Prognostic factors in nonsmall cell lung cancer: insights from the German CRISP registry

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Shareable abstract (@ERSpublications)
Advanced NSCLCs without driver mutations have inferior long-term survival once liver metastases or ⩾4 metastatic sites are present. In patients with <4 metastatic organ sites, liver metastases also represent a negative prognostic factor. https://bit.ly/3Ui4v9m

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Abstract

Introduction Understanding prognosis, especially long-term outcome, in advanced nonsmall cell lung cancer (NSCLC) is crucial to inform patients, guide treatment and plan supportive and palliative care.

Methods Prognostic factors influencing overall survival (OS) and progression-free survival (PFS) in 2082 patients with wild-type (WT)-NSCLC (629 M1a, 249 M1b, 1204 M1c) are reported. Patients were included in the prospective German CRISP registry recruiting in >150 centres. Analysis for pre-therapeutic factors was based on results from Cox proportional hazard models.

Results Current M-descriptors of the Union for International Cancer Control-8 staging system were validated: M1a and M1b patients had significantly longer median time to events compared to M1c (OS/PFS 16.4/7.2 months, 17.8/6.7 months and 10.9/5.4 months, respectively). OS and PFS were influenced by number and location of metastatic organ systems. M1c and four or more metastatic organs involved had shorter OS and PFS than M1c with one to three organs (OS hazard ratio (HR) 1.69, p<0.001; PFS HR 1.81, p<0.001). M1b-liver metastases had shorter OS/PFS than M1b involving other organs (OS HR 2.70, p=0.006; PFS HR 2.48, p=0.007). Based on number of involved organs (orgsys) and liver metastases, two risk groups (low-risk: M1a, M1b-non-liver, M1c-1-3-orgsys-non-liver; high-risk: M1c-liver, M1b-liver, M1c-4+-orgsys) with significantly different prognoses could be amalgamated (median OS/PFS 14.3/6.5 months and 7.7/4.1 months, respectively). Other favourable factors were female gender

and Eastern Cooperative Oncology Group stage 0, with age showing no impact. Those with T1- or N0-status were associated with longer OS than T2–4 or N2–3.

Conclusion In this large observational dataset, we further defined factors for outcome in WT-NSCLC, including increased number of involved metastatic organ systems and liver metastases, as those with overall poorer prognosis and reduced survival chance.

Introduction

Data from the latest Union for International Cancer Control (UICC)/International Association for the Study of Lung Cancer (IASLC) lung cancer staging convincingly demonstrated that small subsets of advanced nonsmall cell lung cancer (NSCLC) patients may experience long-term survival [1, 2]. Selected patients with stage IVa disease based on pleural and intrapulmonary extension (M1a) or a single involved distant metastatic lesion outside the thorax (M1b), can achieve 5-year survival rates of ∼10% [1, 2]. In parts, this has been prospectively confirmed by at least one small prospective phase-II study with ∼8% 5-year survival rate for a group of predominantly M1b NSCLCs [3, 4]. Besides systemic therapies, local treatments for the primary tumour and metastases seem to be a prerequisite for achieving long-term survival [5, 6]. Whole-body stereotactic radiotherapy (SBRT) has emerged as an alternative ablative local treatment to selected tumour lesions besides their complete surgical removal [7, 8]. Moreover, systemic strategies such as immunotherapy and chemoimmunotherapy may alone significantly increase long-term survival based on durable effects of immunotherapy [9, 10]. Furthermore, patients with treatable molecular driver alterations and, therefore, strong predictive factors (epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) translocations, ROS1-translocations, Braf-V600E-mutations) experience much better long-term survival rates now even reported for landmark points at 3 and 4 years from the time of diagnosis [11–14].

The exact clinical definition of so-called oligometastatic disease (OMD) in NSCLC, based on overall survival (OS) prognosis of patients, is a matter of ongoing discussion even among lung cancer experts [15]. The current typical clinical approach is to include patients with one to three metastatic lesions into this oligometastatic subset [16]. Other investigations have chosen broader inclusion criteria with up to five metastatic sites/lesions [16, 17]. The number of metastatic organs involved has also been identified as an important prognostic factor [18]. The individual organ system affected by metastases and its implication for OS seems to be of further impact [19].

As pre-therapeutic prognostic factors for survival in advanced wild-type (WT)-NSCLC (NSCLC stage IVa/b without EGFR mutations, ALK translocations, ROS-1 translocations, Braf-V600E mutations) have important and valuable implications to plan the multimodal and overall treatment strategy in the individual patient, a more differentiated patient selection in these substages may be a pivotal issue for achieving further therapeutic progress in the future. Therefore, we evaluated data from the large prospective German CRISP registry including patients with advanced WT-NSCLC to pragmatically define important selection factors with prognostic information on the survival outcome in this setting.

Material and methods

Data collection and sample

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 registry. The study was reviewed by responsible ethics committees and registered at ClinicalTrials.gov (identifier NCT02622581). All patients provided written informed consent. CRISP is documenting and monitoring patients' demographic characteristics, initial stage of disease, histopathological and molecular biomarker of the tumour, response to different therapy lines and overall disease history. Treatments, outcomes and additional molecular test results are updated every ⩾3 months. All patients receive follow-up until death, loss to follow-up or end of project. Radiological analyses are performed according to local German standards. Additionally, patients complete questionnaires regarding symptom burden and quality of life. More than 150 certified lung and comprehensive cancer centres, hospital- and office-based oncological practices in Germany participate in CRISP; therefore, a large and representative landscape of NSCLC patients is recorded. All sites recruit patients consecutively. The first patient was included into CRISP on 17 December 2015. The registry does not enforce individual diagnostic and therapeutic procedures at participating facilities. However, all patients were diagnosed, staged and received treatment according to German and international lung cancer guidelines. CRISP and its data recruitment have been described in detail elsewhere [20, 21].

Data cut for this analysis was 31 December 2021. Eligible patients were aged ⩾18 years with confirmed diagnosis of squamous or nonsquamous NSCLC in stage IVa (M1a or M1b) or IVb (M1c) according to

the eighth edition of the UICC/IASLC classification and, for the outcome cohort of interest, had to be under follow-up in CRISP for ⩾30 months (latest start of first-line treatment was 30 June 2019). Patients whose tumours were harbouring a therapeutically druggable EGFR-, ALK-, BRAF- or ROS1-mutation were strictly excluded from the manuscript analyses. However, these patients were looked at separately in an analysis included in supplementary figure S4 to make the findings in the wild-type patients better comparable also to data from the current staging system (UICC/IASLC eighth edition) (figure 1). To analyse a cohort of patients principally eligible for an oligometastatic therapeutic strategy (including for example combined systemic treatment, radiochemotherapy and/or surgical procedures), patients with an Eastern Cooperative Oncology Group (ECOG) performance status of >1 were also excluded. All study patients had received at least one line of systemic therapy.

