Advances in systemic treatment of melanoma

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After decades of phase III trials failing to demonstrate an impact on survival of various drugs in metastatic melanoma there are finally significant advances in systemic therapies for melanoma emerging. Novel ways to modulate the immune system by monoclonal antibodies as well as various signalling pathway inhibitors are responsible for creating a whole new therapeutic landscape. For the first time it is likely that a number of new drugs with completely different mechanisms of action will be approved in the near future. The imminent candidates are the anti-CTLA-4 antibody ipilimumab, and the highly selective BRAF inhibitor PLX4032. But in each class other molecules are under development with good perspectives. Various new combinations will have to be explored and it is reasonable to expect synergies between the different classes of drugs as well as between novel molecules within the same class of drugs. Here, an overview of current developments and the most important new drugs under consideration is provided.

Key words: adjuvant therapy, anti-CTLA-4, BRAF inhibition, drug development, melanoma, systemic therapy

a brief history of chemotherapy, cytokine therapy and biochemotherapy in advanced metastatic melanoma

Melanoma with dissemination to distant sites and visceral organs is, with the exception of rare cases of surgery for oligometastatic disease, almost invariably incurable, with a median survival time of only 8–9 months and a 3-year survival rate of only 10%–15% [1]. By and large, increased response rates observed with combinations of chemotherapy and immunotherapy have not translated into survival benefits. Combination chemotherapy regimens with or without tamoxifen have not been shown to be superior to mono-chemotherapy with dacarbazine (DTIC) alone in a number of phase III trials [2]. Twenty-one phase III trials evaluating the addition of interferon (IFN)-α alone or of interleukin (IL)-2 or of the combination of IL-2 and IFN with mono- or combination chemotherapy failed to provide proof of a survival benefit, in spite of improved response rates and at the cost of significant toxicity [3].

In Europe DTIC is the only approved drug. Fotemustine is approved in only some countries on the basis of a phase III trial delaying the onset of brain metastases [4]. IFN and IL-2 are not approved for advanced metastatic disease. In the USA, IL-2 is approved based on phase II studies in 277 patients, showing lasting complete response (CR) in 7% of patients [5]. All in all a desperate situation waiting for new drugs to break the deadlock of decades.

advances in immunotherapy

immunoregulatory monoclonal antibodies

anti-CTLA-4. An immune signal will only be generated when an antigen is presented by a major histocompatibility (MHC) molecule and a co-stimulatory molecule, B7.1 or B7.2, binds to CD28 to provide the signal for T-cell activation. After activation, T cells upregulate CTLA-4, which competes for binding to B7, resulting in inhibition of T-cell receptor (TCR) signalling, IL-2 gene transcription and T-cell proliferation. Monoclonal antibodies that bind to CTLA-4 can block the interaction between B7 and CTLA-4. Inhibition of this negative switch may break peripheral tolerance to self-tissues and induce anti-tumour responses. Two fully human IgG monoclonal antibodies recognizing CTLA-4, ipilimumab (MDX-010) and tremelimumab (CP-675,206) have been tested, alone or in combination, in phase II/III trials.

Iiplimumab. Iiplimumab can induce long-lasting responses: out of 72 chemotherapy-naïve patients who were treated with ipilimumab (3 mg/kg every 4 weeks for 4 months) alone (median survival 11.5 months) or in combination with DTIC (median survival 13 months) in a randomized phase II trial, seven patients (10%) were still alive after 2 to >4 years [6]. Iiplimumab in combination with a vaccine (3 mg/kg every 3 weeks or a 3 mg/kg initial dose of ipilimumab followed by 1 mg/kg every 3 weeks, with both cohorts receiving concomitant vaccination with two modified, HLA-A*0201-restricted peptides) was assessed in a randomized phase II study in 56 patients. Overall response rate was 13%; better clinical responses were observed in patients with grade 3/4 autoimmune toxicity, an observation confirmed in a 139-patient study at the National Cancer Institute (NCI) [7].
The most common grade 3/4 immune-related adverse events were colitis/diarrhoea and dermatitis that responded to systemic steroids without significantly affecting the efficacy of ipilimumab therapy [8, 9]. These studies suggest that induction of manageable autoimmunity in patients with metastatic melanoma treated with ipilimumab could be a surrogate marker of objective and durable clinical responses.

