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JOURNAL OF CANCEROLOGY HOT TOPIC

ASCO 2015: Special Award Lecture Abstracts

Central Nervous System Tumors. 2071 Poster Session (Board #60)

Mon, 1:15 PM-4:45 PM

IDENTIFICATION OF GLIOBLASTOMA PATIENTS WHO STAND TO BENEFIT FROM PARP INHIBITOR THERAPY

FIRST AUTHOR: KERRIE LEANNE MCDONALD

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Background: The development of effective targeted drugs for the treatment of glioblastoma (GBM) represents a major unmet need. Veliparib (ABT-888; AbbVie) inhibits both PARP1 and PARP2 (poly[ADP-ribose] polymerase). The successful clinical application of veliparib and other PARP inhibitors (PARPi) will be assisted by the identification of predictive biomarkers. **Methods:** Efficacy of veliparib in combination with radiotherapy (RT) was tested on a panel of primary and recurrent GBM patient-derived cell lines (PDCL). In order to screen for potential biomarkers for PARPi, we performed whole genome sequencing (WGS) on sensitive and resistant PDCLs and also measured the expression of 96 candidate DNA repair pathway genes using the RT2 Profiler PCR Array (Human DNA Repair; Qiagen). **Results:** Differential sensitivity to veliparib and RT was observed amongst the panel of PDCLs. Three out of 16 PDCLs showed hypersensitivity to veliparib/RT. The PDCLs sensitive to treatment exhibited a large number of structural variation (SV) events (> 200). The average SV events identified in the resistant PDCLs were < 50. We detected mutations in genes involved in mismatch repair (MMR): *MLH1*, *MSH2*, *MSH6* and *PMS2*. We also detected mutations in other genes involved in DNA maintenance such as *XRCC4*, *FANCA*, *FANCD2*, *ATR*, *RPA1*, *REV3L,* and *PARP1* only in the sensitive PDCLs. **Conclusions:** Mutations in DNA maintenance pathways may be a method for selecting patients for therapies involving the combination of DNA-damaging agents such as radiotherapy and PARP inhibitors. Additionally, the signature associated with genomically unstable GBM may be a method of identifying potential responders to PARP inhibitor therapy.

2074 Poster Session (Board #64)

Mon, 1:15 PM-4:45 PM

ANALYSIS OF BRAF ALTERATIONS AND MOLECULAR PROFILING IN GLIOBLASTOMA AND ASTROCYTOMA

First author: Nadia Faiq

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Background: Although well characterized in pilocytic astrocytoma and pleomorphic xanthoastrocytoma, the prevalence of BRAF alterations in glioblastoma (GBM) and astrocytoma is not well established. Characterization of BRAF mutations in glioblastoma and astrocytoma may identify a subgroup of patients with sensitivity to BRAF inhibitors. **Methods:** DNA was extracted from 95 diffuse gliomas (grade II-IV) at our institution and an independent set of 714 gliomas, and was subjected to hybrid capture for 315 or 265 cancer-related genes plus select intronic regions. Sequencing was performed to a mean coverage depth of > 500x and analyzed for the presence of base substitutions, insertions/deletions, copy number alterations, and rearrangements. **Results:** Seven of 95 gliomas (7.4%) analyzed harbored BRAF alterations; 6 (6.3%) were identified with either a V600E mutation (3 GBM + 1 gliosarcoma) or a D594G mutation (2 GBM). One glioma with a BRAF rearrangement was identified (astrocytoma grade II). There were no alterations found in oligodendrogliomas. Molecular profiles in all six tumors with BRAF point mutations were similar; all were wild-type for IDH1/2 and exhibited CDKN2A/B loss. Conversely, the BRAF rearrangement was IDH1 mutated and CDKN2A/B intact. To confirm the frequency of BRAF alterations, an independent database of 714 gliomas was queried. Thirty-four (4.8%) tumors were found to have BRAF alterations, including 24 BRAF point mutations. Of those, 96% (n = 23) were IDH1/2 wild-type and 83% (n = 21) harbored CDKN2A/B loss. Conversely, BRAF rearrangements and amplifications (n = 10) did not share this profile. Forty percent harbored IDH1/2 mutations and only 40% displayed CDKN2A/B loss. In our patients, five of the six with BRAF point mutations are alive. The median overall survival is 28.8 months (10.7-40.6). One patient with recurrent GBM and V600E mutation was treated with the BRAF inhibitor vemurafenib with a progression-free survival = 12 months. **Conclusions:** BRAF alterations occur in GBM and astrocytoma. BRAF point mutations are associated with a specific molecular profile, specifically IDH1/2 wild-type, and CDKN2A/B loss. This profile identifies a molecular subgroup of gliomas that may exhibit improved survival and are amenable to targeted therapy with BRAF inhibitors.

