HealthACE Pharma Business Intelligence

Oncology Intelligence Report

March 24, 2014 Monday

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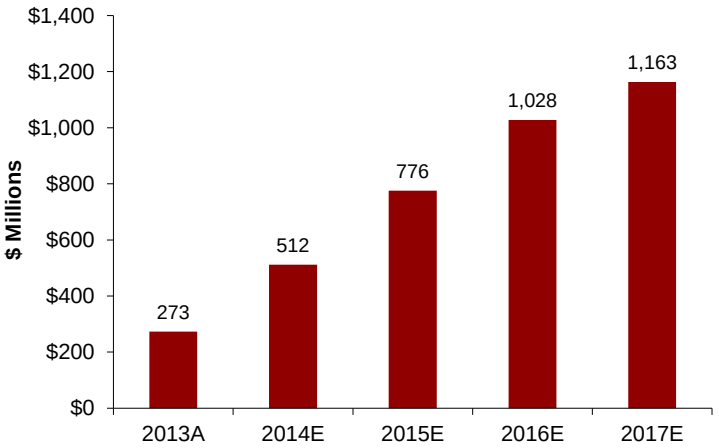
Medivation - Annual Revenues Forecast



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

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Medivation/Astellas: Xtandi Approved in Japan for Post-Chemo CRPC; First-to-Market Advantage May Not Be as Substantial as Expected

Astellas announced that prostate cancer drug Xtandi had been approved in Japan for treatment of castration-resistant prostate cancer. Precautions regarding the indication include 1) efficacy and safety have not been established in prostate cancer patients who have not received chemotherapy and 2) physicians should be sufficiently knowledgeable of the safety and efficacy record of Xtandi and determine eligible patients based on details from clinical trial results. Furthermore, the dosage regimen section notes efficacy and safety has not been established for prostate cancer patients that have not undergone surgical or pharmaceutical castration. Medivation stands to receive USD15mn in development milestone payments. Normally, a drug is price-listed on the NHI drug tariff within 60 days of approval.

The first-to-market advantage for Xtandi may not be as substantial as we had expected. Astellas will have to limit sales promotion to the post-chemotherapy indication and, given the conservative nature of Japanese physicians, off-label use will likely be relatively minimal. JNJ submitted a domestic new drug application (NDA) for Zytiga in July 2013 and likely included data from the pre-chemotherapy clinical trial (COU-AA-302) in the application package, in our view. This could result in Zytiga being approved in summer 2014 and obtaining approval for the pre-chemo indication ahead of Xtandi. Moreover, JNJ has enlisted AstraZeneca as it co-promotion partner in Japan (a good choice given its established presence in the anticancer agent market with Casodex). Consequently, the advantages of Xtandi being approved first could be much more limited than we had anticipated.

Astellas provided no comments on its strategy for obtaining expanded approval for pre-chemo therapy but we see two possible options: 1) a formal amended NDA application could be submitted based on data from the PREVAIL study once it has been completed or 2) Astellas could petition the regulatory authorities to amend the product label based on data from the interim analysis of the PREVAIL study. Obviously, the latter option could result in a faster possible approval.

Reimbursement price is key issue. An overseas price adjustment will likely be applied when the initial NHI reimbursement price is set for Xtandi. We assume the similar efficacy comparison calculation method will be used and estimate the annual cost per patient at around JPY1-1.2mn. If the cost calculation method were used instead, we estimate it would boost the annual cost to JPY2-4mn. The NHI price will likely be announced at a Central Social Insurance Medical Council meeting in May.

$1.00 = JPY102.32

Source: Barclays Capital/Seki, March 24, 2014
Oncology Indication: Prostate
Keyword: FDA/Regulatory Issues

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Medivation: Xtandi's Future Growth Depends on Oncology-to-Urology Transition; Seeking Out a 2nd Asset in Either Oncology or Neurology

Key issues discussed at investor meetings with Medivation management included: 1) reasons the 2014 guidance was lower than expected; 2) the key for Xtandi sales growth is the upcoming oncology-to-urology transition, not the distinction of pre-chemo and post-chemo settings of metastatic castration resistant prostate cancer (mCRPC); 3) most of Xtandi's future sales will eventually come from urology, and Xtandi will be a foundation therapy for prostate cancer spanning the entire prostate cancer continuum; 4) Xtandi should have a strong advantage over Zytiga in the urology setting based on its profile; 5) breast cancer remains a key second indication for Xtandi, and Phase II data release in 2015 could add meaningfully to Xtandi's peak sales estimate; and 6) the company continues its efforts to identify a second asset to bring to the clinic.

