Impact of co-alterations on first-line treatment in PD-L1 high KRAS G12C mutated lung adenocarcinoma in Real World Data within the Precision-Oncology-Program

Abstract category: Clinical solid tumor oncology

L. Boos[1], C. Doerig[2], G. Gut[1, 3], N. Miglino[1], L. Fabregas-Ibanez[4], M. Zoche[4], C. Früchtenicht[2], S. Rizzo[5], C. Berardo[2], M. Bodmer[2], D. Glinz[2], L. Hempel[1], P. Rahimzadeh[3], B. Gosztonyi[3], U. Richter[1], L. Bankel[1], A. Wicki[1, 3]

[1]Medical Oncology, University Hospital Zurich, Zurich, CH; [2] Hoffmann-La Roche Ltd., Basel, CH; [3] Faculty of Medicine, University of Zurich, Zurich, CH; [4] Pathology - Molecular Tumor Profiling, University Hospital Zurich, CH; [5] Genentech, South San Francisco, CA, USA.

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INTRODUCTION

Advanced PD-L1 high KRAS G12C mutated lung adenocarcinoma (LUAD) are currently treated with chemo-immunotherapy (C-ICI) or immunotherapy (ICI) in the first treatment line (1L), without genomic biomarkers to support treatment choice. Co-occurring alterations in STK11 and KEAP1 are known to affect treatment response in LUAD (Ricciuti et al., 2022); CDKN2A/B alterations were reported to impact the effectiveness of ICI in solid tumors (Adib et al., 2021), (Balli et al., 2017), (Liu et al., 2022). Here, we present insights from the Precision Oncology Program (POP) on the impact of STK11, KEAP1 and CDKN2A/B on the mean duration of treatment (DOT) of 1L C-ICI or ICI in PD-L1 high LUAD depending on KRAS G12C status based on patient-matched Real World Data (RWD) obtained from a large-scale clinicogenomic database.

METHODS

This study matched individual patients treated at the University Hospital Zurich (USZ) to the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine advanced NSCLC CGDB (FH-FMI CGDB) based on disease characteristics patients (stage, oncogenic mutations, PD-L1). The de-identified FH-FMI data originated from approximately 280 US cancer clinics (~800 sites of care). Using the POP framework to extract a FH-FMI RWD matched cohort, we assessed DOT in 1L for LUAD with PD-L1 ≥ 50% and with or without KRAS G12C. This assessment included a comparison of cases with and without co-alterations in STK11, KEAP1, or CDKN2A/B, using a t-test for analysis. (Table 1.)

RESULTS

In FH-FMI CGDB, we found 468 KRAS G12C mutant (m) LUAD, 183 of which were PD-L1 high. In KRAS G12C wildtype (wt) and KRAS G12C m LUAD without co-alterations DOT on ICI and C-ICI is comparable. In KRAS G12C wt LUAD, CDKN2A/B and KEAP1 alterations are associated with a significantly shorter DOT on ICI while in KRAS G12C m LUAD co-alterations in CDKN2A/B, STK11 and KEAP1 were associated with a shorter DOT on C-ICI.

PD-L1 ≥ 50%	C-ICI DOT	ICI DOT	p-value	n C-ICI	n ICI
No oncogenic driver*	13.5	14.7	0.5	116	208
. CDKN2A/B	20.1	8.8	0.02	28	42
. STK11	10.4	8.9	0.62	28	32
. KEAP1	15.3	6.7	0.04	21	44
KRAS G12C	15.5	17.2	0.57	55	81
. CDKN2A/B	9.5	16.8	0.24	9	18
. STK11	4.7	11.1	0.13	9	6
. KEAP1	3.1	6.6	0.35	5	8

Table 1. DOT of C-ICI, ICI in stage IV CGDB LUAD with PD-L1 ≥ 50% depending on co-alterations. C-ICI, carboplatin, pemetrexed, pembrolizumab. ICI, pembrolizumab.
*No oncogenic driver was defined as lack of the following molecular alterations: EGFR exon 19 deletion, EGFR L858R, EGFR T790M, EGFR exon 20 insertion, ALK fusion, ROS1 fusion, RET rearrangement, MET exon 14 skipping, MET amplification, KRAS G12C, BRAF V600E, HER2 alteration.

CONCLUSION

In this large PD-L1 high LUAD RWD cohort, we identified CDKN2A/B and KEAP1 status with or without KRAS G12C as biomarkers associated with altered DOT in 1L ICI or C-ICI. These molecular insights suggest a need for escalation / de-escalation of the treatment choice for PD-L1 high LUAD based on the molecular tumor profile.

REFERENCES

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