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Early View

Original research article

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Original article

Prognostic Factors in Non-small-cell Lung Cancer: Insights From the German CRISP Registry

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Summary of the “take home message”

Advanced NSCLC without driver mutations have inferior long-term survival once liver metastases or ≥4 metastatic sites are present. In patients with less than 4 metastatic organ sites liver metastases also represent a negative prognostic factor.

Abstract

Introduction

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

Methods

Prognostic factors influencing overall (OS) and progression-free survival (PFS) in 2,082 patients with Wild-type(WT)-NSCLC (629 M1a, 249 M1b, 1,204 M1c) are reported. Patients were included in the prospective German CRISP-registry recruiting in over 150 centers. Analysis for pretherapeutic factors was based on results from Cox proportional hazard models.

Results

Current M-descriptors of UICC-8 staging system were validated: M1a and M1b patients had significantly longer time to events compared to M1c (OS/PFS, medians 16.4/7.2; 17.8/6.7; 10.9/5.4months). OS and PFS were influenced by number and location of metastatic organ systems. M1c and ≥4 metastatic organs involved had shorter OS and PFS than M1c with 1 to 3 organs (OS HR 1.69,p<·001; PFS HR 1.81,p<·001). M1b-liver metastases had shorter OS/PFS than M1b-involving other organs (OS HR 2.70, p=·006;PFS HR 2.48, p=·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 prognosis could be amalgamated (OS/PFS, medians 14.3/6.5; 7.7/4.1 months). Other favourable factors were female gender and ECOG 0 with age

showing no impact. 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.

Keywords: Non-small-cell lung cancer, metastatic disease, pretreatment prognostic factor, survival

Introduction

Data from the latest 8th UICC/IASLC lung cancer staging convincingly demonstrated that small subsets of advanced non-small-cell lung cancer (NSCLC) patients may experience long-term survival[1,2]. Selected patients with IVA-disease based on pleural and intrapulmonary extension (M1a) or a single involved distant metastatic lesion outside the thorax (M1b), can achieve five-year survival rates of about ten percent[1,2]. In parts, this has been prospectively confirmed by at least one small prospective phase-II study with about eight percent five-year survival rate for a group of predominantly M1b NSCLC[3,4]. Besides systemic therapies, local treatments for the primary tumour and also 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 tumor 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]. Further, patients with treatable molecular driver alterations and, therefore, strong predictive factors (EGFR-mutations, ALK-translocations, ROS1-translocations, Braf-V600E-mutations) experience much better long-term survival rates now even reported for three and four years[11,12,13,14].

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 on OS seems to be of further impact[19].

As pretherapeutic 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 "**C**linical **R**esearch Platform **I**nto Molecular Testing, Treatment and Outcome of Non-**S**mall Cell Lung Carcinoma **P**atients" (CRISP) (AIO-TRK-0315) is an open, prospective, non-interventional, multicenter registry. The study was reviewed by responsible ethics committees and registered at ClinicalTrials.gov (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, outcome, and additional molecular test results are updated at least every three months. All patients receive follow up until death, lost to follow up or end of project, respectively. Radiological analyses are performed according to local German standards. Patients also complete questionnaires regarding symptom-burden and quality of life. Over 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 December 17, 2015. The registry does not enforce individual diagnostic and therapeutical procedures to 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 in detail been described elsewhere[20,21].

Data cut for this analysis was December 31, 2021. Eligible patients were ≥ 18 years with confirmed diagnosis of squamous or non-squamous NSCLC in stage IVA (M1a or M1b) or IVB (M1c) according to UICC 8th edition and, for the outcome cohort of interest, had to be under follow-up in CRISP for at least 30 months (latest start of first-line treatment was June 30, 2019). Patients whose tumors were harboring a therapeutically druggable EGFR-, ALK-, BRAF- or ROS1-mutation were strictly excluded from the manuscript analyses. These patients were, however, separately looked at in an analysis included in the supplement to make the findings in the wild-type patients better comparable also to data from the current staging system (8th edition IASLC/UICC) (see Figure 1). To analyse a cohort of patients, principally eligible for an oligometastatic therapeutic strategy (including e.g. 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.

Analytic Approach

Tumour (T-, N-, M-descriptors, different M-descriptor subtypes (UICC8), histology) and patient characteristics (age, body mass index (BMI), sex, ECOG performance status, Charlson comorbidity index (CCI), [4] smoking status), 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]. PFS was defined as the interval between start of first-line treatment and the date of progression or death. Patients without such event before start of second-line treatment were censored at start of second-line or time of last contact. OS was defined as interval between start of first-line and date of death from any cause. Patients alive or lost to

follow-up at data cut (December 31, 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 Consort diagram for all patients is given in Figure 1. At the data cut point on December 31, 2021, 2082 patients who have been observed for at least 30 months (i.e. recruited until June 30, 2019) constitute the outcome sample of wild-type patients. For better comparison with the staging classification dataset we also included in the supplement data of 458 patients with targetable mutations with all other inclusion criteria similar (see also Figure 1and Supplement Figure 4).

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 non-squamous histology (table 1). Among M1b patients, brain (80 (32.1%)), adrenal gland (58 (23.3%)) and bone (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 EBUS-staging intervention with biopsy/cytology in 239 patients from the outcome sample (M1a 53 (8.4%), M1b 27 (10.8%), M1c 159 (13.2%); data not shown).

First-line treatment and outcome

Supplement Figure 1 and Supplement Table 2 sum up first-line treatment protocols. About 40% of all patients received treatment including a checkpoint inhibitor within first-line and about 60% received standard platinum-based combination chemotherapy as first-line. In M1a 46 (7.3%) patients, 18 (7.2%) in M1b and 112 (9.3%) in M1c had to discontinue therapy due to relevant side effects or toxicities (Suppl. Fig.1 and 2). 184 (29.3%) 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%) 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 Supplement Table 3A+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 for 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 Supplement table 4 A and B. Surgery was received by 40 (6.4%) patients in M1a, 29 (11.6%) in M1b and 98 (8.1%) in M1c. Here, 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.

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 ($p = \cdot001$) and an ECOG performance status of 0 ($p<\cdot001$). The respective PFS-results are presented in figure 3A-C.

Tumour size (T-status) and lymph node-status (N-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-, respectively (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 OS (mOS) was 16.4 months (95% CI: 14.3-18.3), for M1b mOS was 17.8 months (95% CI: 15.0-21.4) and for M1c 10.9 months (95% CI: 9.8-11.9), respectively (Figure 4A and HR for OS 1.34 (95% CI: 1.19-1.52), Figure 2 A). For M1a and M1b, median PFS (mPFS) was 7.2 months (95% CI: 6.5-7.9) and 6.7 months (95% CI: 5.7-9.4) compared to 5.4 months (95% CI: 5.1-5.8) for M1c (Figure 4B and HR for PFS 1.38 (95%CI: 1.22-1.56), Figure 3 A). Details regarding mPFS and mOS of M1a stage groups based on different M-1c-descriptor parameters see Supplement Figure 2. In our outcome sample (n = 2082 patients) the number of events for PFS (all events: 1462) included 408 deaths and 1054 patients with progressive disease. In stage M1a (all together: 629) the endpoint definition was: events 405, deaths 108, progressive disease 297 patients. In stage M1b (n = 249) these endpoint data were: events n=170, deaths 51, progressive disease 119 patients. In stage M1c (n = 1204) data were: events n=887, deaths 249, and progressive disease 638, respectively.

Within the M1b group, patients with liver metastasis had a significantly shorter OS and PFS than patients with metastases in other organs/non-liver metastases (OS: HR 2.70 (95% CI: 1.33-5.49), Figure 2B, mOS in months 4.5 (95% CI: 1.8-12.2) vs 18.8 months (95% CI: 16.1-23.7), Figure 4E). 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 Figure 3B and 4F.

Patients in this M1b-liver subgroup – even though only 19 patients - had a shorter mOS than patients in the total M1c cohort (mOS in months 4.5 (95% CI: 1.8-

12.2) vs 10.9 months (95% CI: 9.8-11.9) Figure 4A+C) and demonstrated also shorter PFS (Figure 4B+D). Within the M1c cohort, the number of the metastatic sites and the affected organs also strongly influenced OS (Figure 2C and 4E). Patients in the M1c cohort with ≥4 affected organ systems had a significant worse OS than patients with only 1-3 affected organs ((HR 1.69 (95% CI: 1.36-2.10), Figure 2C). A number of ≥4 affected organs was associated with shorter PFS, respectively (Figure3C and 4F). However, M1c-staged patients with 1-3 affected organ sites had again shorter OS when the liver was involved compared to M1c-patients with 1-3 affected organs without involvement of the liver (OS 8.2 months (95% CI: 7.2-10.0) vs 12.2 months (95% CI: 11.1-13.6) Figure 4E). Regarding PFS-data are demonstrated in Figure 4F. The OS of patients staged M1c with 1-3 affected organs, including the liver, was comparably shorter than that of M1c staged patients with ≥4 metastatic organs (8.2 months (95% CI: 7.2-10·0) vs 6.6 months (95% CI: 4.0-7.3) Figure 4E). A subgroup analyses 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 ≥4 metastatic sites in the M1c group (Supplement Figure 3A-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 1-3 affected organs (without involvement of the liver) and the prognostic unfavourable factors stage M1b with liver metastases, M1c with 1-3 affected organs with involvement of the liver and M1c with ≥4 metastatic organs were amalgamated into a low-risk group and a high-risk group of patients, respectively. Comparing these

two groups, the low-risk group showed a nearly twofold as long median OS than the high-risk group (mOS: 14.3 months (95% CI: 13.6-15.7) vs 7.7 months (95% CI: 6.9-8.9) Figure 5C). PFS was also significantly longer in the low-risk group (6.5 months (95% CI: 6.2-7.0) vs 4.1 months in the high-risk group (95% CI: 3.4-4.8) Figure 5D). Supplement Figure 4 B and C show 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 for staging of advanced wild-type 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 8th UICC staging system amalgamations and to investigate this also in a non-driver-altered NSCLC wild-type population[3-6].

