

March 27, 2014 Thursday

**Today's Intelligence at a Glance**

**1. Merck & Co.:** Initiates Early Access Program for Anti-PD-1 in Melanoma; Also Initiates Additional Trial Comparing MK-3475 Monotherapy vs. Combinations

Leerink/Fernandez, March 27, 2014

[HealthACE Abstract](#)

Indication: Skin

**2. Bristol-Myers:** Yervoy (Phase III/Adjuvant Melanoma) Expected to Show a Significant Improvement in Relapse Free Survival

Citigroup/Baum, March 25, 2014

[HealthACE Abstract](#)

Indication: Skin

**3. Market Overview:** PD-1/L1 Monotherapy May Successfully Manage Many PD-L1+ Patients, But Patients with PD-L1 Negative & PD-1/L1 Monotherapy Failures Will Likely Depend on Combination IO

Leerink/Fernandez, March 27, 2014

[HealthACE Abstract](#)

Indication: Lung

**4. Innate Pharma:** Lirilumab (Phase I, Anti-KIR) Moves Forward with Nivolumab Combo at High Dose & Higher Enrollment

Goldman Sachs/Chesney, March 26, 2014

[HealthACE Abstract](#)

Indication: Solid Tumors

**5. Clovis Oncology:** CO-1686 (Phase I/NSCLC) Data Impressive at ELCC; Anti-T790M Drugs Should Move to 1st-Line; Street Underappreciates Full Market Potential

Citigroup/Werber, March 27, 2014

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Indication: Lung

**6. Chugai:** Direct Comparison Difficult But Alectinib (Phase I/II/ALK+ NSCLC) Looks Superior to Novartis' LDK378

Barclays Capital/Seki, March 27, 2014

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Indication: Lung

**7. Genmab:** Milestone Underlines Rapid Progress of Daratumumab (MM) Pivotal Trials; Approval May Occur Ahead of Expectations

Deutsche Bank/Parkes, March 27, 2014

[HealthACE Abstract](#)

Indication: Hematologic

**8. Pharma-Global:** Brazil's Cristalia Gains ANVISA Approval for Production of Biosimilar Drugs – Trastuzumab (Herceptin), Etanercept (Enbrel), and Somatropin (Norditropin)

The Pharma Letter, March 24, 2014

[HealthACE Abstract](#)

Indication: Breast

**Additional Analysis**

**Clinical Trials for Lambrolizumab (MK-3475)**

Study Name Design	Indication	Endpts	Estimated Completion Date
NCT01866319 Phase III; Two Different Dosing Schedule; vs. Ipilimumab	Melanoma (Advanced)	1 <sup>o</sup> : PFS, OS 2 <sup>o</sup> : ORR	March 2016
NCT01905657 Phase II/III; vs. Docetaxel	NSCLC (Two Doses; Previously- Treated Participants)	1 <sup>o</sup> : OS, PFS Adverse events; 2 <sup>o</sup> : ORR, DOR	January 2020 Recruiting
NCT01704287 Phase II; vs. Chemo	Melanoma (Advanced)	1 <sup>o</sup> : PFS, OS 2 <sup>o</sup> : ORR, DOR	January 2016 Active, Not Recruiting
NCT02039674 Phase II; Combination with Chemo or Immunotherapy	NSCLC	1 <sup>o</sup> : PFS, ORR	July 2018 Recruiting
NCT01848834 Phase I	Solid Tumors (TNBC, H&N, Urothelial Tract, Gastric)	1 <sup>o</sup> : Adverse events, ORR	October 2014 Recruiting
NCT01840579 Phase I	Part A: Solid Tumors Part B: NSCLC (Combo with Chemo)	1 <sup>o</sup> : DLTs	April 2015 Recruiting
NCT02054806 Phase I	Solid Tumors (Advanced)	1 <sup>o</sup> : Best overall response; 2 <sup>o</sup> : PFS, OS, DOR	November 2015 Not Yet Recruiting
NCT01295827 Phase I	Solid Tumors (Five Parts)	1 <sup>o</sup> : DLTs, Adverse events, RR, DCR	February 2016 Recruiting
NCT01953692 Phase I	Blood Cancers (MDS, HL, NHL)	1 <sup>o</sup> : Adverse events, ORR	March 2016 Recruiting
NCT02007070 Phase I	NSCLC (Advanced)	1 <sup>o</sup> : ORR, Adverse events; 2 <sup>o</sup> : PFS, OS, Duration of response	August 2016 Not Yet Recruiting
NCT02036502 Phase I; Combination with Lenalidomide and Dexamethasone	Multiple Myeloma	1 <sup>o</sup> : DLTs, Adverse events; 2 <sup>o</sup> : ORR, CR, TTP, DOR, PFS, OS, Change in PD-L1 expression	March 2017 Not Yet Recruiting

