Immune Checkpoint Inhibitors in Melanoma Define a New Era in Immunotherapy Aiming for Cure

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17.1 The New Paradigm: Breaking Tolerance Is the Prerequisite

Advances in melanoma therapies are at present mainly in the field of immunotherapy and mutation-driven drug development (Eggermont et al. 2014). Breaking tolerance represents a major paradigm shift and the impact of the first checkpoint inhibitors, i.e. anti-CTLA-4 (cytotoxic T lymphocyte antigen-4) and anti-PD1/anti-PDL1 (programmed death-1 receptor and its ligand PD-L1) is unprecedented (Pardoll 2012). In only 5 years, advanced melanoma has been transformed from an incurable disease into a curable disease (Eggermont et al. 2013; Robert et al. 2013). Breaking tolerance has a transversal impact throughout solid tumor oncology.

17.2 Anti-CTLA4

17.2.1 Ipilimumab in the Therapeutic Setting of Advanced Melanoma

Monoclonal antibody blocking of cytotoxic T lymphocyte antigen 4 (CTLA-4) leads to breaking immune tolerance and can induce tumor regressions. In 2011, the fully humanized monoclonal anti-CTLA4 antibody ipilimumab was approved in the USA in first- and second- line for patients with advanced melanoma and in second

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line in Europe at a dose of 3 mg/kg. The approval was based on randomized controlled trial (RCT) results that showed that ipilimumab alone or combined with a peptide vaccination provided a significant survival benefit of about 33 % compared to vaccination alone (Hodi et al. 2010). In another RCT, but in first-line, ipilimumab at 10 mg/kg combined with dacarbazine provided only a small, albeit statistically significant, benefit over treatment with dacarbazine alone, but there seems no reason to advocate the use of this combination (Robert et al. 2011). Mature data in thousands of patients indicate that about 20 % of patients treated with ipilimumab have the potential to survive for at least 3 years and up to 10 years from treatment initiation (Schadendorf et al. 2015). Also the efficacy in patients with brain metastases has been established and reported (Margolin et al. 2012). Ipilimumab responses can occur after the initial tumor progression or the appearance of new lesions. For this reason, immune-related response criteria (irRC) have been developed to avoid premature treatment cessation (Wolchok et al. 2009; Hoos et al. 2010).

Adverse events (AE) occur in about 40 % of patients and are mostly immune-related (irAE), such as skin rashes, colitis, hepatitis, and hypophysitis. Grades 3–4 adverse events occur in about 20 % of patients and can, in rare cases, be fatal. Usually, they resolve spontaneously or after steroid therapy. Endocrinopathies behave differently and pituitary–adrenal axis failure usually requires permanent hormonal substitution. High-dose steroids are indicated for severe irAEs, but other immunosuppressive agents, like anti-TNF-alpha antibodies may also be needed, especially in the context of severe colitis (Weber et al. 2012).

Good biomarkers for response to ipilimumab therapy still remain to be established. Immune-related adverse events, an increase in lymphocyte counts, an increase in eosinophil counts, the presence of NY-ESO-1 antigen, and the resistance in vitro to T-regulatory cell functions seem to be associated with higher response rates (Attia et al. 2005; Ku et al. 2010; Delyon et al. 2013; Ménard et al. 2008). Recently, the high levels of soluble CD25 in the serum, especially in combination with high levels of LDH, were demonstrated to be a very strong prognostic factor for poor outcome (Hannani et al. 2015).

Even the optimal dose and schedule for ipilimumab remain to be established. A randomized phase II trial comparing 0.3 mg/kg, 3 mg/kg, and 10 mg/kg suggested 10 mg/kg to be the more effective dose, but associated it with more toxicity (Wolchok et al. 2010). The results of the RCT comparing 3 mg/kg versus 10 mg/kg are not yet mature. The value of four thrice-weekly administrations (induction) compared to induction followed by further administrations (maintenance) has not been established.

