February 4, 2014 Tuesday

Today's Intelligence at a Glance

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UBS/Hauber, February 4, 2014
HealthACE Abstract *Indication: Lung*

2. Market Overview: PD-1: First-to-Market and Ease of Use Likely to Capture Best Opportunity; Bodes Well for Merck & Co.'s Lambrolizumab (Melanoma)
Jefferies/Holford, February 3, 2014
HealthACE Abstract *Indication: Multiple*

3. Celgene: Results from Revlimid & Rituxan Combo (Phase III/iNHL) Impressive; May Support Its Use in More Than 50% of Eligible First-Line Patients
BMO Capital Markets/Birchenough, February 4, 2014
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6. Market Overview: KOL: Ongoing Xtandi vs. Casodex Studies are Brilliant Marketing Studies and Could Help Position Xtandi with Urologists
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7. Roche: U.K. NICE Says Relapsed NSCLC Patients Should No Longer Have Access to Tarceva as It Does Not Meet Criteria for Clinical & Cost Effectiveness
PharmExec.com/Upton, February 4, 2014
HealthACE Abstract *Indication: Lung*

8. Pharma-Europe: Roche's Kadcyla, Bayer's Xofigo, and GSK's Tafinlar Can Now Be Accessed on NHS Through the Cancer Drugs Fund
PharmaTimes/McKee, February 4, 2014
HealthACE Abstract *Indication: Multiple*

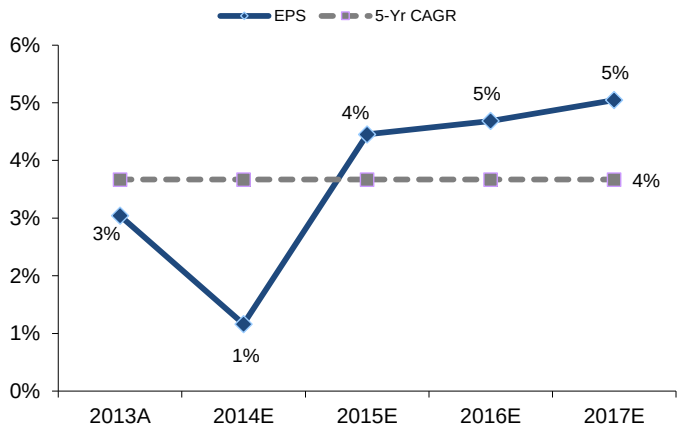
Additional Analysis

Roche's MPDL3280A in Development

Indication		Stage	Trial Name
NSCLC	Phase III; vs. Taxotere	OS, ORR, PFS, Duration of response	OAK Study
	Phase II; Single-arm study	Objective response, Duration of response, PFS, PK	FIR Study
	Phase II; vs. Taxotere	OS, ORR, PFS	POPLAR Study
	Phase II; Single-arm, biomarker study	ORR, Duration of response, PS, OS	NCT02031458
	Phase I; Combo with oral dosing of Tarceva	Safety, PK/PD, PFS, OS, ORR	NCT02013219
Melanoma	Phase I; Combo with Zelboraf; Dose-escalation & cohort-expansion study	Safety, Autoimmunity, Vital signs, ECG	NCT01656642
RCC	Phase II; Monotherapy or Combo with Avastin	PFS, ORR, OS, Duration of response	NCT01984242
Various Tumors	Phase II; Combo with Avastin and/or Chemo	Safety, PK, ORR, PFS, Duration of response	NCT01633970
	Phase I; Dose-escalation study	Safety	NCT01375842
	Phase I; Combo with Cobimetinib	Safety, PK	NCT01988896

Source: Company Reports, www.clinicaltrials.gov

Roche - Annual Pharma Sales Growth Rate (%)



Sources: Company Reports; 5+ Brokerage Analyst Reports

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Roche: MPDL3280A (Anti-PD-L1): Rolling Submission for NSCLC in Early 2015 Could Result in a 2016 Launch, But Label Likely to Be Narrow

Roche's FY13 results last week were unremarkable: solid sales, Perjeta strong, R&D spend high, decent guidance leading to <1% changes to our estimates despite an incremental FX of -1%. The main focus, however, was around Roche's highly anticipated anti-PD-L1 (MPDL3280A) for cancer. The market opportunity is enormous (we estimate >$15 bn in lung cancer alone), though we have so far only seen early data on all competing molecules (from Bristol-Myers, Merck & Co., AstraZeneca and Roche). With a best-case early market entry for Roche within 18-24 months, and increasing newsflow on Roche and competitor molecules, we now include U.S. forecasts for PD-L1 (in lung cancer only) for the first time, from 2016. This adds CHF 600m sales, and 2% to our Core EPS in 2018.

