overall survival (OS). To explore the effect of prior treatment with docetaxel on immune response and OS, data for the subset of pts with prior docetaxel use from the IMPACT study (NCT00065442) were analyzed.
Materials and Methods: 512 pts were randomized 2:1 to sipuleucel-T or control. The trial was sponsored by Dendreon; enrollment and follow-up are complete. Pts treated with chemotherapy ⩾3m prior to registration were eligible provided they received ⩽2 chemotherapy regimens. Pts received 3 infusions of sipuleucel-T or control at approx. 2-wk intervals, and were followed for safety and clinical endpoints. Product parameters ($CD54^+$ count, CD54 upregulation, and total nucleated cell count) were evaluated by flow cytometry in the wk 0, 2, and 4 products. Immune response was measured by ELISA, IFNγ ELISPOT, and stimulation index, OS was analyzed using a Cox regression model.
Results: The majority of pts with prior chemotherapy received docetaxel: 15.5% of sipuleucel-T and 12.3% of control pts had prior docetaxel (last dose a median of 10.2m before randomization [10.6m for sipuleucel-T and 9.6m for control pts], range 2.8–73.0m). Pts with prior docetaxel had slightly less favorable prognostic features. Adverse events within 1 day of sipuleucel-T infusion were similar between groups (79.2% for pts with prior docetaxel and 79.6% for pts without prior docetaxel). 86.8% of prior docetaxel pts received the 3 planned infusions of sipuleucel-T vs 92.7% of pts without prior docetaxel. Sipuleucel-T product parameters and immune responses were similar for pts with and without prior docetaxel. The OS hazard ratio (HR) for sipuleucel-T was consistent (interaction P = 0.638) in pts with prior docetaxel (HR = 0.672 [95% CI: 0.364, 1.241]) and without prior docetaxel (HR = 0.788 [95% CI: 0.612, 1.014]).
Conclusions: Sipuleucel-T can be administered safely and successfully manufactured for pts previously treated with docetaxel. While the limited sample size of pts with prior docetaxel precludes definitive conclusions, the results of this study suggest that pts who received prior docetaxel appear to generate immune responses and experience a survival benefit.

7013 POSTER DISCUSSION

A Phase 1 Study of DI17E6, an Antibody Targeting AV Integrins, in Progressive Castrate-resistant Prostate Cancer With Bone Metastases (mCRPC) After Chemotherapy

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Background: The αv integrin subfamily is composed of at least five members, including αvb1, αvb3, αvb5, αvb6, and αvb8. These integrins exhibit classical integrin functions such as regulation of cell adhesion to extra-cellular matrices, cell spreading, and cell migration. Over-expression of αv integrins has been demonstrated in a number of human cancers including melanoma and breast, renal, cervical, gastric, lung, and prostate tumours. DI17E6 (EMD 525797) is a de-immunized monoclonal IgG2 antibody specifically targeting αv integrins involved in tumour progression.
Methods: This study assessed the safety, tolerability, pharmacokinetics and effect of DI17E6 on e.g. PSA and tumour size (by RECIST 1.0 criteria) in mCRPC patients (pts) progressing after chemotherapy in salvage setting (clinicaltrials.gov identifier NCT00958477). 26 pts were treated with iv infusions of 250, 500, 1000 or 1500 mg DI17E6 given over 1 hour. 24 pts (43−80 years) received 3 doses (weeks 1, 3 and 5) prior to response assessment at the end of week 6. Pts without progressive disease could receive further doses every 2 weeks. Dose-limiting toxicities (DLTs) were assessed over the first 6 weeks and pts were followed for safety until 4 weeks after the last administration of DI17E6.

Table 1: Treatment days per cohort

Pt	250 mg	500 mg	1000 mg	1500 mg
1	42	297	113	91
2	42	380+	121	84+
3	42	85	198+	72+
4	42	142	41	64+
5	56	140	56	77+
6	98	56	43	57+
7	14*			
8	28*			

+ = ongoing treatment; * dropped out pts (1 and 2 infusions only).