17.2.2 Ipilimumab in the Adjuvant Setting of Resected Stage III Melanoma

The results of a double-blind placebo-controlled adjuvant trial EORTC18071 in stage III patients at high risk for relapse were recently published (Eggermont et al. 2015). In 951 patients with high-risk stage III disease (palpable nodal disease or sentinel node positive disease with metastases >1 mm in diameter according to the

Rotterdam Criteria (van Akkooi et al. 2008; van der Ploeg et al. 2011, 2014)), ipilimumab was dosed at 10 mg/kg and administered every 3 weeks over the first 12 weeks (induction) and thereafter every 12 weeks for up to 3 years or relapse. A significant impact on RFS (HR 0.75, $p=0.0013$) for the ITT population was reported. Most patients came off treatment after four to five administrations of ipilimumab. The potential value of maintenance therapy will therefore remain unanswered. irAEs were consistent with what has been observed in advanced melanoma trials, but at a higher frequency, especially regarding endocrinopathies. Post hoc analyses demonstrated a significant impact both in patients with sentinel node-positive disease and palpable node-positive disease. Similar to EORTC adjuvant trials 18952 and 18991 with IFN and pegylated-IFN, patients with sentinel-positive disease derived a greater benefit (Eggermont et al. 2005, 2008, 2012a). Patients with an ulcerated primary derived the greatest benefit like in the meta-analysis of the IFN trials 18952 and 18991, indicating that ulcerated melanoma is a separate biologic entity (Eggermont et al. 2012b, c). In contrast, however, to the experience in the adjuvant IFN trials EORTC 18952 and 18991, patients with non-ulcerated melanomas also derived a benefit in the adjuvant ipilimumab setting (van Akkooi et al. 2008). This is in contrast to the total lack of benefit in IFN trials, which has also recently been confirmed in the individual patient data (IPD) meta-analysis of all adjuvant IFN versus observation trials (Suciu et al. 2014).

17.2.3 Combination Therapies with Ipilimumab

Various combinations of ipilimumab with other immune-modulating, anti-angiogenic or chemotherapeutic, or targeted agents have been reported or are ongoing. Guiding principles for combination treatment designs could be to use drugs that lead to immunogenic cell death (Kroemer et al. 2013; Vacchelli et al. 2014a; Galluzzi et al. 2012; Zitvogel et al. 2013). Since radiotherapy can also induce immunogenic cell death, the reported observation of abscopal antitumor effects after radiotherapy and ipilimumab has led to a number of clinical studies to further investigate this phenomenon (Postow et al. 2012).

17.2.3.1 Chemotherapy

Three studies regarding the combination of chemotherapy with ipilimumab in melanoma patients have been published thus far.

1. *Dacarbazine*: A phase III trial comparing DTIC versus DTIC plus ipilimumab at 10 mg/kg in first-line in patients with advanced melanoma showed a survival benefit for patients treated with the combination (Robert et al. 2011). The median benefit of only 2.1 months was, however, disappointing and the combination is not believed to bring a benefit over ipilimumab alone.
2. *Fotemustine*: In an open-label, single-arm phase II trial, 86 patients with advanced melanoma, 20 of them with asymptomatic brain metastases, received induction treatment of 10 mg/kg intravenous ipilimumab every 3 weeks for a total of four

doses, and 100 mg/m^2 intravenous fotemustine weekly for 3 weeks and then every 3 weeks from week 9 to week 24 (Di Giacomo et al. 2012). Patients with a confirmed clinical response were eligible for maintenance treatment from week 24, with ipilimumab every 12 weeks and fotemustine every 3 weeks. Forty patients (46.5 %) in the study population achieved disease control, as did 10 patients with brain metastases (50 %). Toxicity was considerable with 47 patients (55 %) having grade 3 or 4 treatment-related adverse events.

3. *Carboplatin/taxol*: Very preliminary results of a randomized phase II trial comparing concurrent carboplatin plus paclitaxel and ipilimumab (four doses at 3 mg/kg) with sequential treatment of these agents were reported recently (Jamal et al. 2014). In 31 patients, response rates (RR) and disease control rates (DCR) for 14 evaluable patients at 24 weeks were 21.4 % and 42.9 % by mWHO, and 35.7 % and 64.3 % by irRC, respectively. Grades 3 to 4 AEs were observed in 63 % of patients.

17.2.3.2 Antiangiogenic Agents

Bevacizumab Four dosing cohorts of ipilimumab (3 or 10 mg/kg) with four doses at 3-week intervals and then every 12 weeks, and bevacizumab (7.5 or 15 mg/kg) every 3 weeks, were studied in 46 patients with metastatic melanoma (Hodi et al. 2014a). There were 8 PRs and 22 SDs, and a disease control rate of 67.4 %. Median survival was 25.1 months. Extensive CD8(+) and macrophage cell infiltration were observed in on-treatment tumor biopsies. From this initial experience, it appears that the combination of bevacizumab and ipilimumab can be safely administered. VEGF-A blockade influences inflammation, lymphocyte trafficking, and immune regulation that should be studied further.

