REAL-WORLD DATA ANALYSED WITH PROPENSITY SCORES TECHNIQUE FROM THE GERMAN PROSPECTIVE MULTICENTRE REGISTRY STUDY (CRISP AIO-TRK-0315)

COMBINED CHEMO-IMMUNOTHERAPY VERSUS MONOIMMUNOTHERAPY IN ADVANCED HIGH PD-L1 POSITIVE NSCLC

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BACKGROUND

Checkpoint-Inhibitors alone (IO) or in combination with chemotherapy (C-IO) are standards of care for advanced NSCLC with a high PD-L1 expression (TPS › 50 %) and no driver-mutation. Both regimens improved significantly the overall survival (OS) when compared to chemotherapy alone. However, it is unclear if these group of patients needs the combination of a checkpoint-inhibitor and chemotherapy or if IO alone would be sufficient. No randomized clinical trials have addressed this question so far and compared C-IO and IO directly in this treatment situation. Due to existing side effects of chemotherapy, longer treatment-application times and costs, it should be evaluated which regimen is best or if there are subgroups of patients that are more benefitting from IO or C-IO.

METHODS

The Clinical Research Platform Into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP) (AIO-TRK-0315) is an open, prospective, noninterventional, multicentre lung cancer registry. Since 2016, representative data on patient and disease characteristics, molecular testing, therapies, including systemic treatments and other modalities, and their respective outcomes are being documented across all sectors of cancer care including oncology practices, hospitals, and comprehensive cancer centers. CRISP and its data recruitment have previously been described in detail[1,2]. All patients included in this analysis were diagnosed with stage IVA/B NSCLC, with high expression of PD-L1 (TPS ≥ 50 %), no driver-mutation, starting first-line treatment after 9/4/2018 and were treated with IO or C-IO. Subsequent propensity score matching resulted in 212 patients per treatment strategy. This represents a selection of the total patient numbers accrued within the CRISP registry from December 2015 until June 2021. All patients had a follow-up of at least 18 months.

In another former analysis from CRISP, a high- and low-risk group of stage IVA/B NSCLC patients has been identified[3]. This analysis included patients with NSCLC stage IVA/B with no driver mutation and every expression of PD-L1. In this analysis, patients with liver metastasis and/or more than 4 metastatic sites had been identified as prognostically unfavourable and therefore been classified as a high-risk group.

The analysis presented here evaluated the association of treatment (IO or C-IO) with OS and progression free survival (PFS) in each risk group and analysed other risk factor categories like age, gender, stage, histology, ECOG and Charlson-Comorbidity Index (CCI) independently, trying to identify subgroups which might benefit from a certain treatment.

RESULTS

Two propensity score matched groups could be created. Every group contained of 212 patients. Patient characteristics are given in table 1. In the IO and C-IO group 55.2 % and 62.7 % were male. Median age in the IO group was 63.5 (58.5 – 69.1) years and 63.6 (57.8 – 68.4) years in the C-IO group. Majority of patients presented with ECOG 1 (51.9 %/48.6 % in the IO/C-IO group). Adenocarcinoma was the predominant histology in both groups (76.2 %/78.8 % in the IO/C-IO group).

By reason of drug approval at the timepoint of patient inclusion, all patients were treated with pembrolizumab alone or in combination with chemotherapy. The details of therapy are given in **table 2**.

No statistically significant and clinically relevant differences regarding OS and PFS could be detected between the whole patient groups **(figure 1 A and B)**. The decline of the PFS-curve was in the first 6 months by trend (not significant) faster in the IO group.

The PFS and OS in the high- and low risk group are given in **figure 2 A – D**. IO showed a favourable outcome in the high-risk group regarding PFS and OS (months: 13.8 vs, 5.2 and 25.1 vs. 6.9; **figure 2B and D**). This effect should be considered with maximum caution, due to the very limited number of patients. In the low-risk group there was a not significant, slightly trend for C-IO regarding PFS (months: 16.1 vs. 8.5; **figure 2A**).

For the covariates age, gender, histology, stage, ECOG and CCI no significant differences in OS and PFS between the two treatments could be detected.

