PROSPECTIVE GERMAN REGISTRY CRISP, AIO-TRK-0315

# RELIABLE SEGREGATION OF SURVIVAL UNDER IMMUNOTHERAPY IN NSCLC USING SIMPLE CLINICAL PARAMETERS


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none


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## BACKGROUND

Immune checkpoint inhibitors (CPI) have significantly improved the survival of patients with metastatic non-small-cell lung cancer (NSCLC), but reliable prognosticators are lacking. The PD-L1 expression on tumor cells (PD-L1 tumor proportion score [TPS]) is the only approved biomarker so far, however correlation with patient outcomes is weak. Objectives of this study were: i) to characterize patients with advanced NSCLC and longer responses to first line PD-(L)1 inhibitors as monotherapy (IO) or combined with platinum-based chemotherapy (CHTIO), and ii) to explore whether a composite clinicopathologic score could be used for stratification at initial diagnosis. He hypothesized that the large number of patients captured in CRISP combined with the comprehensive, deep clinical annotation of this registry could provide the prognostic information necessary for this task.

## CONCLUSION

**Several clinical, laboratory and pathologic characteristics correlate with PFS and OS and can be used in combination to improve segregation of PFS and OS for patients with NSCLC receiving immunotherapy. Reliable predictive tools could support individualized decisions about the addition of chemotherapy in the treatment of PD-L1 positive tumors. Prospective studies will be necessary to validate these results and define thresholds for clinical use.**

## METHODS

Patients with advanced NSCLC from the CRISP registry receiving first-line IO (n=507) or CHTIO (n=1000) were analyzed with a data cut-off in 06/2022. Inclusion criteria for the IO cohort were: (1) stage IIIB/C-IV NSCLC who received first-line CPI mono treatment before 30.06.2022 (FAS), (2) no ALK/EGFR alteration, (3) up-to-date documentation, (4) completed first-line treatment or experienced progression/death in the first-line treatment, (5) PD-L1 TPS ≥ 50 %. Inclusion criteria for the CHTIO cohort were: (1) stage IIIB/C-IV NSCLC who received first-line CPI+chemotherapy treatment before 30.06.2022 (FAS), (2) no ALK/EGFR alteration, (3) up-to-date documentation, (4) completed first-line treatment or experienced progression/death in the first-line treatment. Potential predictors were identified by Cox regression and combined to build prognostic models of progression-free (PFS) and overall survival (OS) in predefined derivation (80 %) and validation (20 %) datasets using a Bayesian information criterion-based strategy that penalizes model complexity and will select smaller models that may prevent overfitting. Covariates were selected using the derivation dataset and augmented backward elimination with a relative change-in-estimate threshold of $\tau$=0.05 to achieve less biased regression coefficients than backward elimination.

## RESULTS

**Association of baseline characteristics with PFS for the IO cohort**
The following characteristics were significantly associated with higher risk for progression/death: ECOG ≥ 2 (HR (95 % CI) = 2.13 (1.48, 3.06)) as well as unknown ECOG (HR (95 % CI) = 1.53 (1.05, 2.23)) compared to ECOG of 0, LDH > ULN (HR (95 % CI) = 1.49 (1.17, 1.91)) compared to LDH ≤ ULN or missing, bone metastasis (compared to no/missing, HR (95 % CI) = 1.53 (1.19, 1.96)), intrathoracal metastasis (compared to no/unknown/missing, HR (95 % CI) = 1.40 (1.10, 1.79)).

**Association of baseline characteristics with PFS for the CHTIO cohort**
The following characteristics are significantly associated with higher risk for progression/death: male (compared to female, HR (95 % CI) = 1.27 (1.09, 1.49)), PD-L1 tumour proportion score ≥1 % and <50 % (HR (95 % CI) = 1.54 (1.19, 1.97)), <1 % (HR (95 % CI) = 1.60 (1.19, 2.14)) and not tested (HR (95 % CI) = 1.53 (1.19, 1.97)) compared to PD-L1 tumour proportion score ≥50 %, ECOG performance status of 1 (HR (95 % CI) = 1.34 (1.12, 1.61)), ≥ 2 (HR (95 % CI) = 2.25 (1.74, 2.93)) and unknown performance status (HR (95 % CI) = 1.48 (1.15, 1.92)) compared to performance status of 0, LDH > ULN (compared to no/missing, HR (95 % CI) = 1.26 (1.07, 1.48)), ASAT/CA/CRP/HGB outside normal range (compared to no, HR (95 % CI) = 1.30 (1.11, 1.52)), brain metastasis (compared to no/missing, HR (95 % CI) = 1.47 (1.23, 1.76)), liver metastasis (compared to no/missing, HR (95 % CI) = 1.60 (1.31, 1.96)).