Roche's key focus - especially its fast-to-market strategy - has been on lung cancer (NSCLC). The company may be able to file a rolling submission in the U.S. for NSCLC patients with PDL1 expression in early 2015 (based on the FIR study), which could result in "best plausible case" accelerated approval by late 2015/early 2016 though only in patients with high level (IHC3) PDL1 expression (c. 12% of lung cancer patients).

Label expansion into broader lung cancer population from 2017/18. The POPLAR (p2) and OAK (p3) studies conducted in unselected refractory NSCLC populations could result in label expansion & European approval in 2017/ 2018. MPDL's unique lung safety profile may be critical, especially in NSCLC. We model as an upside scenario a 30% (US) and 40% (Europe) share in NSCLC, for a further CHF 4.8bn sales (another 16% to Core EPS) by 2020 for MPDL3280A in lung cancer alone (not included in our numbers). Additional tumor types (e.g., renal cancer from 2019, plus another yet to be disclosed tumor type) could add further upside. If the latter is CRC, the additional market potential could exceed even the NSCLC opportunity.

Source: UBS/Hauber, February 4, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

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Market Overview: PD-1: First-to-Market and Ease of Use Likely to Capture Best Opportunity; Bodes Well for Merck & Co.'s Lambrolizumab (Melanoma)

We hosted a lunch on February 3, 2014, with a leading PD-1 expert in New York. Our expert has extensive experience working with anti-PD-1 and anti-CTLA-4 drugs in melanoma and renal cell carcinoma patients. We have summarized our expert's key thoughts from the meeting. More information is available from the team on request.

Takeaways from PD-1 Expert Event:

First and easiest could be best. Our expert believes that the first anti-PD-1 that reaches the market could have an advantage, which we think bodes well for Merck & Co.'s [MRK] lambrolizumab in melanoma (rolling submission to complete in H1'14). He also believes that ease of use is important for physician adoption, which could be unfavorable for combo regimens, such as Bristol-Myers' [BMY] ipilimumab/nivolumab, that may be difficult to administer in a community setting. Our expert also opined that being 3rd or later to market in any category/class may result in little commercial use. We don't see a winner yet in the PD-1 vs. PD-L1 debate. Our expert presented arguments in favor of each.

- **Arguments in favor of PD-1s included:** 1) anti-PD-1 drugs have better access to immune cells, which are in circulation, whereas anti-PD-L1 drugs would need to penetrate the stroma and reach the tumor microenvironment to have optimal activity; 2) targeting PD-1 receptors could help target tumors that depend on the PD-L2 pathway to evade the immune response.
- **Argument in favor of PD-L1s included:** targeting the PD-L1 pathway could spare PD-L2, which may have a protective effect on bronchial endothelial cells and help reduce pulmonary adverse events.

Our expert prefers PD-1 as a future backbone of therapy. Our expert stated that he envisages that almost all immunotherapy will require a PD-1 or PD-L1 backbone in the future, which we believe bodes well for companies with such an asset as well as a broad array of other immunotherapeutic agents, such as BMY.

Anti-PD-1 use may not be restricted to PD-L1 positive tumors. At present, there is confusion with the PD-L1 biomarker as the developers use different markers for their assays, according to our expert. Furthermore, PD-L1 expression varies by cancer type and could also be inducible. The doctor noted that there is much activity in PD-L1 negative tumors, which suggests that the use of this class of drugs may not be limited to PD-L1 positive patients.

Comparison within the PD-1 and CTLA-4 inhibitor classes. Within the PD-1 inhibitors, our expert thinks the efficacy of lambrolizumab could be slightly better than nivolumab, and within the CTLA-4 inhibitors, he thinks AstraZeneca's [AZN] tremelimumab could be as good as BMY' ipilimumab, if optimally dosed.