DISCUSSION

Two propensity matched groups, which were prospectively collected, with each 212 patients with NSCLC stage IVA/B, high expression of PD-L1 and treated with either IO or C-IO have been analysed.

Thereby no statistical and clinically significant difference, favouring one regimen of therapy, could be detected. However, signals, that subgroups of patients might benefit from one regimen of therapy more than from the other, could be observed.

A weakness of our analyses was the partially small group of patients, especially in the high-risk subgroup.

To answer the question, if IO or C-IO is more beneficial for patients with PD-L1 high expressing NSCLC, prospectively randomized clinical trials are necessary especially for the high- and low-risk group.

References:
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Conflicts of Interest:
Honoraria for Advisoryboards (outside the submitted eposter) from:

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Table 1: Characteristics at start of first-line treatment[a]

	PBZ			PBZ + CT		
	Female n = 95 (44.8 %)	Male n = 117 (55.2 %)	Total n = 212	Female n = 79 (37.3 %)	Male n = 133 (62.7 %)	Total n = 212
Age in years, median (25 – 75 % quantile)	62.8 (55.9 – 68.2)	64.9 (59.6 – 69.5)	63.5 (58.5 – 69.1)	61.8 (56.7 – 69.0)	63.8 (57.9 – 68.2)	63.6 (57.8 – 68.4)
‹ 65 years	61 (64.2 %)	59 (50.4 %)	120 (56.6 %)	45 (57.0 %)	78 (58.6 %)	123 (58.0 %)
≥ 65 years	34 (35.8 %)	58 (49.6 %)	92 (43.4 %)	34 (43.0 %)	55 (41.4 %)	89 (42.0 %)
Patients with any comorbidity	78 (82.1 %)	102 (87.2 %)	180 (84.9 %)	64 (81.0 %)	115 (86.5 %)	179 (84.4 %)
Comorbidities according to the CCI[b]						
0	51 (53. 7%)	67 (57.3 %)	118 (55.7 %)	51 (64.6 %)	80 (60.2 %)	131 (61.8 %)
1	24 (25.3 %)	32 (27.4 %)	56 (26.4 %)	21 (26.6 %)	30 (22.6 %)	51 (24.1 %)
2	12 (12.6 %)	10 (8.5 %)	22 (10.4 %)	6 (7.6 %)	11 (8.3 %)	17 (8.0 %)
3	5 (5.3 %)	3 (2.6 %)	8 (3.8 %)	1 (1.3 %)	6 (4.5 %)	7 (3.3 %)
4	0 (0.0 %)	4 (3.4 %)	4 (1.9 %)	0 (0.0 %)	2 (1.5 %)	2 (0.9 %)
≥ 5	2 (2.1 %)	1 (0.9 %)	3 (1.4 %)	0 (0.0 %)	4 (3.0 %)	4 (1.9 %)
Missing	1 (1.1 %)	0 (0.0 %)	1 (0.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
ECOG at therapy start						
ECOG 0	26 (27.4 %)	36 (30.8 %)	62 (29.2 %)	22 (27.8 %)	45 (33.8 %)	67 (31.6 %)
ECOG 1	45 (47.4 %)	65 (55.6%)	110 (51.9 %)	38 (48.1 %)	65 (48.9 %)	103 (48.6 %)
ECOG ≥ 2	6 (6.3 %)	9 (7.7 %)	15 (7.1 %)	8 (10.1 %)	6 (4.5 %)	14 (6.6 %)
Unknown	17 (17.9 %)	7 (6.0 %)	24 (11.3 %)	11 (13.9 %)	16 (12.0 %)	27 (12.7 %)
Missing	1 (1.1 %)	0 (0.0 %)	1 (0.5 %)	0 (0.0 %)	1 (0.8 %)	1 (0.5 %)
Smoking status						
Current smoker	35 (36.8 %)	36 (30.8 %)	71 (33.5 %)	32 (40.5 %)	49 (36.8 %)	81 (38.2 %)