CR: Complete Response  
DCR: Disease Control Rate  
DLTs: Dose-Limiting Toxicities  
DOR: Duration of Response  
NSCLC: Non-Small Cell Lung Cancer  
OS: Overall Survival  
ORR: Objective Response Rate  
PFS: Progression-Free Survival  
TTP: Time to Progression

Source: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

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## **Merck & Co.: Initiates Early Access Program for Anti-PD-1 in Melanoma; Also Initiates Additional Trial Comparing MK-3475 Monotherapy vs. Combinations**

Providing anti-PD1, MK-3475, to metastatic melanoma patients who have failed standard of care therapy (including Yervoy), we view Merck & Co.'s (MRK) Early Access Program (EAP) as the beginning of a sea-change in melanoma – with MRK at the forefront. **The FDA's approval of this program serves as both a positive indicator for the rolling-BLA filing MRK plans to complete by mid-year, as well as the company's ability to gain rapid market uptake upon accelerated approval (expected late-2014)**, in our opinion. Not only does the program mark the first PD-1 broadly available to melanoma patients outside of clinical trials, but it may serve to "raise the bar" for future trials and therapies in melanoma. Though the EAP (NCT02083484) is currently only available in the U.S. (at no cost to patients), MRK is already collecting interest in international markets and confirmed its intention to broaden this program OUS in 2014.

In addition to the EAP, MRK is also initiating a randomized Phase I/II trial in 345 patients to compare MK-3475 monotherapy with combination therapy including a MK-3475 + PEGINTRON arm and a MK-3475 + Yervoy (NCT02089685) arm. Finally an investigator-sponsored trial to be led by Yale will mirror yet significantly lag "Arm M" of BMY's CHECKMATE-012 study evaluating the anti-PD1 in patients with brain metastases (NCT02085070). BMY's CHECKMATE-012 is expected to have data at ASCO 2014.

**Source:** Leerink/Fernandez, March 27, 2014

**Oncology Indication:** Skin

**Keyword:** Clinical Trials/Pipeline

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## **Bristol-Myers: Yervoy (Phase III/Adjuvant Melanoma) Expected to Show a Significant Improvement in Relapse Free Survival**

We anticipate that EORTC-run 950-patient Phase 3 Yervoy adjuvant melanoma trial will show a very significant improvement in relapse free survival for Yervoy 10mg/kg dose compared with placebo in high-risk stage III melanoma patients. We anticipate outcome measures to look materially superior and better tolerated compared with historic controls with IFN alpha, the current and meager gold standard. As with Roche's Avastin in breast cancer, we assume Bristol-Myers (BMY) will adopt patient price caps to offset 3-year treatment duration and higher 10mg/kg dosing.

**What do we expect?** We anticipate that Yervoy will demonstrate at least a 30- 40% improvement in relapse free survival compared with the placebo treated patients. The historical improvement with IFN is a dubious c.10%. The anticipated clinical benefit of Yervoy will likely offset the expected immune related adverse event profile typical for Yervoy, even with prolonged usage. The predictive relevance of baseline tumor ulceration for Yervoy is unclear.

**What next?** We anticipate BMY to initiate a three-arm trial with Yervoy, nivolumab and the combination in a similar adjuvant melanoma setting. A trial evaluating two different doses of Yervoy (3mg/kg and 10mg/kg) in adjuvant melanoma is ongoing. We anticipate competitors AstraZeneca, Merck & Co. and Incyte to follow suit with various combinations but we don't expect Yervoy to face significant competition until 2019.

**\$3bn opportunity for Yervoy, with c.95% margins.** We estimate a total commercial opportunity for Yervoy of \$3bn in the adjuvant melanoma indication, on top of the opportunity in metastatic melanoma. There are c.45,000 patients with Stage III melanoma diagnosed every year in the U.S. and EU-5 (roughly 2.5x Stage IV metastatic melanoma patients) with stage IIIB and IIIC constitute a third of all Stage III patients. BMY is evaluating Yervoy 10mg/kg dose over a maximum duration of 3 years (15 injections in total). We have conservatively assumed only a year of treatment (7 injections) and model the same pricing for the 10mg/kg dose as for the 3mg/kg dose approved for the metastatic indication. We expect BMY to introduce price caps similar to Avastin in breast cancer.