We maintain our estimate of Xtandi's peak worldwide sales of $7.7 billion in prostate cancer alone. Further, we believe that key catalysts such as 2014 quarterly sales, Xtandi's label expansion into pre-chemo mCRPC, and potential data readouts from Phase II studies TERRAIN and STRIVE (comparing Xtandi with Casodex) should provide near-term interest following the stock's recent weakness.

Xtandi guidance for 2014 appeared confusing to the Street because it was a "perfect storm" of overstated demand in second half 2013 and the Street had unrealistic expectation of high Xtandi off-label use by urologists in the pre-chemo setting before its formal approval. Management commented that Xtandi awareness and use in the oncology segment is very high; major further growth for Xtandi would have to come from the use by urologists.

Xtandi has largely saturated the oncology setting in the U.S. since its launch 18 months ago, and the off-label use in the pre-chemo setting is already substantial in the oncology setting. **With the pre-chemo approval, the key for Xtandi's next leg of growth is the oncology-to-urology transition, and the penetration into urology will be slower to accomplish as compared with the oncology setting.** Management noted that urologists typically take care of prostate cancer patients for a much longer duration (10-12 years) than oncologists (1-2 years), and patients are referred to oncologists only following signs of symptomatic disease. The company anticipates Xtandi to reach peak penetration in the urology segment in approximately three to four years from its formal approval, or roughly the midway point between the time Zytiga and Xtandi reached peak penetration in the oncology segment (12 to 18 months) and Casodex reached peak penetration following its launch (roughly five to six years).

The majority of Xtandi's future market opportunity should reside in the urology setting, in our opinion. The approval in the pre-chemo mCRPC (or M1) setting will introduce Xtandi into the urologists' offices, and further studies in progress in the earlier settings, including the M0 setting (PROSPER study), the metastatic hormone-sensitive setting (TERRAIN and STRIVE studies), the neoadjuvant setting, and the frontline hormonal setting, will continue to drive Xtandi use in urology and across the prostate cancer disease continuum.

Sales mix will flip to 80% urology following the pre-chemo approval, and the commercial team will also be upsized. Currently, Medivation has a 60-person sales organization with 80% targeting oncology. Following the pre-chemo approval, the company plans to expand its commercial salesforce from 60 to 90 representatives, and 80% will target urology. In addition, partner Astellas is expected to increase its dedicated 90-person salesforce as well.

Xtandi in breast cancer provides upside; we expect Phase II data reveal in 2015 to add meaningfully to the Street's Xtandi estimates, if promising. Management noted that the focus on developing Xtandi for the treatment of advanced breast cancer is high priority, and beyond the ongoing Phase II study of monotherapy Xtandi in AR+, triple-negative breast cancer (TNBC), and Xtandi in combination with the aromatase inhibitor (AI) exemestane in postmenopausal women with advanced breast cancer that are estrogen receptor positive (ER+) or progesterone receptor positive (PgR+) and human epidermal growth factor receptor 2 negative (HER2-), the company plans to initiate enrollment of a third Phase II study evaluating Xtandi in combination with Roche's (RHBBY $37.42) Herceptin (trastuzumab) in HER2+, AR+, ER- metastatic, or locally advanced breast cancer.

Medivation continues to seek out a second asset in either oncology or neurology to bring to the clinic behind Xtandi. Management reiterated that the company has several research programs in progress and continues to evaluate

potential in-licensing opportunities in indications such as oncology and neurology, with the goal of identifying a second asset that would help diversify and bolster the pipeline. No guidance was provided regarding a potential announcement related to the pipeline; however, we believe a strategic decision might be announced by year-end 2014.

Source: William Blair/Xu, March 24, 2014
Oncology Indication: Prostate
Keyword: Management/Strategy/Financials

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Incyte: Panelists Positive on IDO Inhibition Because of Its Benign AE Profile and Preclinical Synergy with Current Immune Checkpoint Targets; '360 Combo Data with MRK's Lambrolizumab Could Be in 2015

We hosted Incyte (INCY) and two immune checkpoint specialists as part of our immunooncology summit in Boston.

