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1290 CLINICAL RESPONSE TO THE MAGE-A3 IMMUNOTHERAPEUTIC IN METASTATIC MELANOMA PATIENTS IS ASSOCIATED WITH A SPECIFIC GENE PROFILE PRESENT PRIOR TO TREATMENT

J. Louahed[1], B. Dréno[2], S. Gaulis[1], T. Helleputte[3], P. Dupont[3], O. Gruselle[1], A. Spatz[4], W. Kruit[5], F. Lehmann[1], V.G. Brichard[1]

[1]*Cancer Immunotherapeutics, GlaxoSmithKline Biologicals, Rixensart/BELGIUM,* [2]*Unit of Skin Cancer, University Hospital Nantes, Nantes/FRANCE,* [3]*Machine Learning Group, University of Louvain, Louvain-La-Neuve/BELGIUM,* [4]*Academic Unit of Clinical Oncology, Institut Gustav Roussy, Villejuif/FRANCE,* [5]*Medical Oncology, Erasmus University Medical Centre, Rotterdam/NETHERLANDS*

Objectives: Gene expressions profiling by microarrays are used to identify biomarkers predictive of the observed clinical activity of the MAGE-A3 Antigen-Specific Cancer Immunotherapeutic (ASCI) recorded in a Phase II study in metastatic melanoma (EORTC 16032-18031). Clinical activity to MAGE-A3 ASCI treatment in metastatic melanoma patients and a gene signature discriminating between clinical benefit and non clinical benefit patients were previously demonstrated (ASCO 2008). The predictive signature improved significantly the median time to treatment failure (2.3 months in the GS (-) and 10.3 months in the GS (+) population. Here we report on a new improved classifier to select patients with a higher likelihood of clinical response to treatment.

Methods: 75 patients with progressive, unresectable stage III or stage IV M1a MAGE-A3 (+) melanomas, were randomized as 1st line therapy between immunization with MAGE-A3 recombinant protein combined with GSK Adjuvant Systems AS15 or AS02B. Gene expression profiling was performed on tumor biopsies taken prior to any immunization.

Results: Supervised classification experiments were conducted on a subset of 62 patients. A multivariate gene selection process was embedded in the estimation of a mathematical predictive model (linear support vector machine). Using bootstrap resamplings, gene selection was repeated on 30 independent sample sets. A final gene signature of 33 probes was derived from genes appearing most frequently after the various resamplings. The vast majority of the identified genes are immune-related. The final classifier correctly predicts clinical response with 91% sensitivity, 95% specificity and 91% positive predictive value. These performances were estimated on new independent resamplings of the same data.

Conclusions: The gene signatures found in metastatic melanoma patients are strongly correlated with the response to the MAGE-A3 ASCI treatment, reflecting an immune microenvironment in the tumor present prior to any therapeutic intervention. Such signatures and associated classifier could be used to select patients with a higher likelihood of response to MAGE-A3 ASCI treatment.

1300 GENE EXPRESSION SIGNATURE IS A POTENTIAL PREDICTIVE FACTOR FOR EFFICACY OF MAGE-A3 ANTIGEN-SPECIFIC CANCER IMMUNOTHERAPEUTIC (ASCI) AS ADJUVANT THERAPY IN RESECTED STAGE IB/II NON-SMALL CELL LUNG CANCER (NSCLC)

J. Jassem[1], J. Vansteenkiste[2], M. Zielinski[3], J. Dahabreh[4], A. Linder[5], F. Lehmann[6], B. Dizier[7], P. Therasse[8], J. Louahed[6], V.G. Brichard[6]

[1]*Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND,* [2]*Respiratory Oncology Unit, University Hospital Leuven, Leuven/BELGIUM,* [3]*Chest Disease Hospital, ., Zakopane/POLAND,* [4]*Thoracic Surgery Department, Athens Medical Center, Athens/GREECE,* [5]*., LungenKlinik Hemer, Hemer/GERMANY,* [6]*Cancer Immunotherapeutics, GlaxoSmithKline Biologicals, Rixensart/BELGIUM,* [7]*Rixensart, GlaxoSmithKline Biologicals, Rixensart/BELGIUM,* [8]*Clinical, GlaxoSmithKline Biologicals, Rixensart/BELGIUM*

Objective: A phase II randomized trial in 182 NSCLC patients (pts) with completely resected stage IB or II MAGE-A3 positive tumors showed a strong positive signal for activity of postoperative MAGE-A3 recombinant protein combined with an Adjuvant System (q3w x 5, followed by q3m x 8), compared to placebo. Analysis of gene expression profiling of primary tumors was performed to identify a predictive signature that possibly correlates with clinical activity of MAGE-A3 ASCI treatment.

