Specific Antigen
SRE: Skeletal-Related Event

Source: www.clinicaltrials.gov

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Medivation: Xtandi a "Better Drug" Than Zytiga, But Currently in 2nd Position After Zytiga; Disappointing Results from Early Studies of Sequential Use, in Either Direction

Given the current competitive dynamics and treatment landscape, we have been exploring the data for the performance of Xtandi and Zytiga when administered after each other. This question is important for several reasons. First, as JNJ is more and more successful in the pre-chemotherapy setting, so more and more patients coming through to Xtandi in the post-chemotherapy setting are Zytiga experienced, and therefore Xtandi's use will be affected by any change in the likelihood of response or duration of response as a result of that pre-treatment. Second, the relative benefits of either drug in the two settings will materially affect their revenue potential, depending on their share in the two settings at any point in time, and the proportion of patients pre-treated with either of the two agents beforehand.

Small observational studies addressing this question are starting to emerge and they are showing relatively consistent results. To assess this question thoroughly, we searched the literature and presentations at the recent ASCO GU meeting for posters and presentations about the clinical results for metastatic prostate cancer patients treated with one or other of these two drugs, given after prior treatment with its rival.

The results from these small observational and retrospective trials (Exhibit 1) suggested to us that responses to sequential use of Zytiga and Xtandi, in either direction, would be much attenuated compared to those seen in pivotal trials in patients naïve to both agents. This analysis also suggests the somewhat surprising insight that Xtandi is a better drug after Zytiga, than Zytiga is after Xtandi. This prompts one of the enduring questions in oncology, which is when do you use the best drugs – early when the patient is most likely to benefit or later when the patient has fewer options and choices. Typically, the conclusion of such debates (after multiple trials, several years and hundreds of millions of dollars) is to use the best drugs first to maximize the beneficial impact for the most patients, but this remains to be confirmed in this disease (Exhibit 2).

1. Response rates to both drugs are dramatically lower when either follows the other, compared to response rates in patients naïve to both.
2. The duration of such responses, when they occur, is much shorter than in doubly naïve patients, which compounds the negative revenue effect of being used second.
3. At the margin, Xtandi works better after Zytiga than Zytiga does after Xtandi, which is a surprising finding.
4. Xtandi's response rates are not materially reduced by chemotherapy.
5. Parenthetically, prior treatment with other anti-androgens does not appear to negatively impact responses to Xtandi.

Our conclusions from the analysis of these various trials is that Xtandi is still a "better drug" than Zytiga, being pound-for-pound more potent, more effective, easier to use and better tolerated. However, it is in second position after Zytiga in most patients today, and that position has limited upside until Astellas and Medivation can leapfrog Zytiga into the pre-chemotherapy setting in 2015. When that happens, the consequences for Zytiga will be very negative, with dramatic loss of penetration and duration, and hence revenue (with the converse upside outlook for Medivation). Despite their benefits, both drugs have limited duration of effect in most patients, and hence the prostate cancer field remains ripe for further innovation from incremental improvements in duration and depth of response. Whether the combined use of these two drugs could offer those improvements will depend on the progress and results of the recently opened ALLIANCE multi-center trial; even with rapid enrollment this trial is likely to take several years to reach a possible result for its primary endpoint of overall survival.

Exhibit 1:

Novel Hormone Therapy Cross Over Studies Identified in Literature

Zytiga --> Xtandi		Xtandi --> Zytiga	
Reference/Location of Patients	**Patient Number**	**Reference/Location of Patients**	**Patient Number**
Schrader et al, European Urology 65, 2014 - Germany	35	Loriot et al, Annals of Oncology, 2013 - France	38
Bianchini et al, European Journal of Cancer, 2014 - UK	39	Noonan et al, Annals of Oncology 2013 - North America	30
Cheng et al, ASCO GU Poster - US	122 (prior Zytiga and Chemo)		
Thomson et al, ASCO GU 2013 Poster Presentation - UK	23		
Stevenson et al, ASCO GU 2013 - UK	69 (prior Zytiga and chemo)		

Source: Medical Literature, SCB Analysis

Exhibit 2:

Summary of Results of Treatment with Xtandi *After* Zytiga and Zytiga *After* Xtandi

Xtandi appears to have some residual activity and benefit after Zytiga has failed; duration of responses 50% lower and responses in 25-30% of patients --> can justify trial of Xtandi post Zytiga and continue if patients respond