17.2.3.3 Cytokines

1. *Interleukin-2 (IL-2):* The most mature data on the combination of IL-2 and ipilimumab regard 36 patients treated at the NCI Surgery Branch (Prieto et al. 2012). There were six complete responders (17 %), which was higher than the 6 % CR rate in 56 patients treated with ipilimumab alone and the 7 % CR rate among 85 patients who received ipilimumab with gp100 peptide vaccination. All CRs except one were ongoing at 54+ to 99+ months at the time of the report. The combination with IL-2 did not seem to increase toxicity. The combination with IL-2 should be explored further.
2. *Interferon-alpha (IFN):* The first phase II trial report on the combination of IFN was a study with the anti-CTLA4 drug tremelimumab (Tarhini et al. 2012). In this study, 37 stage IV melanoma patients received tremelimumab 15 mg/kg/course (three cycles [one cycle = 4 weeks]) intravenously every 12 weeks. High-dose interferon alfa-2b (HDI) was administered concurrently, at 20 MU/m^2/day i.v. for 5 days/week for 4 weeks followed by 10 MU/m^2/day s.c. three times a week for 8 weeks per course. In 35 evaluable patients, overall response rate was 24 % (four CRs and five PRs), 38 % SD, with a median progression-free survival of 6.4 months and a median overall survival of 21 months. These results seemed to indicate additive antitumor activity.

3. *Pegylated-IFN*: In 31 patients, ipilimumab (3 mg/kg for four doses) was administered in combination with peg-interferon alfa-2b at 3 mcg/kg weekly for up to 156 weeks (Kudchadkar et al. 2014). Among 26 evaluable patients, there were two CRs, nine PRs, three SDs, and twelve PDs. Peg-interferon alfa-2b added to ipilimumab resulted in a response rate of 42.3 % and was well tolerated except for a high grade 3 rash rate of 20 %. The combination warrants further exploration.
4. *GM-CSF:* In a randomized phase II trial, conducted by ECOG in 245 patients with unresectable stage III/IV melanoma, ipilimumab plus GM-CSF (sargramostim) treatment was compared with ipilimumab alone (Hodi et al. 2014b). Patients received ipilimumab at 10 mg/kg, intravenously on day 1 plus sargramostim, 250 μg subcutaneously, on days 1–14 of a 21-day cycle versus ipilimumab alone. Ipilimumab treatment included induction for four cycles followed by maintenance every fourth cycle. At a rather short median follow-up of 13.3 months, overall survival was superior for the combination treatment (17.5 months versus 12.7 months), the 1-year survival rates were 68.9 % versus 52.9 %. Surprisingly, no differences for PFS were observed (median PFS of 3.1 months for both treatment arms). The combination treatment was associated with less toxicity. Further studies are needed to elucidate these observations, which is true for all combinations with cytokines (Vacchelli et al. 2014b).

17.2.3.4 Vaccines

1. *gp100 vaccines*: Theoretically, a combination of a vaccine with anti-CTLA4 is very attractive. Yet the results from the RCT comparing ipilimumab versus ipilimumab plus gp100 vaccine versus gp100 vaccination alone did not show a benefit for the combination of ipilimumab plus the vaccine compared to ipilimumab alone (Hodi et al. 2010) and similar observations were made with the mature results of the NCI Surgery Branch experience (Prieto et al. 2012).
2. *Laherparepvec (T-VEC):* The first combination study of ipilimumab with the vaccine laherparepvec (T-VEC) was reported at the 2014 ASCO annual meeting (Puzanov et al. 2014a). In 17 patients, the response rate was 41 % (24 % CR, 18 % PR); and 35 % had SD. Median time to response was 2.9 months. No DLTs were reported. Grade 3/4 AEs occurred in 32 %, with only two patients having irAEs at grades 3/4. These very preliminary results seem promising, but more mature data are awaited.

17.2.4 BRAF and MEK Inhibitors

Combinations of BRAF inhibitors and MEK inhibitors with immune checkpoint inhibitors such as anti-CTLA are theoretically attractive, but have, in practice, proven to be not so simple to develop.

1. *Vemurafenib*: A phase I trial combining vemurafenib and ipilimumab was stopped early, after only 11 patients, because of several cases of grades 3–4 hepatitis (Ribas et al. 2013).

2. *Dabrafenib + Trametenib*: A phase I trial with dabrafenib + ipilimumab did not evoke a high rate of hepatitis, and an expansion cohort is ongoing (Puzanov et al. 2014b). However, the combination of dabrafenib + trametenib + ipilimumab phase I study was stopped because of life-threatening colitis in three of the first seven patients (Puzanov et al. 2014b).