**OS stratified by risk group in the IO cohort**
The following characteristics are significantly associated with higher risk for progression/death: age (HR (95 % CI) = 1.02 (1.01, 1.04)), ECOG performance score at inclusion of 1 (HR (95 % CI) = 1.44 (1.04, 1.99)), ≥ 2 (HR (95 % CI) = 2.57 (1.70, 3.89)) and unknown score (HR (95 % CI) = 1.78 (1.16, 2.72)) compared to performance score of 0, ASAT/CA/CRP/HGB outside normal range (compared to no, HR (95 % CI) = 1.48 (1.13, 1.94)), affected lymph nodes at inclusion N3 (HR (95 % CI) = 1.81 (1.16, 2.81)) compared to no affected lymph nodes at inclusion, bone metastasis (compared to no/missing, HR (95 % CI) = 1.64 (1.25, 2.15)), intrathoracal metastasis (HR (95 % CI) = 1.46 (1.13, 1.89)) compared to no/unknown/missing.

**OS stratified by risk group in the CHTIO cohort**
The following characteristics are significantly associated with higher risk for death: male (compared to female, HR (95 % CI) = 1.25 (1.05, 1.48)), PD-L1 tumour proportion score <1 % (HR (95 % CI) = 1.64 (1.21, 2.24)) and not tested (HR (95 % CI) = 1.37 (1.05, 1.79)) compared to PD-L1 tumour proportion score ≥50 %, Co-mutation of KRAS and P53 (compared to no, HR (95 % CI) = 1.94 (1.20, 3.14)), ECOG performance at inclusion ≥2 (HR (95 % CI) = 2.16 (1.64, 2.84)) compared to ECOG 0, LDH > ULN (compared to no, HR (95 % CI) = 1.25 (1.05, 1.49)), ASAT/CA/CRP/HGB outside normal range (compared to no, HR (95 % CI) = 1.36 (1.14, 1.61)), brain metastasis (compared to no/missing, HR (95 % CI) = 1.45 (1.19, 1.76)), liver metastasis (compared to no/missing, HR (95 % CI) = 1.57 (1.26, 1.95)). When all other covariates are being held constant, alteration for KRAS (HR (95 % CI) = 0.75 (0.59, 0.95)) is significantly associated with lower risk for death compared to no alteration for KRAS.

**Table 1: Association of baseline characteristics with PFS for the IO cohort**

| Variable | HR (95 % CI) |
|---|---|
| **Sex (ref = Female)** | |
| Male | 1.06 (0.84, 1.34) |
| **Biomarker alteration for KRAS (ref = No)** | |
| Yes | 0.77 (0.54, 1.11) |
| **Co-mutation of KRAS and P53 (ref = No)** | |
| Yes | 0.86 (0.51, 1.45) |
| **ECOG performance score at inclusion (ref = 0)** | |
| 1 | 1.28 (0.96, 1.71) |
| ≥2 | 2.13 (1.48, 3.06) |
| Unknown to site | 1.53 (1.05, 2.23) |
| **Smoking status (ref = Never Smoker)** | |
| Ex-Smoker (light) | 1.16 (0.70, 1.92) |
| Ex-Smoker (intensity unknown) | 0.88 (0.51, 1.51) |
| Ex-Smoker (heavy) | 0.77 (0.50, 1.20) |
| Current Smoker | 0.78 (0.49, 1.22) |
| Unknown to site | 1.18 (0.66, 2.13) |
| **LDH > ULN (ref = No/missing)** | |
| Yes | 1.49 (1.17, 1.91) |
| Unknown to site | 1.24 (0.87, 1.76) |
| **Brain metastasis (ref = No/missing)** | |
| Yes | 1.31 (0.99, 1.72) |
| **Liver metastasis (ref = No/missing)** | |
| Yes | 1.03 (0.74, 1.45) |
| **Bone metastasis (ref = No/missing)** | |
| Yes | 1.53 (1.19, 1.96) |
| **Intrathoracal metastasis (ref = No/unknown/missing)** | |
| Yes | 1.40 (1.10, 1.79) |