An induction regimen consisting of 10 mg/kg every 3 weeks for 4 months (Q3W×4) along with a maintenance treatment of 10 mg/kg ipilimumab every 12 weeks starting at week 24 (Q12W) has emerged as the most effective schedule and been used in most ongoing phase II and phase III clinical trials [10].

In 2009, remarkable 2-year overall survival (OS) was reported for >50% of patients receiving ipilimumab in first line and for >30% of patients receiving ipilimumab in second line [11]. Overall positive results of ipilimumab in patients with metastatic melanoma led to the initiation of a pivotal trial in first line comparing dacarbazine with or without ipilimumab. Another phase III trial of ipilimumab alone or in combination with a gp100 peptide vaccine as second-line therapy is also ongoing. This trial in second line has now been analysed and reported at ASCO in 2010 [12]. A remarkable survival benefit was observed for the ipilimumab-containing treatment arms. It thus seems likely that ipilimumab will be the first drug in the history of melanoma that will be approved on the basis of a demonstrated survival benefit in patients with advanced metastatic melanoma. It also means that the likelihood that the pivotal trial comparing DTIC versus DTIC plus ipilimumab will be successful is increased, which would lead to the introduction of a drug with proven survival benefit in the complete landscape of melanoma since these trials did not limit the patient populations on the basis of mutations, HLA types, lactate dehydrogenase (LDH) serum levels or other tumour-related factors.

tremelimumab. Early-phase clinical studies of tremelimumab demonstrated acceptable toxicity [immune-related adverse events (irAEs)] and similar efficacy of 10 mg/kg monthly and 15 mg/kg quarterly doses of the antibody with median survival of 10.3 and 11 months, respectively [13]. In 246 patients single-agent tremelimumab (15 mg/kg quarterly, one or more dose, 44% of patients two or more doses) resulted in a response rate of only 8.3%. However, the duration of the response (183+ to 540+ days) and the median OS of 10.1 months suggested activity [38]. This schedule was evaluated in comparison with standard dacarbazine or temozolomide chemotherapy in previously untreated 324 and 319 patients, respectively. The trial was stopped, based on a second interim analysis, for futility in March 2008. Median OS by intent-to-treat was 11.8 months in the tremelimumab arm, and 10.7 months in the chemotherapy arm, with a hazard ratio (chemotherapy over tremelimumab) of 1.04 [14]. Yet at longer follow-up and further analysis it was found that patients with a C-reactive protein (CRP) of <1.5 times the upper normal limit seemed to derive a significant survival benefit from treatment with tremelimumab. On this basis and in this patient population a phase III trial comparing tremelimumab versus DTIC is being planned.

new response criteria
The observation that new lesions in patients receiving ipilimumab or tremelimumab may not always indicate progressive disease and treatment failure as defined by modified WHO criteria is an important one. Four patterns of response have been observed: (i) response in baseline lesions; (ii) stable disease (SD) with slow, steady decline in total tumour burden; (iii) response after initial increase in total tumour burden; (iv) response in index and new lesions after the appearance of new lesions. Importantly, in 17 out of 26 patients who developed new lesions after 12 weeks of treatment, regression or stabilization of disease was observed. Novel, immune-related response criteria (irRC) may more accurately describe response to immunotherapy and avoid premature treatment cessation in patients with disease progression before response. Contrary to WHO criteria, irRC (i) only consider measurable lesions (>1 cm), (ii) define total tumour burden as the sum of index lesions identified at baseline and new lesions detected after baseline and (iii) aim for follow-up after progressive disease to detect late activity [15].

other immunoregulatory monoclonal antibodies
anti-PD-1. Another monoclonal antibody that has been developed acts against the programmed death-1 receptor (PD-1R), the ligand of which (PD-1L) can be directly expressed on melanoma cells. PD-1R is a part of the B7: CD28 family of costimulatory molecules that regulate T-cell activation and tolerance and thus anti-PD-1R can play a role in breaking tolerance [16].