17.2.5 Anti-PD1 and Anti-PDL1

PD1 protein is another immune checkpoint expressed in many tumor-infiltrating lymphocytes in response to inflammation. It has two ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC). The engagement of PD1 on the lymphocyte surface by PD-L1 on melanoma cells delivers inhibitory signals down-regulating T-cell function (Topalian et al. 2012a). Remarkable results of phase I trials evaluating two anti-PD1 antibodies (nivolumab and pembrolizumab) reported response rates of 30 % (Topalian et al. 2012b; Robert et al. 2014). Anti-PD-L1 antibody also gave an encouraging long-term response rate of 17.3 % in melanoma patients in a phase I study (Brahmer et al. 2012). Importantly, the safety profile is very favorable compared to ipilimumab, with much lower rates of irAEs, in particular the troublesome colitis and hypophysitis. Both pembrolizumab and nivolumab have been reported to induce response rates around 30 % in advanced melanoma patients, even in patients that previously failed ipilimumab (Hamid et al. 2013; Topalian and Sznol 2014). Responses tend to be very durable, up to 2 years. Moreover, PDL-1 expression in the tumor is a good biomarker for response for monotherapy with either agent. Nivolumab proved to be vastly superior dacarbazine in first-line in a RCT in 418 patients with advanced non-BRAF-mutant melanoma (Robert et al. 2015a). Pembrolizumab proved to be superior to therapy of choice in ipilimumab failures (Ribas et al. 2015). Moreover, in a cohort of 655 patients treated with pemborlizumab it was demonstrated that response rates in BRAF wild-type patients and in BRAF-mutant patients are similar (45 % and 50 %, respectively) (Daud et al. 2015). Moreover, pembrolizumab has been shown to be superior to ipilimumab in a phase III trial (Robert et al. 2015b). Overall, it leads to the conclusion that anti-PD1 can be considered to be proposed to all patients with advanced melanoma in first-line, irrespective of mutational status, perhaps with the only exception of patients with bulky rapidly progressive BRAF-mutant melanoma. However, the incredible impact of anti-PD1 and anti-PDL1 monoclonal antibodies lies in its broad transversal impact in oncology, now with activity demonstrated against a wide panel of neoplasms other than melanoma, including lung cancer, renal cell cancer, bladder cancer, stomach cancer, head and neck cancer, ovarian cancer, and colorectal cancer with microsatellite instability and Hodgkin lymphoma (Lorenzo Galluzzi et al. 2014).

17.2.6 Anti-PD1 Plus Anti-CTLA4

Very impressive data have been reported on the efficacy of the combination of ipilimumab and nivolumab in the last 2 years (Wolchok et al. 2013; Sznol et al. 2014). The rationale to combine these two checkpoint inhibitors is that they have different

mechanisms of action, with anti-CTLA4 mainly acting at the central level in the lymph node compartment, perpetuating and/or restoring the induction and proliferation of activated T-cells, and with anti-PD1 mainly acting at the peripheral level at the tumor site, preventing the neutralization of cytotoxic T cells by PDL1 expressing tumor cells and PDL2 expressing plasmoid dendritic cells in the tumor infiltrate. Very deep and long-lasting responses are observed, and in the update on the current experience presented by Sznol et al. at the 2014 ASCO annual meeting, with impressive survival rates of >90 % at 1 year and >80 % at 2 years in advanced melanoma patients (Sznol et al. 2014). In 2015, the RCT comparing nivolumab + ipilimumab versus nivolumab versus ipilimumab in advanced melanoma patients was published and demonstrated that the combination is superior to either monotherapy and that nivolumab alone is superior to ipilimumab regarding PFS (Larkin et al. 2015). The trial is not mature regarding OS data. Importantly, patients with PDL1-positive tumors seemed to benefit equally from nivolimumab monotherapy compared with combination therapy. PDL-1-negative patients had the best results with the combination therapy. It will be very interesting to have the mature results of this trial in 1–1.5 years' time. Clearly, all these results are unprecedented in the melanoma world and demonstrate the power of the current concepts of breaking tolerance.

Immunotherapy combinations in general are expected to be perhaps the most dynamic drug development field for years to come. Once breaking tolerance is achieved, or even further improved with candidate molecules such as anti-LAG3 and others, the door is open to combine with agonists such as OX40, CD137, and others. Deepening breaking tolerance and combining with various agonistic approaches is a complex scenario to work out, but obviously, smart immune combos are the future (Eggermont and Robert 2014).

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