HR: Hazard ratio, CI: Confidence interval, ref: Reference level

**Table 2: AAssociation of baseline characteristics with PFS for the CHTIO cohort**

| Variable | HR (95 % CI) |
|---|---|
| **Sex (ref = Female)** | |
| Male | 1.27 (1.09, 1.49) |
| **PD-L1 tumor proportion score (ref = TPS ≥50%)** | |
| TPS ≥1 % and <50 % | 1.54 (1.19, 1.97) |
| TPS <1 % | 1.60 (1.19, 2.14) |
| Not tested | 1.53 (1.19, 1.97) |
| **Co-mutation of KRAS and P53 (ref = No)** | |
| Yes | 0.97 (0.69, 1.35) |
| **ECOG performance status at inclusion (ref = 0)** | |
| 1 | 1.34 (1.12, 1.61) |
| ≥2 | 2.25 (1.74, 2.93) |
| Unknown to site | 1.48 (1.15, 1.92) |
| **Smoking status (ref = Never Smoker)** | |
| Ex-Smoker (light) | 0.94 (0.63, 1.38) |
| Ex-Smoker (intensity unknown) | 0.93 (0.63, 1.36) |
| Ex-Smoker (heavy) | 0.82 (0.60, 1.11) |
| Current Smoker | 0.76 (0.56, 1.03) |
| Unknown to site | 0.71 (0.49, 1.04) |
| **LDH > ULN (ref = No/missing)** | |
| Yes | 1.26 (1.07, 1.48) |
| Unknown to site | 1.02 (0.81, 1.29) |
| **ASAT/CA/CRP/HGB outside normal range (ref = No)** | |
| Yes | 1.30 (1.11, 1.52) |
| **Brain metastasis (ref = No/missing)** | |
| Yes | 1.47 (1.23, 1.76) |
| **Liver metastasis (ref = No/missing)** | |
| Yes | 1.60 (1.31, 1.96) |

HR: Hazard ratio, CI: Confidence interval, ref: Reference level

**Fig. 1A + B: PFS stratified by risk group in the IO cohort**

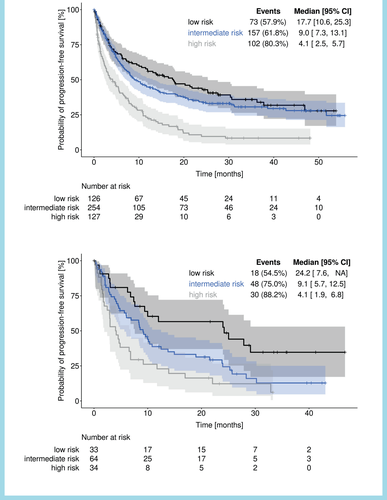


**Fig. 3A + B: OS stratified by risk group in the IO cohort**

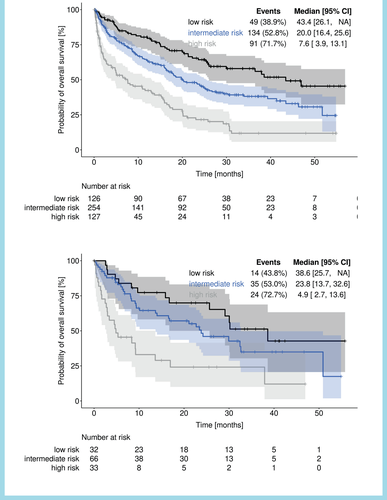


**Fig. 2A + B: PFS stratified by risk group in the CHTIO cohort**

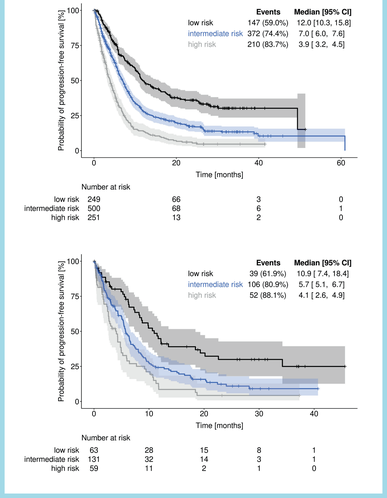


**Fig. 4A + B: OS stratified by risk group in the CHTIO cohort**