Currently, it is widely discussed amongst experts to separately analyse in the future advanced NSCLC patients with strong genetic driver alterations (EGFR, ALK, ROS1, BRAF). 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 overall

survival data in Supplement Figure 4 A, B and C). Survival data 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 WT-population of metastatic NSCLC patients, which makes this 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 the 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[23,24]. The IASLC staging database, that has historically been dominated by surgical databases, had unfortunately 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 1,204 in 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 – 1,204 patients - could be separately analysed regarding number of metastatic organ systems involved. Patients with 1-3 metastatic organ systems involved had a significantly better outcome than those with $\geq$4 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[25]. However,

most studies finally recruited more than 85% of patients with only one or two distant metastases at the time of diagnosis (at least less than three organs), therefore, current available evidence for more metastatic lesions is rather confined[26].

In our database, the number of patients with one to three distant metastatic organ systems involved, showed a comparably better outcome in two- and three-years survival results in contrast to those with $\geq$ 3 metastatic organs involved. Even if these data currently still represent intermediate outcome landmarks - as valid four to five-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 into comparable directions than 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 EORTC/ESTRO expert consensus also reported similar statements[16]. However, as already mentioned, based on current evidence, more than 85% of the patients had either 1 or 2 distant metastatic sites at time of diagnosis[7–10,15]. Therefore, a more conservative interpretation of the term “oligometastatic” seems to be currently somehow 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[17,26]. Size of metastases may be important to be taken into consideration based on their impact on diagnostic findings, treatment options and overall tumour burden[26].

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 ≥4 metastatic organs or those with liver metastases (M1b or M1c) represent a more advanced metastatic disease with poor chances of two to three-years survival outcome and, therefore, a significantly reduced chance of four- to five-year long-term survival (high risk-group). Our results are also supported by the fact that these prognostic factors (M1a, M1b, M1c, number of metastatic organ systems, and liver metastases, low-risk vs. 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 (Supplement Table 2). Even though response criteria reported in a registry trial may not be of the same rigorousness 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 also have early information on the patient groups that received the newly evolved standard of care since 2017 with first-line systemic chemoimmunotherapy[27,28]. However, as first-line therapy with chemoimmuno-therapy only became available based on pivotal trials and approval by EMA in 2016 and 2017, our population may not have had full availability of such new systemic first-line approaches already.[27,28] Future analyses of this in our patients and other datasets should look in detail into this pivotal issue of inclusion of immunotherapy into the first-line treatment but also the impact of inclusion as second-line or later administration. We all have currently learned that administration of immunotherapy alone even in second-line can result in five-year survival results of around 13 to 14 percent[29].

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 local treatments choice to primary tumour as well as to individual metastatic sites. Currently, we do only have some preliminiary data on radiotherapy given (type, area,

dose, intention; see Supplemental Table 4 A, B, C, D). Longer follow-up with more valid four and five-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.

Small, randomized trials have given a clear signal that for longer overall survival within the patient's groups with restricted metastatic disease, definitive local treatments are clearly necessary for metastatic sites and the primary tumour [5, 6, 30,31]. The two randomized trials looking at local treatment versus no local treatment - although including small patient numbers - have convincingly paved that way to give most optimal systemic treatment (today accepted: chemoimmunotherapy) as well as local treatments to primary tumor and metastasis in this patient population [5, 6]. Both randomized trials included ablative radiotherapy techniques for the primary and the metastases. No consensus is currently existing what may be the best choice of local therapy – surgery or ablative radiation techniques [30] but possibly an individualized descision 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 five-years survival of around ten percent in the staging database for M1b, the five-year survival results of around eight percent in that trial´s population seems quite realistic[1].

Summarizing, the optimal treatment strategies in patients with more restricted metastatic disease will only be available from large prospective randomized trials

with well-defined inclusion criteria in the future. Our current recommendation, based on our multicentre real-world experience in CRISP, would strongly be to confine patient selection in wild-type NSCLC patients to those a) with M1a-disease, b) with M1b-disease (without liver metastases) and c) with 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 improved prognosis patients (low-risk group). WT-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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The study was reviewed by the responsible ethics committees and registered at ClinicalTrials.gov (NCT02622581).

Appendix

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Conflict of interest:

M M:
Has received **honoraria for advisory boards** from Astra Zeneca, BMS, Boehringer Ingelheim, MSD, Novartis, Pfizer, Roche, Sanofi Aventis, Takeda.

F G:
Has received **research funding to institution** from Astra Zeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Siemens,
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C E:
Declares that there is no conflict of interest

H S:
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M d W:

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U K:
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J K:

Has received **honoraria for scientific meetings** from Astra Zeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda,
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M J:
Declares that there is no conflict of interest

L S:
Declares that there is no conflict of interest

S Z:
Declares that there is no conflict of interest

A K-O:
Declares that there is no conflict of interest

A G :
Has received **research funding to the employer AIO-Studien-gGmbH** from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Janssen-Cilag, Lilly, MSD Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda.

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G Z:
Declares that there is no conflict of interest

S D:
Declares that there is no conflict of interest

B G:

Has received **advisory board honoraria:** MSD Oncology, Roche Pharma AG, Amgen

L M:
Declares that there is no conflict of interest.

J U:
Has received **honoraria for advisory boards and workshops** from:
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M T:
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Figure legends

Figure 1

Patient flow chart of all patients with advanced stage IV NSCLC included in this analysis, starting from the total number of patients recruited into the CRISP registry from December 2015 until December 31, 2021. Outcome analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019 (outcome sample). *All patients with alterations in EGFR, 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 until June 30, 2019 and are included in Suppl. Fig. 4.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ous, outcome sample.

Figure 2

Cox proportional hazards models for overall survival for (**A)** the whole outcome sample (n=2,082), for (**B**) patients with M1b by selected organ sites (n=249) and for (**C**) patients with M1c by number of metastatic organ sites (n=1,204). Analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. The parameters shown are an exhaustive list of co-variables used for the Cox proportional hazards models. * $p \leq 0{\cdot}05$, ** $p \leq 0{\cdot}01$, *** $p \leq 0{\cdot}001$. **Abbreviations**: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

Figure 3

Cox proportional hazards models for progression-free survival for the whole outcome sample (**A**), patients with M1b by selected organ sites (**B**) and for patients with M1c by number of metastatic organ sites. Analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. The parameters shown are an exhaustive list of co-variables used for the Cox proportional hazards models. * $p \leq 0{\cdot}05$, ** $p \leq 0{\cdot}01$, *** $p \leq 0{\cdot}001$. **Abbreviations**: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

Figure 4

First-line Registry-OS and first-line PFS in patients with advanced NSCLC by M1a, M1b, M1c stage (**A** and **B**), by selected organ sites (for M1b) (**C** and **D**), by number of extrathoracic metastatic sites (for M1c) [n=1,189; n=15 of 1,204 are missing: patients with documented M1c but without information on the type of affected organs] for M1a and for M1b liver and non-liver (**E** and **F**). Analysis is based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. **Abbreviations**: CI, confidence interval; PFS, progression-free survival; OS, overall survival; 3- sit. liver, up to three metastatic sites including liver metastases; 3- sit. non-liv, up to three metastatic sites excluding liver metastases; 4+ sites, four and more metastatic sites;

Figure 5

First-line Registry-OS and first-line PFS in patients with advanced NSCLC by IVa and IVb stage according to recent IALSC staging system (**A** and **B**), for the amalgamated low-risk group (consisting of stage M1a, M1b non-liver and M1c 1-3 organ sites without liver) and the

high-risk group (consisting of M1b liver, M1c 1-3organ sites with liver and M1c with ≥4 organ sites) (**C** and **D**). Analysis is based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. **Abbreviations**: CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Supplement Figure 1

Top first-line treatment regimens for patients with M1a, M1b and M1c stage (outcome sample). Checkpoint inhibitors: pembrolizumab, atezolizumab, or nivolumab; platinum agents: carboplatin or cisplatin; taxanes: nab-paclitaxel or paclitaxel. **Abbreviations**: CPI, checkpoint inhibitor; CT, chemotherapy; PEM, pemetrexed.

Supplement Figure 2

First-line Registry-OS and first-line PFS in patients with advanced NSCLC by different variations of M1a or M1b or M1c (**A** and **B**). Analysis is based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. **Abbreviations**: CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Supplement Figure 3

Cox proportional hazards models for the subgroup of patients who received a checkpoint inhibitor (alone or in combination with chemotherapy) in the first or second line of therapy. Overall survival for (**A)** the whole subgroup sample (n=1,344), for (**B**) patients with M1b by selected organ sites (n=147) and for (**C**) patients with M1c by number of metastatic organ sites (n=786). Analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. The parameters shown are an exhaustive list of co-variables used for the Cox proportional hazards models. * p ≤0·05, ** p ≤0·01, *** p ≤0·001. **Abbreviations**: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

Supplement Figure 4

First-line Registry-OS in patients with advanced NSCLC, whose tumours harbouring *a driver-mutation,* by M1a, M1b, M1c stage (**A**), by number of extrathoracic metastatic sites (for M1c) **(B)** and for the amalgamated low-risk and high-risk group **(C)** are given. Analysis is based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019.

In **(B)** 5 patients could not be allocated to the specific subgroups because of partial missing data.

Abbreviations: CI, confidence interval; PFS, progression-free survival; OS, overall survival; 3- sit. liver, up to three metastatic sites including liver metastases; 3- sit. non-liv, up to three metastatic sites excluding liver metastases; 4+ sites, four and more metastatic sites;

Table legends

Table 1

Data are number (%), unless otherwise indicated. Data cut for this analyzes was December 31, 2021.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; TPS, tumor proportion score; ULN, upper limit of normal.

[a] unless otherwise indicated

[b] Charlson comorbidity index (CCI) according to Quan et al., 2011

[c] multiple answers possible

Supplement Table 1

Data are number (%), unless otherwise indicated.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; TPS, tumor proportion score; ULN, upper limit of normal.

[a] unless otherwise indicated

[b] Charlson comorbidity index (CCI) according to Quan et al., 2011

[c] multiple answers possible

Supplement Table 2

Analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019 (outcome sample). Data are number (%), unless otherwise indicated. Only patients with a documented date for the end of first line therapy were feasible for the analyzes “Treatment duration”, “Reason for end of treatment” and “Registry-maximum clinical response”.