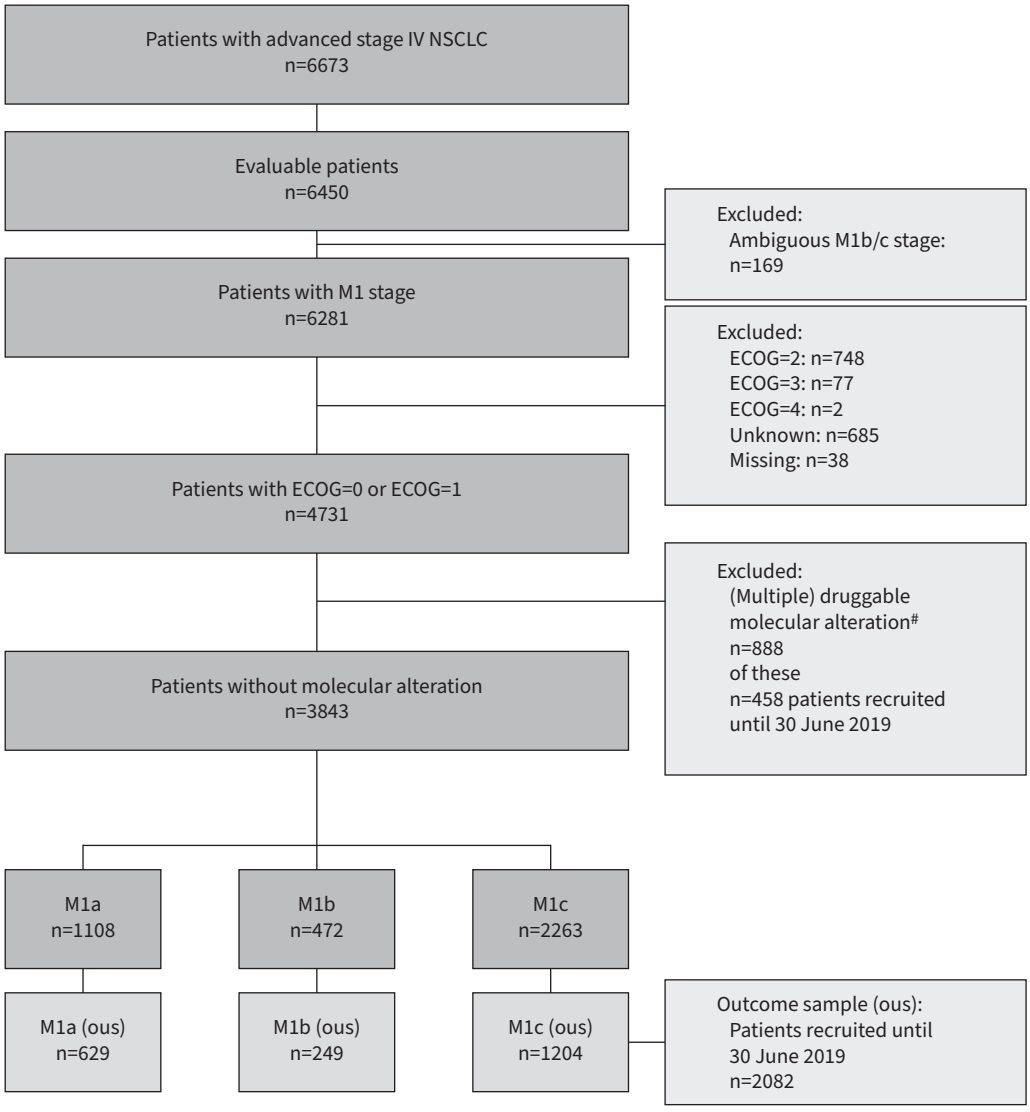

FIGURE 1 Patient flow chart of all patients with advanced stage IV nonsmall cell lung cancer (NSCLC) included in this analysis, starting from the total number of patients recruited into the CRISP registry from December 2015 until 31 December 2021. Outcome analyses are based on data of those patients who have been observed for ⩾30 months, *i.e.* starting first-line treatment until 30 June 2019 (outcome sample). #: all patients with alterations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1 or BRAF (n=859) or treatment with a tyrosine kinase inhibitor, but not (yet) documented targetable mutation (n=29) have been excluded. Of these, n=458 patients had been recruited before 30 June 2019 and are included in supplementary figure S4. ECOG: Eastern Cooperative Oncology Group; ous: outcome sample.

Analytical approach

Tumour (T-, N-, M-descriptors, different M-descriptor subtypes (UICC/IASLC), histology) and patient (age, body mass index (BMI), sex, ECOG performance status, Charlson comorbidity index (CCI), smoking status) characteristics were analysed.

Descriptive statistical analysis was performed by M1a-, M1b- or M1c-disease status. Time to events were calculated using the Kaplan–Meier method [22]. Progression-free survival (PFS) was defined as the interval between start of first-line treatment and the date of progression or death. Patients without such events before start of second-line treatment were censored at start of second-line treatment or time of last contact. OS was defined as interval between start of first-line treatment and date of death from any cause. Patients alive or lost to follow-up at data cut (31 December 2021) were censored at time of last contact. First-line treatment was defined as any systemic treatment, *e.g.* chemotherapy, checkpoint inhibitors or a combination of both. Cox proportional hazard model was used to identify potential prognostically independent factors for survival in the outcome cohort. The validity of the proportional hazards assumption was checked graphically and by Kolmogorov-type supremum test for the presented Cox models. To further analyse the influence of location and number of involved metastatic organ systems, we applied additional Cox models for the subgroups of M1b and M1c patients and for those who received immunotherapy as part of first-line therapy.

Results

Patients and tumour characteristics

The Consolidated Standards of Reporting Trials diagram for all patients is given in figure 1. At the data cut point on 31 December 2021, 2082 patients who had been observed for ⩾30 months (*i.e.* recruited before 30 June 2019) constitute the outcome sample of wild-type patients. For better comparison with the staging classification dataset we also included the data of 458 patients with targetable mutations with all other inclusion criteria similar (figure 1 and supplementary figure S4).

