Anti-tumor activity of cetuximab plus avelumab in non-small cell lung cancer patients involves innate immunity activation: findings from the CAVE-Lung trial

Carminia Maria Della Corte[1], Morena Fasano[1], Vincenza Ciaramella[1], Flora Cimmino[2], Robert Cardnell[3], Carl M. Gay[3], Kavya Ramkumar[3], Lixia Diao[4], Raimondo Di Liello[1], Giuseppe Viscardi[1], Vincenzo Famiglietti[1], Davide Ciardiello[1], Giulia Martini[1], Stefania Napolitano[1], Teresa Troiani[1], Erika Martinelli[1], Jing Wang[4], Lauren Byers[3] , Floriana Morgillo[1] and Fortunato Ciardiello[1] Corresponding author: fortunato.ciardiello@unicampania.it

[1]Medical Oncology, Department of Precision Medicine, Università degli Studi della Campania "Luigi Vanvitelli", Napoli, Italy; [2]CEINGE Institute, Napoli, Italy; [3]Department of Thoracic Head and Neck Medical Oncology, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA ; [4]Department of Bioinformatics, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA

BACKGROUND AND AIM

We recently conducted Cetuximab-AVElumab-Lung (CAVE-Lung), a proof-of-concept, translational and clinical trial, to evaluate the combination of two IgG1 monoclonal antibodies (mAb): avelumab, an anti-PD-L1 drug, and cetuximab, an anti-epidermal growth factor receptor (EGFR) drug, as second- or third-line treatment in non-small cell lung cancer (NSCLC) patients. We have reported clinically relevant anti-tumor activity in 6/16 patients. Clinical benefit was accompanied by Natural Killer (NK) cell-mediated antibody-dependent cell cytotoxicity (ADCC). Among the 6 responding patients, 3 had progressed after initial response to a previous treatment with single agent anti-PD-1, nivolumab or pembrolizumab.

METHODS

We report long-term clinical follow-up and additional findings on the anti-tumor activity and on the immune effects of cetuximab plus avelumab treatment for these 3 patients. .

CONCLUSIONS

DDR mutations may contribute to DDR-induced STING pathway with sustained innate immunity activation following cetuximab plus avelumab combination in previously treated, PD-1 inhibitor responsive NSCLC patients.

RESULTS

As of November 30, 2021, 2/3 patients were alive. One patient was still on treatment from 34 months, while the other two patients had progression free survival (PFS) of 15 and 19 months, respectively. Analysis of serially collected peripheral blood mononuclear cells (PBMC) revealed long-term activation of NK cell-mediated ADCC (Fig.1). Comprehensive genomic profile analysis found somatic mutations and germline rare variants in DNA damage response (DDR) genes. Furthermore, by transcriptomic analysis of The Cancer Genome Atlas (TCGA) dataset we found that DDR mutant NSCLC displayed high STING pathway gene expression. In NSCLC patient-derived three-dimensional in vitro spheroid cultures, cetuximab plus avelumab treatment induced additive cancer cell growth inhibition as compared to single agent treatment. This effect was partially blocked by treatment with an anti-CD16 mAb, suggesting a direct involvement of NK cell activation. Furthermore, cetuximab plus avelumab treatment induced 10-, 20-, and 20-fold increase, respectively, in the gene expression of CCL5 and CXCL10, two STING downstream effector cytokines, and of interferon b, as compared to untreated control samples (Fig.2).

Figure 1 Biomarkers from CAVE-Lung trial

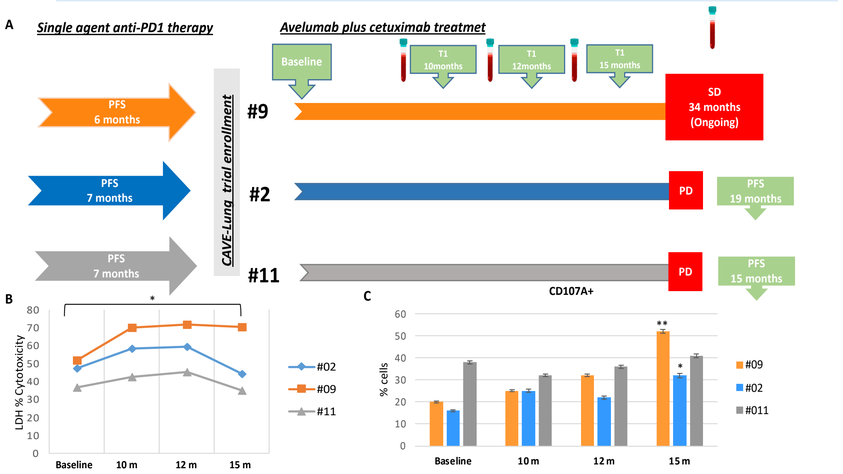
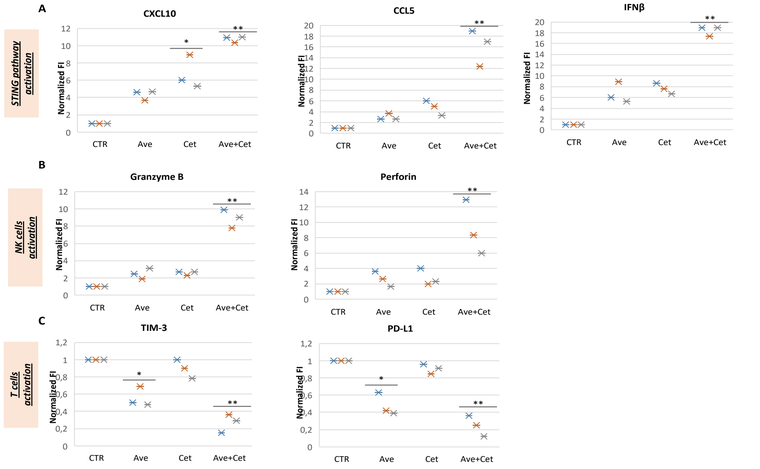


Figure 2 NSCLC patients' derived 3D cultures



Competing interests. CMDC, advisory board MSD; MF, family relationship Merck, advisory board for MSD and Merck Serono; CMG, Advisory Board - Jazz Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Speaker's Bureau - AstraZeneca, BeiGene; RDL, Advisory Board Astellas; EM, advisor and speaker for Astra Zeneca, Amgen, Bayer, Merck-Serono, Roche, Sanofi, Servier, Pierre Fabre; TT, advisor and speaker for Roche, Merck-Serono, Sanofi, Servier, Novartis, Bayer; L.A.B., advisory committees for AstraZeneca, AbbVie, GenMab, BergenBio, Pharma Mar SA, Sierra Oncology, Merck, Bristol-Myers Squibb, Genentech, and Pfizer and has research support from AbbVie, AstraZeneca, GenMab, Sierra Oncology, Tolero Pharmaceuticals; FM: advisory boards: MSD, Lilly; institutional research grants: AstraZeneca; FC, advisor and speaker for Roche, Amgen, Merck-Serono, Pfizer, Sanofi, Bayer, Servier, BMS, Cellgene, Lilly, institutional Research Grants form Bayer, Roche, Merck-Serono, Amgen, AstraZeneca, Takeda. Other authors have no conflicts of interest to declare.