

Key Events

Oncology

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Date	Event	Status
1 st - 5 th June 2007	American Society of Clinical Oncology (ASCO) 43 rd Annual Meeting	Reported

The low-down on ASCO 2007

Wood Mackenzie opinion

The 43rd American Society of Clinical Oncology (ASCO) annual meeting was held in Chicago at the beginning of June 2007. The conference was well attended, with over 5,000 abstracts presented. ASCO's theme for the meeting was "translating research into clinical practice", and many of the delegates and speakers called for more energy and funding to be put into finding new directions for research. In terms of the clinical data presented, the meeting can perhaps best be described as steady rather than spectacular. The star of the meeting was Bayer/Onyx Pharmaceuticals' tyrosine kinase inhibitor Nexavar, which demonstrated a significant survival benefit in advanced liver cancer – the first treatment to do so in nearly 30 years. Celgene's thalidomide-derived drug Revlimid also created a stir after achieving the best one-year survival rates ever seen in first-line multiple myeloma patients.

There were a number of underlying themes at ASCO. Perhaps the most interesting was the rising popularity of combinations of targeted drugs, with many oncologists optimistic that "mixing and matching" targeted drugs will enable them to minimize or even eliminate the use of harsher chemotherapeutic regimens, while still delivering better cancer treatment to their patients. Amongst the dozen or so presentations on this subject, the most advanced was the Phase III AVOREN trial of Avastin in combination with interferon alpha for the treatment of kidney cancer. We believe that this trend will accelerate as more targeted drugs are approved in various cancer subtypes. Although, we also note that combinations of targeted drugs may result in additional side effects, offsetting the therapeutic benefit. Furthermore, targeted drugs are typically expensive, and combinations of two or more will multiply the cost. The gains in therapeutic value of such combinations will have to be very significant if they are not to face reimbursement difficulties with many government agencies.

Another common problem noted by many speakers was the dearth of suitable predictive biomarkers, and several sessions were devoted to new technologies and approaches under development for the identification of predictive biomarkers. However, it was clear that these approaches, while innovative, are far from ready for prime time. As one investigator noted, there is an urgent need for new paradigms for cancer biomarker development. The ultimate success of "mix and match" combinations of targeted drugs is likely to be constrained by the availability of predictive biomarkers which will allow reliable patient screening.

ASCO's biggest winner – Nexavar

The results of the SHARP trial were easily the most exciting to come out of this year's ASCO. SHARP (sorafenib HCC Assessment Randomised Protocol) looked at the overall survival of patients with hepatocellular carcinoma (HCC) treated with Bayer/Onyx' Nexavar (sorafenib) compared to placebo.

The data from this Phase III study showed that Nexavar offered a 2.8-month survival benefit over placebo. While an extra 2.8-month life expectancy may seem of minor consequence, this actually equates to a 44% increase in survival in a patient population where survival rates are very low and where there are few treatment options apart from surgery. The results were so striking that the SHARP trial was halted in February 2007, and patients on placebo were offered Nexavar. This will form the basis of a regulatory submission by Bayer and Onyx in this additional indication (Nexavar is already approved for treating GIST and renal cell carcinoma). However, we believe that the results of this trial will translate into an immediate boost in sales due to off-label use.

But what about the competition? Pfizer's Sutent and Roche/Genentech's Avastin are hot on Nexavar's heels, both having completed Phase II trials in HCC. It is too soon to tell if these drugs can produce results as impressive as Nexavar – both have different mechanisms of action, and Sutent also has the added complication of potentially causing heart problems. Whatever the outcome of these trials, Nexavar has opened up a whole new approach to the treatment of HCC – one that is badly needed in this area of high unmet clinical need. With a likely first-to-market advantage, Bayer and Onyx have an opportunity to entrench Nexavar in the market prior to the approval of additional targeted drugs. We note that price may be a concern, with Nexavar costing just under \$5,000 per month of treatment. It remains to be seen whether an extra three months of life will be deemed reimbursable by various government agencies.

The changing face of renal cell carcinoma

The treatment of renal cell carcinoma (RCC) has changed dramatically in recent years, and appeared as a leading theme at this year's ASCO annual meeting. Although a rarer form of cancer, much research has been ploughed into this tumour type and it is now reaping rewards. Historically, treatment has been restricted to immunotherapy in the form of interferon-alpha and/or Interleukin-2. However, the arrival onto the market of two tyrosine kinase inhibitors – Pfizer's Sutent (sunitinib) and Bayer's Nexavar (sorafenib) – has heralded the dawn of a new era of targeted therapy in RCC.