Table 1 gives in detail the relevant patient and tumour characteristics for the wild-type outcome sample. More patients were male, with ECOG performance status 1 and nonsquamous histology (table 1). Among M1b patients, brain (n=80, 32.1%), adrenal gland (n=58, 23.3%) and bone (n=56, 22.5%) were the most frequent (single) metastatic sites. Of all patients with M1a included in the outcome sample (n=629), 276 (43.9%) were diagnosed with contralateral lung metastasis, 178 (28.3%) with pleural carcinosis, 154 (24.5%) with proven malignant pleural effusion and 21 (3.3%) with pericardial effusion (data not shown in table 1). Diagnostic pathology was based on initial endobronchial ultrasound staging intervention with biopsy/cytology in 239 patients from the outcome sample (M1a n=53, 8.4%; M1b n=27, 10.8%; M1c n=159, 13.2%; data not shown).

First-line treatment and outcome

Supplementary figure S1 and supplementary table S2 sum up first-line treatment protocols. Approximately 40% of all patients received treatment including a checkpoint inhibitor within first-line therapy and ∼60% received standard platinum-based combination chemotherapy as first-line treatment. 46 (7.3%) patients in M1a had to discontinue therapy due to relevant side-effects or toxicities; 18 (7.2%) did so in M1b, and 112 (9.3%) in M1c (supplementary figures S1 and S2). 184 (29.3%) patients in M1a, 85 (34.1%) in M1b and 349 (29.0%) in M1c achieved an objective clinical response. In M1c, 457 (38.0%) patients terminated their first-line treatment due to disease progression compared to 223 (35.5%) in M1a and 83 (33.3%) in M1b). 601 (95.5%) patients in M1a, 239 (96.0%) in M1b and 1151 (95.6%) in M1c completed the planned first-line therapy. Data regarding long-term OS and long-term follow-up are given in supplementary table S3a and b.

Local treatment

Radiotherapy was performed in 169 (26.9%) patients in M1a, 125 (50.2%) in M1b and 656 (54.5%) in M1c. This status had not yet been fully documented at the time of this data cut for 75 (11.9%) patients in M1a, 25 (10.0%) in M1b and 78 (6.5%) in M1c. For the subgroups of M1a, M1b and M1c, more detailed data on the type of radiotherapy, area, dose and intention are outlined in supplementary table S4a and b. Surgery was received by 40 (6.4%) patients in M1a, 29 (11.6%) in M1b and 98 (8.1%) in M1c. For 90 (14.3%) patients in M1a, 39 (15.7%) in M1b and for 143 (11.9%) in M1c this information had not yet been fully documented at the time of this data cut. All other patients received neither radiotherapy nor surgery. More detailed data on the type of surgery and surgical techniques were not documented for this patient group of advanced and metastatic disease patients in our CRISP registry.

TABLE 1 Patient and tumour characteristics of patients at start of first-line treatment[#] in the outcome sample (recruited until 30 June 2019)

	M1a	M1b	M1c
Patients	629	249	1204
Age years	67.9 (60.9–74.7)	65.9 (59.6–73.1)	64.3 (58.4–70.7)
<65	246 (39.1)	111 (44.6)	646 (53.7)
⩾65	383 (60.9)	138 (55.4)	558 (46.3)
Sex			
Female	219 (34.8)	105 (42.2)	457 (38.0)
Male	410 (65.2)	144 (57.8)	747 (62.0)
BMI kg·m^{-2}	25.4±5.07	24.8±4.69	25.1±5.01
<20	76 (12.1)	35 (14.1)	141 (11.7)
20–25	259 (41.2)	102 (41.0)	533 (44.3)
25–30	195 (31.0)	77 (30.9)	380 (31.6)
⩾30	95 (15.1)	34 (13.7)	147 (12.2)
Missing	4 (0.6)	1 (0.4)	3 (0.2)
Patients with any comorbidity	552 (87.8)	207 (83.1)	1017 (84.5)
Comorbidities according to the CCI[¶]			
CCI 0	311 (49.4)	139 (55.8)	723 (60.0)
CCI 1–2	244 (38.8)	84 (33.7)	388 (32.2)
CCI 3–4	59 (9.4)	23 (9.2)	70 (5.8)
CCI ⩾5	15 (2.4)	3 (1.2)	23 (1.9)
Other comorbidities[+]			
Arterial hypertension	302 (48.0)	107 (43.0)	535 (44.4)
Diabetes without end-organ damage	85 (13.5)	28 (11.2)	146 (12.1)
Vasosclerosis	114 (18.1)	37 (14.9)	168 (14.0)
Performance status			
ECOG 0	218 (34.7)	101 (40.6)	427 (35.5)
ECOG 1	411 (65.3)	148 (59.4)	777 (64.5)
Smoking status (at inclusion)			
Current smoker	175 (27.8)	81 (32.5)	420 (34.9)
Former smoker (heavy)	235 (37.4)	112 (45.0)	429 (35.6)
Former smoker (intensity unknown)	45 (7.2)	9 (3.6)	72 (6.0)
Former smoker (light)	63 (10.0)	19 (7.6)	102 (8.5)
Never-smoker	61 (9.7)	11 (4.4)	76 (6.3)
Unknown	50 (7.9)	17 (6.8)	105 (8.7)
LDH >ULN			
Yes	206 (32.8)	91 (36.5)	529 (43.9)
Unknown	64 (10.2)	34 (13.7)	143 (11.9)
Histology			
Nonsquamous	454 (72.2)	192 (77.1)	972 (80.7)
Adenocarcinoma	428 (94.3)	175 (91.1)	891 (91.7)
Large cell carcinoma	5 (1.1)	6 (3.1)	25 (2.6)
Others	21 (4.6)	11 (5.7)	56 (5.8)
Squamous	175 (27.8)	57 (22.9)	232 (19.3)
T status (at inclusion)			
T1	34 (5.4)	31 (12.4)	130 (10.8)
T2	103 (16.4)	51 (20.5)	233 (19.4)
T3	123 (19.6)	49 (19.7)	226 (18.8)
T4	281 (44.7)	99 (39.8)	491 (40.8)
TX	88 (14.0)	19 (7.6)	124 (10.3)
N status (at inclusion)			
N0	110 (17.5)	34 (13.7)	120 (10.0)
N1	57 (9.1)	25 (10.0)	113 (9.4)
N2	196 (31.2)	80 (32.1)	387 (32.1)
N3	172 (27.3)	86 (34.5)	460 (38.2)
NX	94 (14.9)	24 (9.6)	124 (10.3)
Selected metastatic sites (at inclusion)[+]			
Adrenal gland	0 (0.0)	58 (23.3)	346 (28.7)
Bone	0 (0.0)	56 (22.5)	540 (44.9)
Brain	0 (0.0)	80 (32.1)	420 (34.9)