Abbreviations: CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TTNT, time to next treatment.

[a] unless otherwise indicated

[b] of those patients with documented other reason for end of treatment and without second-line

treatment (n=516), 74% (n=381) had died. “Other” is often chosen if the reason for discontinuation is a general deterioration in the patient’s overall condition which cannot unambiguously linked to progression or toxicity.

[c] 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.

Supplement Table 3 A+B

Analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019 (outcome sample). Data are number (%), unless otherwise indicated.

Abbreviations: CI, confidence interval; FU, follow-up

Supplement Table 4 A-D

Data regarding radiotherapy applied in the outcome sample (recruited until June 30, 2019) are given. Data are given for patients staged M1a, M1b and M1c (A+B) and for the amalgamated low-risk and high-risk group (C+D).

Tables

Table 1. Patient and tumour characteristics of patients in the outcome sample (recruited until June 30, 2019)

Characteristics at start of first-line treatment [a]	***M1a*** **n=629**	***M1b*** **n=249**	***M1c*** **n=1,204**
Age in years, median (25-75% quantile)	67.9 (60.9-74.7)	65.9 (59.6-73.1)	64.3 (58.4-70.7)
< 65 years	246 (39.1%)	111 (44.6%)	646 (53.7%)
≥ 65 years	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 in kg/m^2, mean (±StD)	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%)	1,017 (84.5%)
Comorbidities according to the CCI [b]			
CCI =0 [b]	311 (49.4%)	139 (55.8%)	723 (60.0%)
CCI =1-2 [b]	244 (38.8%)	84 (33.7%)	388 (32.2%)
CCI =3-4 [b]	59 (9.4%)	23 (9.2%)	70 (5.8%)
CCI ≥5[b]	15 (2.4%)	3 (1.2%)	23 (1.9%)
Other comorbidities [c]			
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			
Non-squamous	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) [c]			
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%)
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%)
Wildtype	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%)
Wildtype	82 (13.0%)	24 (9.6%)	139 (11.5%)
Unknown/No testing	474 (75.4%)	194 (77.9%)	880 (73.1%)

Supplement Table 1

Table S1. Patient and tumour characteristics of the total cohort

Characteristics at start of first-line treatment [a]	***M1a*** **n=1,108**	***M1b*** **n=472**	***M1c*** **n=2,263**
Age in years, median (25-75% quantile)	68.2 (61.3-74.6)	66.1 (60.3-73.3)	64.6 (58.6-70.8)
< 65 years	418 (37.7%)	204 (43.2%)	1,174 (51.9%)
≥ 65 years	690 (62.3%)	268 (56.8%)	1,089 (48.1%)
Sex			
Female	388 (35.0%)	192 (40.7%)	876 (38.7%)
Male	720 (65.0%)	280 (59.3%)	1,387 (61.3%)
BMI in kg/m^2, mean (±StD)	25.3 (5.05)	25.0 (4.81)	25.1 (5.01)
<20	126 (11.4%)	64 (13.6%)	277 (12.2%)
20-25	458 (41.3%)	184 (39.0%)	967 (42.7%)
25-30	357 (32.2%)	149 (31.6%)	695 (30.7%)
≥30	158 (14.3%)	67 (14.2%)	296 (13.1%)
Missing	9 (0.8%)	8 (1.7%)	28 (1.2%)
Patients with any comorbidity	982 (88.6%)	392 (83.1%)	1,901 (84.0%)
Comorbidities according to the CCI [b]			
CCI =0 [b]	561 (50.6%)	259 (54.9%)	1,330 (58.8%)
CCI =1-2 [b]	430 (38.8%)	170 (36.0%)	759 (33.5%)
CCI =3-4 [b]	93 (8.4%)	36 (7.6%)	136 (6.0%)
CCI ≥5[b]	24 (2.2%)	7 (1.5%)	35 (1.5%)
Missing	0 (0.0%)	0 (0.0%)	3 (0.1%)
Other comorbidities [c]			
Arterial hypertension	533 (48.1%)	202 (42.8%)	986 (43.6%)
Diabetes without end organ damage	162 (14.6%)	61 (12.9%)	273 (12.1%)
Vasosclerosis	220 (19.9%)	68 (14.4%)	326 (14.4%)
Performance status			
ECOG 0	394 (35.6%)	182 (38.6%)	816 (36.1%)
ECOG 1	714 (64.4%)	290 (61.4%)	1,447 (63.9%)
Smoking status (at inclusion)			
Current smoker	319 (28.8%)	150 (31.8%)	819 (36.2%)
Former smoker (heavy)	418 (37.7%)	193 (40.9%)	795 (35.1%)
Former smoker (intensity unknown)	81 (7.3%)	31 (6.6%)	162 (7.2%)
Former smoker (light)	102 (9.2%)	33 (7.0%)	173 (7.6%)
Never smoker	108 (9.7%)	24 (5.1%)	134 (5.9%)
Unknown	79 (7.1%)	39 (8.3%)	177 (7.8%)
Missing	1 (0.1%)	2 (0.4%)	3 (0.1%)
LDH > ULN			
Yes	353 (31.9%)	178 (37.7%)	1028 (45.4%)
Unknown	117 (10.6%)	67 (14.2%)	289 (12.8%)
Missing	0 (0.0%)	0 (0.0%)	5 (0.2%)

Histology			
Non-squamous	799 (72.1%)	351 (74.4%)	1,833 (81.0%)
Adenocarcinoma	752 (94.1%)	318 (90.6%)	1,676 (91.4%)
Large cell carcinoma	10 (1.3%)	10 (2.8%)	54 (2.9%)
Others	37 (4.6%)	23 (6.6%)	103 (5.6%)
Squamous	309 (27.9%)	121 (25.6%)	430 (19.0%)
T status (at inclusion)			
T1	84 (7.6%)	59 (12.5%)	236 (10.4%)
T2	170 (15.3%)	91 (19.3%)	423 (18.7%)
T3	205 (18.5%)	94 (19.9%)	429 (19.0%)
T4	500 (45.1%)	190 (40.3%)	931 (41.1%)
TX	149 (13.4%)	38 (8.1%)	242 (10.7%)
Missing	0 (0.0%)	0 (0.0%)	2 (0.1%)
N status (at inclusion)			
N0	203 (18.3%)	65 (13.8%)	223 (9.9%)
N1	99 (8.9%)	53 (11.2%)	219 (9.7%)
N2	335 (30.2%)	150 (31.8%)	701 (31.0%)
N3	317 (28.6%)	154 (32.6%)	875 (38.7%)
NX	154 (13.9%)	50 (10.6%)	245 (10.8%)
Selected metastatic sites (at inclusion) [c]			
Adrenal gland	0 (0.0%)	94 (19.9%)	656 (29.0%)
Bone	0 (0.0%)	112 (23.7%)	1,044 (46.1%)
Brain	0 (0.0%)	147 (31.1%)	798 (35.3%)
Extrathoracic lymph nodes	0 (0.0%)	56 (11.9%)	512 (22.6%)
Liver	0 (0.0%)	43 (9.1%)	529 (23.4%)
Lung (contralateral)	490 (44.2%)	20 (4.2%)	475 (21.0%)
Pleura	299 (27.0%)	15 (3.2%)	266 (11.8%)
PD-L1 expression (at inclusion)			
TPS ≥50%	215 (19.4%)	121 (25.6%)	511 (22.6%)
TPS 1-49%	274 (24.7%)	112 (23.7%)	542 (24.0%)
TPS <1%	131 (11.8%)	37 (7.8%)	243 (10.7%)
TPS unknown, documented positive	42 (3.8%)	17 (3.6%)	65 (2.9%)
TPS unknown, documented negative	138 (12.5%)	51 (10.8%)	272 (12.0%)
Test result documented as unknown	4 (0.4%)	0 (0.0%)	7 (0.3%)
No PD-L1 testing	303 (27.3%)	134 (28.4%)	623 (27.5%)
Missing	1 (0.1%)	0 (0.0%)	0 (0.0%)
KRAS mutation status (at inclusion)			
Mutant	236 (21.3%)	92 (19.5%)	503 (22.2%)
Wildtype	267 (24.1%)	134 (28.4%)	621 (27.4%)
Test result documented as unknown	1 (0.1%)	1 (0.2%)	1 (0.0%)
Unknown/No testing	604 (54.5%)	245 (51.9%)	1,138 (50.3%)
TP53 mutation status (at inclusion)			
Mutant	165 (14.9%)	76 (16.1%)	402 (17.8%)
Wildtype	167 (15.1%)	62 (13.1%)	314 (13.9%)
Unknown/No testing	776 (70.0%)	334 (70.8%)	1,546 (68.3%)
Missing	0 (0.0%)	0 (0.0%)	1 (0.0%)

Toxicity	46 (7.7%)	18 (7.5%)	112 (9.7%)
Progression	223 (37.1%)	83 (34.7%)	457 (39.7%)
According to protocol/guidelines	127 (21.1%)	60 (25.1%)	205 (17.8%)
Other [b]	203 (33.8%)	75 (31.4%)	372 (32.3%)
Missing	2 (0.3%)	3 (1.3%)	5 (0.4%)
First line treatment ongoing			
Registry-maximum clinical response [c]			
CR	12 (2.0%)	6 (2.5%)	12 (1.0%)
PR	172 (28.6%)	79 (33.1%)	337 (29.3%)
SD	184 (30.6%)	77 (32.2%)	290 (25.2%)
PD	107 (17.8%)	32 (13.4%)	249 (21.6%)
Unknown	126 (21.0%)	45 (18.8%)	263 (22.8%)
Not yet documented			
Time to second line treatment			
Events (start of second line treatment or death)	508 (80.8%)	188 (75.5%)	975 (81.0%)
Duration in months, median (95% CI)	7.1 (6.5-7.8)	8.0 (6.4-9.6)	5.7 (5.4-6.1)

Supplement Table 2

Table S2: Treatment characteristics and best response of patients in the outcome sample (recruited until June 30, 2019)