agonistic antibodies OX 44 and anti-CD137 (4-1BB). The antibodies anti-OX44 and anti-4–1BB have an agonistic action on T-cell activation and the anti-CD25 antibody that targets T-regulatory cells that constitutionally overexpress CD25. It has been demonstrated that combinations of these antibodies can significantly optimize T-cell responses; thus, we are most likely witnessing an emerging field of immunomodulation that holds great promise [17]. A phase I dose-escalation study of BMS-663513, an agonist anti-CD137 human monoclonal antibody (up to 15 mg/kg), in 54 metastatic melanoma patients reported manageable toxicity with fatigue, transaminitis and neutropenia being the most common AEs, and clinical activity that justifies its further development both as a single agent and in combination [18].

other developments in immunotherapy
adoptive immunotherapy. Rosenberg and coworkers at the Surgery Branch of the NCI have developed an evolutionary programme in adoptive immunotherapeutic approaches to treat cancer, melanoma in particular, that has demonstrated significant progress in insights and results over the years. The most important recent developments have demonstrated that conditioning the patient by mild myeloablative chemotherapy with cyclophosphamide and fludarabine will induce lymphopenia under which conditions the adoptive transfer of T-cell clones derived from the tumours of the patient will expand vividly in vivo after transfer into the patient and lead to overall response rates of 50% with >10% CRs. When total body
irradiation is added to precondition the patient further, to eliminate or reduce also the lymphocyte populations in the bone marrow that would compete for IL-2, response rates as high as 72% have been observed with 16% CRs [19]. Confirmatory studies outside the NCI are ongoing. Conversion of normal peripheral blood lymphocytes (PBLs) into anti-tumour lymphocytes by transduction with genes encoding one of the TCRs relevant to tumour cells is another development in adoptive immunotherapy. Rosenberg’s group reported on four tumour responses in 31 patients with metastatic melanoma treated by autologous PBLs transduced by MART-1-specific TCR following mildly myeloablative conditioning [20].

vaccine development in stage IV. The development of an effective therapeutic vaccine for metastatic melanoma continues to be the elusive ‘holy grail’ in a disease where now signalling pathway inhibitors and anti-CTLA-4 antibodies are emerging as effective therapies. The anti-CTLA-4 and other immunomodulatory antibodies may come to the rescue of the vaccine development field, as they may play a crucial role in maintaining an immune response initiated by a vaccine. Yet there have been some advances reported that should be mentioned here. A randomized phase III trial comparing vaccination with the gp100: 209–217 (210M) peptide in combination with high dose IL-2 with treatment with IL-2 alone was reported to improve progression-free survival (PFS) significantly without a clear impact on survival [21]. Also a recombinant MAGE–A3 fusion protein combined with an immunological adjuvant—AS02B or AS15—has been assessed in the EORTC 16032–18031 randomized phase II trial as first-line treatment for 68 patients with unresectable stage III or stage IV M1a melanoma. The combination with AS15 yielded higher anti-MAGE3 antibody titres, stronger T cell induction and some long-lasting clinical responses [22]. A gene-signature derived from pretreatment tumour biopsies has been developed and shown to predict clinical benefit [23]. A randomized trial in patients with resected stage IIIB and IIIC melanoma is ongoing.

Interest has been generated by the 28% overall response rate observed in a recent phase II study with intratumoral injections of OncoVEXGMP-CSF—an oncolytic herpes simplex virus vector encoding granulocyte monocyte colony-stimulating factor (GM-CSF)—into 43 stage IIIC and IV patients [24]. Injected tumours routinely responded, often with local CR, within 2 months of therapy. Importantly, systemic long-term responses were observed independent of the disease stage: six CR, six partial response (PR), seven SD of injected tumours. A phase III trial in 360 previously treated, unresectable melanoma patients is ongoing. Another vaccination trial with intratumoral gene delivery is ongoing in M1a patients with Allovectin-7®. This is a plasmid/lipid complex containing the DNA sequences encoding HLA-B7 and β2-microglobulin, which together form a MHC class I.