Continued

TABLE 1 Continued

	M1a	M1b	M1c
Extrathoracic lymph nodes	0 (0.0)	34 (13.7)	284 (23.6)
Liver	0 (0.0)	19 (7.6)	303 (25.2)
Lung (contralateral)	276 (43.9)	9 (3.6)	244 (20.3)
Pleura	178 (28.3)	6 (2.4)	156 (13.0)
PD-L1 expression (at inclusion)			
TPS ⩾50%	106 (16.9)	52 (20.9)	261 (21.7)
TPS 1–49%	143 (22.7)	50 (20.1)	250 (20.8)
TPS <1%	68 (10.8)	20 (8.0)	116 (9.6)
TPS unknown, documented positive	23 (3.7)	8 (3.2)	37 (3.1)
TPS unknown, documented negative	85 (13.5)	36 (14.5)	148 (12.3)
Test result documented as unknown	2 (0.3)	0 (0.0)	5 (0.4)
No PD-L1 testing	202 (32.1)	83 (33.3)	387 (32.1)
KRAS mutation status (at inclusion)			
Mutant	118 (18.8)	46 (18.5)	236 (19.6)
Wild-type	129 (20.5)	55 (22.1)	285 (23.7)
Unknown/no testing	382 (60.7)	148 (59.4)	683 (56.7)
TP53 mutation status (at inclusion)			
Mutant	73 (11.6)	31 (12.4)	185 (15.4)
Wild-type	82 (13.0)	24 (9.6)	139 (11.5)
Unknown/no testing	474 (75.4)	194 (77.9)	880 (73.1)

Data are presented as n, median (interquartile range), n (%) or mean±SD. BMI: body mass index; CCI: Charlson comorbidity index; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ULN: upper limit of normal; TPS: tumour proportion score. [#]: unless otherwise indicated; [¶]: CCI according to QUAN *et al.* [23]; [+]: multiple answers possible.

Patient-dependent prognostic factors

Figure 2a–c demonstrates Cox proportional hazards models for OS in the whole outcome sample, in M1b by selected organ sites and in M1c by the number of metastatic organ systems. Age showed no influence on OS. Significant factors associated with a benefit for OS were in the whole outcome sample and in the M1c subgroup female sex (p=0.001) and an ECOG performance status of 0 (p<0.001). The respective PFS-results are presented in figure 3a–c.

Tumour size (T-status) and lymph node (N-status) status

T1-status was a significant positive prognostic factor compared to T2/3/4 in the whole-outcome sample and in the M1c subgroup (figure 2a,c and figure 3a,c). The whole-outcome sample demonstrated an OS benefit for N0- in comparison to N2/3-status (figure 2a). N3-status turned out unfavourable in M1b, and N2- in M1c compared to N0-status (figure 2b,c and figure 3b,c).

Location and number of metastatic organs are highly independent prognostic factors

In our analysis, M1a and M1b were favourable prognostic factors regarding OS and PFS compared to M1c. For M1a median (m)OS was 16.4 months (95% CI 14.3–18.3 months), for M1b mOS was 17.8 months (95% CI 15.0–21.4 months) and for M1c 10.9 months (95% CI 9.8–11.9 months) (figure 4a); hazard ratio (HR) for OS was 1.34 (95% CI 1.19–1.52) (figure 2a). For M1a and M1b, median (m)PFS was 7.2 months (95% CI 6.5–7.9 months) and 6.7 months (95% CI 5.7–9.4 months) compared to 5.4 months (95% CI 5.1–5.8 months) for M1c (figure 4b); HR for PFS was 1.38 (95% CI 1.22–1.56 (figure 3a). Details regarding mPFS and mOS of M1a stage groups based on different M1c descriptor parameters (supplementary figure S2). In our outcome sample (n=2082 patients) the number of events for PFS (all events n=1462) included 408 deaths and 1054 patients with progressive disease. In stage M1a (altogether n=629) the end-point definition was events n=405, deaths n=108, progressive disease n=297 patients. In stage M1b (n=249) these end-point data were events n=170, deaths n=51, progressive disease n=119 patients. In stage M1c (n=1204), the data were events n=887, deaths n=249, progressive disease n=638.

Within the M1b group, patients with liver metastasis had a significantly shorter OS and PFS than patients with metastases in other organs/nonliver metastases (OS: HR 2.70, 95% CI 1.33–5.49 (figure 2b); mOS: 4.5 months, 95% CI 1.8–12.2 months *versus* 18.8 months, 95% CI 16.1–23.7 months (figure 4e)).