Thoughts on different combination regimens. Our expert believes the ipi/nivo combo produces higher response rates in melanoma patients than single agent anti-PD-1s, and the response is more rapid, deeper, and more durable in a high percentage of patients. He thinks combining immunotherapy with chemotherapy is sub-optimal and could lead to lost immune function. The PD-1/ Avastin combo could have the best efficacy in kidney cancer (or renal cell carcinoma), due to overexpression of VEGF in this tumor type, and could present an easy path to first line approval in this tumor type, according to our expert.

Anti-PD-1 market opportunity. Anti-PD-1s are in development for multiple solid and hematological tumor types. We see a significant opportunity for BMY' nivolumab (peak sales c$13bn) across the indications in development, and strong peak sales potential for MRK's lambrolizumab (c$4bn), which could be the first anti-PD-1 approved for melanoma. We project respectable sales for Roche's [ROG] MPDL3280A and AZN's MEDI-4736 (peak sales of $2bn and $1bn, respectively), which we think could be the 3rd and 4th drugs in this class to be approved.

Source: Jefferies/Holford, February 3, 2014
Oncology Indication: Multiple
Keyword: Market Overview

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Celgene: Results from Revlimid & Rituxan Combo (Phase III/iNHL) Impressive; May Support Its Use in More Than 50% of Eligible First-Line Patients

The BMO Capital Markets US biotech team hosted a diligence call late last week with a prominent lymphoma expert. The focus of the call was on the evolving standard-of-care and new emerging treatment options for patients with indolent non-Hodgkins Lymphoma (iNHL). With a particular focus on Celgene's Revlimid, our expert is impressed with the activity of Revlimid + Rituxan (R2), where a complete response (CR) rate of ~80% has been observed in treatment-naïve iNHL patients. Responses are described as durable as compared with Rituxan + CHOP (R-CHOP) for which our expert suggested a CR rate of 40%-60% with about 30%-40% of patients losing response over three years. Validation of the durable 30-month CR has occurred recently, according to our expert, with correlation with overall survival, and should support approval of R2 if phase 3 data are positive. With regard to the ongoing phase 3 trial of R2 our expert suggested two ways for Revlimid to win, with either a comparable durable CR rate, with better safety/tolerability, or with a superior durable CR rate.

Revlimid use for iNHL is not contemplated in long-term guidance or Street consensus estimates and could provide $2.5B in incremental sales in the U.S. alone at peak, particularly given 30-month dosing in phase 3. Based on our expert feedback we believe that a comparable CR + better tolerability alone would support R2 use in more than 50% of eligible first-line iNHL patients, and we believe that 30%+ superiority is achievable given higher, more durable CR rates versus R-CHOP. While final data are not expected until 2017, interim data could come earlier in 2015/2016.

Source: BMO Capital Markets/Birchenough, February 4, 2014
Oncology Indication: Hematologic
Keyword: Market Overview

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OncoMed: USPTO Grants Patent on RSPO-LGR Pathway; New Antibody Could Be Selected Under Celgene's Alliance

OncoMed was granted a 4th U.S. patent #8,628,774 on the RSPO-LGR pathway. This is a method patent that covers antibodies targeting Leucine-rich repeat-containing G protein-coupled Receptor (LGR) proteins in order to disrupt the RSPO-LGR signaling pathway. OncoMed expects to file an IND for an anti-RSPO3 antibody in late 2014/early 2015, which could be selected under the Celgene Mega-alliance. We look for additional clinical validation of OncoMed's pipeline with multiple data read-outs at ASCO in June.

Transformative Alliance with Celgene. In November, OncoMed signed a transformative alliance with Celgene covering demcizumab, the bi-specific anti-DLL/VEGF antibody, plus 4 preclinical antibodies targeting either RSPO-LGR and/or an undisclosed CSC pathway. OncoMed received $177 million upfront and stands to receive up to $3.15 billion in milestones. Importantly, OncoMed maintained development control. If Celgene opts in, OncoMed retains a 50/50 profit split in the U.S. with healthy double-digit OUS royalties.