Z-->X			X-->Z		
	Bianchini (UK)			*Loriot (France)*	
	Z	*X*		*X*	*Z*
PSA decline >/=50%	38%	13%	*PSA decline >/=50%*	55%	8%
Duration of Treatment	6.4 months	2.9 months	*Duration of Treatment*	8 months	3 months
	Cheng (US)			*Noonan (Canada)*	
	Z	*X*		*X*	*Z*
PSA decline>/=50%	54%	26%	*PSA decline>/=50%*	60%	3%
	Stevenson (UK)		*Treatment Duration*	41 weeks	13 weeks
	Z	*X*	*Median % change in PSA*	-67%	+18%
Time to progression	7.5 months	4.5 months			
	Schrader (Germany)				
	Z	*X*			
Duration of treatment	9 months	4.9 months			
PSA decline >/= 50%	46%	29%			

Very little activity for Zytiga after Xtandi; short duration of effect, very few responses (<10%), mostly rising PSA --> hard to justify

Source: Medical Literature, ASCO GU, NEJM, SCB Analysis

Source: Bernstein Research/Porges, February 7, 2014
Oncology Indication: Prostate
Keyword: Market Overview

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Medivation: Both Xtandi and Zytiga are Being Tested in ER+/Her2- Breast Cancer; Role of Androgen Signaling Unclear

Xtandi and Zytiga are being tested in two sub-populations within breast cancer. The first is triple- negative breast cancer that is positive for androgen receptor expression, which accounts for ~ 3% of breast cancer. The second is ER+/Her2- breast cancer, which accounts for ~45% of breast cancer.

The role of AR signaling is TNC is based on limited preclinical data. In 2005-2006, two research groups used microarray analysis to identify a breast cancer subtype characterized by negative ER and positive AR expression (ER-/AR+). One of the groups, at Memorial Sloan Kettering, also showed that ER-/AR+ breast cancer cell lines proliferated in response to androgens, and the proliferation was inhibited by an anti-androgen.

Results from phase II study testing Xtandi predecessor bicalutamide in AR+ TNC were underwhelming. The study, conducted by the Memorial group, took five years and enrolled 26 patients who had ER-/AR+ breast cancer. Of the 26 patients, none achieved complete or partial response, and only 5 achieved stable disease greater than 6 months; median PFS was 12 weeks.

Xtandi and Zytiga are more likely than bicalutamide to show benefit in AR+ TNC. Both drugs are being tested in small phase II studies based on the belief that they are more effective at inhibiting AR signaling. We expect readout from these studies in late 2014 to the first half of 2015. Assuming androgen signaling does play a role in AR+ TNBC in humans, we would expect Xtandi and Zytiga to show a clinical benefit in these studies in this patient population.

Pre-clinical data demonstrate conflicting roles of AR signaling in ER-positive breast cancer. In ER+ tumors, estrogen signaling is the predominant oncogenic pathway, while androgen signaling is thought to act in a tumor-suppressive fashion. Therefore, it would seem paradoxical that blocking AR signaling would inhibit the growth of this cancer subtype. On the other hand, a group from the University of Denver, in collaboration with MDVN, recently published contrasting evidence, suggesting that Xtandi decreased estrogen-mediated growth of ER+/AR+ breast cancer, while bicalutamide had the opposite effect. The latest data are based on cell lines and xenografts, and have not been independently verified or proven in human studies. Experts we consulted believe the role of AR signaling in ER+ breast cancer is very much open to debate and the potential of this research is highly speculative.

Both Xtandi and Zytiga are being tested in initial proof-of-concept studies in ER+/Her2- breast cancer. In both studies, the androgen inhibitor is being given on top of the aromatase inhibitor exemestane vs. exemestane alone. In a prior drug-drug interaction study, Xtandi was shown to reduce exposure to exemestane by 40%; to compensate, exemestane dosage was doubled in the combination arm, which could lead to issues in interpreting the results. Both the Xtandi and Zytiga trials are enrolling ER+/Her2- breast cancer patients regardless of AR status, even though preclinical data from the U of Denver group were based on ER+/AR+ cell lines. This suggests that the companies and study investigators may have limited understanding of the role of AR signaling in ER+ breast cancer patients. Experts we consulted were highly skeptical that either study would lead to a positive outcome.

Revenue opportunity for Xtandi in breast cancer pales in comparison to opportunity in prostate cancer. According to published literature, AR positivity is identified in 11-30% of Triple Negative BC cases, or 2-5% of all breast cancer cases. As the total incidence of breast cancer and prostate cancer is similar, the simplistic view of the revenue opportunity in TNBC may be as little as 1/30th of the opportunity in metastatic prostate cancer (where all patients are likely to be eligible for androgen inhibition). Considering the need for a confirmatory phase III study, the earliest launch of any breast cancer indication would be in the 2018-2019 timeframe. We believe it is too early to ascribe any value to MDVN based on the breast cancer indications, and at this stage it is hard to see Xtandi being competitive with the many targeted agents in development for the many subsets of breast cancer.