Characteristic at start of first-line treatment [a]	***M1a*** **n=629**	***M1b*** **n=249**	***M1c*** **n=1,204**
Patients with completed first-line treatments	601 (95.5%)	239 (96.0%)	1,151 (95.6%)
Treatment duration [months], median (25-75% quartile)	3.4 (2.0-6.0)	3.0 (1.6-5.6)	3.0 (1.4-5.5)
Reason for end of treatment			
Toxicity	46 (7.3%)	18 (7.2%)	112 (9.3%)
Progression	223 (35.5%)	83 (33.3%)	457 (38.0%)
According to protocol/guidelines	127 (20.2%)	60 (24.1%)	205 (17.0%)
Other [b]	203 (32.3%)	75 (30.1%)	372 (30.9%)
Missing	2 (0.3%)	3 (1.2%)	5 (0.4%)
First-line ongoing	28 (4.5%)	10 (4.0%)	53 (4.4%)
Registry-best response [c]			
CR	12 (1.9%)	6 (2.4%)	12 (1.0%)
PR	172 (27.3%)	79 (31.7%)	337 (28.0%)
SD	184 (29.3%)	77 (30.9%)	290 (24.1%)
PD	107 (17.0%)	32 (12.9%)	249 (20.7%)
Unknown	126 (20.0%)	45 (18.1%)	263 (21.8%)
First-line ongoing	28 (4.5%)	10 (4.0%)	53 (4.4%)
Time to next treatment (TTNT)			
Events (start of next treatment or death)	508 (80.8%)	188 (75.5%)	975 (81.0%)
TTNT in months, median (95% CI)	7.1 (6.5-7.8)	8.0 (6.4-9.6)	5.7 (5.4-6.1)

Supplement Table 3

Table S3: Long-term overall survival (A) and long-term follow up (B)

A

	M1a	M1b	M1c	Total
Patients (N)	**629**	**249**	**1204**	**2082**
Overall Survival (months)				
Events n (%)	399 (63.4%)	144 (57.8%)	830 (68.9%)	1373 (65.9%)
Median [95% CI]	16.4 [14.3, 18.3]	17.8 [15.0, 21.4]	10.9 [9.8, 11.9]	13.2 [12.1, 14.0]
25% quantile [95% CI]	7.0 [5.8, 7.9]	6.3 [5.3, 9.0]	4.6 [4.2, 5.2]	5.4 [5.1, 5.7]
75% quantile [95% CI]	37.0 [32.1, 46.3]	49.4 [37.6, NA]	28.7 [24.8, 33.4]	33.3 [30.3, 40.4]
3-months rate [95% CI]	90.4% [87.8, 92.5]	88.5% [83.8, 91.9]	84.3% [82.1, 86.3]	86.7% [85.1, 88.1]
6-months rate [95% CI]	77.9% [74.4, 81.1]	75.6% [69.6, 80.6]	67.6% [64.8, 70.3]	71.7% [69.7, 73.6]
9-months rate [95% CI]	68.9% [65.0, 72.4]	69.8% [63.5, 75.3]	55.9% [52.9, 58.8]	61.5% [59.3, 63.6]
12-months rate [95% CI]	59.1% [54.9, 63.0]	64.7% [58.2, 70.5]	46.6% [43.6, 49.6]	52.6% [50.3, 54.8]
24-months rate [95% CI]	37.4% [33.2, 41.6]	40.7% [33.9, 47.4]	29.1% [26.3, 31.9]	33.0% [30.8, 35.3]
36-months rate [95% CI]	25.4% [21.3, 29.6]	32.6% [25.6, 39.7]	21.7% [19.1, 24.5]	24.0% [21.9, 26.3]
48-months rate [95% CI]	20.1% [15.8, 24.8]	25.8% [18.1, 34.3]	17.6% [14.5, 20.9]	19.3% [16.8, 21.8]
60-months rate [95% CI]	19.2% [14.7, 24.1]	22.6% [14.1, 32.4]	14.4% [10.3, 19.1]	17.0% [14.1, 20.1]

B

	M1a	M1b	M1c	Total
Patients (N)	**629**	**249**	**1204**	**2082**
Follow-up time (months)				
Events n (%)	399 (63.4%)	144 (57.8%)	830 (68.9%)	1373 (65.9%)
Median [95% CI]	32.4 [30.2, 34.9]	29.0 [27.0, 32.3]	32.5 [30.7, 33.6]	32.2 [30.7, 32.9]
25% quantile [95% CI]	19.6 [16.5, 22.6]	19.0 [14.6, 24.6]	21.1 [17.3, 23.2]	19.9 [17.8, 21.7]
75% quantile [95% CI]	43.3 [40.2, 48.6]	39.7 [33.4, 47.1]	41.1 [39.5, 43.2]	41.7 [39.9, 43.5]
3-months FU rate [95% CI]	95.7% [93.7%, 97.0%]	95.3% [91.7%, 97.4%]	95.5% [94.1%, 96.5%]	95.5% [94.5%, 96.3%]
6-months FU rate [95% CI]	93.2% [90.8%, 95.0%]	91.4% [86.8%, 94.4%]	91.3% [89.3%, 92.9%]	91.9% [90.5%, 93.1%]
9-months FU rate [95% CI]	88.6% [85.6%, 91.1%]	88.0% [82.8%, 91.8%]	86.9% [84.5%, 89.0%]	87.6% [85.9%, 89.1%]
12-months FU rate [95% CI]	86.4% [83.1%, 89.2%]	83.1% [77.0%, 87.8%]	84.5% [81.8%, 86.8%]	84.9% [83.0%, 86.6%]
24-months FU rate [95% CI]	68.9% [63.7%, 73.5%]	68.1% [59.8%, 75.0%]	71.4% [67.4%, 75.0%]	70.0% [67.1%, 72.7%]
36-months FU rate [95% CI]	42.1% [35.5%, 48.5%]	28.4% [19.6%, 37.7%]	38.3% [32.9%, 43.6%]	38.0% [34.2%, 41.8%]
48-months FU rate [95% CI]	19.8% [14.1%, 26.2%]	14.0% [7.3%, 22.7%]	10.9% [7.3%, 15.2%]	14.2% [11.3%, 17.5%]
60-months FU rate [95% CI]	5.8% [2.6%, 10.8%]	1.8% [0.2%, 8.1%]	1.2% [0.2%, 3.7%]	2.8% [1.5%, 4.9%]

Supplement Table 4

Table S4: Radiotherapy in the outcome sample (recruited until June 30, 2019) (A+B) and in the amalgamated low-risk and high-risk group (C+D)

A

	M1a	M1b	M1c	Total
Patients (N)	**629**	**249**	**1204**	**2082**
Any palliative radiotherapy				
Yes n (%)	169 (26.9%)	125 (50.2%)	656 (54.5%)	950 (45.6%)
Potential n (%)	75 (11.9%)	25 (10.0%)	78 (6.5%)	178 (8.5%)
No n (%)	380 (60.4%)	99 (39.8%)	463 (38.5%)	942 (45.2%)
Missing n (%)	5 (0.8%)	0 (0.0%)	7 (0.6%)	12 (0.6%)
Area of radiation				
Brain n (%)	55 (8.7%)	67 (26.9%)	349 (29.0%)	471 (22.6%)
Bone n (%)	39 (6.2%)	33 (13.3%)	251 (20.8%)	323 (15.5%)
Thorax n (%)	93 (14.8%)	48 (19.3%)	157 (13.0%)	298 (14.3%)
Other n (%)	24 (3.8%)	27 (10.8%)	99 (8.2%)	150 (7.2%)
Missing n (%)	2 (0.3%)	0 (0.0%)	2 (0.2%)	4 (0.2%)
Type of radiotherapy				
Brachytherapy n (%)	3 (0.5%)	5 (2.0%)	6 (0.5%)	14 (0.7%)
Conventional RT n (%)	108 (17.2%)	76 (30.5%)	469 (39.0%)	653 (31.4%)
Stereotactic RT n (%)	19 (3.0%)	40 (16.1%)	113 (9.4%)	172 (8.3%)
Radio-Chemotherapy n (%)	26 (4.1%)	16 (6.4%)	57 (4.7%)	99 (4.8%)
Other n (%)	19 (3.0%)	9 (3.6%)	55 (4.6%)	83 (4.0%)
Unknown n (%)	10 (1.6%)	11 (4.4%)	46 (3.8%)	67 (3.2%)
Missing n (%)	2 (0.3%)	0 (0.0%)	4 (0.3%)	6 (0.3%)

B

	M1a	M1b	M1c	Total
Patients (N)	**629**	**249**	**1204**	**2082**
Total dose (Gy)				
n	176	149	705	1030
Mean	39.7	38.0	34.3	35.8
± StD	19.32	14.73	12.72	14.50
Median	38.3	35.0	30.0	35.0
25-75% quantiles	30.0 - 50.0	30.0 - 48.0	30.0 - 40.0	30.0 - 42.0
Number of treatment days (fractions)				
n	169	144	680	993
Mean	14.5	12.4	11.0	11.8
± StD	9.64	9.40	7.00	7.98
Median	13.0	10.0	10.0	10.0
25-75% quantiles	8.0 - 20.0	5.0 - 18.5	5.0 - 14.0	5.0 - 15.0

C

	Low risk	High risk	Unknown risk	Total
Patients (N)	**1731**	**336**	**15**	**2082**
Any palliative radiotherapy				
Yes n (%)	806 (46.6%)	140 (41.7%)	4 (26.7%)	950 (45.6%)
Potential n (%)	164 (9.5%)	12 (3.6%)	2 (13.3%)	178 (8.5%)
No n (%)	755 (43.6%)	180 (53.6%)	7 (46.7%)	942 (45.2%)
Missing n (%)	6 (0.3%)	4 (1.2%)	2 (13.3%)	12 (0.6%)
Area of radiation				
Brain n (%)	405 (23.4%)	65 (19.3%)	1 (6.7%)	471 (22.6%)
Bone n (%)	250 (14.4%)	71 (21.1%)	2 (13.3%)	323 (15.5%)
Thorax n (%)	271 (15.7%)	25 (7.4%)	2 (13.3%)	298 (14.3%)
Other n (%)	131 (7.6%)	19 (5.7%)	0 (0.0%)	150 (7.2%)
Missing n (%)	4 (0.2%)	0 (0.0%)	0 (0.0%)	4 (0.2%)
Type of radiotherapy				
Brachytherapy n (%)	14 (0.8%)	0 (0.0%)	0 (0.0%)	14 (0.7%)
Conventional RT n (%)	543 (31.4%)	107 (31.8%)	3 (20.0%)	653 (31.4%)
Stereotactic RT n (%)	152 (8.8%)	19 (5.7%)	1 (6.7%)	172 (8.3%)
Radio-Chemotherapy n (%)	91 (5.3%)	7 (2.1%)	1 (6.7%)	99 (4.8%)
Other n (%)	68 (3.9%)	15 (4.5%)	0 (0.0%)	83 (4.0%)
Unknown n (%)	60 (3.5%)	7 (2.1%)	0 (0.0%)	67 (3.2%)
Missing n (%)	6 (0.3%)	0 (0.0%)	0 (0.0%)	6 (0.3%)

