Lung Cancer 124 (2018) 117–124

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Rare targetable drivers (RTDs) in non-small cell lung cancer (NSCLC): Outcomes with immune check-point inhibitors (ICPi)

Elizabeth Dudnik[a,*,1], Elias Bshara[b,1], Ahuva Grubstein[c], Ludmila Fridel[d], Tzippy Shochat[e], Laila C. Roisman[f], Maya Ilouze[a], Anna Belilovski Rozenblum[b], Smadar Geva[b], Alona Zer[a], Ofer Rotem[a], Aaron M. Allen[a,b], Nir Peled[f,g]

[a] Thoracic Cancer Service, Davidoff Cancer Center, Rabin Medical Center, Beilinson Campus, Petah Tikva 49100, Israel
[b] Sackler Faculty of Medicine, Tel Aviv University, POB 39040 Ramat Aviv, Tel Aviv 69978, Israel
[c] Department of Diagnostic Radiology, Rabin Medical Center, Beilinson Campus, Petah Tikva 49100, Israel
[d] Department of Pathology, Rabin Medical Center, Beilinson Campus, Petah Tikva 49100, Israel
[e] Statistical Consulting Unit, Rabin Medical Center, Beilinson Campus, Petah Tikva 49100, Israel
[f] Cancer Institute, Soroka University Medical Center, Beer-Sheva 84101, Israel
[g] Ben Gurion University of Negev, POB 653 Beer-Sheva 8410501, Israel

ARTICLE INFO

Keywords:
Mutation
Lung cancer
PD-1
PD-L1
Tumor mutational burden
Immunotherapy

ABSTRACT

Objectives: Efficacy of immune check-point inhibitors (ICPi) in NSCLC with rare targetable drivers (RTDs) is largely unknown.

Materials and Methods: Consecutive patients with NSCLC and RTDs (non-*EGFR/ALK*, n-82) were selected from the Davidoff Cancer Center database. ORR, PFS, OS with ICPi, OS since advanced disease diagnosis, TMB, MSI, and PD-L1 expression were analyzed; uni- and multivariate PFS and OS analyses were done. OS with ICPi was compared between the RTD cohort and the non-selected NSCLC cohort (n-278).

Results: Of 50 tumors tested, 32%, 38%, and 30% were associated with ≥50%, 1–49% and < 1% PD-L1 expression, respectively. Median TMB (n-48) comprised 4 muts/Mb (0–57); TMB ≥ 10 muts/Mb was seen in 19% of tumors. Both TMB and PD-L1 expression varied across different RTDs. All the 47 tumors were MSI stable. ORR with ICPi (n-44) was 16%, median PFS was 3.2 months (95% CI, 2.6–5.0), median OS was 16.2 months (95% CI, 8.4-NR). No correlation was seen between OS with ICPi and PD-L1 expression ($p > 0.4$), TMB ($p > 0.8$), or RTD type ($p > 0.3$). In the multivariate analysis, ECOG PS (p-0.005), targeted agents exposure (p-0.005), and ICPi exposure (p-0.04) were the only variables which correlated with OS since advanced disease diagnosis. Median OS since advanced disease diagnosis comprised 32 months (95% CI, 19.9–44.9) and 13 months (95% CI, 6.6–15.9) for patients who were and were not exposed to ICPi, respectively (log-rank test-6.3; p-0.01). In the inter-cohort comparison, for patients matched for ECOG PS (0/1), median OS with ICPi comprised 17.5 months (95% CI, 8.1-NR) and 8.6 months (95% CI, 6.7-NR) for RTD and non-selected patients, respectively (log-rank test-2.4, p-0.1).

Conclusion: In NSCLC with RTD, ICPi have favorable efficacy and independent impact on OS. NSCLC with RTD is associated with MSI stable status and variable levels of PD-L1 expression and TMB; their predictive value remains to be determined.