Demcizumab Active in Pancreatic Cancer. Last month, OncoMed reported initial Phase Ib data on anti-DLL4 antibody demcizumab in combination with gemcitabine and Abraxane at ASCO-GI. An impressive 50% (3/6) of patients achieved a partial response (PR) plus 2 patients with stable disease for an DCR of 83%. Based on these results, OncoMed will initiate a Phase II trial of demcizumab + gemcitabine + abraxane in 1st-line pancreatic cancer in 2H:14. Celgene could opt in to co-promote Demcizumab at any point after the Phase II trials.

OMP-59R5 Active in Pancreatic Cancer. Also at ASCO-GI, OncoMed reported Phase Ib ALPINE data on OMP-59R5 (anti-Notch 2/3). A total of 27 patients were evaluable at OMP-59R5 doses ranging from 2.5-12.5mg/kg, of whom 18 were combined with gemcitabine + Abraxane. No DLTs have been observed to date and 6/13 (46%) evaluable triple combo patients achieved a PR and 3 had stable disease equating to a DCR of 77%. OncoMed will begin the Phase II portion of the ALPINE trial in 2Q:14.

Source: PiperJaffray/Tenthoff, February 3, 2014
Oncology Indication: General
Keyword: Market Overview

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OncoGenex: Custirsen's Chance of Success (Phase III/Prostate Cancer) May be Under-Appreciated; Market Opportunity Likely to Improve with Results from ECOG Study

Feedback from a MEDACorp prostate cancer key opinion leader (KOL) during from ASCO-GU:

The KOL believes the upcoming OncoGenex's (OGXI) custirsen Phase III trial in combination with Taxotere (data by mid-2014) has a more than a 50:50 chance based in part on his own experience from the Phase II, which included some dramatic responses. He believes that the previous failed trials in the Taxotere add-on setting were due to unclear mechanistic rationale and he believes there is a clear basis for combining custirsen and Taxotere. The KOL also believes that the second compound apatorsen (OGX-427, HSP27 inhibitor) from OGXI has shown clear single-agent activity and he is positive on its outlook.

While the utility of custirsen is not necessarily limited to combination with chemotherapy, it is the initial setting for this agent. Additional ASCO GU data show that using Xtandi or Zytiga one after another has some modest activity. Although Xtandi and Zytiga are increasingly used sequentially before chemotherapy, the KOL believes that results of the E3805 trial announced on Dec. 5, 2013, and to be presented at ASCO 2014 may lead to earlier use of Taxotere. While Taxotere had only been approved and used in "hormone-resistant" patients, E3805 compared androgen deprivation therapy (ADT) in hormone-sensitive patients with or without 6 cycles of Taxotere at the start of standard hormonal therapy. It was announced that the Independent Data and Safety Monitoring Committee had recommended the early termination of the study due to improved overall survival in an interim analysis. The KOL stated that he is keenly interested in the full results of this study at ASCO as the improvement in survival appears to be dramatic. The NIH press release reported a 3-year survival of 69.0% vs. 52.5% in the overall population, which likely corresponds to a very substantial median survival improvement (potentially on the order of ~20 months by our rough estimate). The press release further stated that most of the benefit can be accounted for by patients who have a high extent of metastatic disease at study entry (3-year survival of 63.4% vs. 43.9%).

Source: Leerink Swann/Liang, February 3, 2014
Oncology Indication: Prostate
Keyword: Clinical Trials/Pipeline

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Market Overview: KOL: Ongoing Xtandi vs. Casodex Studies are Brilliant Marketing Studies and Could Help Position Xtandi with Urologists

Feedback from a MEDACorp prostate cancer key opinion leader (KOL) during from ASCO-GU:

The KOL believes Xtandi will win the majority of overall market share vs. Zytiga. He further commented that **market share will be determined by not only physician perception but also reimbursement, noting that some insurers currently require Xtandi to be used after Zytiga due to cost difference**. He noted that the tumor response data and PSA data will play especially well with urologists who are "PSAcentric". He emphasized that urologists have a very different mindset compared to oncologists. This may explain the slow penetration of Zytiga into urologists who may have been referring patients to oncologists, but Xtandi could have a better chance of winning an audience with urologists. Urologists already reach for Casodex, and it helps that Xtandi is in the same class as Casodex. He commented that the ongoing Xtandi vs. Casodex head-to-head studies are "brilliant" marketing studies. These studies are highly likely to be successful clinically and could help position Xtandi with urologists.