In addition, the approval of Wyeth's Torisel (temsirolimus) immediately prior to the ASCO conference, together with results presented at ASCO on the experimental use of Roche/Genentech's Avastin in this setting, offers an exciting new range of treatment options. Targeted therapies are no longer just experimental therapies but are now the mainstay of treating advanced renal cell carcinoma (see new treatment algorithm in Table 1 below).

Table 1: Advanced Renal Cell Carcinoma Treatment

Advanced RCC	Setting	Treatment
1 st line therapy	Low and intermediate risk	Sutant or high-dose IL-2
	High risk	Torisel
2 nd line therapy	Prior cytokine	Nexavar
	Prior VEGFR	Phase III trials in progress

The question now is how should these newer agents be combined? And in what sequence should they be used? A myriad of trials are currently attempting to answer these questions. Interestingly, data thus far suggest that the use of Nexavar followed by Sutent appears to produce a secondary response, whereas the reverse i.e. using Sutent followed by Nexavar, is not true. Thus, we believe this could be an opportunity for Bayer to leverage these data to encourage earlier, and thus increased, use of Nexavar in the treatment of RCC.

Roche recently applied for approval of Avastin in combination with interferon for the first-line treatment of advanced/metastatic RCC. Further data in this setting from the AVOREN trial were released at ASCO. As expected, the combination of Avastin with interferon, although offering a survival benefit, remains in line with the current gold standard Sutent. Because this combination also appears to present a more severe side-effect profile than that of Sutent, which also has the advantage of being administered orally, we do not expect Avastin to have a major impact on this segment of the oncology market. However, it does give oncologists an additional string to their bow when looking at treatment options for advanced RCC.

A number of clinicians are contemplating or have initiated clinical trials involving combinations of the newer targeted drugs e.g. Sutent + Avastin, Nexavar + Avastin, Avastin + Torisel, and Sutent + TroVax. There was a general feeling at ASCO that combinations of targeted therapies are likely to offer the best future treatment advances. The race is now on to determine the best combination or sequence of therapies in this setting. No doubt much more interesting data are still to come in this area. We expect ASCO 2008 will provide further food for thought.

Cancer vaccines – the way forward?

Prophylactic cancer vaccines are currently making a splash on the market – witness the strong uptake of Merck & Co's HPV vaccine Gardasil, launched in 2006 for the prevention of cervical cancer, and the success of hepatitis B vaccination in reducing the incidence of liver cancers. Many other prophylactic cancer vaccines are currently in development and making good headway, generating immense public interest in the process. These vaccines act by reducing the incidence of infections that lead to the development of virally induced cancers. However, taking this concept one step further and developing therapeutic cancer vaccines, which target an individual's own tissue rather a virus, is proving to be much more challenging.

The most notable therapeutic cancer vaccine data to be presented at ASCO was from two Phase II trials involving TroVax, under development by Oxford BioMedica and sanofi-aventis. The trials looked at the use of TroVax given alone or in combination with interleukin-2 or interferon-alpha, in metastatic RCC patients. TroVax targets the tumour antigen 5T4, which is broadly distributed in a wide range of tumours and is generally associated with a poor prognosis. Results from these trials were described as "very encouraging" with no serious adverse events attributable to the treatment. 91% of patients experienced an anti-5T4 antibody response, with 68% of clear cell carcinoma patients demonstrating disease control – supporting the rationale that the induction of a 5T4-specific immune response by TroVax has a therapeutic benefit. A phase III trial of TroVax in patients with clear cell renal cell carcinoma (TRIST) is now underway, and further trials are planned in metastatic colorectal cancer, which also frequently over expresses the 5T4 antigen. We believe that the ability of Oxford BioMedica to secure a licensing deal with sanofi-aventis – a major player in the oncology market – is indicative of the commercial potential of TroVax.

ASCO also threw up a mountain of data on earlier clinical trials involving therapeutic vaccines across a variety of tumour types, but most of these were from Phase I trials. Provenge, the hormone-refractory prostate cancer vaccine from Dendreon, was notable by its absence, which was not surprising given the recent delays with the FDA approval of this vaccine. All in all, therapeutic cancer vaccines were a hot topic at ASCO, but we believe there is still a long way to go before this translates into viable clinical treatment options for cancer.