Former smoker (heavy)	30 (31.6 %)	49 (41.9 %)	79 (37.3 %)	33 (41.8 %)	50 (37.6 %)	83 (39.2 %)
Former smoker (intensity unkn)	6 (6.3 %)	15 (12.8 %)	21 (9.9 %)	4 (5.1 %)	8 (6.0 %)	12 (5.7 %)
Former smoker (light)	5 (5.3 %)	4 (3.4 %)	9 (4.2 %)	4 (5.1 %)	9 (6.8 %)	13 (6.1 %)
Never smoker	9 (9.5 %)	6 (5.1 %)	15 (7.1 %)	3 (3.8 %)	4 (3.0 %)	7 (3.3 %)
Unknown/Missing	10 (10.5 %)	7 (6.0 %)	17 (8.0 %)	3 (3.8 %)	13 (9.8 %)	16 (7.5 %)
Histology						
Adenocarcinoma	72 (75.8 %)	82 (70.1 %)	154 (72.6 %)	63 (79.7 %)	104 (78.2 %)	167 (78.8 %)
Squamous carcinoma	15 (15.8 %)	27 (23.1 %)	42 (19.8 %)	10 (12.7 %)	19 (14.3 %)	29 (13.7 %)
Large cell carcinoma	3 (3.2 %)	2 (1.7 %)	5 (2.4 %)	2 (2.5 %)	2 (1.5 %)	4 (1.9 %)
Others	5 (5.3 %)	6 (5.1 %)	11 (5.2 %)	4 (5.1 %)	8 (6.0 %)	12 (5.7 %)
Metastasis (at inclusion)						
1	44 (46.3 %)	51 (43.6 %)	95 (44.8 %)	32 (40.5 %)	59 (44.4 %)	91 (42.9 %)
2	27 (28.4 %)	32 (27.4 %)	59 (27.8 %)	24 (30.4 %)	40 (30.1 %)	64 (30.2 %)
3	15 (15.8 %)	21 (17.9 %)	36 (17.0 %)	13 (16.5 %)	20 (15.0 %)	33 (15.6 %)
≥4	9 (9.5 %)	13 (11.1 %)	22 (10.4 %)	10 (12.7 %)	14 (10.5 %)	24 (11.3 %)
Affected organ systems (at inclusion)[c]						
Brain	27 (28.4 %)	34 (29.1 %)	61 (28.8 %)	26 (32.9 %)	47 (35.3 %)	73 (34.4 %)
Bone	34 (35.8 %)	51 (43.6 %)	85 (40.1 %)	22 (27.8 %)	41 (30.8 %)	63 (29.7 %)
Lung – contralateral	26 (27.4 %)	32 (27.4 %)	58 (27.4 %)	19 (24.1 %)	40 (30.1 %)	59 (27.8 %)
Lymph node – extrathoracale	24 (25.3 %)	24 (20.5 %)	48 (22.6 %)	19 (24.1 %)	30 (22.6 %)	49 (23.1 %)
Lymph node – thoracale	0 (0.0 %)	1 (0.9 %)	1 (0.5 %)	1 (1.3 %)	1 (0.8 %)	2 (0.9 %)
Liver	17 (17.9 %)	21 (17.9 %)	38 (17.9 %)	12 (15.2 %)	18 (13.5 %)	30 (14.2 %)
Pleura metastases	10 (10.5 %)	18 (15.4 %)	28 (13.2 %)	12 (15.2 %)	19 (14.3 %)	31 (14.6 %)
Pleural effusion	5 (5.3 %)	6 (5.1 %)	11 (5. 2%)	2 (2.5 %)	7 (5.3 %)	9 (4.2 %)
Skin	2 (2.1 %)	1 (0.9 %)	3 (1.4 %)	2 (2.5 %)	0 (0.0 %)	2 (0.9 %)
Adrenal gland	21 (22.1 %)	27 (23.1 %)	48 (22.6 %)	30 (38.0 %)	35 (26.3 %)	65 (30.7 %)
Pericardial effusion	0 (0.0 %)	1 (0.9 %)	1 (0.5 %)	1 (1.3 %)	2 (1.5 %)	3 (1.4 %)
Other	14 (14.7 %)	16 (13.7 %)	30 (14.2 %)	18 (22.8 %)	17 (12.8 %)	35 (16.5 %)
KRAS test results						
No/unknown/missing test	34 (35.8 %)	62 (53.0 %)	96 (45.3 %)	62 (46.6 %)	34 (43.0 %)	96 (45.3 %)
Wildtype	23 (24.2 %)	32 (27.4 %)	55 (25.9 %)	35 (26.3 %)	18 (22.8 %)	53 (25.0 %)
Alteration	38 (40.0 %)	23 (19.7 %)	61 (28.8 %)	36 (27.1 %)	27 (34.2 %)	63 (29.7 %)
G12C (Druggable)	7 (7.4 %)	13 (11.1 %)	20 (9.4 %)	16 (12.0 %)	5 (6.3%)	21 (9.9 %)
Unknown druggability	5 (5.3 %)	3 (2.6 %)	8 (3.8 %)	3 (2.3 %)	2 (2.5 %)	5 (2.4 %)
Non-druggable	26 (27.4 %)	7 (6.0%)	33 (15.6 %)	17 (12.8 %)	20 (25.3 %)	37 (17.5 %)