KOL seems more convinced about immunotherapy in prostate cancer as a result of ASCO GU data. Before Phase III data in the post-chemo setting, the KOL noted that he was not enthusiastic about Yervoy (BMY) for prostate cancer. He commented that the Yervoy post-chemo trial (presented again at ASCO GU) "almost made it" and he was hopeful that immunotherapy like Yervoy has the promise to work early in the pre-chemotherapy setting. On Dendreon's Provenge, the KOL liked the antigen spread data presented at ASCO GU that show that Provenge also elicits immune responses to secondary antigens (which are not targets for the vaccine itself) after tumor cell death during the initial response to Provenge and antigen spread is associated with survival. The KOL commented that this type of correlative data provides additional evidence for the efficacy of Provenge.

Source: Leerink Swann/Liang, February 3, 2014
Oncology Indication: Prostate
Keyword: Market Overview

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Roche: U.K. NICE Says Relapsed NSCLC Patients Should No Longer Have Access to Tarceva as It Does Not Meet Criteria for Clinical & Cost Effectiveness

The U.K. National Institute for Health and Care Excellence's (NICE) decision that relapsed non-small cell lung cancer patients should no longer have access to Roche's cancer drug Tarceva (erlotinib) is a setback for lung cancer care in England and Wales, where "over 1,000 patients a year will be left without an active treatment option after their first-line therapy has failed", a Roche press statement says.

NICE arrived at the decision because erlotinib does not meet its criteria for clinical and cost-effectiveness. However, patients in Scotland and the rest of Europe will continue to benefit from the drug.

The decision will leave patients with access to only the chemotherapy, docetaxel, which many patients are too sick to tolerate, says the statement. "It seems perverse that this NICE guidance will limit the treatment options available to only docetaxel, given that the independent evidence review shows the total NHS treatment costs of docetaxel to be higher than those of erlotinib… The cost of managing treatment side effects is also greater with docetaxel, especially for life-threatening febrile neutropenia, which normally requires hospitalization for antibiotic therapy."

Roche points out that lung cancer treatment rates in the U.K. are already low, with less than 40% of patients receiving any kind of active treatment when their cancer relapses. The NICE decision, says the drug maker, "would reduce this even further".

Clinicians, patients and the public have until 24 February to respond to the preliminary NICE decision. NICE will publish its final decision in June.

Source: PharmExec.com/Upton, February 4, 2014
Oncology Indication: Lung
Keyword: Policy/Legal

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Pharma-Europe: Roche's Kadcyla, Bayer's Xofigo, and GSK's Tafinlar Can Now Be Accessed on NHS Through the Cancer Drugs Fund

Cancer patients in England will no doubt welcome news that three new drugs can now be accessed on the National Health Service through the Cancer Drugs Fund (CDF). The latest update to the Fund has seen the inclusion of Roche's Kadcyla (trastuzumab emtansine) for breast cancer, Bayer's Xofigo (radium-223) for prostate cancer and GlaxoSmithKline's Tafinlar (dabrafenib) for unresectable or metastatic melanoma.

The CDF provides an extra £200 million each year to so that cancer patients in England can access drugs that are not routinely funded by their local NHS. Cancer specialists update the list regularly to ensure uniform and speedy access to the latest and most innovative medicines.

"Better access to effective medicine is a priority for the government, and we are delighted that these new drugs will mean more patients will join over 38,000 cancer sufferers who have already benefitted from the fund," noted Health Secretary Jeremy Hunt.

The Fund was set to originally set to expire in 2014 but an additional cash pot of $400 million was put up by the government to keep it going until March 2016.

The Rarer Cancers Foundation expects that it will benefit more than 33,000 patients in just two years.

Source: PharmaTimes/McKee, February 4, 2014
Oncology Indication: Multiple
Keyword: Policy/Legal