Erbix – CRYSTAL doesn't sparkle

The data from the Phase III CRYSTAL trial of Erbitux (cetuximab) in combination with the Folfiri chemotherapy regimen for first-line treatment of colorectal cancer patients was much anticipated, after ImClone/BMS/Merck KGaA announced in January that the trial had met its primary endpoint of increased progression-free survival. However the details, first presented at ASCO, showed only a modest improvement. Median progression-free survival was 8.9 months in the Erbitux + Folfiri arm, compared to 8 months in the Folfiri-only arm – a reduction of only 15%.

This is insufficient to differentiate Erbitux from the gold-standard treatment, Avastin (Roche/Genentech) which, when used in combination with multiple chemotherapy regimens, has a median progression-free survival of between nine and 11 months, or a benefit of three to four months over chemotherapy alone. More importantly, use of Avastin in these colon cancer patients prolonged survival by up to four or five months, depending on the precise chemotherapy regimen used (survival benefit data are not yet available from the CRYSTAL trial). Based on the data, Erbitux is unlikely to take significant market share from Avastin in the first-line colorectal cancer setting – but may become the preferred drug for second-line use, although here it will have to compete with Amgen's Vectibix. Erbitux is already approved for second- and third-line use in metastatic colorectal cancer in the US and for third-line use in Europe.

On a brighter note, the companies presented data from the Phase III EXTREME trial of Erbitux in patients with metastatic and/or recurrent head & neck cancer. In the first-line setting, patients treated with Erbitux plus cisplatin- or carboplatin-based chemotherapy showed an increase in median overall survival to 10.1 months, compared to 7.4 months for platinum-based chemotherapy alone - a 20% reduction in risk of death. Although the study investigators were rightly enthusiastic about the survival data (and the trial was very heavily promoted at the conference), we note that head and neck cancer is a relatively small market.

Roche/Genentech – steady but unspectacular

Roche and partner Genentech had a major presence at ASCO 2007, reflecting their industry-leading portfolio of cancer drugs. The company's pipelines are dominated by line-extension programmes for their key marketed products Avastin, Herceptin and MabThera/Rituxan. Avastin in particular is being trialled in a wide range of cancer indications; however, while still a critically important drug, the data presented at ASCO lacked the lustre of previous meetings.

As noted above, full data from the Phase III AVOREN trial of Avastin in first-line RCC were presented. In combination with the standard interferon alpha 2a treatment, Avastin led to a doubling of median progression free survival, from 5.4 months for interferon alone to 10.2 months for the combination treatment. While this is good news for Avastin, we note that RCC patients are now being treated with several new targeted drugs – in short, this has become a crowded field, and the Avastin/interferon regimen is just one of several treatment options. On a more positive note, physicians were enthusiastic about the potential for combinations of these drugs, particularly Avastin and Sutent, while noting that the lack of biomarkers remained a critical problem.

Data were presented from the Roche-sponsored Phase III AVAiL trial investigating high and low doses of Avastin, in combination with the European standard gemcitabine and cisplatin chemotherapy, in patients with advanced non-small-cell lung cancer. The data showed an improvement in median progression-free survival: 6.7 months on the low dose, versus 6.5 months in the high-dose group and 6.1 months among those on chemotherapy alone. Although small, oncologists at ASCO viewed the improvement as clinically significant. The catch is that as well as equal efficacy, the low dose had reduced toxicity, which is likely to lead to physicians in both Europe and the US using the lower dose, slowing the drug's sales growth. Avastin (at the higher dose) is already approved in the US to treat non-small-cell lung cancer, in combination with the US standard carboplatin and paclitaxel chemotherapy regimen.

Herceptin remains the class leader in HER2-positive breast cancer. A joint analysis of data from two Phase III trials (NCCTG N9831 and NSABP B-31) showed that the addition of Herceptin to standard adjuvant therapy continued to significantly reduce the risk of breast cancer recurrence, the primary endpoint of the studies, by 52% in women with HER2-positive, node-positive breast cancer, compared to patients who received standard adjuvant therapy alone. Herceptin (plus chemotherapy) is the first, and so far only, treatment to show an overall survival benefit in adjuvant breast cancer (this study), as well as in first-line metastatic breast cancer. Furthermore, a Phase III trial from the National Surgical Adjuvant Breast and Bowel Project (NSABP) showed that, after five years, the risk of congestive heart failure associated with adding Herceptin to combination chemotherapy for early-stage breast cancer did not increase.