Abbreviations: ALK, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; *cMET*, tyrosine-protein kinase Met/hepatocyte growth factor receptor; CT, computer tomography; ECOG, PS Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; *ERBB2/3*, erythroblastic leukemia viral oncogene homolog 2/3; ICPi, immune check-point inhibitors; IHC, immunohistochemistry; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSI-I, - microsatellite instability-intermediate; MS-S, microsatellite instability-stable; Muts, mutations; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine kinase receptor; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PET-CT, positron emission tomography-computer tomography; PFS, progression-free survival; *RET*, "rearranged during transfection" proto-oncogene; *ROS1*, c-Ros oncogene 1; RTD, rare targetable drivers; TMB, tumor mutational burden; TPS, tumor proportion score

* Corresponding author at: Thoracic Cancer Service, Davidoff Cancer Center, Rabin Medical Center, Kaplan St., Petah Tikva 49100, Israel.
E-mail address: elizabetadu@clalit.org.il (E. Dudnik).

[1] Authors with equal contribution.

https://doi.org/10.1016/j.lungcan.2018.07.044
Received 19 May 2018; Received in revised form 26 July 2018; Accepted 31 July 2018

1. Introduction

Incorporation of immune check-point inhibitors (ICPi) into the management of non-small cell lung cancer (NSCLC) represents a milestone in the advancement of NSCLC treatment. Anti-PD-1 (programmed cell death-1)/anti-PD-L1 (programmed cell death ligand-1) ICPi efficacy in NSCLC has been proven in several large randomized controlled trials across different stages and settings [1–6].

The role of ICPi in NSCLC harboring a driver mutation, however, is controversial. For instance, epidermal growth factor receptor (*EGFR)*-driven NSCLC patients do not derive a significant benefit from treatment with ICPi [7,8]. Objective response rate (ORR) and median progression-free survival (PFS) with ICPi in tumors with *EGFR* mutations and anaplastic lymphoma kinase (*ALK)*-rearrangements stay in the range of 3.6–12.2%, and 1.9 months, respectively [9].

The data regarding ICPi efficacy in other oncogene-driven NSCLC (e.g., aberrations in c-Ros oncogene 1 (*ROS1)*, v-Raf murine sarcoma viral oncogene homolog B *(BRAF)*, tyrosine-protein kinase Met (*cMET)*, erythroblastic leukemia viral oncogene homolog 2/3 (*ERBB2/3)*, "rearranged during transfection" proto-oncogene *(RET)*, and neurotrophic tyrosine kinase receptor *(NTRK)* genes) is limited. Because of low prevalence of these molecular subtypes (in the range of 1–4%) [10–17], this question cannot be addressed in a prospective manner, which makes the cancer registries the only existing data source in these NSCLC subtypes. NSCLC harboring rare targetable drivers (RTD) are generally associated with never-smoking status and low tumor mutational burden (TMB) [18–20], and therefore, tend to be seen as “immunotherapy-resistant” despite the paucity of data. Indeed, as reported by Sabari et al., patients with *cMET* exon 14 altered NSCLC treated with ICPi only have an ORR of 6.7% and a median PFS of 2.3 months [19]. On the other hand and according to our data, ICPi in *BRAF*-driven NSCLC are associated with an ORR of 25%–33% and a median PFS in the range of 3.7–4.1 months [21], which is comparable to the results observed in the 2nd-line setting in the unselected population of NSCLC patients (ORR of 15–20% and median PFS of 2.3–4 months) [1–3]. Ross et al. [20] also reported favorable ICPi outcomes in cMET and BRAF-driven NSCLC.

PD-L1 expression in the tumor cells represents a well-established predictive biomarker which is widely used in conjunction with anti-PD-1 therapy in advanced NSCLC [2,4,5]. TMB has recently emerged and been validated as an important predictive biomarker as well [8,18,22–24]. The predictive value of microsatellite instability (MSI) across wide range of histological tumor subtypes has been proven recently [25]. The data regarding the PD-L1 expression, TMB and MSI status in NSCLC with RTD is scarce [8,18,20]. Therefore, further research exploring the efficacy of ICPi in NSCLC with RTD in correlation with different predictive parameters is warranted.

Here, we report clinical outcomes with anti-PD-1/anti-PD-L1 ICPi and prevalence of PD-L1 expression, TMB and MSI in a cohort of advanced NSCLC patients with RTDs.