Patient characteristics are given in Table 1
Data are number (%), unless otherwise indicated. | Abbreviations: CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group. | a unless otherwise indicated | b Charlson comorbidity index (CCI) according to Quan et al. 2011 | c multiple answers possible.

Table 2: Treatment

	PBZ			PBZ + CT		
	Female n = 95 (44.8 %)	Male n = 117 (55.2 %)	Total n = 212	Female n = 79 (37.3 %)	Male n = 133 (62.7 %)	Total n = 212
Prior systemic treatment (curative)						
Yes (Platinum-based CT)	6 (6.3 %)	7 (6.0 %)	13 (6.1 %)	2 (2.5 %)	3 (2.3 %)	5 (2.4 %)
No	87 (91.6 %)	109 (93.2 %)	196 (92.5 %)	76 (96.2 %)	127 (95.5 %)	203 (95.8 %)
Unknown to site	2 (2.1 %)	1 (0.9 %)	3 (1.4 %)	0 (0.0 %)	2 (1.5 %)	2 (0.9 %)
Missing	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (1.3 %)	1 (0.8 %)	2 (0.9 %)
First-line treatment strategy						
PBZ+CAR+PEM	-	-	-	48 (60.8 %)	70 (52.6 %)	118 (55.7 %)
PBZ+CAR+NAB	-	-	-	4 (5.1 %)	17 (12.8 %)	21 (9.9 %)
PBZ+CAR+PAC	-	-	-	7 (8.9 %)	13 (9.8 %)	20 (9.4 %)
PBZ+CAR+PAC+NAB	-	-	-	1 (1.3 %)	0 (0.0 %)	1 (0.5 %)
PBZ+CAR+PAC+PEM	-	-	-	0 (0.0 %)	1 (0.8 %)	1 (0.5 %)
PBZ+CAR	-	-	-	0 (0.0 %)	1 (0.8 %)	1 (0.5 %)
PBZ+CAR+GEM	-	-	-	0 (0.0 %)	1 (0.8 %)	1 (0.5 %)
PBZ+CIS+PEM	-	-	-	16 (20.3 %)	22 (16.5 %)	38 (17.9 %)
PBZ+CAR+CIS+PEM	-	-	-	2 (2.5 %)	6 (4.5 %)	8 (3.8 %)
PBZ+CIS+PAC	-	-	-	1 (1.3 %)	1 (0.8 %)	2 (0.9 %)
PBZ+CIS+VIN	-	-	-	0 (0.0 %)	1 (0.8 %)	1 (0.5 %)
PBZ Dose at start of treatment						
200 mg	91 (95.8 %)	113 (96.6 %)	204 (96.2 %)	78 (98.7 %)	130 (97.7 %)	208 (98.1 %)
400 mg	3 (3.2 %)	1 (0.9 %)	4 (1.9 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Other	0 (0.0 %)	1 (0.9 %)	1 (0.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	1 (1.1 %)	2 (1.7 %)	3 (1.4 %)	1 (1.3 %)	3 (2.3 %)	4 (1.9 %)
Dose modifications						
Yes	6 (6.3 %)	15 (12.8 %)	21 (9.9 %)	7 (8.9 %)	13 (9.8 %)	20 (9.4 %)
No	70 (73.7 %)	94 (80.3 %)	164 (77.4 %)	63 (79.7 %)	96 (72.2 %)	159 (75.0 %)
Missing	19 (20.0 %)	8 (6.8 %)	27 (12.7 %)	9 (11.4 %)	24 (18.0 %)	33 (15.6 %)
Type of modification						
Dose reduction	0 (0.0 %)	1 (0.9 %)	1 (0.5 %)	1 (1.3 %)	0 (0.0 %)	1 (0.5 %)