**Source:** Citigroup/Baum, March 25, 2014

**Oncology Indication:** Skin

**Keyword:** Clinical Trials/Pipeline

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## **Market Overview: PD-1/L1 Monotherapy May Successfully Manage Many PD-L1+ Patients, But Patients with PD-L1 Negative & PD-1/L1 Monotherapy Failures Will Likely Depend on Combination IO**

AstraZeneca (AZN) shows steady progress through initiation of MEDI4736 Phase II in NSCLC and exploration of the anti-PDL1 in combination with Iressa. Though we will not see additional data from AZN's Phase I study of anti-PDL1 MEDI4736 until ASCO, the initiation of a NSCLC-specific Phase II (ATLANTIC) is reassuring for a product where we had only seen data on 6 NSCLC (non-small cell lung cancer) patients at ESMO 2013. Only U.S. sites are listed currently, yet ATLANTIC (NCT02087423) is referenced as a global study targeting n=210. Additionally, AZN initiated a Phase I trial combining MEDI4736 with its 1<sup>st</sup> Gen TKI, Iressa (NCT02088112). Similar to Phase I trials initiated in the past month by Roche (MPDL3280a + Tarceva) and AZN (tremelimumab + Iressa), this trial displays AZN's continued intent to combine across small and large molecules where there is scientific rationale and clear unmet need.

Broader inclusion of CTLA4 in PD1/L1 combination trials is supportive of combination IO. In this rapidly moving field, it is encouraging that Merck & Co. (MRK) has initiated two trials in the past month, which include MK-3475 + Yervoy arms in both melanoma and NSCLC. We remain of the view that PD1/L1 monotherapy may successfully manage many PDL1 (+) biomarker patients, but PDL1 (-) and PD1/L1 monotherapy failures are where combination IO will shine. As this represents 70-85% of lung cancer patients, we remain bullish on long-term prospects for combination IO and for the continued relevance of CTLA4 antibodies. Recall, early melanoma data from Bristol-Myers (BMY) showed higher response rates (particularly in PDL1-negative tumors) with nivolumab + Yervoy. Critically important data remains to be presented in 2014 at ASCO (in June) and ESMO (in late September), including data from both BMY and AstraZeneca (PDL1 + tremelimumab) in the critically important lung cancer population.

**Source:** Leerink/Fernandez, March 27, 2014

**Oncology Indication:** Lung

**Keyword:** Clinical Trials/Pipeline

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## **Innate Pharma: Lirilumab (Phase I, Anti-KIR) Moves Forward with Nivolumab Combo at High Dose & Higher Enrollment**

Clinicaltrials.gov published an update to the on-going Phase I trial investigating Innate's lirilumab (anti-KIR) in combination with Bristol-Myers' nivolumab (anti-PD1) indicating, in our view, that: 1) The dose escalation portion of the trial has likely completed and lirilumab will be dosed at the highest dose (3mg/kg) alongside nivolumab (3mg/kg). 2) Trial enrollment will also increase from 150 to 162 patients. 3) The various solid tumor cohort expansion groups are now listed collectively instead of individually.

Recall that the Phase I trial was designed to have two phases: a dose escalation study investigating lirilumab 0.1, 0.3, 1 and 3mg/kg in combination with nivolumab 3mg/kg, which is primarily focused on establishing the maximum tolerated dose (MTD). The second phase of the trial is intended to investigate anti-tumor activity of the MTD of the combo in six tumor types (squamous and non-squamous lung cancer, kidney cancer, melanoma, colorectal cancer and ovarian cancer).

The fact that the dose escalation portion of the study has now apparently concluded is in-line with previous management commentary that they expected to see some data from this trial by the end of 2014/early 2015. Furthermore, we are encouraged by the fact that the MTD was established at the high dose, implying there was no dose limiting toxicities seen so far. We are also encouraged by the fact that enrolment has increased, implying investigator comfort with the combo in a broader patient population. The motivation behind listing the solid tumor types collectively rather than individually is unclear. However, this move coupled with the increase in patient enrolment could potentially indicate they are investigating the combination in additional tumor types that they are not currently prepared to disclose.