D

	Low risk	High risk	Unknown risk	Total
Patients (N)	**1731**	**336**	**15**	**2082**
Total dose (Gy)				
n	876	149	5	1030
Mean	35.9	34.8	38.5	35.8
± StD	14.82	12.43	17.12	14.50
Median	35.0	32.4	37.5	35.0
25-75% quantiles	30.0 - 43.1	30.0 - 40.0	30.0 - 39.0	30.0 - 42.0
Number of treatment days (fractions)				
n	845	143	5	993
Mean	12.0	10.5	12.4	11.8
± StD	8.21	6.38	7.99	7.98
Median	10.0	10.0	13.0	10.0
25-75% quantiles	5.0 - 15.0	5.0 - 14.0	10.0 - 15.0	5.0 - 15.0

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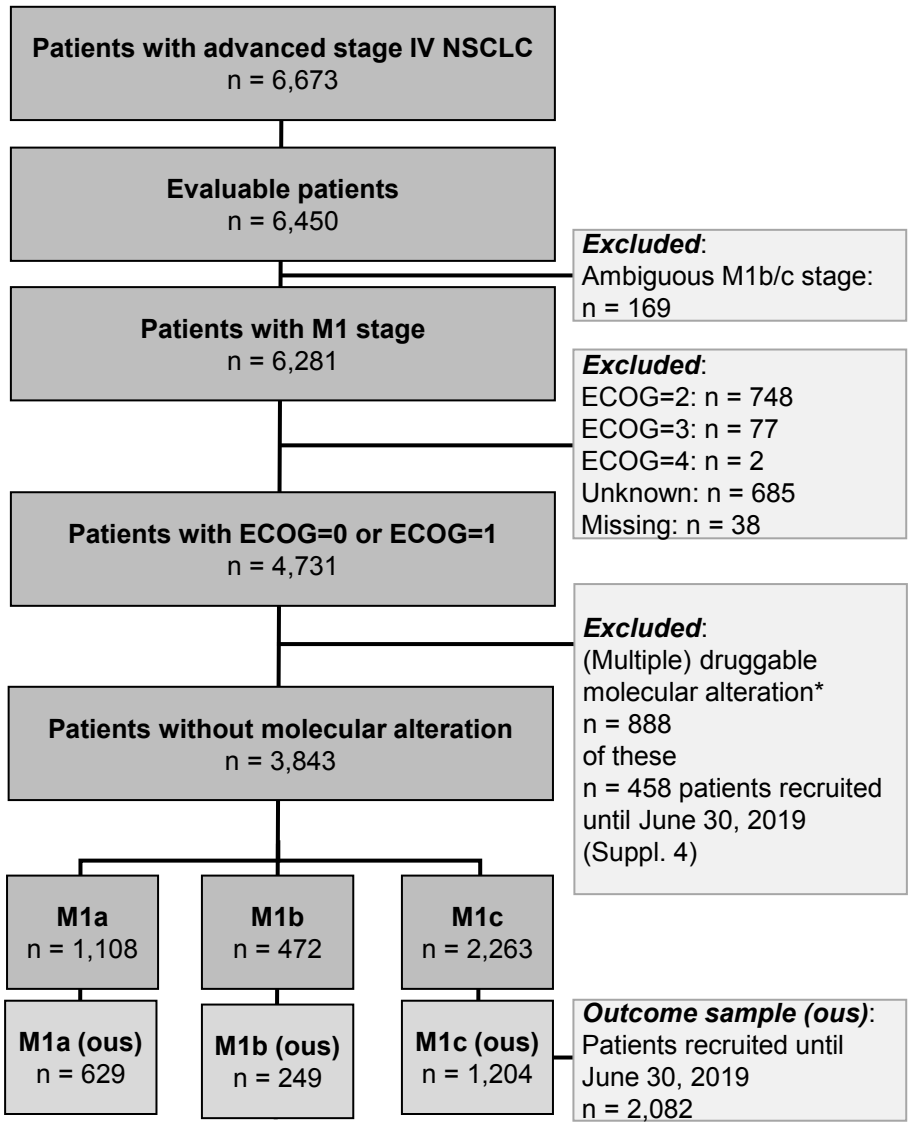
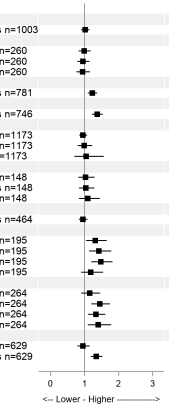

Patients with advanced stage IV NSCLC
n = 6,673
Evaluable patients
n = 6,450
Excluded:
Ambiguous M1b/c stage:
n = 169
Patients with M1 stage
n = 6,281
Excluded:
ECOG=2: n = 748
ECOG=3: n = 77
ECOG=4: n = 2
Unknown: n = 685
Missing: n = 38
Patients with ECOG=0 or ECOG=1
n = 4,731
Excluded:
(Multiple) druggable molecular alteration*
n = 888
of these
n = 458 patients recruited until June 30, 2019 (Suppl. 4)
Patients without molecular alteration
n = 3,843
M1a
n = 1,108
M1b
n = 472
M1c
n = 2,263
M1a (ous)
n = 629
M1b (ous)
n = 249
M1c (ous)
n = 1,204
Outcome sample (ous):
Patients recruited until June 30, 2019
n = 2,082

Figure 1
Patient flow chart of all patients with advanced stage IV NSCLC included in this analysis, starting from the total number of patients recruited into the CRISP registry from December 2015 until December 31, 2021. Outcome analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019 (outcome sample). *All patients with alterations in EGFR, 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 until June 30, 2019 and are included in Suppl. Fig. 4 **Abbreviations**: ECOG, Eastern Cooperative Oncology Group; ous, outcome sample.

A

Cox proportional hazards model

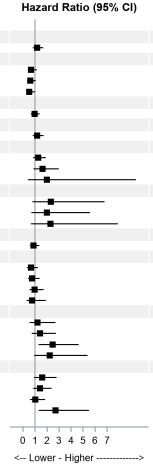
Variable		Hazard Ratio (95% CI)	HR	95% CI	p
Age group					
>=65 years vs <65 years	n=1079 vs n=1003		1.02	0.90-1.14	0.798
BMI group					
20-25 vs <20	n=885 vs n=260		0.99	0.83-1.18	0.902
25-30 vs <20	n=655 vs n=260		0.94	0.79-1.14	0.546
>=30 vs <20	n=282 vs n=260		0.94	0.76-1.16	0.561
Sex					
Male vs female	n=1301 vs n=781		1.23	1.10-1.37	<0.001***
ECOG Performance Status					
1 vs 0	n=1336 vs n=746		1.37	1.22-1.54	<0.001***
Charlson score					
1-2 vs 0	n=716 vs n=1173		0.95	0.85-1.07	0.417
3-4 vs 0	n=152 vs n=1173		0.99	0.80-1.22	0.921
>=5 vs 0	n=41 vs n=1173		1.04	0.70-1.56	0.842
Smoking status					
Current smoker vs Never smoker	n=676 vs n=148		1.03	0.82-1.29	0.811
Ex-smoker vs Never smoker	n=1086 vs n=148		1.04	0.84-1.29	0.737
Unknown/Missing vs Never smoker	n=172 vs n=148		1.10	0.83-1.44	0.516
Histology					
Non-squamous vs Squamous	n=1618 vs n=464		0.95	0.83-1.08	0.438
T status					
T2 vs T1	n=387 vs n=195		1.31	1.05-1.65	0.019*
T3 vs T1	n=398 vs n=195		1.42	1.13-1.78	0.003**
T4 vs T1	n=871 vs n=195		1.48	1.20-1.82	<0.001***
TX vs T1	n=231 vs n=195		1.18	0.90-1.55	0.236
N status					
N1 vs N0	n=195 vs n=264		1.15	0.90-1.46	0.258
N2 vs N0	n=863 vs n=264		1.45	1.20-1.75	<0.001***
N3 vs N0	n=718 vs n=264		1.33	1.10-1.61	0.003**
NX vs N0	n=242 vs n=264		1.40	1.09-1.79	0.008**
M status					
M1b vs M1a	n=249 vs n=629		0.95	0.79-1.15	0.618
M1c vs M1a	n=1204 vs n=629		1.34	1.19-1.52	<0.001***