Results: At cut-off for analysis, the mean duration on treatment was 95.4 days (26 pts). 4 out of 6 pts in cohort 2 (500 mg) and 3 out of 6 pts in cohort 3 had >16 weeks on treatment (Table 1). No DLTs occurred. Pt 1 and 2 of cohort 2 (500 mg) had a marked decrease in PSA and stabilization. Pt 2 also had primary tumour shrinkage and normalisation of lymph node size. These pts had long term anti-integrin treatment (21 infusions and 27 infusions, respectively). Both subjects additionally showed signs of clinical benefit in term of quality of life and pain reduction.
Conclusions: Clinical single agent activity of DI17E6 in salvage therapy was observed in dose cohort 2 and higher. This supports further investigations in mCRPC. DI17E6 is well tolerated without premedication and did not show clinically relevant dose-related changes in safety parameters assessed.

7014 POSTER DISCUSSION

Evaluation of Circulating Tumour Cells (CTCs) in Chemotherapy-naïve Patients With Metastatic Castration-resistant Prostate Cancer (mCRPC) Receiving TAK-700, an Investigational 17,20-lyase Inhibitor

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Background: CTC enumeration provides prognostic information in patients with metastatic prostate cancer. In particular, the categorical shift from ⩾5 to <5 cells per 7.5 mL of whole blood may represent a better predictor of overall survival than changes in prostate-specific antigen (PSA) levels. In a phase 1/2 study in chemotherapy-naïve patients with mCRPC (TAK-700_201, NCT00569153), the investigational 17,20-lyase inhibitor TAK-700 was well tolerated (the most common AE was fatigue) and resulted in profound reductions in circulating concentrations of testosterone and the adrenal androgen DHEA-S. PSA response rate (⩾50% decrease) at 12 weeks was observed in 52% of patients receiving TAK-700 at 400 mg BID plus prednisone. Here we report preliminary data on candidate biomarkers of response from this study.
Materials and Methods: Patients received oral TAK-700 at 100–600 mg BID, 400 or 600 mg BID plus prednisone 5 mg BID, or 600 mg QD. Blood samples were collected on a 28-day cycle (at baseline and on Day 1 of cycles 2, 4, and every 3 cycles thereafter) for evaluation of biomarkers of response to TAK-700. CTCs were enumerated using the CellSearch methodology.
Results: As of November 2010, CTCs could be enumerated in 99 (90%) of 110 patients enrolled in the study. CTC at baseline was ⩾5 in 43 (43%) patients and <5 in 56 (57%) patients. Of those with CTC ⩾5 at baseline, 21 (49%) achieved CTC <5 at follow-up. Overall, 31 (72%) patients with baseline CTC ⩾5 had a ⩾50% reduction in CTCs at follow-up. Of patients with CTC <5 at baseline, the majority (51, 91%) maintained CTC <5 at follow-up.
Conclusions: TAK-700 treatment resulted in CTC reductions in the majority of patients. Notably, approximately half of patients with CTC ⩾5 at baseline converted to CTC <5 with TAK-700 treatment. Correlation with other biomarkers of clinical outcome, including PSA response, will be presented. Patient follow-up is ongoing.
Funding: Millennium Pharmaceuticals, Inc.

7015 POSTER DISCUSSION

Fatigue Improvement/Reduction With Abiraterone Acetate in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC) Post-docetaxel − Results From the COU-AA-301 Phase 3 Study

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Background: Fatigue is a common, debilitating side effect of prostate cancer and its treatment, particularly androgen deprivation therapy.

Abiraterone acetate (AA), a selective androgen biosynthesis inhibitor, suppresses growth of CRPC through inhibition of persistent androgen synthesis from adrenal and intratumoral sources. In an international double-blind randomised trial of 1195 patients (pts), AA + prednisone (P) improved overall survival (HR = 0.646) in mCRPC progressing after docetaxel (D), compared with placebo + P. Here we retrospectively assess the effect of AA on patient-reported fatigue in this study.