IDO inhibitors have shown a benign adverse event profile compared to CTLA-4 or PD-1 therapy, and IDO has shown synergies with CTLA-4 in melanoma patients and in preclinical models with PD-1/PD-L1. Both panelists were positive on IDO combination regimens. One panelist also expects strong synergies between IDO inhibition and T cell activators, such as vaccines and even chemotherapy, and also highlighted the role of IDO inhibitors as adjuvant therapies post-resection. In these settings, the tumor may not have set up checkpoint blockades and IDO inhibition would potentially maintain a favorable environment for T cells.

INCY will start the Phase 1 portion of a Phase 1/2 trial of '360 with Merck & Co.'s (MRK) PD-1 antibody, lambrolizumab, in 2Q14. Overall, anti-PD-1 antibodies, like lambrolizumab, have had a more benign clinical profile than Yervoy, and thus, we expect INCY will be able to use a higher dose of '360 in this combination study relative to the Yervoy combination study in melanoma. We expect the combined safety profile could allow for more rapid dose escalation than has been observed in the '360-Yervoy combination study, although also the potential for more doses to be studied prior to reaching a maximum tolerated dose.

The design of the trial will likely be a 6+6 design (6 patients enrolled per dose cohort, with the requirement to expand each dose by an additional 6 patients if a certain number of Grade 3 or 4 toxicities are observed) with at least 8 weeks of minimum follow-up for each dose cohort to account for the slow onset of some immune related adverse events. We expect the first dose of '360 will likely be 25 mg twice daily, which was the starting dose of '360 when the melanoma study re-opened after liver enzyme problems at high doses with Yervoy. We believe that clinical activity has been observed at this 25 mg dose in the Yervoy study, and INCY management has indicated that preclinical activity hits a peak effect and plateaus at this dose exposure in animals, and as such, even the first dose cohort may demonstrate additive or synergistic activity.

That said, with a 6+6 design and a 21% expected response rate with lambrolizumab, it would require more than 2 responders at 25 mg for the efficacy data to even start being interpretable, and more likely it would require data from the first 2-3 dose cohorts prior to calling the combination a success. Given the 8 week follow-up per dose cohort, this may take until 1H15 prior to data. The next updates on this program will be during INCY's 1Q14 earnings call in late April/early May and at MRK's R&D day on May 6th.

Source: Jefferies/Wei, March 20, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Biotech: Experts Believe Targeting IDO Inhibitor Alone Unlikely to Drive Efficacy, Best Utilized in Combination with CTLA-4 or PD-1 Strategies

The Jefferies Biotech team hosted an investor summit earlier this week focused on recent developments with chimeric antigen receptor (CAR) T cell immunotherapy and immune checkpoint targets. Our onco-immunology experts at the summit believe IDO is a well characterized target driving immunosuppression in the tumor environment but blocking IDO itself is unlikely to drive efficacy, and is best utilized in combination with CTLA-4/PD-1 strategies.

Newlink Genetics (NLNK) is developing two orally available IDO inhibitors for the treatment of cancer, indoximod (Phase II) and NLG919 (Phase I). Indoximod is probably more of an IDO2 inhibitor vs. targeting IDO1 and may inhibit downstream effects on WARS and mTORc. NLNK is investigating indoximod in combination trials with docetaxel (breast cancer), Provenge (prostate cancer), temozolomide (brain tumors), Yervoy (melanoma), and Abraxane (pancreatic cancer), with the bulk of the preliminary data expected in Q4'14/ Q1'15. NLNK also believes synergy between indoximod and CTLA-4 blockade inhibitors may be possible for stronger responses, which was supported in preclinical models.

NLG919 is in Phase I for solid tumors (data expected in Q4'14/Q1'15. Synergy between NLG919 and indoximod may be possible, and NLNK showed in a mouse model that significant tumor shrinkage can be achieved in combination vs. either agent alone. Furthermore, NLNK is also presenting data at the AACR meeting (Abs #1633; Monday April 7) in which the company has identified selective inhibitors of IDO1 and tryptophan 2, 3 dioxygenase (TDO). While IDO1 converts tryptophan to N-formyl-kynurenine, the catabolism of tryptophan may also occur through TDO according to literature. Both IDO1 and TDO, although functionally similar, appear structurally distinct enzymes, and therefore may represent a third class of IDO pathway compounds in NLNK's pipeline.

We also hosted a panel on chimeric antigen receptor T-cell (CAR-T) immunotherapy with a majority of companies in our panel focused on targeting CD19 antigen in B-cell malignancies. Early data has reported robust responses in patients with refractory disease, and a durable response. Key challenges include addressing cytokine release syndrome (addressed through administration of IL-6 inhibitor) and potential for off-target adverse events.