On the other hand a number of negative experiences with vaccines have been reported the last couple of years, especially in the adjuvant setting, indicating that multiple vaccination can have detrimental effects, perhaps because of induction of tolerance. Such negative outcomes have been reported on the adjuvant use of the GMK vaccine in stage II melanoma [25], the allogeneic cell-based vaccine Canvaxin™ in stage III and resected stage IV disease [26] and with vaccines where GM-CSF was used as the immunoadjuvant [27, 28]. All this leads to the conclusion that we still do not understand fully the complexity of therapeutic vaccine strategies, and that better immune monitoring methodology and concepts such as the use of anti-CTLA-4 antibodies and conditioning of the patient may all be necessary to make clinical progress in this field [29].

advances in pathway-signalling inhibition based on mutation-driven drug development

A large and permanently increasing number of pharmacological inhibitors targeting several of the recently identified mutated signal transduction molecules are being explored in clinical trials in genetically defined subgroups of melanoma patients. In Table 1 the mutated targets (c-KIT, BRAF, MEK, NRAS, PI3K, Akt, mTOR and GNAC) and the signal transduction inhibitors that are being evaluated at present are summarized. The C-KIT and BRAF inhibitors are furthest in their development at the moment.

c-KIT

Activating mutations and/or gene amplification of KIT have been found in 39% of mucosal, 36% of acral and 28% of melanomas that arise in chronically sun-damaged skin [30]. Mucosal and acral melanomas represent <20% of all melanomas in the western world, but >90% of melanomas in Asia. The percentage of c-KIT mutations in patients with chronically sun-damaged skin remains to be confirmed outside California. c-KIT mutations have been described in a series of patients with metastatic melanomas in the western world, but 20% of all melanomas in Asia. The percentage of c-KIT mutations in patients with chronically sun-damaged skin remains to be confirmed outside California.

Table 1. Mutation-driven signalling pathway inhibitors

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<tr>
<th>Oncogene</th>
<th>Drug</th>
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<td></td>
<td>nilotinib</td>
<td>Phase III (ongoing)</td>
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<td>dasatinib</td>
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<td>BRAF</td>
<td>sorafenib</td>
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<td>Non-selective</td>
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<td>PLX4032</td>
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<td></td>
<td>PLX5992</td>
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<tr>
<td>mTOR</td>
<td>Temsirolimus</td>
<td>Phase II</td>
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<tr>
<td>GNAC (uveal melanoma)</td>
<td>MEK inhibitors</td>
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Table 1. Mutation-driven signalling pathway inhibitors

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case reports [31]. Although limited in number thus far, these clinical experiences confirm KIT as a melanoma therapeutic target, with patients experiencing dramatic and durable responses to treatment. This year an interesting phase II study from China reported high response rates and prolonged PFS with imatinib treatment [32]. Also a phase II trial with nilotinib is ongoing and the randomized phase III trial comparing nilotinib with DTIC has recently been activated.

**BRAF**

BRAF mutations are found in ~60% of melanoma patients, primarily in younger individuals, originating on non-chronically sun-damaged skin [30]. As BRAF is a serine-threonine kinase, it was obvious that an inhibitor could be developed. Many have been developed over the last decade, non-selective ones and more recently highly selective ones.

Sorafenib, a non-selective BRAF broad-spectrum kinase inhibitor was originally developed in combination with carboplatin and taxol against lung cancer and demonstrated in phase I also activity against melanoma. Its development went all the way to large phase III trials, but eventually here it failed both in second line [33] and in first line [34].

The first selective BRAF inhibitor to be developed in the clinical setting was PLX4032. Is has been demonstrated to have very impressive single-agent clinical activity with unprecedented response rates of ~80% and a clear impact on PFS [35, 36]. A rather novel side-effect is that it can induce keratoacanthomas and invasive squamous cell cancers. Although easily recognized and managed in the patients with advanced metastatic melanoma, this side-effect may be more difficult to manage in the adjuvant setting. Currently PLX4032 is being further evaluated in a large phase II trial. Moreover, a worldwide phase III trial (BRIM-trial) was activated inearily 2010, comparing PLX4032 with DTIC. Additional highly selective BRAF inhibitors by the same company as well as by other companies are currently under clinical development as listed in Table 1.