Developmental Therapeutics-Clinical Pharmacology and Experimental Therapeutics. 2507 Oral Abstract Session

Tue, 8:00 AM-11:00 AM

PHASE II STUDY WITH WEE1 INHIBITOR AZD1775 PLUS CARBOPLATIN IN PATIENTS WITH P53-MUTATED OVARIAN CANCER REFRACTORY OR RESISTANT (< 3 MONTHS) TO STANDARD FIRST-LINE THERAPY

First author: Suzanne Leijen

The Netherlands Cancer Institute, Amsterdam, Netherlands

Background: AZD1775 (formerly MK-1775) is a potent and selective inhibitor of Wee1, a kinase that phosphorylates CDC2. Phosphorylation of CDC2 inactivates the CDC2/cyclin B complex and is therefore essential for normal G2 checkpoint function. As most p53-deficient tumors lack a functional G1 checkpoint, they rely on the G2 checkpoint for cell cycle arrest in response to DNA damage. G2 checkpoint abrogation, using a Wee1 inhibitor, may therefore sensitize p53-deficient tumor cells to DNA-damaging anticancer agents. In a phase I study, the maximum tolerated dose (MTD) of AZD1775 in combination with carboplatin demonstrated target engagement (NCT00648648). **Methods:** Patients (pts) with p53 mutated ovarian cancer refractory or resistant (_ 3 months) to standard first-line therapy (carboplatin plus paclitaxel) were re-exposed to carboplatin (AUC 5), plus five twice-daily doses of 225 mg AZD1775 in a 21 day cycle (MTD) (NCT01164995). The p53 mutation status was analyzed by both sequencing analysis (TP53 exons 2-10) and AmpliChip TP53 array (TP53 exons 2-11). Response evaluation was performed according to RECIST 1.0, volumetric tumor measurement (enhanced RECIST), and CA-125 blood levels. **Results:** Bone marrow toxicity, fatigue, diarrhea, nausea, and vomiting were the most common adverse events. Out of 24 pts enrolled, 22 pts were evaluable for study endpoints. As best response (RECIST 1.0), 6 pts (27%) showed confirmed partial response (PR) with a median progression-free survival (PFS) of 10.9 months. Nine pts (41%) had stable disease and 7 pts (32%) had progressive disease as best response, with a median PFS of 5.3 and 1.3 months, respectively. **Conclusions:** AZD1775 is a first in class Wee1 inhibitor that in combination with carboplatin is well tolerated and shows promising antitumor activity in p53-mutated ovarian cancer refractory or resistant (< 3 months) to standard first-line therapy.

Clinical trial information: **NCT01164995.**

2523 Poster Session (Board #239)

Sat, 8:00 AM-11:30 AM

MOLECULAR CHARACTERISTICS IN BREAST CANCER TUMORS TREATED WITH NEOADJUVANT CHEMOTHERAPY WITH AND WITHOUT BEVACIZUMAB: RESULTS FROM NEOAVA-RANDOMIZED PHASE II STUDY

First author: Olav Engebraaten

Oslo University Hospital, Oslo, Norway

Background: The molecular characteristics of responding and non-responding breast cancers when treated with antiangiogenic therapy are largely unknown. **Methods:** To investigate molecular alterations in tumors treated with antiangiogenic therapy, the NeoAva study included patients with HER2-negative primary tumors of ≥ 25 mm that were randomized (1:1) to receive chemotherapy (4 x FEC100 + 12 weeks of taxane-based therapy) with or without bevacizumab. Tumor material was obtained at screening, 12 weeks into treatment, and at surgical removal at 25 weeks. Micro-RNA expression profiling was performed (Agilent). In this study, 131 patients were evaluable for tumor response. **Results:** pCR in breast and axilla were obtained in 14 (21.1%) patients in the chemo_bev arm, and in 7 (10.6%) patients in the chemo-only arm. The overall pCR rates were higher in the ER-negative tumors compared to ER-positive tumors (9 of 23 vs. 12 of 108). Addition of bevacizumab seemed to improve pCR in the ER-positive patient group (9 vs. 3) but not in the ER-negative patient group (5 vs. 4). Tumors that achieved pCR showed a significantly higher expression of genes (n = 362) enriched for immune response-related pathways, compared to the tumors that did not achieve pCR in the ER-positive group. The identified immune gene signature predicted response independent of the PAM50 proliferation signature and VEGF pathway signature, particularly in the bevacizumab-treated group ($p < 0.001$). Proliferation scores regressed across time-points in response to therapy ($p < 0.001$) and bevacizumab treatment accelerated the reduction of the proliferation score in the ER-positive tumors. In response to therapy, tumors achieved a better prognosis profile, i.e. luminal A or normal-like profile. The ER-positive tumors, particularly luminal B, showed significant differences in gene expression and associated pathways between two treatment arms (chemo only and chemo_bev), while minimal change was observed for ER-negative/basal-like tumors. **Conclusions:** The immune signature was found to be a strong predictor of response in ER-positive tumors, particularly in tumors treated with chemotherapy combined with bevacizumab.