Source: Bernstein Research/Porges, February 10, 2014
Oncology Indication: Breast
Keyword: Market Overview

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Bristol-Myers: Positive Outlook for Immuno-Oncology Pipeline; Multiple Immune-Modulators, in Addition to Yervoy, That Can Combine with Nivolumab

We are upgrading Bristol-Myers (BMY) based on our more positive outlook for the company's immuno-oncology (IO) pipeline and lower market expectations following the recent update on the Checkmate-012 trial.

The turning point for us was Merck & Co.'s (MRK) recent announcement regarding its four new collaborations for MK-3475 because we believe it strongly suggests that even though we don't know which PD-1 combos are optimal, there is growing evidence that combos will be meaningfully better than PD-1 monotherapy, and BMY probably has the most promising combos. We believe the market's initial high expectations for Nivo+Yervoy and the recent negative reaction following the Checkmate-012 update were both premature. IO drugs work slower than targeted treatments; therefore, it is rational for BMY to continue the study to focus on durability of responses and survival because these attributes are the strengths of IOs and they are ultimately more clinically relevant than Overall Response Rate.

Moreover, Yervoy does not have to be the other piece of a Nivo-based combo. BMY has a number of other immune-modulators in its pipeline (e.g., anti-LAG-3) that it can combine with Nivo, and MRK's decision to partner with Incyte for its IDO inhibitor strengthens the case for dual-immunotherapy. Overall, we believe this will be one of the largest biopharma markets, with a number of effective PD-1 based regimens that could exceed $30B because IO drugs will probably work in multiple tumors, move up to earlier-stage patients, and command a significant pricing premium because they meaningfully improve cancer survival. We forecast Nivo risk-adjusted sales of ~$11B by 2023, and are introducing risk adjusted sales of ~$2.5B by 2023 for the rest of the IO pipeline.

Source: BMO Capital Markets/Arfaei, February 9, 2014
Oncology Indication: Multiple
Keyword: Management/Strategy/Financials

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Sunesis: Hires New COO to Lead Commercial Efforts for Vosaroxin (AML); Phase III VALOR to Be Unblinded in 3Q Due to Slower-Than-Expected Rate of OS Events

Sunesis (SNSS) issued a press release announcing the hiring of its new EVP/Chief Commercial Officer, Joseph I. DePinto, who will lead commercial efforts for vosaroxin. Based on Mr. DePinto's experience at Dendreon (Provenge), ImClone Systems (Erbitux), and Abraxis Bioscience (Abraxane), this appears to be a solid hire by SNSS.

In addition, SNSS noted the unblinding of the Phase III VALOR study will now occur in Q3 vs. Q2 2014 based on slower than expected rate of Overall Survival (death) events. Due to the double-blinded nature of the study, size (largest R/R AML study in history), when a patient was randomized, and what treatment arm the patient is randomized to, we believe there are too many unknown variables to determine if today's news provides a definitive read-through on the likely outcome for VALOR.

Of recent note, during 2012/2013, the potential timing of unblinding of the Revlimid MM-020 results varied over different quarters based on the fluctuation of the PFS (and OS) events in the three arms. As a result, we believe today's announcement by SNSS most likely reflects a fluctuating OS rate overall (based on various factors), an issue inherent in oncology studies where PFS and OS are the primary endpoint(s).

SNSS indicated that it still expects to be able to complete submission of the various NDA modules to the FDA by the end of 2014 (no change in timing), setting the stage for a potential FDA decision by mid-2015E. Recall vosaroxin has been granted Fast Track designation by the FDA.

We continue to believe VALOR has a 65% probability of success.

Source: Wells Fargo Securities/Andrews, February 10, 2014
Oncology Indication: Hematologic
Keyword: Clinical Trials/Pipeline

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Pharmacyclics: Imbruvica Scipts Suggest $45-$49M Sales in 1Q14, and Estimate 2014 Sales at $260-$390M vs. Recent Consensus of $208M

Analysts' calculations also imply ~44% (last week 54%) use of Imbruvica in CLL patients. NRx were down 10% at 201 vs. 223 last week while TRx were flat at 299 vs. 296 last week. According to IMS data for Imbruvica, new patient starts stood at 201, week ending 1/31. If we assume average patient flow at 200/week through 2014, we calculate 2014 Imbruvica sales at $260-$390M. We assume 2014 discontinuations at 25%- 50%/year. We assume CLL and MCL breakup at 50% each. At average new patient flow at 150/week, we see 2014 sales at $200-$300M. Key unknowns: Refill rates, compliance and capture rate.

Analysis of new patient starts indicate 1Q14 sales at $49M. We expect new scripts to grow to ~240 by end of Feb and accelerated growth (~10%/week) increase post CLL approval. We model 50% of prescriptions for high dose (MCL) and 50% of prescriptions for low dose (CLL).