Material and Methods: In this study of oral AA (1 g QD) + P (5 mg BID) vs placebo + P in mCRPC post-D, fatigue was assessed at baseline and each treatment cycle until discontinuation, using the Brief Fatigue Inventory (BFI) questionnaire. Fatigue intensity (worst fatigue item only) and fatigue interference (average of interference with general activity, mood, walking, work, relationships, enjoyment of life) were evaluated; scores were analysed post hoc for changes over time. All analyses were conducted using responder definitions (founded on distribution-based calculations) of clinically significant changes in eligible pts (i.e. with baseline score of $\geqslant 5$ on BFI worst fatigue item/interference scale).

Results: 797 pts were randomised to AA and 398 to placebo. Median treatment duration was 8 and 4 months, respectively. Baseline BFI scores were not different between groups. AA yielded significantly better fatigue outcomes than placebo (Table). With AA, time to improvement in fatigue intensity was shorter and more pts showed improvement in fatigue intensity and interference. AA also delayed progression of fatigue intensity and interference. The fatigue profile of AA was superior to placebo from Cycles 1 to 15.

Conclusions: In post-D mCRPC, in addition to overall survival benefits, therapy with AA + P delays fatigue progression and produces clinically significant improvements in fatigue scores compared to baseline. Furthermore, AA improved fatigue more rapidly than placebo.

	AA N = 797	Placebo N = 398	p Value
BFI-Intensity			
Improvement, improved/eligible pts (%)	221/384 (58)	75/186 (40)	0.0001[a]
Time to improvement [median], days	59	194	0.0114[b]
Time to progression [25th percentile], days	232	139	0.0014[b]
BFI-Interference			
Improvement, improved/eligible pts (%)	103/189 (55)	35/92 (38)	0.0096[a]
Time to improvement [median], days	57	113	0.0809[b]
Time to progression [25th percentile], days	281	139	0.0006[b]

[a] Chi-square test; [b] Log-rank test.

Poster Presentations (Sun, 25 Sep, 14:00−16:30)
Genitourinary Malignancies − Prostate Cancer

7016 POSTER

Second Line Chemotherapy After Docetaxel Among Symptomatic Castration-Resistant Prostate Cancer (CPRC) Patients − GETUG-P02 Randomized Phase II Trial

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Background: Most patients (pts) relapse after first-line treatment with docetaxel. Trials with alternative agents were conducted among healthy pts (80% with OMS < 2, 80% <70-year old, <50% without pain). We designed a pragmatic second-line chemotherapy randomized phase II trial among symptomatic CRPC pts either old or with comorbidities.

Material and Methods: We assessed 3 routinely used drugs: mitoxantrone (MX:12 mg/m^2/3 wk), oral etoposide (VP:25 mg bid/d1 to 14/3 wk), oral vinorelbine (VN:60−80 mg/m^2/d1 & d8/3 wk). The primary objective was objective palliative response defined by a decrease pain and/or analgesic consumption without disease progression. We prospectively assessed quality of life [QoL, (QLQ-C30, PR25)] and, for elderly, autonomy (ADL, IADL) and depression (GDS). The arms were stratified on progression-free interval from docetaxel and PSA doubling time.

Results: 92 pts were equally included in the 3 arms. 48 (52%) were more than 70-year old. Median time from docetaxel was 5.8 months. Pts and disease initial characteristics were similar in each arm: 28% of pts had comorbidities, median baseline EVA for pain was 4, median concomitant treatments number was 3. Median cycles number was 3 in VP and 5 in MX and VN. Respectively 1, 3 and 1 pts withdrawn due to toxicities in MX, VP and VN arm. Grade 3−4 neutropenia occurred for 21% and 23% of MX and VN pts. Grade 3−4 anemia and asthenia were respectively observed for 16% and 13% of VP pts, and for 3% in MX and VN arms. Objective and global palliative response rates were respectively 17%, 22% (MX), 14%, 18% (VP) and 11%, 22% (VN). Corresponding median palliative response durations were 4.3, 4.9 and 2.1 months. Analgesic (partial+stable) response was respectively 92%, 93% and 77% in MX, VP and VN arm and corresponding median analgesic response duration were 10.6, 6.5 and 10.5 months. Median palliative PFS (OS) was respectively 3.4, 2.0 and 2.3 (10.6, 8.4, 12.6) months in MX, VP and VN arm. QoL did not decline over treatment for 89% of pts.