Clinical trial information: **NCT00773695.**

2524 Poster Session (Board #240)

Sat, 8:00 AM-11:30 AM

BEVACIZUMAB PLUS LETROZOLE (LEA CLINICAL TRIAL PHASE III). USING HYPERTENSION FOR FINDING BIOMARKERS OF EFFICACY

First author: Juan de la Haba Rodriguez

Medical Oncology Department University Reina Sofia Hospital; Biomedical Research Institute Maimonides, Cordoba, Spain

Background: The LEA study compares the combination of endocrine therapy plus bevacizumab (ET-B) against endocrine therapy (ET), as first-line treatment in patients (pts) with advanced breast cancer. It failed to demonstrate superiority for the combination (JCO 2015, in press). Some retrospective studies have shown that pts developing hypertension (HT) whilst on antiangiogenic treatment have a better outcome. Polymorphisms in several HT-related genes might contribute to inter-individual differences in response to these treatments. The aim

of this study is to analyze the predictive value of HT for bevacizumab efficacy. Associations between polymorphisms in genes related with HT and bevacizumab efficacy were assessed. **Methods:** The LEA study randomized 380 pts in two treatment arms, ET-B (191 pts) and ET (189 pts). We collected Grade 1-4 HT in all pts and genotyped 11 polymorphisms in HT-related genes (ACE, AGTR1, AGT, VEGF, ADRB1, ADRB2, GNB3, NOS3) in germinal DNA from 117 of these pts (ET-B:67/ ET:50). **Results:** A higher rate of HT was associated with the bevacizumab combination arm (17 vs. 62% pts ET vs. ET-B arm; $p < 0.001$). Patients developing HT had a better response rate (45 vs. 27% in pts with HT vs. no HT; $p < 0.001$), as well as a longer progression-free survival (PFS) (21.9 vs. 12.0 months; HR: 0.55; 95% CI: 0.43-0.71; $p < 0.001$) and overall survival (OS) (48.6 vs. 41.6 months; HR: 0.55; 95% CI: 0.380.79; p_0.0010). The association found between HT and ET-B, and between HT and efficacy was maintained in the genotyped subpopulation. The variants in the angiotensin converted enzyme (ACE) rs1799752 (287pbIN/DEL) and in the angiotensin receptor type 1 (AGTR1) rs5186 (M235T) were associated with HT ($p < 0.05$). In the ET-B arm, we found a correlation between rs1799752 ACE IN/DEL and PFS ($p = 0.04$), and between VEGF2578 and OS ($p = 0.0045$). **Conclusions:** Hypertension is correlated with better clinical outcomes in pts treated with the ET-B combination. These results provide preliminary evidence of the predictive role of polymorphisms in HT-related genes in bevacizumab efficacy. The real significance of these polymorphisms should be further elucidated in larger prospective studies.