Therapy interruption	1 (1.1 %)	0 (0.0 %)	1 (0.5 %)	1 (1.3 %)	3 (2.3 %)	4 (1.9 %)
Dose escalation	4 (4.2 %)	14 (12.0 %)	18 (8.5 %)	6 (7.6 %)	8 (6.0 %)	14 (6.6 %)
Missing	1 (1.1 %)	0 (0.0 %)	1 (0.5 %)	0 (0.0 %)	2 (1.5 %)	2 (0.9 %)
Reason for modification						
Toxicity	2 (2.1 %)	1 (0.9 %)	3 (1.4 %)	1 (1.3 %)	2 (1.5 %)	3 (1.4 %)
Other	5 (5.3 %)	14 (12.0 %)	19 (9.0 %)	6 (7.6 %)	11 (8.3 %)	17 (8.0 %)
Missing	88 (92.6 %)	102 (87.2 %)	190 (89.6 %)	72 (91.1 %)	120 (90.2 %)	192 (90.6 %)
Completed first-line treatment	n = 67	n = 95	n = 162	n = 63	n = 94	n = 157
Treatment duration, median (25 – 75 % quantiles) [months]	2.1 (0.7 – 6.2)	3.7 (0.7 – 8.3)	3.0 (0.7 – 7.9)	4.2 (2.2 – 10.6)	3.6 (2.0 – 7.7)	3.9 (2.1 – 9.0)
Reason for end of treatment						
Toxicity	4 (6.0 %)	17 (17.9 %)	21 (13.0 %)	3 (4.8 %)	8 (8.5 %)	11 (7.0 %)
Progression	29 (43.3 %)	35 (36.8 %)	64 (39.5 %)	24 (38.1 %)	30 (31.9 %)	54 (34.4 %)
Guidelines	4 (6.0 %)	8 (8.4 %)	12 (7.4 %)	14 (22.2 %)	11 (11.7 %)	25 (15.9 %)
Other	29 (43.3 %)	35 (36.8 %)	64 (39.5 %)	19 (30.2 %)	44 (46.8 %)	63 (40.1 %)
Missing	1 (1.5 %)	0 (0.0%)	1 (0.6 %)	3 (4.8 %)	1 (1.1 %)	4 (2.5 %)
Best response[d]						
CR	1 (1.5 %)	2 (2.1 %)	3 (1.9 %)	0 (0.0 %)	3 (3.2 %)	3 (1.9 %)
PR	12 (17.9 %)	31 (32.6 %)	43 (26.5 %)	32 (50.8 %)	37 (39.4 %)	69 (43.9%)
SD	12 (17.9 %)	20 (21.1 %)	32 (19.8 %)	8 (12.7 %)	12 (12.8 %)	20 (12.7 %)
PD	18 (26.9 %)	14 (14.7 %)	32 (19.8 %)	7 (11.1 %)	14 (14.9 %)	21 (13.4 %)
Unknown	24 (35.8 %)	28 (29.5 %)	52 (32.1 %)	15 (23.8 %)	28 (29.8 %)	43 (27.4 %)
Missing	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (1.6 %)	0 (0.0 %)	1 (0.6 %)

Data are number (%), unless otherwise indicated. | Abbreviations: CAR, carboplatin; CIS, cisplatin; CT, chemotherapy; CR, complete response; GEM, gemcitabine; NAB, nab-paclitaxel; PAC, paclitaxel; PBZ, pembrolizumab; PEM, pemetrexed; PD, progressive disease; PR, partial response; SD, stable disease; VIN, vinorelbine. | a there are no specifications as to the timing, frequency or criteria of tumor assessment, thus registry response data should be considered as the best clinical approximation and might not be identical to the response determined in clinical trials.