Methods: Microarray analysis (Affymetrix) was performed on 159 fresh-frozen tumor biopsies (MAGE-A3: 108; placebo: 51; stage IB: 109; stage II: 50). Clinical data on relapse are based on a median follow-up of 44 months.

Results: Study of tumor samples from pts in the placebo arm led to identification of a prognostic gene profile (GP) associated with a high risk of postoperative relapse. The absence of this profile correlated with a very low relapse rate in stage IB pts: placebo 0%; MAGE-A3 4%. In the MAGE-A3 treated pts with the high risk of relapse signature, we compared 10 stage IB pts with recurrence to 10 pts without recurrence. A 25-gene probe predicted benefit from MAGE-A3 treatment. The relevance of this signature was confirmed first on the remaining 139 stage IB and secondly on stage II biopsies. The hazard risk (HR) for disease-free interval in the ASCI arm was 0.57 and 0.78 in the GP+ and GP- groups, respectively, with no impact on relapse rate in the placebo arm. Immune related genes associated to the tumor microenvironment prior to treatment seem critical.

Conclusions: we identified prognostic markers associated with high risk of relapse. Stage IB pts with tumors not presenting this signature have a very low risk of relapse after surgery (<3%). We also described another gene expression signature that may predict clinical response the MAGE-A3 ASCI treatment. Selection of pts with this signature results in a 2 fold increase in clinical efficiency. This signature is also associated to clinical activity of MAGE-A3 in a Phase II study in metastatic melanoma. Data will be validated in the ongoing NSCLC adjuvant phase III study (MAGRIT).

1310 TP53 AND KRAS MUTATIONS AS MARKERS OF OUTCOME OF ADJUVANT CISPLATIN-BASED CHEMOTHERAPY IN COMPLETELY RESECTED NON-SMALL-CELL LUNG CANCER (NSCLC): THE INTERNATIONAL ADJUVANT LUNG CANCER TRIAL (IALT) BIOLOGICAL PROGRAM

X. Ma[1], A.L. Vataire[2], H. Sun[3], A. Dunant[2], E. Brambilla[4], J. Soria[5], M. Filipits[6], P. Hainaut[1]

[1]*Molecular Carcinogenesis and Biomarkers Group, International Agency for Research on Cancer, Lyon/FRANCE,* [2]*Biostatistics, Institut Gustave Roussy, Villejuif/FRANCE,* [3]*Epigenetics Group, International Agency for Research on Cancer, Lyon/FRANCE,* [4]*Pathology, CHU Grenoble, Grenoble/FRANCE,* [5]*Institute Gustave Roussy, Villejuif/FRANCE,* [6]*Department of Medicine I, Medical University Vienna, Vienna/AUSTRIA*

Background: Adjuvant cisplatin-based therapy improves survival among patients with completely resected NSCLC, but there is a lack of biological predictors of the benefit. We have analysed mutations in TP53 (exons 5 to 8) and KRAS (codons 12 and 13) in archived specimens of patients enrolled in IALT, a randomized trial of adjuvant cisplatin-based chemotherapy against observation.

Methods: Genomic DNA was extracted from 783 paraffin-embedded sections. Mutations were detected by direct sequencing and independently confirmed by a second sequencing for TP53 or by Restriction Fragment Length Polymorphism (RFLP) for KRAS. Prognostic and predictive analyses were based on Cox models adjusted for clinical and pathologic variables.

Results: TP53 mutations were found in 240 of 524 patients (46%) for whom exons 5 to 8 could be entirely sequenced. TP53 mutation status had no prognostic or predictive value for survival in all NSCLC grouped together. However, in non-adenocarcinoma patients, there was a borderline significant interaction between TP53 status and treatment effect on disease-free survival (DFS) (test for interaction TP53 and treatment, p=0.05 and p=0.25 for overall survival (OS)). The effect of chemotherapy was not different in TP53 mutated and wild type patients (p=0.18 for OS and p=0.13 for DFS), but a trend of benefit in TP53 wild type and of harm in TP53 mutated patients were observed. The prevalence of KRAS mutation was 14% (98/718). The prognostic effect of KRAS on DFS was different among the 3 histology groups, adenocarcinoma, squamous cell carcinoma and non-adenocarcinoma/ non-squamous cell carcinoma (p=0.03 for DFS and p=0.31 for OS), with the worst prognostic effect in the latter. Mutation of KRAS was not predictive of the effect of chemotherapy.

Conclusions: Patients with non-adenocarcinoma and TP53 wild type might benefit from cisplatin-based adjuvant chemotherapy, whereas chemotherapy might be harmful in patients with mutated TP53. KRAS mutation might be a biomarker of poor prognosis factor in patients with non-adenocarcinoma. Mutation detection may help in assigning patients to appropriate treatment protocol.