**Source:** Goldman Sachs/Chesney, March 26, 2014

**Oncology Indication:** Solid Tumors

**Keyword:** Clinical Trials/Pipeline

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## **Clovis Oncology: CO-1686 (Phase I/NSCLC) Data Impressive at ELCC; Anti-T790M Drugs Should Move to 1<sup>st</sup>-Line; Street Underappreciates Full Market Potential**

We are attending the ELCC conference in Geneva where phase 1 data for CO-1686 was presented in 53 patients who got the new HBr formulation of which 44 are still on therapy. The OR was 64% and mPFS was still not reached after > 6 months on therapy in 22 T790M+ patients. The OR was 52% if 7 patients whose T790M status was unknown (n=29) were included. Encouragingly, only 1/12 patients who is T790M- showed a response highlighting the selectivity of this drug. The reviewer called the data impressive since 10/14 of the T790M+ responders started CO-1686 immediately after failing a previous TKI. The drug was very well tolerated as only 1 patient stopped therapy due to an adverse event. The new HBr formulation has less GI side effects and better PK than the previous free base formulation. Our impression is that the audience received this data very well and that the potency and durability of the drug's efficacy is a big step forward to the field with an acceptable side effect profile.

We continue to believe that the Street is not fully appreciating the market opportunity in 1<sup>st</sup>- and 2<sup>nd</sup>-line especially since CO-1686 will likely become the standard of care and will replace the current TKI drugs. In our view, the market is lucrative for CO-1686 to share with AZN9291 as we estimate that the 1<sup>st</sup>-line market opportunity is \$4B-\$5B and the 2<sup>nd</sup>-line market opportunity is \$1.5B.

**Clearly Eyeing the 1<sup>st</sup>-Line Market.** At the conference, there is a lot of discussion that patients should be carefully evaluated for T790M+ mutations at baseline and after failing 1<sup>st</sup>-line therapy. This can be done with biopsy now or by using sensitive PCR blood assays in the future. More so, there is an appreciation that there is a need for new T790M+ targeted TKIs to use in both 1<sup>st</sup>-/2<sup>nd</sup>-line especially since Tarceva and Giotrif (afatinib) do not work on this mutation, which occurs in 50% of patients who fail those drugs. The TIGER-1 phase 2/3 study will test CO-1686 vs. Tarceva in 1<sup>st</sup>-line patients with EGFR mutations (not just T790M mutation). Based on the higher activity on T790M mutation and similar activity on all EGFR mutations, CO-1686 should beat Tarceva on both PFS and possible OR. This should lead to its use in 1<sup>st</sup>-line patients.

**Hyperglycemia in Focus.** The main side effect which was discussed at the Q&A session was asymptomatic hyperglycemia which was seen in 15%/7%/18% (gr 1/2/3). This was easily managed with dose reduction or by starting oral metformin. The side effect typically occurred during the first 1-2 weeks of initiating therapy. Only 1 patient who was pre-diabetic at baseline required insulin. In future studies, this side effect will be monitored carefully during the first month of therapy and the incidence of grade 3 will likely be reduced by starting metformin early.

**CO-1686 Development Plans.** Clovis will initiate 3 registration studies in 2014. The TIGER2 study, in T790M+ patients directly after progression on their first and only TKI therapy, is expected to start in Q2. TIGER1 will also start in Q2 testing CO- 1686 vs. Tarceva in 1st line EGFR mutant patients who have not had TKI therapy but who may have received one type of chemotherapy. TIGER3 will test CO-1686 vs. chemotherapy in later-line patients with or w/o the T790M mutation and will start in H2. We expect Clovis to file for approval in H2:15 and foresee approval in H2:16.

**Source:** Citigroup/Werber, March 27, 2014

**Oncology Indication:** Lung

**Keyword:** Clinical Trials/Pipeline

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## **Chugai: Direct Comparison Difficult But Alectinib (Phase I/II/ALK+ NSCLC) Looks Superior to Novartis' LDK378**

The New England Journal of Medicine (NEJM) has published clinical trial results for Novartis' LDK378 in treating anaplastic lymphoma kinase positive metastatic non-small cell lung cancer (ALK+ NSCLC). LDK378 achieved an overall response rate of 56% (95% confidence interval: 45-67%) and progression-free survival of 7.0 months (95% CI: 5.6–9.5 months). LDK378 received a breakthrough therapy designation from the U.S. FDA in March 2013 and was filed for approval with the FDA in 4Q13.

Chugai has already announced phase 1/2 results for alectinib, which uses the same action mechanism as LDK378. Differences in patient populations and trial methodologies make it generally difficult to compare clinical results for the two, but a comparison based on the usable data shows alectinib to be superior to LDK378. Chugai filed alectinib for approval in Japan last October and began phase 1/2 trials in the U.S. in 3Q13. Alectinib was designated a breakthrough therapy by the FDA in 2Q13 in a first for a Japanese drugmaker.