B

Cox proportional hazards model

Variable		Hazard Ratio (95% CI)	HR	95% CI	p
Age group					
>=65 years vs <65 years	n=138 vs n=111		1.17	0.81-1.68	0.404
BMI group					
20-25 vs <20	n=101 vs n=35		0.66	0.39-1.13	0.130
25-30 vs <20	n=78 vs n=35		0.61	0.35-1.06	0.080
>=30 vs <20	n=35 vs n=35		0.51	0.26-1.00	0.049*
Sex					
Male vs female	n=144 vs n=105		0.95	0.65-1.38	0.797
ECOG Performance Status					
1 vs 0	n=148 vs n=101		1.18	0.81-1.71	0.402
Charlson score					
1-2 vs 0	n=84 vs n=139		1.27	0.85-1.89	0.244
3-4 vs 0	n=23 vs n=139		1.62	0.88-2.96	0.121
>=5 vs 0	n=3 vs n=139		1.99	0.42-9.40	0.385
Smoking status					
Current smoker vs Never smoker	n=81 vs n=11		2.32	0.80-6.79	0.123
Ex-smoker vs Never smoker	n=140 vs n=11		1.99	0.71-5.60	0.194
Unknown/Missing vs Never smoker	n=17 vs n=11		2.30	0.67-7.90	0.187
Histology					
Non-squamous vs Squamous	n=192 vs n=57		0.87	0.56-1.35	0.534
T status					
T2 vs T1	n=51 vs n=31		0.65	0.34-1.23	0.182
T3 vs T1	n=49 vs n=31		0.75	0.41-1.39	0.367
T4 vs T1	n=99 vs n=31		0.96	0.54-1.70	0.888
TX vs T1	n=19 vs n=31		0.75	0.30-1.89	0.543
N status					
N1 vs N0	n=25 vs n=34		1.21	0.54-2.70	0.649
N2 vs N0	n=80 vs n=34		1.41	0.73-2.73	0.301
N3 vs N0	n=86 vs n=34		2.45	1.30-4.62	0.006**
NX vs N0	n=24 vs n=34		2.24	0.93-5.38	0.072
Selected organ sites					
Bone vs Other	n=51 vs n=49		1.61	0.92-2.80	0.094
Brain vs Other	n=77 vs n=49		1.41	0.83-2.38	0.205
Gland vs Other	n=54 vs n=49		1.03	0.57-1.85	0.933
Liver vs Other	n=18 vs n=49		2.70	1.33-5.49	0.006**



C

Cox proportional hazards model

Variable		Hazard Ratio (95% CI)	HR	95% CI	p
Age group					
>=65 years vs <65 years	n=558 vs n=646		0.99	0.85-1.15	0.894
BMI group					
20-25 vs <20	n=527 vs n=146		1.03	0.82-1.29	0.822
25-30 vs <20	n=382 vs n=146		0.95	0.75-1.21	0.679
>=30 vs <20	n=149 vs n=146		0.95	0.71-1.27	0.731
Sex					
Male vs female	n=747 vs n=457		1.25	1.08-1.45	0.003**
ECOG Performance Status					
1 vs 0	n=777 vs n=427		1.37	1.18-1.59	<0.001***
Charlson score					
1-2 vs 0	n=388 vs n=723		0.87	0.75-1.02	0.079
3-4 vs 0	n=70 vs n=723		1.12	0.83-1.50	0.468
>=5 vs 0	n=23 vs n=723		1.34	0.81-2.22	0.254
Smoking status					
Current smoker vs Never smoker	n=420 vs n=76		1.00	0.74-1.36	0.989
Ex-smoker vs Never smoker	n=603 vs n=76		1.05	0.78-1.41	0.740
Unknown/Missing vs Never smoker	n=105 vs n=76		1.04	0.72-1.49	0.833
Histology					
Non-squamous vs Squamous	n=972 vs n=232		0.93	0.78-1.11	0.433
T status					
T2 vs T1	n=233 vs n=130		1.54	1.16-2.03	0.003**
T3 vs T1	n=226 vs n=130		1.67	1.26-2.22	<0.001***
T4 vs T1	n=491 vs n=130		1.57	1.21-2.03	<0.001***
TX vs T1	n=124 vs n=130		1.31	0.93-1.85	0.123
N status					
N1 vs N0	n=113 vs n=120		0.99	0.71-1.38	0.955
N2 vs N0	n=387 vs n=120		1.43	1.10-1.86	0.007**
N3 vs N0	n=460 vs n=120		1.16	0.90-1.50	0.262
NX vs N0	n=124 vs n=120		1.27	0.90-1.78	0.168
Number of metastatic organ sites (total)					
4+ vs 1-3 sites	n=129 vs n=1075		1.69	1.36-2.10	<0.001***

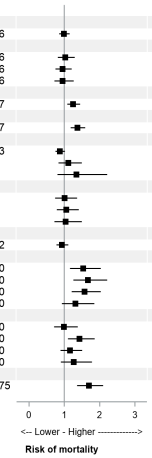


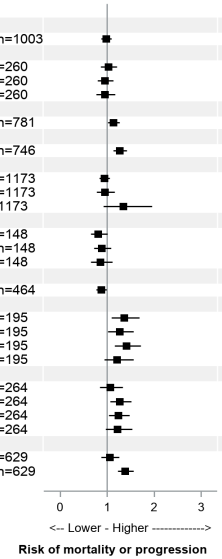
Figure 2

Cox proportional hazards models for overall survival for (**A)** the whole outcome sample (n=2,082), for (**B**) patients with M1b by selected organ sites (n=249) and for (**C**) patients with M1c by number of metastatic organ sites (n=1,204). Analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. The parameters shown are an exhaustive list of co-variables used for the Cox proportional hazards models. * $p \leq 0{\cdot}05$, ** $p \leq 0{\cdot}01$, *** $p \leq 0{\cdot}001$. **Abbreviations**: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

A

Cox proportional hazards model

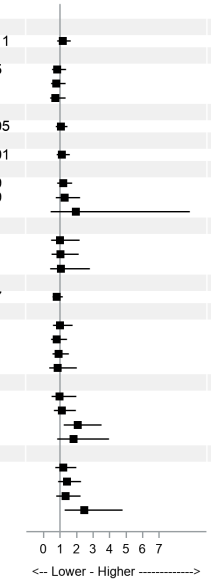
Variable		HR	95% CI	p
Age group				
>=65 years vs <65 years	n=1079 vs n=1003	0.98	0.88-1.10	0.732
BMI group				
20-25 vs <20	n=885 vs n=260	1.02	0.87-1.21	0.780
25-30 vs <20	n=655 vs n=260	0.95	0.79-1.13	0.550
>=30 vs <20	n=282 vs n=260	0.95	0.77-1.17	0.615
Sex				
Male vs female	n=1301 vs n=781	1.13	1.02-1.26	0.025*
ECOG Performance Status				
1 vs 0	n=1336 vs n=746	1.27	1.13-1.42	<0.001***
Charlson score				
1-2 vs 0	n=716 vs n=1173	0.94	0.84-1.05	0.270
3-4 vs 0	n=152 vs n=1173	0.95	0.77-1.16	0.613
>=5 vs 0	n=41 vs n=1173	1.34	0.92-1.95	0.126
Smoking status				
Current smoker vs Never smoker	n=676 vs n=148	0.81	0.65-1.01	0.056
Ex-smoker vs Never smoker	n=1086 vs n=148	0.88	0.72-1.08	0.226
Unknown/Missing vs Never smoker	n=172 vs n=148	0.85	0.65-1.11	0.246
Histology				
Non-squamous vs Squamous	n=1618 vs n=464	0.87	0.76-0.99	0.031*
T status				
T2 vs T1	n=387 vs n=195	1.36	1.10-1.69	0.005**
T3 vs T1	n=398 vs n=195	1.26	1.01-1.57	0.036*
T4 vs T1	n=871 vs n=195	1.41	1.16-1.72	<0.001***
TX vs T1	n=231 vs n=195	1.21	0.94-1.56	0.136
N status				
N1 vs N0	n=195 vs n=264	1.06	0.85-1.34	0.595
N2 vs N0	n=663 vs n=264	1.27	1.06-1.52	0.009**
N3 vs N0	n=718 vs n=264	1.24	1.04-1.48	0.018*
NX vs N0	n=242 vs n=264	1.22	0.97-1.53	0.097
M status				
M1b vs M1a	n=249 vs n=629	1.05	0.88-1.26	0.597
M1c vs M1a	n=1204 vs n=629	1.38	1.22-1.56	<0.001***



B

Cox proportional hazards model

Variable		HR	95% CI	p
Age group				
>=65 years vs <65 years	n=138 vs n=111	1.16	0.82-1.63	0.400
BMI group				
20-25 vs <20	n=101 vs n=35	0.83	0.51-1.37	0.467
25-30 vs <20	n=78 vs n=35	0.78	0.46-1.32	0.351
>=30 vs <20	n=35 vs n=35	0.71	0.39-1.32	0.284
Sex				
Male vs female	n=144 vs n=105	1.04	0.74-1.45	0.823
ECOG Performance Status				
1 vs 0	n=148 vs n=101	1.12	0.80-1.57	0.518
Charlson score				
1-2 vs 0	n=84 vs n=139	1.19	0.83-1.72	0.337
3-4 vs 0	n=23 vs n=139	1.27	0.73-2.22	0.400
>=5 vs 0	n=3 vs n=139	1.95	0.43-8.86	0.385
Smoking status				
Current smoker vs Never smoker	n=81 vs n=11	0.99	0.45-2.17	0.978
Ex-smoker vs Never smoker	n=140 vs n=11	1.01	0.48-2.13	0.982
Unknown/Missing vs Never smoker	n=17 vs n=11	1.05	0.39-2.82	0.920
Histology				
Non-squamous vs Squamous	n=192 vs n=57	0.79	0.53-1.18	0.245
T status				
T2 vs T1	n=51 vs n=31	0.99	0.56-1.75	0.975
T3 vs T1	n=49 vs n=31	0.79	0.44-1.41	0.423
T4 vs T1	n=99 vs n=31	0.91	0.54-1.54	0.725
TX vs T1	n=19 vs n=31	0.84	0.35-2.01	0.702
N status				
N1 vs N0	n=25 vs n=34	0.98	0.48-2.00	0.954
N2 vs N0	n=80 vs n=34	1.11	0.62-1.97	0.729
N3 vs N0	n=86 vs n=34	2.06	1.21-3.52	0.008**
NX vs N0	n=24 vs n=34	1.82	0.83-3.97	0.133
Selected organ sites				
Bone vs Other	n=51 vs n=49	1.18	0.71-1.98	0.518
Brain vs Other	n=77 vs n=49	1.41	0.87-2.27	0.159
Gland vs Other	n=54 vs n=49	1.32	0.78-2.24	0.300
Liver vs Other	n=18 vs n=49	2.48	1.28-4.79	0.007**