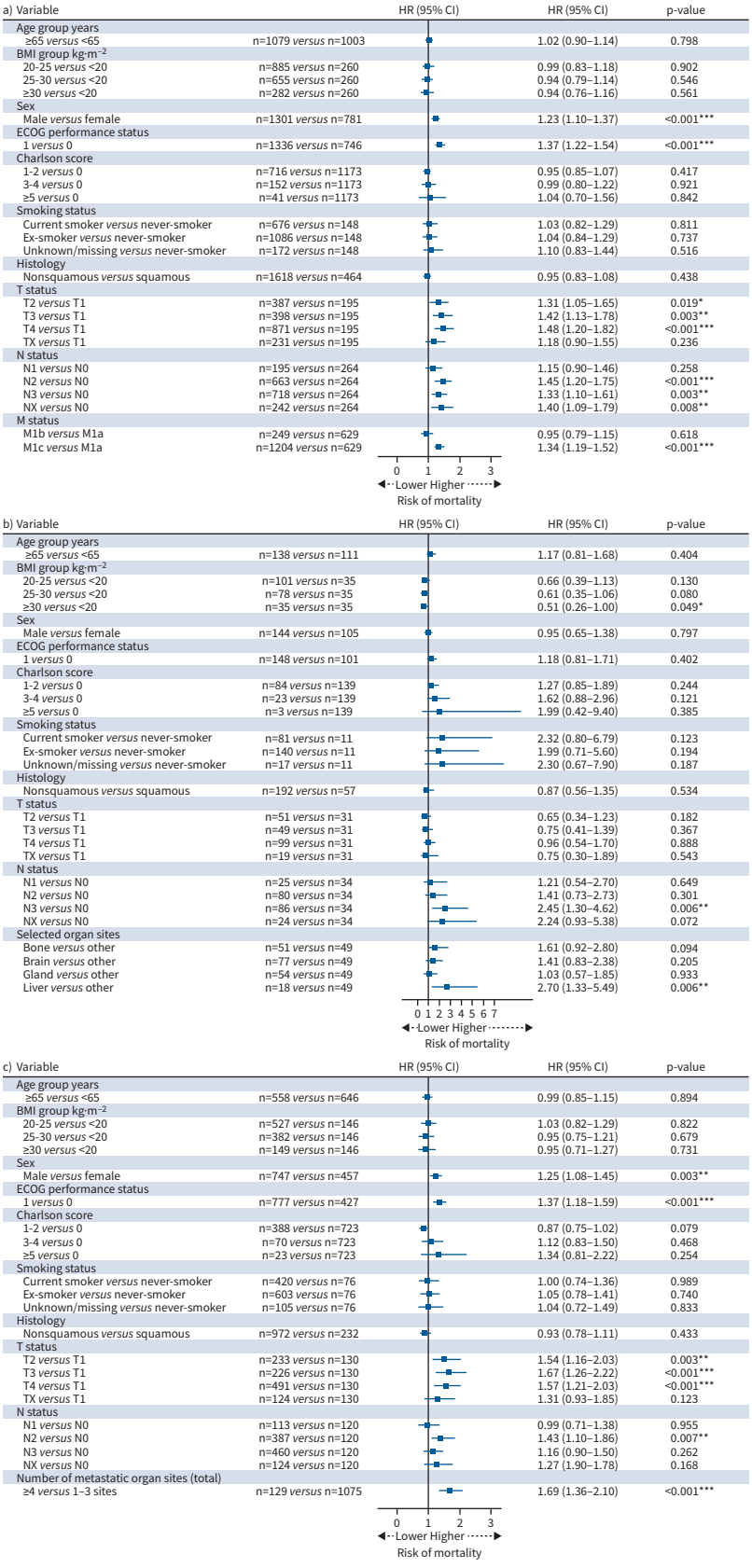

FIGURE 2 Cox proportional hazards models for overall survival for a) the whole outcome sample (n=2082), for b) patients with M1b by selected organ sites (n=249) and for c) patients with M1c by number of metastatic organ sites (n=1204). Analyses are based on data of those patients who have been observed for ⩾30 months,

i.e. starting first-line treatment before 30 June 2019. The parameters shown are an exhaustive list of covariables used for the Cox proportional hazards models. BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio. *: p⩽0.05, **: p⩽0.01, ***: p⩽0.001.

However, the number of patients with M1b and liver metastases was rather small with 19 patients included and these data alone should not be overinterpreted. The PFS data are shown in figures 3b and 4f.

Patients in this M1b-liver subgroup (only including 19 patients) had a shorter mOS than patients in the total M1c cohort (mOS 4.5 months, 95% CI 1.8–12.2 months *versus* 10.9 months, 95% CI 9.8–11.9 months) (figure 4a,c) and demonstrated shorter PFS (figure 4b,d). Within the M1c cohort, the number of the metastatic sites and the affected organs strongly influenced OS (figures 2c and 4e). Patients in the M1c cohort with four or more affected organ systems had a significant worse OS than patients with only one to three affected organs (HR 1.69, 95% CI 1.36–2.10) (figure 2c). Having four or more affected organs was associated with shorter PFS (figures 3c and 4f). However, M1c-staged patients with between one and three affected organ sites had shorter OS when the liver was involved compared to M1c-patients with one to three affected organs without involvement of the liver (OS 8.2 months, 95% CI 7.2–10.0 months *versus* 12.2 months, 95% CI 11.1–13.6 months) (figure 4e). PFS data are demonstrated in figure 4f. The OS of patients staged M1c with between one and three affected organs, including the liver, was comparably shorter than that of M1c staged patients with four or more metastatic organs (8.2 months, 95% CI 7.2–10.0 months *versus* 6.6 months, 95% CI 4.0–7.3 months) (figure 4e). A subgroup analysis in patients who received systemic treatment including a checkpoint-inhibitor, alone or in combination with chemotherapy (as first- or second-line therapy) was performed. Results regarding the unfavourable effect of liver metastasis in the M1b group were confirmed, just like the negative impact of four or more metastatic sites in the M1c group (supplementary figure S3a–c).

In our cohort, stage IVA demonstrated superior OS and PFS when compared to IVB (figure 5a,b).

Considering our results regarding number and location of metastatic organs, the favourable prognostic factors stage M1a and M1b (without liver metastases) and M1c with between one and three affected organs (without involvement of the liver) and the prognostic unfavourable factors stage M1b with liver metastases, M1c with one to three affected organs with involvement of the liver and M1c with four or more metastatic organs were amalgamated into low- and high-risk groups of patients, respectively. Comparing these two groups, the low-risk group showed mOS nearly two-fold that of the high-risk group (mOS 14.3 months, 95% CI 13.6–15.7 months *versus* 7.7 months, 95% CI 6.9–8.9 months) (figure 5c). PFS was also significantly longer in the low-risk group (6.5 months, 95% CI 6.2–7.0 months *versus* 4.1 months, 95% CI 3.4–4.8 months in the high-risk group) (figure 5d). Supplementary figure S4b,c shows the overall survival data for the comparable group of NSCLC patients with targetable mutations.

Discussion

Based on our prospectively recruited large real-world CRISP registry cohort, we could clearly validate the current M-descriptors also for staging of advanced WT-NSCLC [1]. Patients with M1a/b-disease had a significantly better OS and PFS than those with multiple distant metastases of M1c [1]. The current staging, merging M1a/b into stage IVA disease, could also be confirmed and this stage grouping had a significantly better OS than the IVB-disease subset [1]. To our knowledge, our study population is currently one of the largest cohorts to prospectively confirm and validate the latest M-staging descriptors and eighth UICC/IASLC staging system amalgamations and to investigate this in a non-driver-altered NSCLC wild-type population [3–6].