Source: Jefferies/Amin, March 21, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Compugen: Identification of 9 Novel Immune Checkpoint Targets Impressive, But Clinical Trials are Still Years Away

We are impressed that Compugen (CGEN) has identified 9 novel immune checkpoint targets. Bayer signed an early agreement worth up to $540m and royalties for rights to two of these targets. CGEN has begun preclinical work on a third compound CGEN-15049, which it believes will be broadly applicable in cancers. Separately, CGEN has entered into a joint-venture with Merck Serono to develop additional compounds. Although CGEN will enter the clinic with its own proprietary compound until 2016, we believe there is high value in the computational discovery platform and we believe that the value of immune checkpoint targets is likely to increase over time.

CGEN is still a very early stage story and the company will not start clinical trials with its own proprietary candidates until 2016. We note that the lack of clinical data adds another layer of uncertainty to the value of the company's immune checkpoint targets. The field of immune checkpoint targets is evolving quickly, and it is unclear how many immune checkpoint targeting drugs will be necessary and where CGEN's candidates will fit into the treatment paradigm. We see combinability as a key requirement for new immune checkpoint drugs, which will not be apparent until human safety studies are conducted. Separately, it remains unclear if CGEN's patents will block other companies from developing drugs targeting CGEN's newly discovered immune checkpoints.

Source: Jefferies/Wei, March 19, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Pfizer: Bull Scenario Suggests Palbociclib (Breast Cancer) Could Generate $5B By 2020 Across Multiple Tumor Types

Our base case for palbociclib assumes our risk-adjusted forecasts for its use in only the ER+/HER2- breast cancer indication. However, given the number of other tumor types that palbociclib is currently being tested in and, moreover, given it has already demonstrated clinical benefit outside of that specific breast cancer indication (in a phase 2 study that recruited patients with Liposarcoma), we also considered a bull case for palbociclib that assumes efficacy across multiple tumor types. Our 2020E bull case of $5.0bn for palbociclib is 2.3x current consensus. Given palbociclib is a small molecule drug that would only need to be marketed to oncologists, we think our bull case scenario of $5bn by 2020 would also be significantly margin-enhancing for Pfizer as a whole in spite of the associated 8% royalty on global sales due to Amgen.

- PALOMA-1/-2 opportunity assumptions: By 2020, we model 68% penetration at an average monthly price of $7,300 with median treatment duration of c.18 months, giving a potential opportunity value of $4.9bn.
- PALOMA-3 opportunity assumptions: By 2020, we model 65% penetration at an average monthly price of $7,300 with median treatment duration of c. 9 months, giving a potential opportunity value of $2.6bn.
- PENELOPE-B opportunity assumptions: By 2020 we have modelled only $76m from this indication (or 5% of the opportunity value), given we only expect data to mature towards the end of 2019.

Together, these three breast cancer indications could generate ~$9bn in revenue for Palbociclib in the long-run, and potentially as much as ~$7.5bn by 2020. Our new $5bn 2020 forecast for Palbociclib assumes different risk adjustments for each of these three breast cancer opportunities given the varying extent of our current knowledge on the likely success of each one. We have assumed the following specific risk adjustments in arriving at our 2020 forecast:

- PALOMA-1/-2 opportunity: 75% risk adjustment on $4.9bn 2020 opportunity value gives a risk-adjusted $3.68bn forecast.
- PALOMA-3 opportunity: 50% risk adjustment on $2.6bn 2020 opportunity value gives a riskadjusted $1.30bn forecast.
- PENELOPE-B opportunity: 25% risk adjustment on $76m 2020 opportunity value gives a risk-adjusted $0.02bn forecast.

All three indications added together in 2020 generate our new $5.0bn forecast: $3.68bn + $1.30bn + $0.02bn = $5.0bn. Clearly, the magnitude and speed of penetration of this very high margin opportunity will have a material impact on Pfizer's growth outlook. Indeed, it's worth noting that the Palbociclib opportunity in front of Pfizer is by some margin the most impactful single product story the company has had since we took up stock coverage on 6 January 2009.

