Melanoma vaccines: have Roche and BMS moved the goal posts?

LONDON, UK----10th June 2011----ExpertREACT. Newly approved ipilimumab (Yervoy) and dramatic new data from Roche's vemurafenib have improved prognosis for late-stage melanoma patients. Do these advances help or hinder the cause for therapeutic melanoma vaccines?

To coincide with the annual 46th American Society of Clinical oncology (ASCO) meeting recently held in Chicago USA June 3 -7 2011, **VacZine Analytics** has released a new analysis focused on the commercial potential of melanoma vaccines **(1).** Melanoma itself is currently a big subject within oncology with some important advances making the headlines. The following article will discuss these latest topics and what impact, if any, on the development of further immunotherapeutic approaches.

Each year an estimated 200,000 cases of invasive melanoma are diagnosed worldwide **(2).** 75% of these cases occur in developed Western countries affecting mostly people 60 years or older. The incidence of melanoma appears to be rising, particularly in older people although this may be partly due to increased surveillance and early detection. If detected early i.e. at Stage 0/I/II melanoma has a good prognosis because tumours are clinically localised sometimes only affecting the epidermis layer of the skin. Once melanoma has advanced to Stage III there is regional involvement at the lymph nodes, or a Stage IV, widespread metastasis. Here, most patients will not be cured with 5-year % survival rates falling dramatically.

In terms of treatment options, Stage I (and some Stage II) melanomas can often be managed by surgery alone. Surgery again is used for certain "resectable" Stage III melanomas with complete lymph node dissection. For Stage IV patients surgery is generally of limited benefit if there is wide dissemination. At this stage the melanoma is also refractory to systemic therapies such as dacarbazine and interleukin-2. In all patients types there is an increasing risk of disease recurrence which is related to extent of sentinel lymph node involvement **(3).**

Until this year effective options for patients with unresectable Stage III or Stage IV melanoma were virtually non-existent with most being encouraged to enroll in ongoing trials for new adjuvant agents. However, in March, the US FDA approved Bristol Myers Squibb's (BMS) ipilimumab, branded "Yervoy". Yervoy, granted orphan drug status in 2004, is a CTLA-4 monoclonal (mAb) antibody designed to stimulate T-cell mediated anti-tumour immune responses **(4).** In clinical trials, Yervoy demonstrated a statistically significant survival benefit (~4 months) in patients with unresectable or metastatic melanoma who were previously treated with systemic chemotherapeutic agents but has high risk of severe side effects.

Yervoy was also tested in combination with the investigational peptide melanoma vaccine gp100 which according to certain analyses had limited additive benefit. However, another recently published article showed that gp100 enhanced the effect of Interleukin-2 in a Phase III study with locally advanced stage III and stage IV melanoma patients. In the trial the the primary endpoint was centrally verified clinical response (16% vs 6% P=0.03) **(5).** gp100 is a melanoma-associated antigen identified to carry immunogenic epitopes that can induce a CTL response against tumour cells.

Swiss company Roche also recently reported an advance in the treatment of late stage melanoma patients, although this time with a small molecule BRAF inhibitor, vemurafenib (RG7204, PLX4032). BRAF kinase protein is mutated in around 50% of metastatic melanomas. Roche reported data from its BRIM-3 Phase III study which tested the agent in previously untreated BRAF V600 mutation-positive metastatic melanoma patients compared to chemotherapy **(6).** Vemurafenib had a dramatic dual effect of reducing risk of patient death and diseasing worsening by 63% and 74% respectively. The data, once reviewed from a planned interim analysis, prompted an independent data monitoring board to recommend patients from the chemotherapy arm to receive vemurafenib.

Latest advances in the field of melanoma will undoubtedly prompt discussion in many areas over the coming months especially regarding costs. Yervoy being a new immunotherapeutic agent, like

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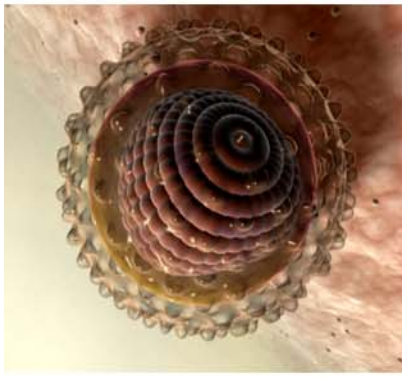

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Dendreon's Provenge (sipuleucel-T) for prostate cancer is very expensive. In fact, before Yervoy's approval, melanoma was cited as one of the most expensive cancers to diagnose, follow and treat **(7).**

Sponsors of other investigational agents for melanoma now may reexamine their positioning strategies relative to Roche and BMS, who recently agreed to join forces with a new Phase I/II study focused on a ipilimumab/vemurafenib combination **(8).** GSK, in particular has an vested interest in new melanoma treatments with another BRAK kinase inhibitor (GSK2118436), but more relevant to immunotherapeutics, the company is developing the MAGE-A3 antigen-specific vaccine (GSK2132231A) which has progressed as far as Phase III.

MAGE-A3, is a tumour specific antigen expressed in a large variety of tumours. Unlike ipilimumab/vemurafenib and gp100/IL-2 studies, the most likely first approved indication of GSK2132231A (based on Phase III enrollment criteria) is to prevent or delay recurrence after successful surgical resection in Stage III (macro) patients. These patients are confirmed to be disease free before randomization and vaccination. As part of a multi-pronged approach, the vaccine is also being tested in a Phase II for survival benefit in Stage III unresectable patients/Stage IV and in Phase I as part of combination with chemotherapy. Mechanistically, having an impact on established tumours is a different proposition than preventing recurrence in disease free patients.

It will be interesting to observe whether GSK can establish its *prevention of recurrence* position before Roche/BMS "invade" downward into other melanoma market segments. In the longer-term GSK could also target Stage III (micro) patients or the larger "uncharted" potential population of Stage II patients (est ~70,000 treated). Pricing thresholds at early disease stages will be lower but higher volume could make the strategy viable. Judging on progress thus far, especially with gp100, GSK will be dragged into further combination trials for late stage patients with GSK2132231A. Medically this is worthwhile but now there now appears to be less room for a expensive vaccine especially with a marginal effect.

References and Notes:

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