The separate analysis of advanced NSCLC patients with strong genetic driver alterations (EGFR, ALK, ROS1, BRAF) in future is widely discussed among experts. These patients are usually treated with specific molecular targeted agents and experience a completely different long-term prognosis, and their standard treatment has different established algorithms [18]. This observation can be confirmed in our dataset, as we looked into a parallel group of 458 patients with targetable driver mutations and comparable inclusion criteria (see also OS data in supplementary figure S4a–c). Survival in the population with targetable mutations is clearly longer than in the wild-type subgroup. A benefit of our reported complete CRISP dataset is the available detailed information on driver mutations of recruited patients. Therefore, we could easily restrict our analysis to the wild-type population of metastatic NSCLC patients, which makes this

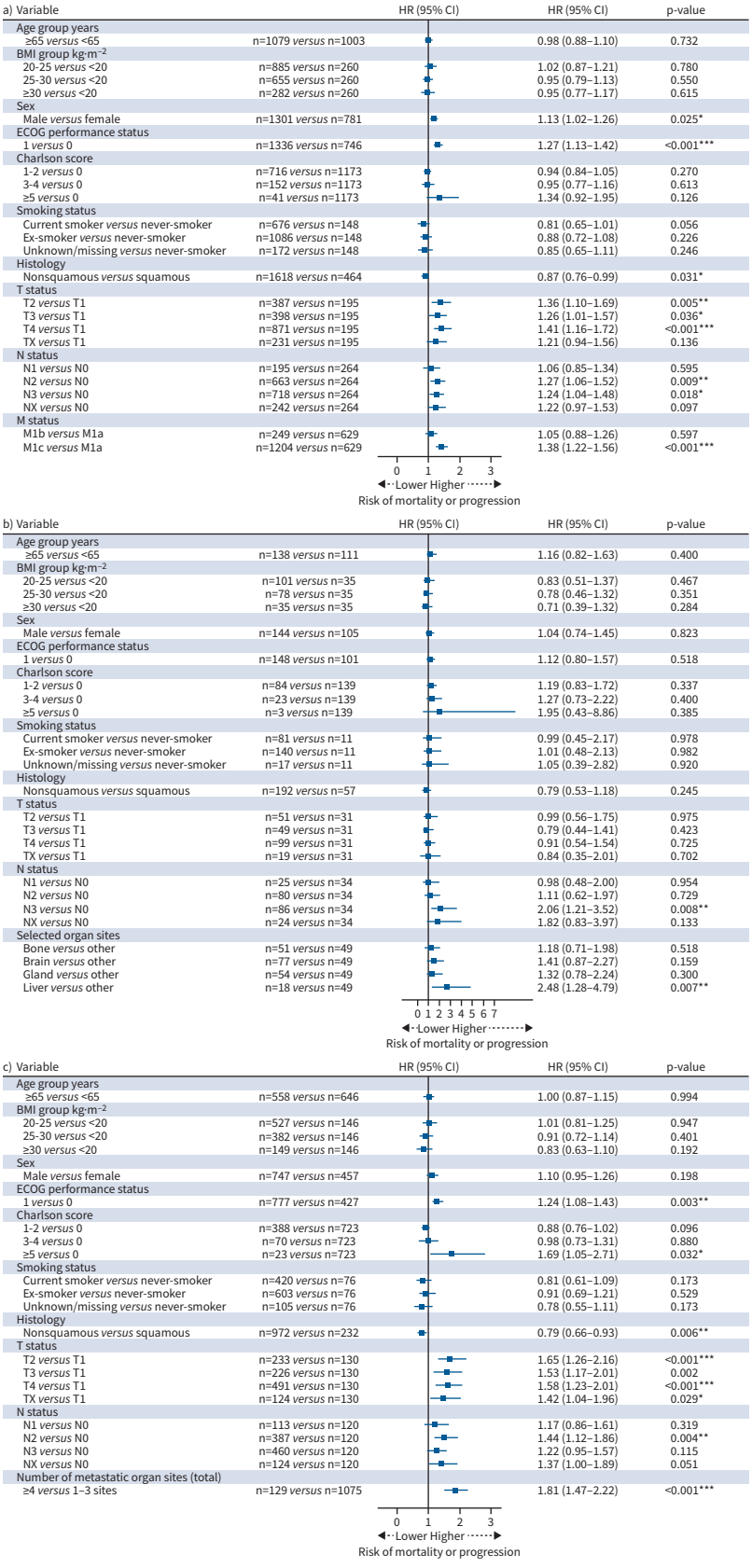

FIGURE 3 Cox proportional hazards models for progression-free survival for a) the whole outcome sample, b) patients with M1b by selected organ sites and c) patients with M1c by number of metastatic organ sites.

Analyses are based on data of those patients who have been observed for ⩾30 months, *i.e.* starting first-line treatment before 30 June 2019. The parameters shown are an exhaustive list of covariables used for the Cox proportional hazards models. BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio. *: p⩽0.05, **: p⩽0.01, ***: p⩽0.001.

dataset the first large patient group with detailed survival data available without existing targetable mutations [7–10, 15].

Besides the M1-descriptors in general we were also able to look at prognostic impact of different metastatic organ sites in the M1b- and M1c-subsets, as well as number of metastatic organ systems involved in the M1c-population. Interestingly, in contrast to the staging paper, but in accordance to other recent reports, we could define those with hepatic metastases as a cohort with clearly inferior survival prognosis [24, 25]. Unfortunately, the IASLC staging database, which has historically been dominated by surgical databases, had too-small patient numbers in stage IVA/B to be able to show such a differential effect of metastatic spread into different organs in M1b and M1c. In this analysis, we had 249 patients with M1b-disease and 1204 with M1c-disease and, therefore, can give quite reliable outcome differences between the individual metastatic organ sites in the joined group.

Moreover, the large M1c-cohort (1204 patients) could be analysed separately regarding number of metastatic organ systems involved. Patients with between one and three metastatic organ systems involved had a significantly better outcome than those with four or more metastatic organs at time of diagnosis. This is of specific interest because the currently available data from prospective clinical trials were unfortunately undefined related to this important issue. Several clinical trials included patient selections with one to five distant metastases into their oligometastatic populations [26]. However, most studies finally recruited >85% of patients with only one or two distant metastases at the time of diagnosis (at least fewer than three organs); therefore, current available evidence for more metastatic lesions is rather confined [27].

In our database, patients with one to three distant metastatic organ systems involved showed a comparably better outcome in 2- and 3-year survival results in contrast to those with three or more metastatic organs involved. Even if these data currently still represent intermediate outcome landmarks (as valid 4–5-year survival cannot be given), the minimal follow-up of our patients on study is already 30 months (2.5 years). Nevertheless, our database evaluation points in comparable directions to those found in several other prospective clinical trials on oligometastatic disease [7–10, 15]. Most clinical trials used as a patient selection criterion the number of three to five distant metastases (metastatic sites) in their inclusion criteria [7–10, 15]. A recent European Organisation for the Research and Treatment of Cancer/European Society for Radiotherapy and Oncology expert consensus also reported similar statements [16]. However, as already mentioned, based on current evidence, >85% of the patients had either one or two distant metastatic sites at time of diagnosis [7–10, 15]. Therefore, a more conservative interpretation of the term “oligometastatic” seems to be currently more appropriate. The upcoming next UICC 9 staging system may be able to give us more detailed insight into the overall prognostic subsets of metastatic disease in all NSCLC patients including the exact number of metastatic lesions and probably also their individual diameter [17, 27]. It may be important to take size of metastases into consideration based on their impact on diagnostic findings, treatment options and overall tumour burden [27].