2530 Poster Session (Board #246)

Sat, 8:00 AM-11:30 AM

SLC1A5 TO PREDICT OUTCOME WITH CHEMOTHERAPY IN EARLY TRIPLE-NEGATIVE BREAST CANCER

First author: Anna Maria Affan

St Vincent Charity Medical Center, Cleveland, OH

Background: Triple-negative breast cancers (TNBC) are high-grade tumors that have a poor prognosis. SLC1A5 is a neutral amino acid transporter found in these tumors, and high levels correlate with aggressive biological behavior. By targeting SLC1A5 function, tumor cell growth can be inhibited and autophagy activated, which should result in improved survival benefit for patients with TNBC. We evaluated the role of SLC1A5 on tumor death rate in patients who were treated with chemotherapy for early TNBC. **Methods:** A retrospective, cohort study of patients with TNBC was performed to evaluate survival compared with the level of expression of SLC1A5. A histogram was constructed to determine a median point that could be used to define a “high” versus “low” score. Five was used as the average cut-point. Thereafter, to determine overall survival, Kaplan-Meier product-moment technique (K-M) was used, with comparisons between groups made by using the log rank test. Statistical significance was taken as $p < 0.05$. **Results:** The cohort consisted of 171 patients with TNBC. The median age was 51 years, with similar distribution between node-positive and node-negative cases. Survival information was available for 112 patients with data available on the SLC1A5 score. There was a significant association of the outcome of interest, overall survival, with the SLC1A5 score, with a worse outcome noted in tumors with higher expression ($p = 0.00189$). Furthermore, 80 patients with TNBC who received chemotherapy with higher levels of SLC1A5 showed worse survival ($p = 0.0005$). Additionally, the relationship between SLC1A5 and hypoxia-induced upregulation of carbonic anhydrase IX (CAIX), was explored using the Welch Two Sample t-test. There was a significant association with higher levels of CAIX associated with higher SLC1A5 ($p = 0.0189$). **Conclusions:** This study suggests that SLCA15 is associated with tumor hypoxia and worse outcome in chemotherapy treated patients. The results emphasize the importance of evaluating proteins involved in cell metabolism and autophagy to aid in the development of novel targets. The relationship of CAIX with SLCA15 implies that the latter may be involved in tumor hypoxia, which needs further exploration in additional cohorts and clinical trials.

2536 Poster Session (Board #252)

Sat, 8:00 AM-11:30 AM

PHASE IB STUDY OF AFATINIB PLUS STANDARD-DOSE CETUXIMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

First author: Anas Gazzah

Drug Development Department, Gustave Roussy, Villejuif, France

Background: Afatinib combined with cetuximab has shown activity in patients (pts) with *EGFR* mutation-positive non-small cell lung cancer (NSCLC) and acquired resistance to EGFR tyrosine kinase inhibitors. Targeting the ErbB pathway may also be beneficial in other tumor types; for example, squamous cancers have high levels of EGFR overexpression. This phase Ib study assessed afatinib plus standard-dose cetuximab in pts with other advanced solid tumors. **Methods:** In Part A, a 3 + 3 design was used to determine the maximum tolerated dose (MTD) of afatinib (from 30 to 40 mg daily) plus cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly). Treatment was administered until disease progression or unacceptable toxicity. Dose-limiting toxicities (DLT) in cycle 1 were used to determine MTD. In Part B, MTD was assessed in three expansion cohorts (squamous NSCLC, squamous cell carcinoma of head and neck [HNSCC], other tumors). **Results:** In Part A, three pts received afatinib 30 mg in cohort 1, and six received afatinib 40 mg in cohort 2. No DLTs were observed in either cohort; MTD was defined as afatinib 40 mg once daily plus standard-dose cetuximab. In Part B, 39 pts have been treated to date at MTD (7 squamous NSCLC, 9 HNSCC and 23 other). Patients were heavily pre-treated (median three lines of prior therapy). Among the 45 pts receiving afatinib 40 mg, the most frequent drug-related adverse events (AEs; all grades [G], n [%]) were rash/acne (37 [82%]), diarrhea (28 [62%]), stomatitis (16 [36%]), and fatigue (13 [29%]). Twelve pts had drug-related G3 AEs, most commonly rash/acne, (5 [11%]) and fatigue (2 [4%]). There were two drug-related G4 AEs (hyperlipasemia and hypersensitivity) and no drug-related G5 AEs. Preliminary efficacy results showed that 38% of pts in the expansion cohort had stable disease (SD); 4/7 (57%) in squamous NSCLC, 3/9 (33%) in HNSCC, 8/23 (35%) in other tumors; no objective responses have been reported to date. Median duration of disease control was 12 weeks. **Conclusions:** MTD was defined as afatinib 40 mg once daily plus cetuximab 250 mg/m^2 weekly (after 400 mg/m^2 loading dose). At MTD, AEs were mild-to-moderate with no unexpected AEs. Stable disease was observed in 38% of heavily pre-treated pts with, squamous NSCLC, HNSCC, and other tumor types. Updated efficacy results will be presented.