EUTrx (actual pills dispensed) calculations also indicate 1Q14 sales at $45M. We note that $10.6M of Imbruvica has already been sold by week #5 in 1Q14 per our IMS calculations. While EUTRx may be a good proxy for next quarter sales, long-term projections could be incorrect due to unknowns such as warehousing/dropouts & overstatement of pills bought vs. used in the quarter.

Source: Deutsche Bank/Karnauskas, February 7, 2014
Oncology Indication: Multiple
Keyword: Sales/Rx Trends

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Ariad: Post-Relaunch Survey: Physicians View Iclusig as Essential Drug for CML Patients with Mutations or Patients Who Have Failed Multiple Agents

Our new post-relaunch survey suggests that physicians view Iclusig as an essential drug for CML patients with T315I or other mutations, or for patients that have failed multiple agents. That said, doctors have become more cautious on the adverse event profile for the drug following the marketing suspension. While use is certainly going to be more restricted than initial expectations, our findings make us incrementally more positive relative to our über bearish view after FDA removed Iclusig from the market.

We polled 50 docs to determine how they perceive Iclusig following the re-launch and to gain insight on how they might now prescribe the drug. The survey results are summarized in the attached slides. Key findings include:

1) Iclusig remains an essential drug for CML,
2) Docs have heighted awareness of safety concerns and report direct experience with SAEs,
3) AEs listed on the label have been observed in real world setting (38% docs report observing at least one),
4) Rate of use is expected to be modestly lower than before the marketing suspension, and
5) A large majority of docs want more safety data before prescribing broadly.

Source: Credit Suisse/Kantor, February 7, 2014
Oncology Indication: Hematologic
Keyword: Clinical Trials/Pipeline

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Roche: Expands Partnership with Cancer Genetics to Be the Sole Provider of Molecular Cancer Diagnostics in Central America & the Caribbean

This morning (2/10), Cancer Genetics announced that it has broadened its partnership with Roche Servicios S.A. to make Cancer Genetics the sole provider of molecular diagnostic cancer testing services for Roche in Central America and the Caribbean. Furthermore, Cancer Genetics is slated to develop a center of excellence for lung cancer testing using the Roche cobas platform, which is FDA-approved.

In our view, this is a significant milestone in Cancer Genetics' development into a leader in the molecular diagnostics sector. The firm is now, in our view, a preferred collaborator for Roche, which in addition to being a top 10 global pharmaceutical firm and a leader in oncology therapeutics development is also the largest purveyor of molecular diagnostics in the world.

The agreement with Roche Servicios S.A., the division of Roche that handles Central America and the Caribbean, is an exclusive provider arrangement that makes Cancer Genetics the sole purveyor of molecular diagnostics-based cancer testing for Roche Servicios over a three-year period. According to the American Cancer Society, there were an estimated 255,900 new cases of cancer in Central America and the Caribbean in 2008, representing over 2% of the overall cancer population globally. In our view, this market represents a fast-growing, under-diagnosed commercial opportunity. We note that even a 10% penetration rate in this sector would substantially increase Cancer Genetics' current test volume base.

Source: Aegis Capital/Selvaraju, February 10, 2014
Oncology Indication: Multiple
Keyword: Partnerships/Business Developments

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Biotech: Aduro BioTech Initiates Phase IIb Combo Study of Its Immunotherapies (CVAX Pancreas & CRS-207) for Pancreatic Cancer

Aduro BioTech today (2/10) announced the initiation of a Phase 2b clinical trial of the company's immunotherapies GVAX Pancreas and CRS-207.

The ECLIPSE trial (Efficacy of Combination Listeria/GVAX Immunotherapy in the Pancreatic Cancer Setting) will enroll approximately 240 adults with previously-treated metastatic pancreatic cancer and will involve over 20 clinical trial sites in the U.S. and Canada. The randomized, controlled 3-arm trial will evaluate the safety, immune response and efficacy of the combination immunotherapy of GVAX Pancreas (with low-dose cyclophosphamide (CY)) and CRS-207 compared to chemotherapy or to CRS-207 alone. The primary endpoint of the trial is overall survival.

In the recently completed, randomized, controlled, multicenter Phase 2 trial in 93 patients in the same population, a statistically significant survival benefit was demonstrated in patients receiving the combination of CY/GVAX Pancreas and CRS-207 immunotherapies (Arm A) compared to patients receiving CY/GVAX Pancreas immunotherapy alone (Arm B). The median overall survival for 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). Moreover, the immunotherapies were well-tolerated, with no treatment-related serious adverse events or unexpected toxicities observed.

Source: Business Wire, February 10, 2014
Oncology Indication: Pancreatic
Keyword: Clinical Trials/Pipeline