The market for ALK+ NSCLC treatments is small (2-5% of that for NSCLC), but our earnings model for Chugai nonetheless assumes peak sales of CHF300mn. Profit margins should also be high since the drug originated with Chugai. Pfizer is already marketing an ALK+ NSCLC treatment in Xalkori (crizotinib), but patients are frequently resistant to it, creating a strong need for an alternative treatment. Chugai expressed confidence in alectinib's safety and low incidence of brain metastasis in remarks at the quarterly results briefing on January 30<sup>th</sup>.

Clinical trial results for LDK378 and alectinib:

1. The overall response rate was 58% for LDK378 and 95.5% for alectinib, with alectinib clearly superior. Note that caution is in order here, as definitions of complete response rate may differ.
2. Progression-free response was 7.0 months for LDK378 versus 7.1 months for alectinib at the time of data analysis and likely to go higher upon follow-up.
3. Differences in patient population warrant strict caution. The alectinib trial had only Japanese patients, while the LDK378 trial had 75% Caucasians and 22% Asians. Most important are patients' pre-trial drug regimens, and both trials used patients with treatment histories. For the LDK378 trial, 68% of patients had been using crizotinib; for the alectinib trial, 22 patients (31%) had a history of chemotherapy with one drug, 19 (27%) with two drugs, and 28 (40%) with three or more drugs.

**Source:** Barclays Capital/Seki, March 27, 2014

**Oncology Indication:** Lung

**Keyword:** Clinical Trials/Pipeline

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## **Genmab: Milestone Underlines Rapid Progress of Daratumumab (MM) Pivotal Trials; Approval May Occur Ahead of Expectations**

Genmab has announced that a milestone has been reached based on “clinical progress” in its potentially pivotal Phase II trial of anti-CD38 antibody daratumumab. The trial is recruiting multiple myeloma (MM) patients who have received at least three different lines of therapy, including both a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double refractory to a PI and an IMiD. Given the unmet need in this patient population, we believe a filing for accelerated approval is likely if initial indications of efficacy are confirmed, supported by the drug’s Breakthrough Therapy Designation from the FDA. A 42% partial response rate was observed in the initial Phase I/II monotherapy trial in relapsed/refractory MM.

We continue to believe that high physician enthusiasm for the CD38 class of drugs could lead to rapid enrollment and early conclusion of this pivotal study. We expect first data to be presented at the ASH. At a minimum this is likely to include data from Part A of the trial. However, if our assumptions are correct then data from a meaningful proportion (if not all) of patients from Part B could also be available. Given the current short expected survival for patients with double refractory multiple myeloma, we see potential for a filing ahead of most investor expectations. This could occur as early as 1H 2015, with a possible approval around end 2015. As a reminder, we currently forecast peak daratumumab sales of \$2.4bn, contributing DKK123 to our NPV valuation based on a 60% probability.

**Source:** Deutsche Bank/Parkes, March 27, 2014

**Oncology Indication:** Hematologic

**Keyword:** Management/Strategy/Financials



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## **Pharma-Global: Brazil's Cristalia Gains ANVISA Approval for Production of Biosimilar Drugs – Trastuzumab (Herceptin), Etanercept (Enbrel), and Somatropin (Norditropin)**

The Brazilian drugmaker Cristalia has just taken another step towards its goal of producing biosimilar drugs domestically, writes Juliane Carvalho on Brazil Pharma News. On March 17, 2014, the company received clearance from the Brazilian National Health Surveillance Agency (ANVISA) to manufacture active pharmaceutical ingredients including trastuzumab (Roche's Herceptin), etanercept (Pfizer/Amgen's Enbrel), and somatropin (Novo Nordisk's Norditropin).

According to Cristalia executives, the new certification of Good Manufacturing Practices (GMP) issued to the company by the ANVISA marks an important step the country is taking to product its first active pharmaceutical ingredients obtained through biotechnology processes.

The laboratory begins to produce this week. The first lots will be used in human clinical trials, which are expected to complete in 2.5 years. Data from these pivotal trials will support the drug market applications with the ANVISA.

For the past two years, the Korean privately-held biotech firm Alteogen has also been participating in this project. Three products are expected to generate sales of 300-400 million real (\$129-\$172 million) each year. These products are also expected to supply the federal government public health demands.

Other large investments were made in two other of the company's production units located in the Sao Paulo state biotechnology complex. Projects include the manufacturing of a therapeutic enzyme which will be exported. Cristalia's industrial complex comprises of active pharmaceutical ingredients production, an oncology products unit, and a center for research and development.

**Source:** The Pharma Letter, March 24, 2014

**Oncology Indication:** Breast

**Keyword:** FDA/Regulatory Issues