Clinical trial information: **NCT02020577**

2550 Poster Session (Board #266)

Sat, 8:00 AM-11:30 AM

SORAVE: A PHASE I TRIAL TO EVALUATE SAFETY AND EFFICACY OF COMBINATION THERAPY WITH EVEROLIMUS AND SORAFENIB

First author: Christian Mattonet

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Background: Combined inhibition of signaling pathways interfering with angiogenesis and cell proliferation may overcome mechanisms of drug resistance in tumors. We evaluated the combination of the multi-kinase inhibitor sorafenib (S) and the mTOR inhibitor everolimus (E) and assessed pharmacodynamic (PD) activity of E by PET. **Methods:** Patients with relapsed solid tumors received escalating doses of E 2.5-10.0 mg/d in a 14-day monotherapy run-in phase followed by combination therapy with a fixed dose of S 800 mg/d from day 15. Further patients were treated with the MTD in an extension phase. The primary aim was to define a safe and feasible combination treatment regimen. Dose-limiting toxicity (DLT) was defined as any drug-related toxicity of CTC IV° or requiring hospitalization or interruption of therapy for > 2 weeks within the first 29 days of treatment. Pharmacokinetic (PK) analyses were performed on days 5, 14, and 29 combined with explorative PD assessment of E by FDG-PET on days 1, 5, and 14 of treatment. Efficacy was assessed by CT (RECIST 1.1) every six weeks of combination treatment. **Results:** 31 patients (mean age 58.5 years) were enrolled and evaluable from October 2009 to December 2013, of which 16 (51.6%) had NSCLC. DLT was not observed according to protocol definition in the dose-finding phase (18 patients), however the MTD for treatment of further patients was defined at 7.5 mg/d E + 800 mg/d S due to toxicities at 10 mg E occurring after the DLT-defining interval (leucopenia/thrombocytopenia III° and pneumonia III°). The median PFS of all treated patients was 99 days (95% CI: 85.7-112.3), the median OS was 178 days (95% CI: 116.9-239.1). In 24 of 29 evaluable patients (82.8%) a decrease in SUV_{max} of the hottest lesion could be observed in PET, the best response as by PERCIST criteria was PR in 7 (21.4%) and SD in 21 (72.4%) patients. No patient reached PR in CT scan whereas 8 of 21 (38.1%) evaluable patients showed confirmed SD over at least 14 weeks. **Conclusions:** Treatment of patients with relapsed solid tumors with a combination of 7.5 mg/d E and 800 mg/d S is safe and feasible. Most tumors show a moderate metabolic decrease in PET; however, this seems to reflect more a pharmacodynamic effect than long-term disease control observed in this group of patients.

Clinical trial information: **NCT00933777**

2572 Poster Session (Board #288)

Sat, 8:00 AM-11:30 AM

IDENTIFICATION OF CANDIDATES FOR SORAFENIB DOSE-ESCALATION USING SORAFENIB PLASMATIC CONCENTRATION MONITORING: PROOF OF CONCEPT

First author: Jennifer Arrondeau

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Background: Sorafenib is approved in various advanced cancers, including hepatocellular carcinoma (HCC), differentiated iodine-resistant thyroid cancer (DTC), and renal cell carcinoma (RCC). We previously described that sorafenib plasmatic concentrations may decrease over months. We examined the inter-individual variability of sorafenib exposure at the time of disease progression to identify a subset of patients likely to benefit from dose increase. **Methods:** Patients treated with sorafenib from October 2008 to December 2014 were included in the analysis. Adverse events were prospectively collected and graded using the National Cancer Institute Common Terminology Criteria. The sorafenib plasma concentrations were prospectively determined by liquid chromatography, 30 days after treatment initiation (Cm1) and at disease progression (Cp). Variations of sorafenib concentrations were analyzed using the Wilcoxon test. **Results:** A total of 124 patients (85 males and 39 females) were studied, 68 having a sorafenib concentration measurement at the time of disease progression. The primary tumors were HCC (n = 46), melanoma (n = 32), DTC (n = 20), RCC (n = 16) or others (n = 9). In the 37 patients without change in dose between treatment initiation and disease progression, the sorafenib dose-normalized concentration decreased significantly over time: median sorafenib Cm1 was 5.54 mg/l while the median sorafenib Cp was 5 mg/l (p = 0.018). When considering all patients at disease progression, 53 patients (43%) had no limiting toxicity, and the inter-individual variation in sorafenib Cp was very large: median Cp 3.82 mg/l; range 2.08-132.9 mg/l. Among the 34 patients with sorafenib Cp < 3.82 mg/l, 22 (65%) had no limiting toxicity, allowing to increase sorafenib dose for treatment optimization, which resulted in clinical benefit in 45% of patients, the more dramatic being one complete response in a choroidal melanoma patient, and a 36.9 months disease control in a DTC patient. **Conclusions:** A subset of patients with disease progression due to sorafenib underexposure and who may respond after dose increase can be identified using sorafenib plasmatic concentration monitoring.