Although GSK reported data from several trials of Tykerb, a potential future rival to Herceptin in breast cancer treatment, none of them clearly differentiated the two drugs, leaving Herceptin with a first-to-market advantage for the time being. Phase III data for Tykerb plus paclitaxel for the first-line treatment of metastatic breast cancer did not significantly improve time to disease progression or overall survival compared to paclitaxel alone. In a Phase II study of Tykerb activity in brain metastases associated with breast cancer, 7% of patients showed a partial response to treatment, a result which one of the study investigators described as not amounting to a "home run".

In keeping with their focus on line extensions, Roche and Genentech have a paucity of novel compounds in late-stage development. However, both have rich early-stage pipelines, with Roche reporting thirteen NMEs in Phase I or II development. As a result, we expect these companies to remain key players in the oncology market for the foreseeable future.

Celgene - Revlimid ups the ante in Multiple Myeloma

Updated data from the ECOG 4A03 Phase III trial of Celgene's thalidomide-derived drug Revlimid in the treatment of multiple myeloma caused quite a buzz. The study compared Revlimid plus a low-dose of the steroid dexamethasone to Revlimid with a standard dose of dexamethasone in first-line treatment of multiple myeloma patients. Overall one-year survival on the Revlimid plus low-dose dexamethasone regimen was 96%, compared to 87% in the Revlimid plus standard-dose dexamethasone arm. Overall survival after two years was 90%. Additional benefits included a lower risk of side effects compared to the high dose steroid arm.

Although still preliminary, one study investigator described the results as the best one-year survival rates ever seen in first-line multiple myeloma. Revlimid (plus standard-dose dexamethasone) is already approved in the US to as a second-line therapy for multiple myeloma. The ECOG 4A03 trial results are likely to form the basis of an FDA filing for approval of Revlimid (plus low-dose dexamethasone) in the first-line setting, with the drug possibly reaching the market by mid-2008. With these data, Revlimid may well become the standard of care in the first-line multiple myeloma setting. The positive impact on sales revenue may well be sufficient to propel Revlimid into the ranks of the blockbuster drugs.

R&D candidates

As always, ASCO brought out a plethora of data on oncology R&D candidates, the most interesting of which are summarised in the following table:

Table 2: Lead oncology R&D candidates

Drug	Trial Sponsors	Drug class	Status	Comments
satraplatin	GPC Biotech	Alkylating agents	Pre-registration	Offers a new treatment option for second-line hormone-refractory prostate cancer patients
ixabepilone	BMS	Other cytotoxics	Phase III	Delays progression of metastatic breast cancer; used in combination with Xeloda (capecitabine)
ipilimumab	BMS	Immunomodulators – Oncology	Phase III	Shows promise in advanced melanoma, an area with limited treatment options
axitinib	Pfizer	Angiogenesis inhibitors	Phase III	Substantial anti-tumour activity in advanced thyroid cancer
S-1	sanofi-aventis	Anti-metabolites	Phase III	Positive results in advanced gastric cancer; used in combination with cisplatin; Already marketed in Japan
enzastaurin	Eli Lilly	Angiogenesis inhibitors	Phase III	Delays progression in diffuse large B-cell lymphoma
ASA404	Novartis	Other novel targets	Phase II	Encouraging Phase II data in hormone-refractory prostate cancer
pertuzumab	Roche	Immunomodulators – Oncology	Phase II	Shows promise in HER2-positive breast cancer when combined with Herceptin
pazopanib	GSK	Angiogenesis inhibitors	Phase II	High response rates seen in a Phase II trial in advanced or metastatic renal cell carcinoma, and in ovarian cancer

Conclusion

The 2007 ASCO meeting reflected steady progress being made in cancer treatment – but much still needs to be done. The keynote speech this year was given by Nancy Brinker, founder of the Susan G. Komen for the Cure Foundation, which raises public awareness of breast cancer with the aim of eradicating it as a life-threatening disease. Her speech was both thought provoking and inspirational, and serves as a useful reminder of the status of cancer treatment in the wider world. Nancy Brinker warned of a growing culture of complacency in the public that cancer is going away – just as the baby-boom generation is becoming the cancer-boom generation. She challenged physicians and researchers to stop conforming and become rebellious in their thinking to find novel new drugs, and delicately reminded the delegates that survival improvements measured in weeks or months, while statistically relevant, are a long way from being a cure.