Total G7 PALOMA-1/-2/-3/PENELOPE-B market

Total G7 PALOMA-1/2/3 & PENELOPE-B Market	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
Total PALOMA-1/2/3 & PENELOPE-B US patients	50,016	48,979	48,271	47,898	47,868	47,830	47,786	47,734
Total PALOMA-1/2/3 & PENELOPE-B Ex-US G7 patients	99,984	97,912	96,496	95,750	95,690	95,616	95,526	95,422
Non-G7 PALOMA-1/2/3 & PENELOPE-B G7 patients			543	1,162	3,876	6,399	8,436	9,541
Global PALOMA-1/2/3 & PENELOPE-B patients	150,000	146,891	145,309	144,810	147,435	149,845	151,748	152,696
Average PALOMA-1/2/3 & PENELOPE-B G7 price per month		0	2,668	7,147	7,229	7,226	7,227	7,233
Average PALOMA-1/2/3 & PENELOPE-B G7 duration of therapy		0	2	8	9	9	10	11
Total G7 PALOMA-1/2/3 & PENELOPE-B Revs	0	0	64,852,376	1,079,670,057	3,603,106,220	5,433,493,306	6,639,033,431	7,522,020,430

Source: Atlantic Equities; SEER database

Source: Atlantic Equities/Purkiss, March 21, 2014
Oncology Indication: Breast
Keyword: Management/Strategy/Financials

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AB Science: Unsuccessful CHMP Appeal for Masitinib in 2nd-Line GIST; Masitinib Could Enter Market in 2016 for Mastocytosis Indication

The decision on the appeal for using masitinib as second-line treatment for GIST (a rare form of gastro-intestinal cancer) has just been handed down by the European Medical Agency's committee. Approval for the GIST indication might be granted after the current phase III trial reaches completion. In 2017, we expect AB Science to make the most of its recent contact with the EMA and be in a position to anticipate the experts' questions.

The CHMP did not budge from its initial position: the phase II trial presented was not deemed to be robust enough to demonstrate efficacy and characterize masitinib's safety profile in GIST. The agency felt that the insufficient number of patients meant that its questions could not be answered comfortably. The company based its case on the scientific rationale underpinning the mechanism (control of the tumor’s environment) but this was not enough to change the agency's mind. We are nevertheless fully confident that GIST will receive the green light, but we now expect this indication to be launched in 2017 in Europe and 2018 in the U.S.

After this failure for GIST, we think that the company is in for another negative event: the CHMP is set to give its decision on the appeal for the pancreatic cancer indication in April. That said, after the decision regarding the pancreatic cancer indication, AB Science's outlook for the next year will be less black and white than was the case in recent months. The main point will be the phase III results for mastocytosis in 2015 (this is a rare inflammatory disease) which is masitinib’s key indication (mast cell-related inflammation) for which we know that the futility analysis was positive (high probability that the phase III trial will be successful). Another key point for 2015 will be the results for ALS (amyotrophic lateral sclerosis, a neuro-degenerative disease). This condition is extremely difficult to treat, but might provide significant upside if the results are positive. All in all, we now believe that masitinib might come on to the market thanks to its mastocytosis indication. The launch might take place in 2016.

Source: Oddo/Malafosse, March 21, 2014
Oncology Indication: Gastrointestinal
Keyword: Clinical Trials/Pipeline

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Tesaro: To Use Myriad Genetics' HRD Test as Companion Dx for Niraparib (Phase III, PARP Inhibitor)

Tesaro has made a deal with Myriad Genetics to use Myriad's homologous recombination deficiency (HRD) test to look for tumor types that may respond to its poly-ADP ribose polymerase (PARP) inhibitor, niraparib. Myriad's HRD test can detect when a tumor can no longer repair double-stranded DNA breaks, making them more susceptible to drugs that damage DNA.

Myriad says this agreement with Tesaro is its fifth collaboration with a major pharmaceutical company to evaluate HRD. The company inked a similar deal with BioMarin back in November to use the HRD test to identify tumor types that may be sensitive to BioMarin's PARP inhibitor BMN-673. Also, a year ago, it made an agreement with PharmaMar to conduct HRD testing on patients enrolled in PharmaMar's Phase II study of PM1183, a drug candidate designed to induce double-stranded DNA breaks.

Niraparib was also the subject of a deal between Myriad and Tesaro in June 2013, when Myriad agreed to conduct BRCA1 and BRCA2 mutation testing using its BRACAnalysis test to identify patients for two separate Phase III clinical studies evaluating the PARP inhibitor.

Source: Genetic Engineering & Biotechnology News, March 24, 2014
Oncology Indication: Breast & Ovarian
Keyword: Partnerships/Business Developments