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Oxidative stress induction: an old idea whose time has come. MOA and clinical correlates of the oxidative stress inducer STA-478

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Background: STA-4783 (4783) is part of a new drug class that causes oxidative stress levels to exceed sustainable levels in cancer cells, inducing apoptosis and expression of immune markers in those cells.
MOA: Details of the molecular pathways activated by 4783 will be presented, including in vitro experiments demonstrating significant activity in numerous tumor cell lines and synergistic activity with taxanes in animal models.
Clinical Study: A multi-center, randomized, double blind study was conducted in patients with stage IV melanoma of cutaneous origin in the US. Patients were treated with weekly paclitaxel $\pm$ 4783 (3 weeks on, 1 week rest), until progression. Patients receiving paclitaxel alone were allowed to cross over to the experimental arm upon progression.
Results: Of 81 patients enrolled, 53 received 4783+paclitaxel and 28 received paclitaxel alone. Of the paclitaxel-alone group, 19 patients crossed-over post-progression to receive 4783 + paclitaxel, and 9 pts did not cross-over. The primary endpoint was achieved: the median progression free survival (PFS) was 3.7 months in the combination arm vs. 1.8 months for paclitaxel alone ($p = 0.035$, 2-sided log-rank test). At the time of analysis, the number of patients alive based on time of last contact were as follows: 4783 + paclitaxel: 16/53 (30%); paclitaxel alone that crossed over to the combination: 6/19 (32%); and paclitaxel alone that did not cross over: 1/9 (11%). Based on the group to which the patient was initially randomized, regardless of cross over status, the ITT analysis showed a median OS of 12.0 months for 4783 + paclitaxel vs. 7.8 months for paclitaxel alone. For those initially randomized to paclitaxel alone who crossed over to the combination after progression, the median OS was 14.3 months vs. 5.6 months in those who did not cross-over. Toxicities were predominantly G1/2 and were typical of paclitaxel alone.
Conclusions: Median survival for patients with metastatic melanoma has been reported as 6−9 months when either DTIC or paclitaxel is used as single agent therapy. The OS in patients randomized to 4783 + paclitaxel was substantially improved compared to historical controls, and the cross-over group also did particularly well. The OS benefit shown in this analysis is supportive of the benefit of 4783 + paclitaxel as demonstrated by the primary PFS endpoint. The survival benefit suggests a promising future role for oxidative stress induction in cancer chemotherapy.

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Ipilimumab (MDX-010) in patients with unresectable stage III or IV malignant melanoma: efficacy and safety data from a phase I trial

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Background: Ipilimumab (MDX-010) is a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4). Treatment with ipilimumab potentiates T cell responses to tumors, resulting in durable objective responses. This open-label study (MDX010−15) examined the efficacy and safety of different ipilimumab preparations and regimens in patients with unresectable stage III or IV melanoma.
Materials and Methods: Thirty-four patients received either 2.8 or 5 mg/kg transfectoma- or 3 mg/kg hybridoma-derived ipilimumab on days 1, 57 and 85. Additionally, 30 patients received single doses of 7.5, 10, 15 or 20 mg/kg transfectoma-derived ipilimumab (N = 6, N = 7, N = 6, and N = 11, respectively). As single doses of up to 20 mg/kg were found to be well tolerated, a further 24 patients were given up to 4 doses of 10 mg/kg ipilimumab on days 1, 22, 43 and 64. Complete or partial responses (CR, PR), stable disease (SD) and adverse events (AEs) were recorded.
Results: Of the 88 patients treated, 1 CR, 3 PRs and 10 durable SDs were confirmed at the time of analysis. ORs were durable (~29+, 34, 38+ and 39+ weeks) and ongoing in 3 patients at study completion. A PR was observed in 1 patient after ~18.5 weeks and developed to an ongoing CR at ~51 weeks. In another patient, SD was observed for ~16 weeks and preceded a ~30-week+ PR. Durable SD ranged from ~21 to 79+ weeks and is ongoing in 4 patients. Patients with OR or SD had immune-related AEs including rash, pruritis (G1/2), diarrhea (G1/2/3) or colitis (G2). AEs were severe in 27 patients, and considered ipilimumab-related (mostly G3/G4 colitis and diarrhea) in 9 (10% of all treated patients).
Conclusions: These preliminary results suggest that ipilimumab is generally well tolerated. Late-onset ORs can occur, sometimes preceded by months of SD. ORs and SDs tend to be durable. Drug-related AEs of an immune nature are similar to those reported previously and are probably related to the biologic effects of ipilimumab. No obvious dose relationship to AEs has been seen to date

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Phase II randomized, placebo controlled study of sorafenib in combination with dacarbazine in subjects with unresectable Stage III or Stage IV melanoma

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Background: Sorafenib (SOR), a potent and selective multi-kinase inhibitor, exerts its anti-tumor and anti-angiogenic effects via inhibition of VEGFR-1, -2, -3, PDGFR-?, -?, and Raf. Dacarbazine (DTIC) is a commonly used cytotoxic agent for advanced melanoma, and previous results in the Phase I/II setting with the combination of SOR + DTIC were encouraging.
Methods: This randomized, double blind, placebo controlled, multicenter, phase II study was undertaken to compare the anti-tumor activity, as measured by PFS, as well as the tolerability of SOR + DTIC vs. DTIC + placebo (PL) in subjects with unresectable Stage III or Stage IV melanoma who had not received prior cytotoxic chemotherapy. Eligibility criteria included measurable disease by RECIST, no prior cytotoxic chemotherapy, and no active brain metastases. Patients (pts) stratified by stage and ECOG PS (0 vs 1) were randomized to receive DTIC 1000 mg/m^2 q 21 days + placebo or SOR 400 mg po bid continuously until the occurrence of progressive disease or intolerable toxicity. The primary endpoint was PFS of DTIC+SOR vs DTIC+PL using a two-sided test, $\alpha = 0.05$; 77 PFS events were needed to detect a hazard ratio (HR) of 0.5 (SOR/PL) with 86% power. Other endpoints included: OS, ORR, TTP, and duration of response.
Results: Accrual occurred over 12 mos. with 101 pts enrolled (51 DTIC+SOR, 50 DTIC+PL). Treatment arms were balanced for age (median 58 y), gender (male 70%), PS (ECOG 1 39%), stage (Stage IV M1c 52%) and baseline LDH (>ULN 29%). By independent assessment, the median PFS of DTIC+PL vs DTIC+SOR was 11.7 wks (95% CI 6.1, 17.9) vs 21.1 wks (95% CI: 16, 28); HR 0.67, $p = 0.07$; PFS rate at Day 180 was 18% vs 41%; and ORR was 12% vs 24%. Survival data are pending. No treatment-related deaths occurred in either arm. Toxicities of Gr 3 or higher (DTIC+PL vs DTIC+SOR) included neutropenia (12% vs 33%), leukopenia (6% vs 14%), thrombocytopenia (18% vs 35%), thrombosis/embolism (0% vs 6%), hypertension (0 vs 8%), hand–foot skin reaction (0 vs 4%), and CNS hemorrhage (0% vs 8%). 3 of 4 pts with CNS hemorrhage had new brain metastases.
Conclusions: In this randomized phase II trial, the combination of DTIC+SOR was well tolerated in chemotherapy-naive pts with advanced melanoma. Further, a strong efficacy trend was seen with DTIC+SOR as compared to DTIC+PL in median PFS, PFS rate at 6 months and ORR. Based on theses results, this regimen warrants further evaluation in larger clinical trial settings.