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Wood Mackenzie attending ASCO in Chicago

Wood Mackenzie will be attending the American Society of Clinical Oncology (ASCO) conference in Chicago between 1st and 5th June 2007. We will be reporting on the key findings of the conference, including breaking clinical data, new R&D compounds, emerging companies in the oncology field and any changes to current clinical guidelines.

We expect some of the highlights of the conference to include:

Breaking data on Erbitux:

- Presentation of results from the CRYSTAL trial, investigating the use of ImClone's Erbitux in previously untreated metastatic colorectal cancer.
- Is ImClone's recent shares tumble due to CRYSTAL data falling short of expectations?
- Does the addition of Erbitux to chemotherapy increase survival in this patient group compared to chemotherapy alone? And are the results stronger than data for Roche's gold standard Avastin?

Tykerb update:

- Phase III results of GSK's Tykerb in first-line treatment of metastatic breast cancer.
- Potentially strong results supporting use of Tykerb as a first-line treatment. Tykerb is also believed to have a moderately better side effect profile than its competitors e.g. less cardiotoxicity.
- Could put significant competitive pressure on Roche/Genentech's Herceptin, which is the current gold standard for HER2+ metastatic breast cancer.

Data from Onyx / Bayer's Nexavar in treating liver cancer

- Full phase III results from SHARP study of Nexavar versus placebo expected to show a sharp improvement in survival in Hepatocellular cancer (HCC) patients given Nexavar. Positive data from this trial will help to drive off-label use of Nexavar in this indication ahead of a formal approval.
- Updates also expected on the use of Nexavar in various other cancer indications – it is currently involved in approximately 60 ongoing clinical trials across 15 different indications. In particular, we hope to see data on its use in metastatic melanoma, and malignant mesothelioma.

New data from Genentech:

- Principally reports of indication-expansion trials for Avastin, Herceptin, Rituxan and Tarceva.
- Endpoint data from AVOREN Phase III trial of Avastin + interferon alpha as first line treatment of metastatic renal cell carcinoma.
- Endpoint data from AVAiL Phase III trial of low versus high doses of Avastin (plus chemotherapy) for the treatment of NSCLC.
- Phase II data for Avastin + Tarceva for second-line treatment of NSCLC.
- Additional clinical details of the Herceptin-DM1 antibody-drug conjugate, from a Phase I trial in Herceptin-resistant breast cancer.

Data on Eli Lilly's Alimta and Gemzar

- Eli Lilly are expected to present data on 76 studies at ASCO this year, including positive Phase III results supporting the use of Alimta in first-line NSCLC. The drug is already approved for second-line treatment in this indication.
- Other data expected to be presented on Alimta includes an early-phase trial of its use in head and neck cancer.
- Phase III trial data expected of Gemzar combination in neoadjuvant breast cancer.

Latest developments from Amgen:

- Results from Phase II studies of AMG 531 in thrombocytopenia associated with Myelodysplastic Syndrome, motesanib diphosphate in patients with locally advanced or metastatic thyroid cancer, and denosumab in patients with bone metastases from prostate cancer.
- Update on developments within Amgen's oncology pipeline – details on Phase I studies including AMG 102, AMG 386, AMG 479, AMG 655 and AP02L/TRAIL.

R&D round-up:

- Presentation of Phase III data for sanofi-aventis' XRP9881 in the treatment of breast cancer. Its oral formulation offers potential advantages over Taxotere.
- Promising Phase II data expected on Eli Lilly's enzastaurin in second and third-line NSCLC.
- Update on the development of mTOR inhibitors, including Wyeth's Torisel (temsirolimus).
- GSK also plan to present Phase III data on their supportive care agent, casopitant, for the treatment of chemotherapy-induced nausea and vomiting. This anti-emetic is claimed to have an improved side effect profile when compared to Merck & Co's Emend.

New kids on the block:

- As well as presentations from big pharma and the biotech sector, we also expect interesting data on novel anti-cancer drugs from smaller companies, such as Arqule, Kosan, Medarex, and ImmunoGen.
- In particular, ImmunoGen are expected to present further data from a Phase I trial of trastuzumab-DMI (Herceptin-DMI), which they are developing in collaboration with Genentech. The compound is believed to increase the effectiveness of Herceptin against drug-resistant cancer cells, meaning that this could have massive potential in a very difficult-to-treat patient population i.e. those patients who have stopped responding to Herceptin.

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