Initial autonomy loss and risk of depression (GDS $\geqslant 5$) were respectively noted for 40% and 47% of elderly, with no relationship with palliative response. Response rate and duration were similar among >70-year old pts.

Conclusions: MX, VP and VN induced palliative response among pts either old or with comorbidities, with a good tolerance profile. However MX seems to be the best compromise in terms of response and profile of toxicities for this group of pts.

7017 POSTER

Establishing and Characterising New in Vitro Models of Docetaxel-resistance in Prostate Cancer

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Introduction: Docetaxel is first-line treatment for hormone-refractory prostate cancer (HRPC). A major limitation of this treatment is that, due to inherent or acquired drug resistance (RD), overall survival is increased by only 2.5 months on average. Here we established docetaxel-resistant prostate cancer cell line variants and characterised them as in vitro models of the clinical situation.

Materials and Methods: Using 22Rv1 (a cell line derived from a primary tumour) and DU145 (from a prostate cancer brain metastasis), we developed docetaxel-resistant variants, 22Rv1RD and DU145RD, respectively, through step-wise exposure to docetaxel over a 6 months period. Initial characterisation of these resistant variants, in comparison to their respective parallel-aged parent cells, included investigating their fold-resistance to docetaxel and their cross-resistance to other chemotherapeutic drugs. Changes in phenotypic characteristics were evaluated using proliferation assays; wound-heal migratory assays; soft agar assays; and invasion through ECM-coated transwells. Exosomes secreted by DU145 and DU145RD were isolated from their corresponding conditioned media, using a combination of filtration and ultracentrifugation. Western blotting was performed to evaluate the success of exosomes isolation and also for assessing cellular expression of the drug efflux pump, MDR1/P-gp.

Results: Docetaxel-conditioned variants were found to be substantially more resistant to docetaxel than their parallel-aged parent cell lines i.e. based on IC_{50} values, 22Rv1RD and DU145RD are 71 ± 8.4 and 107 ± 7.4 fold resistant, respectively. Additionally, both resistant variants conferred cross-resistance to doxorubicin (8.3 ± 1.2 for 22Rv1RD; 4.3 ± 1.0 for DU145RD). While 22Rv1RD display low level cross-resistance to carboplatin (2.1 ± 0.6) and 5-fluorouracil (1.6 ± 0.2), DR145RD does not. DU145RD cells have increased motility ($p < 0.05$), migration ($p < 0.01$) and invasion ($p < 0.05$) capacity compared to DU145. Although 22Rv1RD cells were found to be somewhat less motile, migratory and invasive than 22Rv1, overall these cells are apparently not as aggressive as the DU145/DU145RD pair. Neither parent cell lines nor DU145RD express MDR-1/P-gp, whereas 22Rv1RD cells show low level expression; suggesting that this efflux pump may be in part, but not wholly, responsible for its drug resistance characteristics. Exosome isolation from DU145RD cells modulated the motility ($p < 0.05$) and invasive ($p < 0.05$) capacity of DU145 and invasiveness of 22Rv1 ($p < 0.05$).

Conclusion: New cell line models of docetaxel-resistance that may aid in the investigation of docetaxel-resistance and cross-resistance in prostate cancer have been developed. While MDR-1/P-gp may contribute to resistance and multi-drug resistance in 22Rv1RD, it does not seem to be involved in DU145RD resistance. Docetaxel-resistance in DU145RD is significantly associated with more aggressive cellular characteristics. Furthermore, exosomes released from DU145RD cell line and subsequently isolated from its CM can be taken up by secondary cells and affect the phenotype characteristics of such recipient cells.

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