C

Cox proportional hazards model

Variable		HR	95% CI	p
Age group				
>=65 years vs <65 years	n=558 vs n=646	1.00	0.87-1.15	0.994
BMI group				
20-25 vs <20	n=527 vs n=146	1.01	0.81-1.25	0.947
25-30 vs <20	n=382 vs n=146	0.91	0.72-1.14	0.401
>=30 vs <20	n=149 vs n=146	0.83	0.63-1.10	0.192
Sex				
Male vs female	n=747 vs n=457	1.10	0.95-1.26	0.198
ECOG Performance Status				
1 vs 0	n=777 vs n=427	1.24	1.08-1.43	0.003**
Charlson score				
1-2 vs 0	n=388 vs n=723	0.88	0.76-1.02	0.096
3-4 vs 0	n=70 vs n=723	0.98	0.73-1.31	0.880
>=5 vs 0	n=23 vs n=723	1.69	1.05-2.71	0.032*
Smoking status				
Current smoker vs Never smoker	n=420 vs n=76	0.81	0.61-1.09	0.173
Ex-smoker vs Never smoker	n=603 vs n=76	0.91	0.69-1.21	0.529
Unknown/Missing vs Never smoker	n=105 vs n=76	0.78	0.55-1.11	0.173
Histology				
Non-squamous vs Squamous	n=972 vs n=232	0.79	0.66-0.93	0.006**
T status				
T2 vs T1	n=233 vs n=130	1.65	1.26-2.16	<0.001***
T3 vs T1	n=226 vs n=130	1.53	1.17-2.01	0.002**
T4 vs T1	n=491 vs n=130	1.58	1.23-2.01	<0.001***
TX vs T1	n=124 vs n=130	1.42	1.04-1.96	0.029*
N status				
N1 vs N0	n=113 vs n=120	1.17	0.86-1.61	0.319
N2 vs N0	n=387 vs n=120	1.44	1.12-1.86	0.004**
N3 vs N0	n=460 vs n=120	1.22	0.95-1.57	0.115
NX vs N0	n=124 vs n=120	1.37	1.00-1.89	0.051
Number of metastatic organ sites (total)				
4+ vs 1-3 sites	n=129 vs n=1075	1.81	1.47-2.22	<0.001***

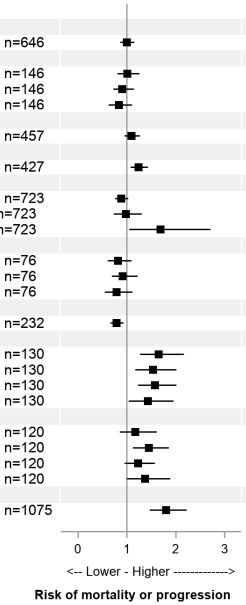
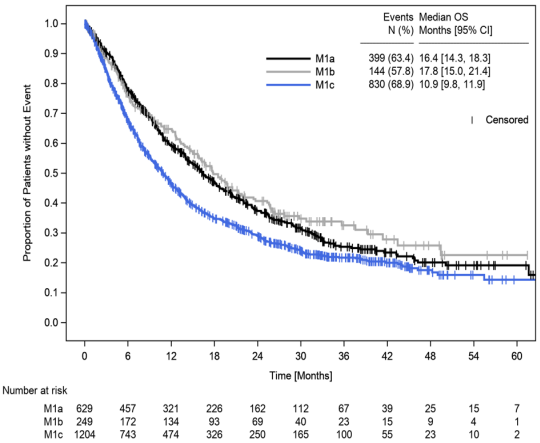


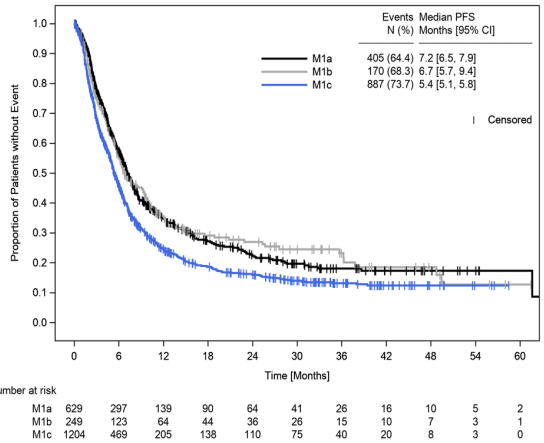
Figure 3

Cox proportional hazards models for progression-free survival for the whole outcome sample (**A**), patients with M1b by selected organ sites (**B**) and for patients with M1c by number of metastatic organ sites. Analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. The parameters shown are an exhaustive list of co-variables used for the Cox proportional hazards models. * $p \leq 0{\cdot}05$, ** $p \leq 0{\cdot}01$, *** $p \leq 0{\cdot}001$. **Abbreviations**: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

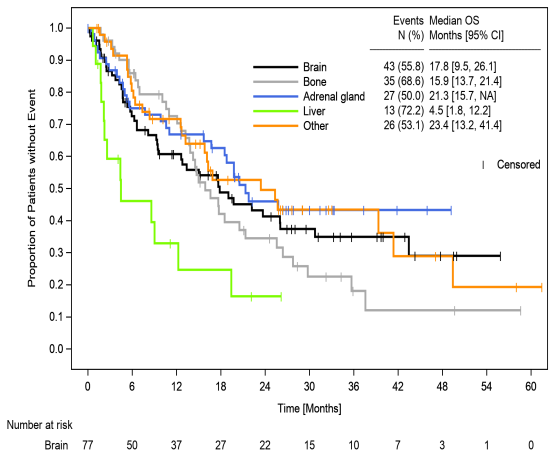
A


Events Median OS
N (%) Months [95% CI]
M1a 399 (63.4) 16.4 [14.3, 18.3]
M1b 144 (57.8) 17.8 [15.0, 21.4]
M1c 830 (68.9) 10.9 [9.8, 11.9]
Censored
Proportion of Patients without Event
Time [Months]
Number at risk
M1a 629 457 321 226 162 112 67 39 25 15 7
M1b 249 172 134 93 69 40 23 15 9 4 1
M1c 1204 743 474 326 250 165 100 55 23 10 2

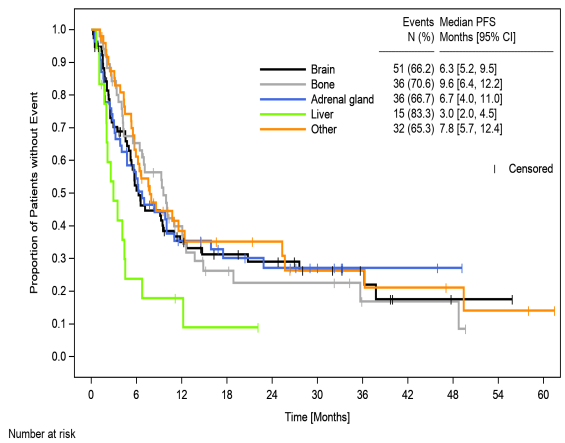
B


Events Median PFS
N (%) Months [95% CI]
M1a 405 (64.4) 7.2 [6.5, 7.9]
M1b 170 (68.3) 6.7 [5.7, 9.4]
M1c 887 (73.7) 5.4 [5.1, 5.8]
Censored
Proportion of Patients without Event
Time [Months]
Number at risk
M1a 629 297 139 90 64 41 26 16 10 5 2
M1b 249 123 64 44 36 26 15 10 7 3 1
M1c 1204 469 205 138 110 75 40 20 8 3 0

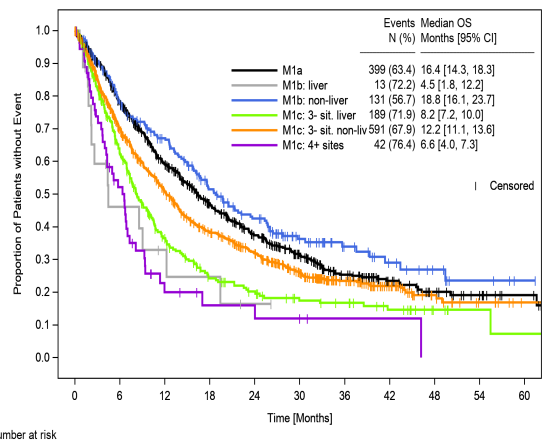
C


Events Median OS
N (%) Months [95% CI]
Brain 43 (55.8) 17.8 [9.5, 26.1]
Bone 35 (68.6) 15.9 [13.7, 21.4]
Adrenal gland 27 (50.0) 21.3 [15.7, NA]
Liver 13 (72.2) 4.5 [1.8, 12.2]
Other 26 (53.1) 23.4 [13.2, 41.4]
Censored
Proportion of Patients without Event
Time [Months]
Number at risk
Brain 77 50 37 27 22 15 10 7 3 1 0
Bone 51 41 32 17 13 7 3 2 2 1 0
Adrenal gland 54 37 33 28 17 10 4 2 1 0
Liver 18 7 4 3 1 0
Other 49 37 28 18 16 8 6 4 3 2 1

D


Events Median PFS
N (%) Months [95% CI]
Brain 51 (66.2) 6.3 [5.2, 9.5]
Bone 36 (70.6) 9.6 [6.4, 12.2]
Adrenal gland 36 (66.7) 6.7 [4.0, 11.0]
Liver 15 (83.3) 3.0 [2.0, 4.5]
Other 32 (65.3) 7.8 [5.7, 12.4]
Censored
Proportion of Patients without Event
Time [Months]
Number at risk
Brain 77 34 20 15 13 9 6 2 1 1 0
Bone 51 30 15 8 6 6 2 2 2 0
Adrenal gland 54 27 15 11 9 6 2 2 1 0
Liver 18 4 2 1 0
Other 49 28 12 9 8 5 5 4 3 2 1

E


Events Median OS
N (%) Months [95% CI]
M1a 399 (63.4) 16.4 [14.3, 18.3]
M1b: liver 13 (72.2) 4.5 [1.8, 12.2]
M1b: non-liver 131 (56.7) 18.8 [16.1, 23.7]
M1c: 3- sit. liver 189 (71.9) 8.2 [7.2, 10.0]
M1c: 3- sit. non-liv 591 (67.9) 12.2 [11.1, 13.6]
M1c: 4+ sites 42 (76.4) 6.6 [4.0, 7.3]
Censored
Proportion of Patients without Event
Time [Months]
Number at risk
M1a 629 457 321 226 162 112 67 39 25 15 7
M1b: liver 18 7 4 3 1 0
M1b: non-liver 231 165 130 90 68 40 23 15 9 4 1
M1c: 3- sit. liver 263 147 76 44 33 23 20 13 5 2 1
M1c: 3- sit. non-liv 871 560 382 269 206 134 77 41 18 8 1
M1c: 4+ sites 55 25 7 4 4 3 1 1 0