Figure 1A

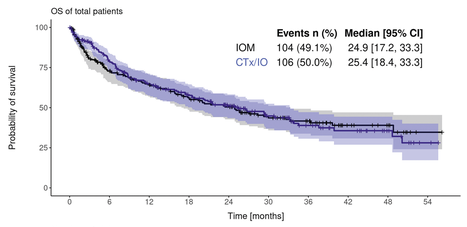
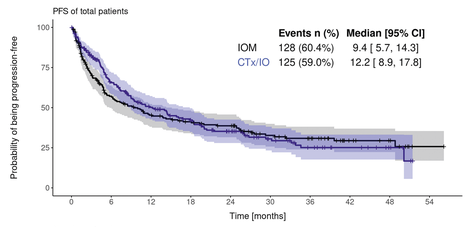


Figure 1B



Time to event analyses are given for the total population regarding OS (A) and PFS (B) | IOM: Therapy with a checkpoint-inhibitor alone | CTx/IO: Combination therapy of checkpoint-inhibitor and chemotherapy | OS: Overavll Survival | PFS: Progression-free survival

Figure 2A

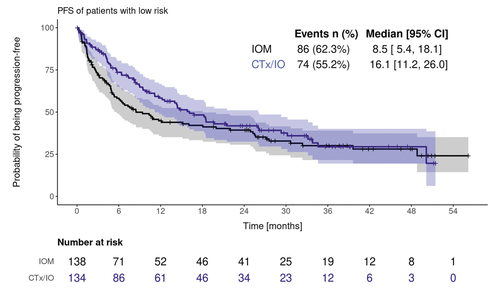


Figure 2B

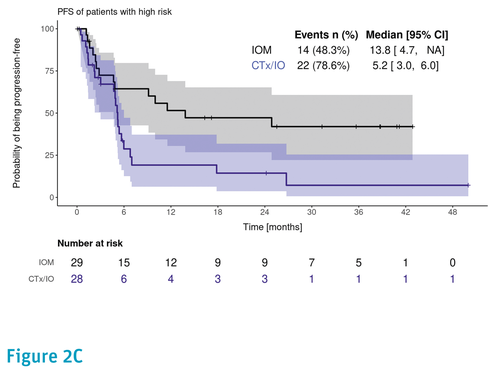


Figure 2C

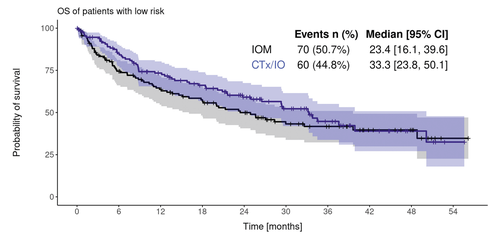
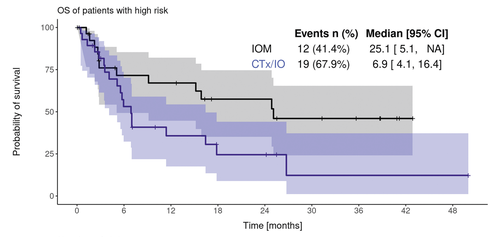


Figure 2D



Time to event analyses for PFS and OS are given for the low risk (A/C) and the high risk-group (B/D) are given.
IOM: Therapy with a checkpoint-inhibitor alone;
CTx/IO: Combination therapy of checkpoint-inhibitor and chemotherapy.
OS: Overavll Survival;
PFS: Progression-free survival
High risk-group: ›4 metastatic sites and/or liver metastases (see reference number 3)