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Family history of cancer correlates with improved outcome from immunotherapy in NSCLC independent of somatic DNA damage response gene status

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Background

Among the few known underlying mechanisms of inherited cancer susceptibility, germline DNA damage response and repair (DDR) genes mutations are the most frequently involved. Acknowledging the immune sensitive phenotype of cancer related to DDR genes defects, we previously showed that high burden of family history of cancer (FHC), namely FHC-high, was independently associated with prolonged overall survival (OS) and progression free survival (PFS) to programmed death-1/programmed death ligand-1 (PD-1/PD-L1) checkpoint inhibitors.

Patients and Methods

We present the outcomes analysis according to FHC from two large multicenter cohorts of patients with metastatic non-small cell lung cancer (NSCLC) receiving either first-line pembrolizumab (PD-L1 expression ≥ 50%) or first-line chemotherapy. Patients were categorized FHC-high (in case of at least one cancer diagnosis in both straight and collateral family lines) and FHC-low/negative. The role of FHC was validated through a random case-control matching. To explore the association between somatic DDR genes alteration and FHC, we gathered relevant baseline clinic-pathologic information and targeted DNA tumour sequencing (FoundationOne CDx assay), from a parallel cohort of patients with NSCLC treated with various regimens at 4 of the participating institutions. The panel of 53 DDR genes defined by Ricciuti et al. was used as reference, identifying 24 genes of interest (MLH1, MSH6, PMS2, ATM, ATR, CHEK1, CHEK2, BAP1, BARD1, BRCA1, BRCA2, BRIP1, PALB2, RAD51, RAD51C, RAD52, FANCA, FANCC, FANCG, FANCL, POLD1, POLE, ERCC4, XRCC2).

Statements

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Results

728 and 652 patients were included in the pembrolizumab and chemotherapy cohort, respectively. We performed a perfect random case-control matching between the two cohorts and 607 patients from each cohort were randomly paired on the basis of the FHC, age (< 70 vs. ≥ 70 years old), ECOG-PS (0-1 vs ≥ 2), and burden of disease (≥ 2 vs < two metastatic sites). As compared to FHC-low/negative patients, FHC high were confirmed to have a significantly longer OS (HR=0.67 [95%CI: 0.46-0.95], p = 0.0281; Figure 1A), a significantly longer PFS (HR=0.65 [95%CI: 0.48-0.89]; p = 0.0074; Figure 1B) and a higher disease control rate (DCR) (86.4 vs 67.5, p = 0.0096; Figure 1C), within the pembrolizumab cohort. On the contrary, no significant associations were found between FHC and OS (HR = 0.75 [95%CI: 0.54 – 1.04], p = 0.0866; Figure 1D), PFS (HR = 1.06 [95%CI: 0.77 – 1.46], p = 0.7039; Figure 1E), and DCR (69.7% vs 63.1%, p = 0.4475; Figure 1F), within the chemotherapy cohort. FHC was not associated with objective response rate (ORR) in either of the matched cohorts.

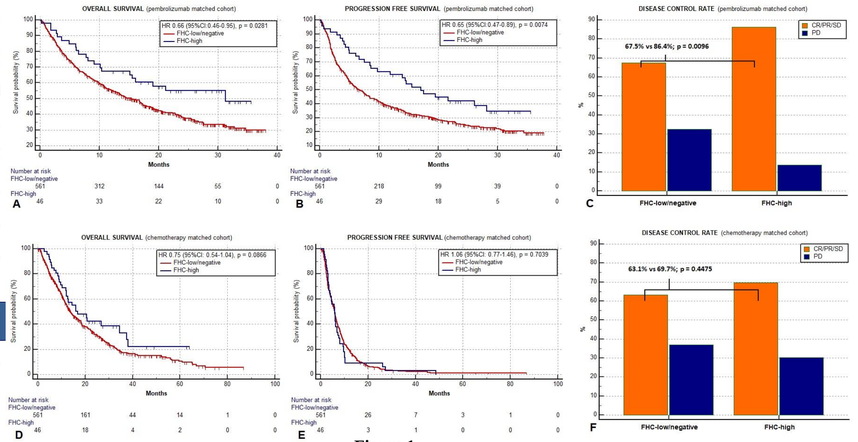
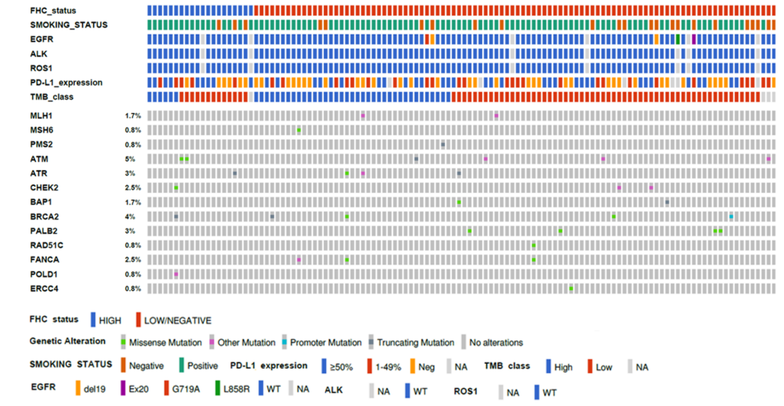


Figure 1

Results

Overall, 118 patients were included in the parallel DDR genes cohort, of which 20 FHC-high (16.9%) and 98 FHC-low/negative (83.1%). Relevant baseline clinic-pathologic characteristics and the DDR genes profile data are summarized in the OncoPrint provided (Figure 2). The prevalence of at least one DDR genes somatic mutations was 20% (4/20) and 24.5% (24/74) for FHC-low/negative and FHC-high patients, respectively (p = 0.6684). The median TMB for FHC-high was 6 Mut/Mb (range: 1 – 18), whilst for the FHC-low/negative was 7.6 Mut/Mb (range: 0 – 42.8) (p = 0.6018) and no association between FHC and PD-L1 tumour expression was reported.

Figure 2



Conclusions

FHC-high status identifies NSCLC patients with improved outcomes to pembrolizumab but not chemotherapy, suggesting its role as a surrogate marker for immunotherapy. Somatic DDR genes alterations are not associated with FHC and further prospective investigations with broader germline testing are warranted.

Reference 1.Cortellini A, Buti S, Bersanelli M, et al. Oncoimmunology. 2020 Jan 7;9(1):1710389. doi: 10.1080/2162402X.2019.1710389. 2.Ricciuti B, Recondo G, Spurr LF, et al. Clin Cancer Res. 2020 Aug 1;26(15):4135-4142. doi: 10.1158/1078-0432.CCR-19-3529. Epub 2020 Apr 24.