2. Materials and methods

2.1. Patients selection

Patients with histologically confirmed NSCLC harboring a RTD were identified through an internal database of Davidoff Cancer Center (tumors with aberrations in *BRAF*, *ERBB2*, *ERBB3*, *cMET*, *RET*, *ROS1*, and *NTRK* genes were included; tumors with alterations in *EGFR* or *ALK* genes were excluded from the analysis).

2.2. Study design and treatment

Baseline demographic, clinical and pathologic characteristics including PD-L1 tumor expression were collected. Additionally, PD-L1 tumor staining was performed in several cases in which it has not been done before and the archival specimen was available for testing. In those cases where FoundationOne™ (Cambridge, MA, USA) testing was done, information regarding the TMB and MSI status was collected based on the formal report. The correlation between the RTD type and TMB, MSI, and PD-L1 expression was analyzed. ORR, PFS, and overall survival (OS) with ICPi were assessed and analyzed in correlation with the RTD type. Additionally, OS since the date of advanced disease diagnosis was assessed and analyzed in correlation with the RTD type. Uni- and multivariate PFS and OS analysis were performed. Finally, another cohort of advanced NSCLC patients unselected for the presence of any molecular aberration and treated with ICPi at five Israeli cancer centers in 2015–2016 was chosen as a comparator; baseline patient characteristics were compared between the two cohorts. OS with ICPi was assessed and compared between the two cohorts; comparison after matching for ECOG PS was done.

2.3. Biomarker and treatment efficacy assessment

PD-L1 by immunohistochemistry (IHC) assessment was done by the pathology specialist using 22C3 PharmDx antibody on either Dako 22C3 PD-L1 IHC platform (Dako, Carpinteria, CA) or Ventana’s BenchMark XT platform (Ventana Medical Systems, Tucson, AZ). The validation of PD-L1 IHC analysis based on the 22C3 PharmDx antibody and Ventana’s BenchMark XT has been published and therefore has been largely adopted in Israel [26]. PD-L1 tumor proportion score (TPS), which is the percentage of tumor cells showing partial or complete membrane staining, was determined and classified as negative, intermediate, or high (TPS of $< 1\%$, 1%–49%, and $> = 50\%$, respectively).

TMB was calculated according to the FoundationOne™ algorithm as previously described in detail [27]. Briefly, TMB was defined as the number of somatic, coding, base substitutions, insertions and deletion mutations per megabase (Mb) of genome examined. Synonymous and non-synonymous alterations were counted; non-coding and germline alterations were not counted; alterations listed in COSMIC as known somatic alterations and truncations in tumor suppressor genes were not counted. To calculate the TMB per Mb, the total number of mutations counted was divided by the size of the coding region of the targeted territory ($\sim$1.1 Mb). TMB results were determined as follows: TMB-High corresponded to greater than or equal to 20 mutations per Mb (muts/Mb); TMB-Intermediate corresponded to 6–19 muts/Mb; TMB-Low corresponded to fewer than or equal to 5 muts/Mb. Following the publication of CheckMate 227 study establishing a new TMB cut-off of greater than or equal to 10 muts/Mb [23], it was added to the report.

MSI was calculated according to the FoundationOne™ algorithm as previously described [27]. To determine MSI status, 114 intronic homopolymer repeat loci with adequate coverage on the comprehensive genomic profiling panel were analyzed for length variability, and compiled into an overall MSI score via principal components analysis. MSI was reported as “MSI-High (MSI-H)”, “MSI-Intermediate (MSI-I)”, and “MS-Stable (MS-S)”.

For patients who had adequate computer tomography (CT)/ positron emission tomography-computer tomography (PET-CT) scans for radiological assessment, the images were reviewed by the radiology specialist; ORR and PFS with ICPi were assessed using RECIST 1.1 [28]. PFS was calculated from the day of ICPi initiation until disease progression, death or start of another systemic treatment; the outcome was censored if a patient was alive without known progression of disease at the time of last follow-up. OS with ICPi was calculated from the day of treatment initiation until death; the outcome was censored if a patient was alive at the time of last follow-up. Additionally, OS calculated from the date of advanced disease diagnosis was assessed.

2.4. Statistical analysis

The sample size was determined by the available patients meeting the inclusion criteria. Categorical variables were presented by numbers