Our analysis presented here currently supports looking at the population with one to three metastatic organ systems involved (M1b, M1c) and no liver metastases (low-risk group) for any combined modality management based on oligometastatic disease status. Patients with four or more metastatic organs or those with liver metastases (M1b or M1c) represent a more advanced metastatic disease with poor chances of 2–3 years survival outcome and, therefore, a significantly reduced chance of 4–5-year long-term survival (high-risk group). In addition, our results are supported by the fact that these prognostic factors (M1a, M1b, M1c, number of metastatic organ systems and liver metastases, low-risk *versus* high-risk group) were confirmed both with the OS data analysis as well as the PFS data available. Another confirmation to this is the overall response rate prospectively reported for all patients (supplementary table S2). Although response criteria reported in a registry trial may not be as rigourous than those for a registrational trial, our observed and reported results seem to be quite realistic for such a large multicentre patient group.

In our analysis, we do have early information on the patient groups that received the newly evolved standard of care since 2017 with first-line systemic chemoimmunotherapy [28, 29]. However, as first-line therapy with chemoimmunotherapy only became available based on pivotal trials and approval by the

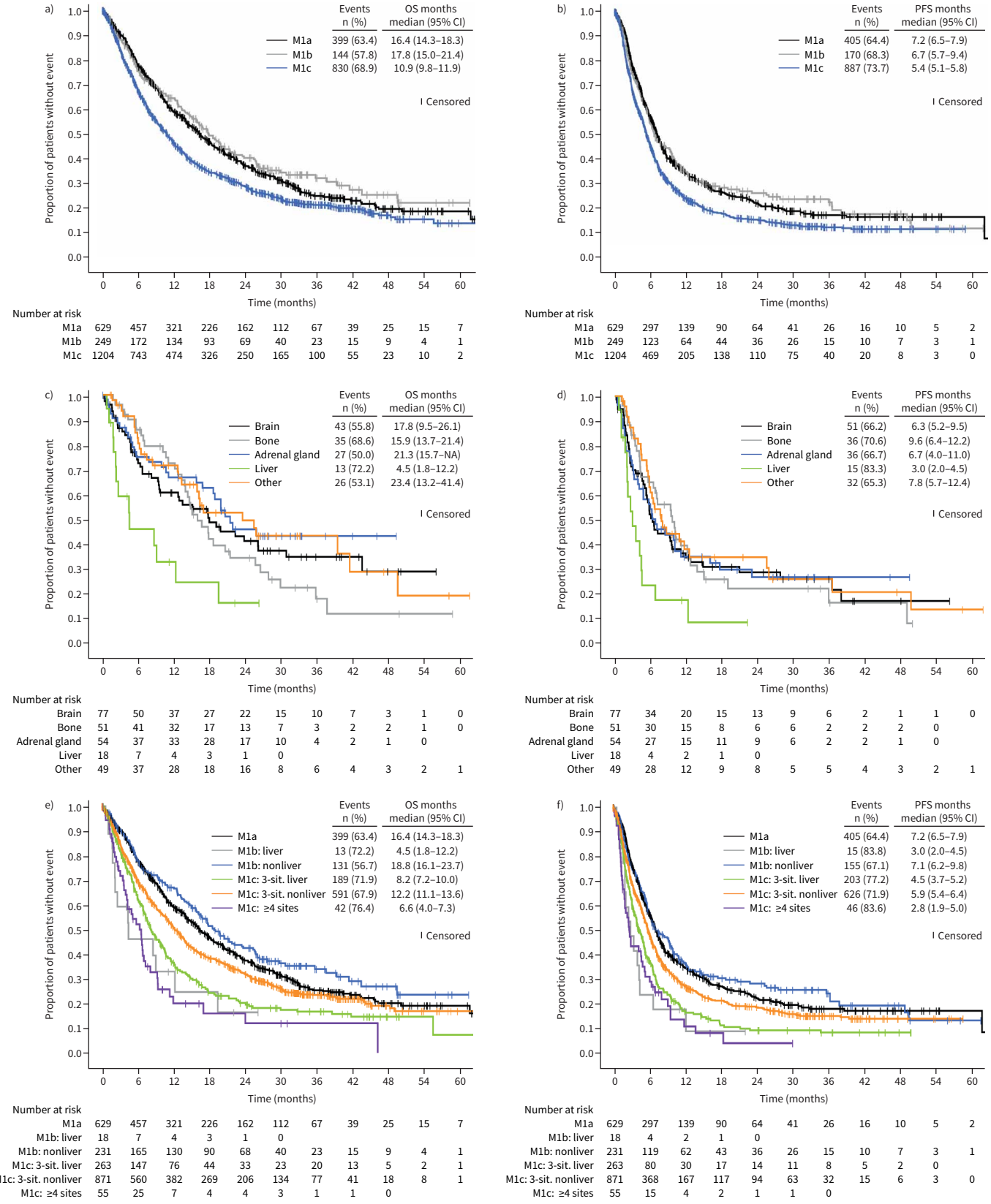

FIGURE 4 First-line registry a, c, e) overall survival (OS) and b, d, f) first-line progression-free survival (PFS) in patients with advanced nonsmall cell lung cancer (NSCLC) by a, b) M1a, M1b, M1c stage, c, d) selected organ sites (for M1b) and e, f) by number of extrathoracic metastatic sites (for M1c) (n=1189; 15 out of 1204 are missing: patients with documented M1c but without information on the type of affected organs) for M1a and for M1b liver

and nonliver. Analysis is based on data of those patients who have been observed for ⩾30 months, *i.e.* starting first-line treatment before 30 June 2019. 3-sit. liv: up to three metastatic sites including liver metastases; 3-sit. non-liv: up to three metastatic sites excluding liver metastases.

European Medicines Agency in 2016 and 2017, respectively, our population may not have had full availability of such new systemic first-line approaches [28, 29]. Future analyses of this in our patients and other datasets should look in detail into this pivotal issue of inclusion of immunotherapy in the first-line treatment, but also the impact of inclusion as second-line or later administration. The administration of immunotherapy alone even as second-line treatment can result in 5-year survival results of ∼13–14% [9].

Future analysis of our registry population will have to look at the detailed treatment history of our patients in their follow-up, which will also include the choice of local treatment of the primary tumour as well as individual metastatic sites. Currently, we do only have some preliminiary data on radiotherapy given (type, area, dose, intention) (supplementary table S4a–d). Longer follow-up with more valid 4- and 5-year OS data will probably give more insight into the possibility of overall curative treatment strategies within these stage groups and even the impact of immunotherapies to this outcome.