**MEK inhibitors**

A popular downstream target with a number of drugs under active development at present in melanoma. A large randomized phase II trial comparing the MEK inhibitor AZD6244 with temozolomide however, did not show a benefit in terms of response rates or impact on PFS [37]. Other agents are currently being evaluated and also tested in various combinations.

**NRAS**

In large series of melanomas analysed for NRAS mutations, the frequency is ~20% [38]. However, RAS remains an elusive target in cancer, with no drugs being available that can directly antagonize its signalling activity. Dual targeting of the MAPK and PI3K pathways might abrogate the effect of RAS mutation [39].

**GNAC**

Uveal melanomas lack mutations in c-KIT, NRAS and BRAF, but they uniquely harbour activating mutations in the α-subunit of a G-protein of the Gq family, GNAQ. In melanoma, activated GNAQ results in MAPK pathway activation [40]. Melanoma cell lines that harbour GNAQ mutations are sensitive to MEK inhibition.

**various other drugs in advanced metastatic disease**

There are a couple of other drugs that are being evaluated for their efficacy in advanced metastatic melanoma that should be mentioned here.

**bevacizumab**

Bevacizumab has been evaluated in a randomized phase II trial (BEAM trial) comparing the combination of carboplatin and paclitaxel with the same drugs in combination with bevacizumab. The addition of bevacizumab led to a significant impact on PFS, and some impact, albeit not significant, on OS [41]. Similar results are being reported for the combination of DTIC with bevacizumab [42, 43]. Whether a pivotal phase III trial for any of these combinations with bevacizumab will be conducted is being discussed.

**nab-paclitaxel**

Nab-paclitaxel [ABI-007 (Abraxane), Abraxis BioScience, LLC, Los Angeles, CA, USA] is a solvent-free, 130-nM albumin-bound (nab) particle formulation of paclitaxel. Compared with solvent-based paclitaxel, nab-paclitaxel was less toxic, allowing a 50% increase in the equitoxic dose in animals [44]. When compared with solvent-based paclitaxel in women with metastatic breast cancer, nab-paclitaxel was associated with higher objective response rates and longer PFS without increased toxicity [45].

The drug has been evaluated in phase II trials in chemo-naïve and in pretreated metastatic melanoma patients. Median survival times and PFS were considered interesting enough to evaluate this agent in a phase III trial [46]. This pivotal trial, in which DTIC is the comparator arm, is currently ongoing.

**advances in systemic adjuvant therapy**

Systemic adjuvant therapy with IFN in melanoma patients with a high risk of relapse has demonstrated modest results. Typically an impact on relapse-free survival (RFS), but not on OS is seen. The meta-analysis of the two largest adjuvant IFN trials ever conducted, EORTC 18952 [47] and EORTC 18991 [48], has demonstrated that lower stage (lower tumour load), i.e. patients with stage IIB or only sentinel node-positive stage III respond better to IFN than patients with advanced stage III (palpable nodes). Moreover, since these trials were stratified for these stages as well as for ulceration of the primary tumour, it showed that ulceration of the primary correlated very strongly with a beneficial effect of adjuvant IFN treatment for all end points (RFS, DMFS and OS), whereas in patients with non-ulcerated primaries, no significant impact on any of the end points could be detected [49]. This has led to the decision to carry out an adjuvant trial with pegylated-IFN-x2b versus observation in patients with an ulcerated primary (EORTC 18081).
This year at ASCO it was reported that adjuvant therapy with GM-CSF in stage III patients resulted in a significant improvement in PFS, but not in OS [50]. As discussed above in the immunotherapy section, the MAGE3 vaccine is currently being evaluated in stage IIIb/IIIc patients in a phase III trial. Lastly, expectations have risen of a potential positive outcome of the EORTC 18071 trial, evaluating adjuvant therapy with ipilimumab in patients with stage IIIA (macroscopic), IIIB and IIIC, because of the significant impact on survival of ipilimumab in advanced metastatic melanoma patients. The EORTC 18071 trial is accruing well and expected to reach full accrual in 2011.

disclosures

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references