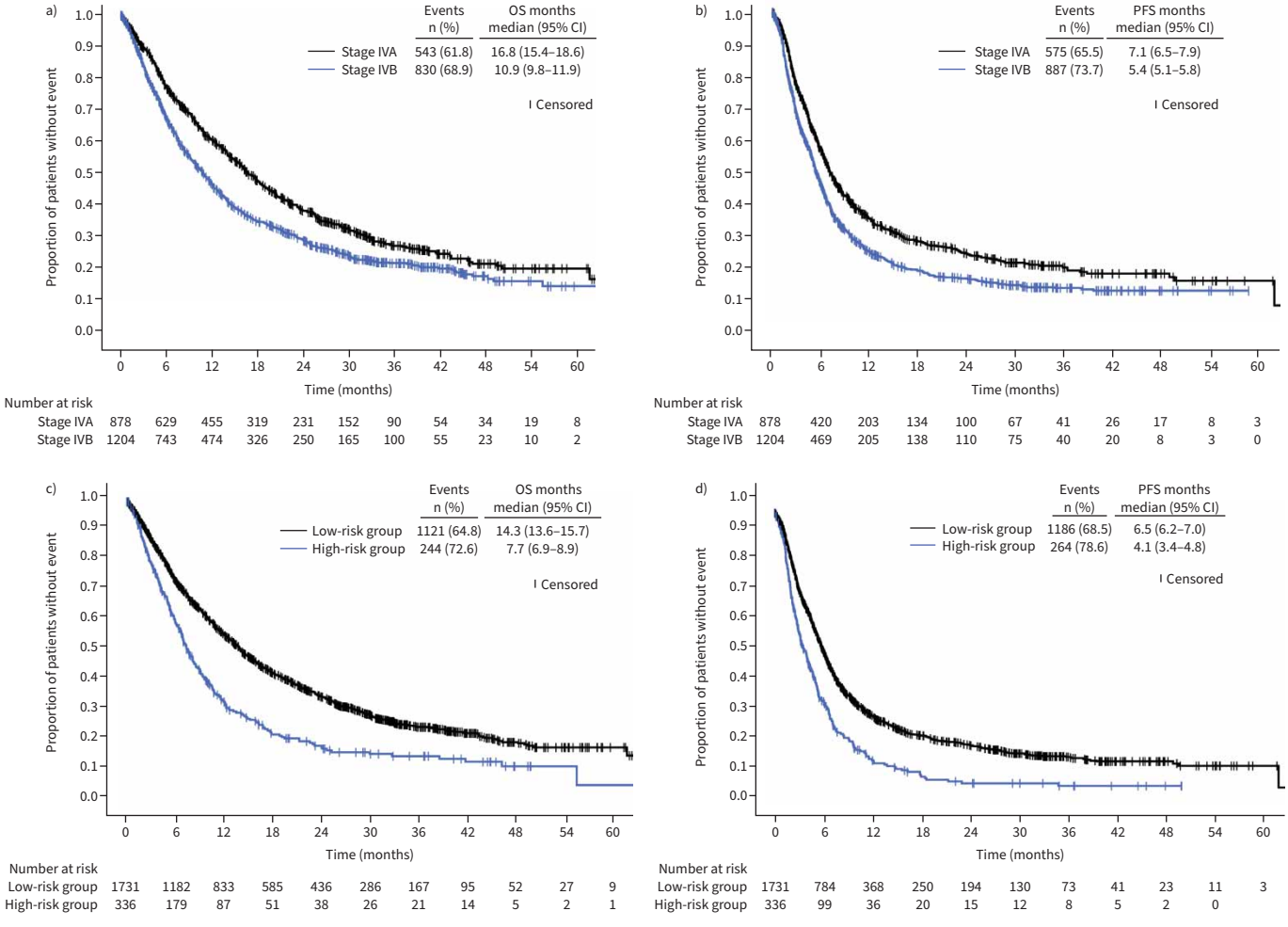

FIGURE 5 First-line registry a, c) overall survival (OS) and b, d) first-line progression-free survival (PFS) in patients with advanced nonsmall cell lung cancer by a, b) IVa and IVb stage according to the recent Union for International Cancer Control/International Association for the Study of Lung Cancer staging system and c, d) for the amalgamated low-risk group (consisting of stage M1a, M1b nonliver and M1c one to three organ sites without liver) and the high-risk group (consisting of M1b liver, M1c one to three organ sites with liver and M1c with four or more organ sites). Analysis is based on data of those patients who have been observed for ⩾30 months, *i.e.* starting first-line treatment before 30 June 2019.

Small, randomised trials have given a clear signal that for longer OS within the patient groups with restricted metastatic disease, definitive local treatments are necessary for metastatic sites and the primary tumour [5, 6, 30, 31]. Despite including small patient numbers, the two randomised trials looking at local treatment *versus* no local treatment have convincingly paved the way to give most optimal systemic treatment (today accepted: chemoimmunotherapy) as well as local treatments to the primary tumour and metastasis in this patient population [5, 6]. Both randomised trials included ablative radiotherapy techniques for the primary tumour and the metastases. Currently, there is no consensus on what may be the best choice of local therapy (surgery or ablative radiation techniques [30]), but it is possible that an individualised decision based on the individual risk profile in the patient will turn out to be a valid strategy for the future.

The largest prospective phase-II trial looking at restricted metastatic NSCLC selected a prognostically rather negative patient group, including mostly locally advanced primaries with lymphatic N2 and N3 involvement and predominantly a single metastatic site and only few patients with two metastatic lesions [7, 32]. Compared to 5-year survival of ∼10% in the staging database for M1b, the 5-year survival results of ∼8% in that trial population seems quite realistic [1].

To summarise, the optimal treatment strategies in patients with more restricted metastatic disease will only be available from large prospective randomised trials with well-defined inclusion criteria in the future. Our current strong recommendation, based on our multicentre real-world experience in CRISP, would be to confine patient selection in wild-type NSCLC patients to those with 1) M1a-disease, 2) M1b-disease (without liver metastases) and 3) one to three distant metastatic organ systems involved at the time of diagnosis from the group of M1c, but only those without liver metastases. This altogether would create an adequately homogenous patient population necessary for valid and meaningful clinical trials in these patients with improved prognosis (low-risk group). Wild-type patients without targetable alterations should be the underlying selection factor to rule out strong predictive factors and, therefore, have rather comparable systemic treatment algorithms for the included patient population.

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