F

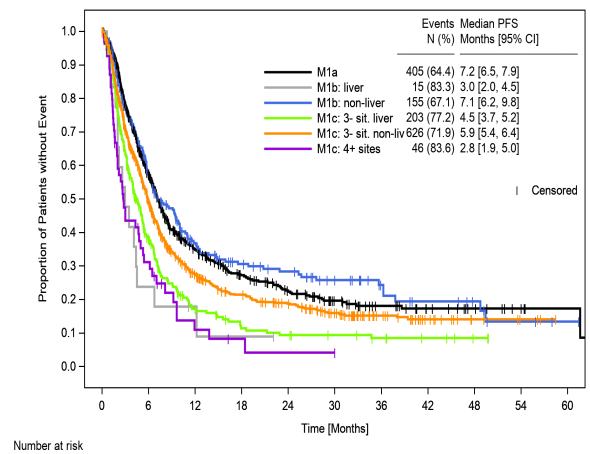
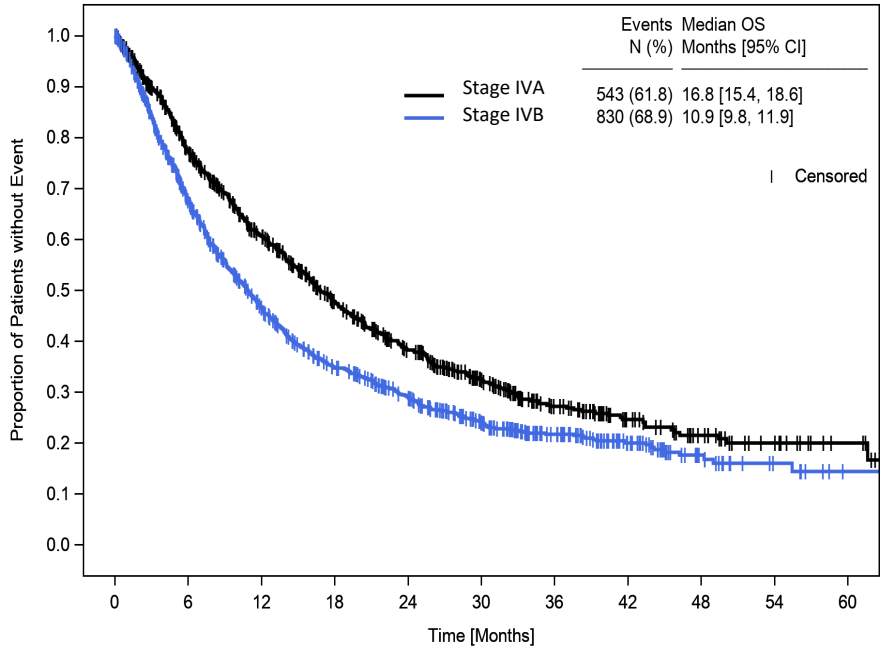

Events Median PFS
N (%) Months [95% CI]
M1a 405 (64.4) 7.2 [6.5, 7.9]
M1b: liver 15 (83.3) 3.0 [2.0, 4.5]
M1b: non-liver 155 (67.1) 7.1 [6.2, 9.8]
M1c: 3- sit. liver 203 (77.2) 4.5 [3.7, 5.2]
M1c: 3- sit. non-liv 626 (71.9) 5.9 [5.4, 6.4]
M1c: 4+ sites 46 (83.6) 2.8 [1.9, 5.0]
Censored
Proportion of Patients without Event
Time [Months]
Number at risk
M1a 629 297 139 90 64 41 26 16 10 5 2
M1b: liver 18 4 2 1 0
M1b: non-liver 231 119 62 43 36 26 15 10 7 3 1
M1c: 3- sit. liver 263 80 30 17 14 11 8 5 2 0
M1c: 3- sit. non-liv 871 368 167 117 94 63 32 15 6 3 0
M1c: 4+ sites 55 15 4 2 1 1 0

Figure 4

First-line Registry-OS and first-line PFS in patients with advanced NSCLC by M1a, M1b, M1c stage (**A** and **B**), by selected organ sites (for M1b) (**C** and **D**), by number of extrathoracic metastatic sites (for M1c) [n=1,189; n=15 of 1,204 are missing: patients with documented M1c but without information on the type of affected organs] for M1a and for M1b liver and non-liver (**E** and **F**). Analysis is based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. **Abbreviations**: CI, confidence interval; PFS, progression-free survival; OS, overall survival; 3- sit. liver, up to three metastatic sites including liver metastases; 3- sit. non-liv, up to three metastatic sites excluding liver metastases; 4+ sites, four and more metastatic sites;

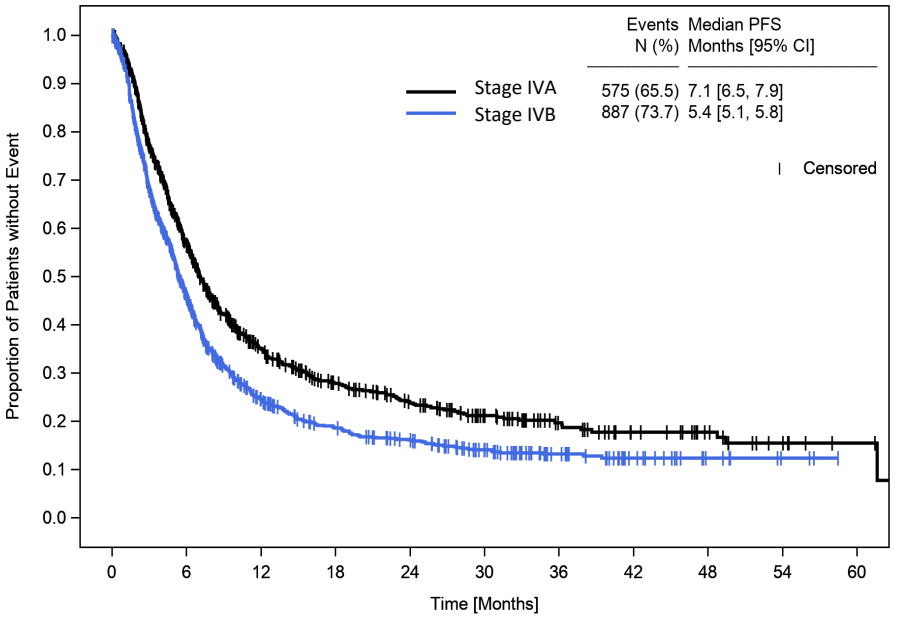
A



Number at risk

Stage IVA	878	629	455	319	231	152	90	54	34	19	8
Stage IVB	1204	743	474	326	250	165	100	55	23	10	2

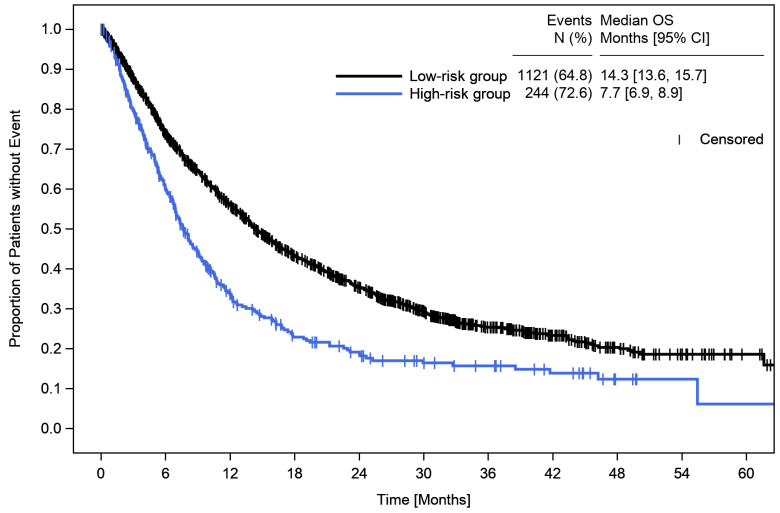
B



Number at risk

Stage IVA	878	420	203	134	100	67	41	26	17	8	3
Stage IVB	1204	469	205	138	110	75	40	20	8	3	0

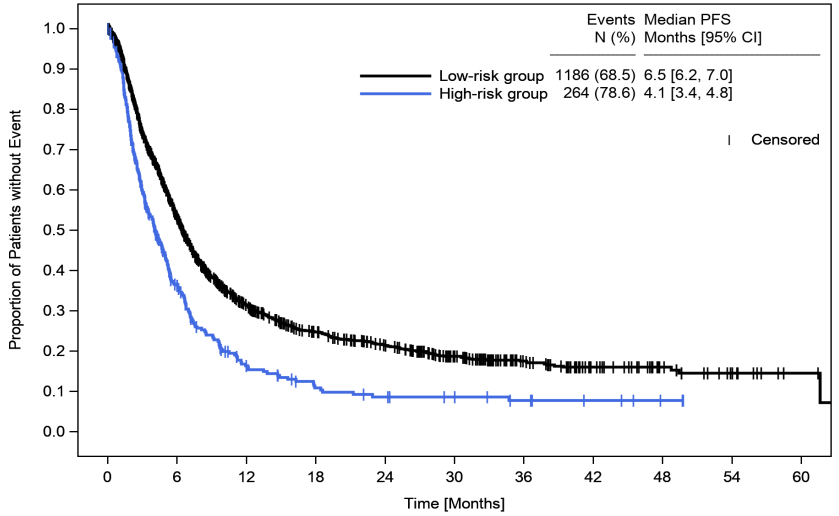
C



Number at risk

Low-risk group	1731	1182	833	585	436	286	167	95	52	27	9
High-risk group	336	179	87	51	38	26	21	14	5	2	1

D

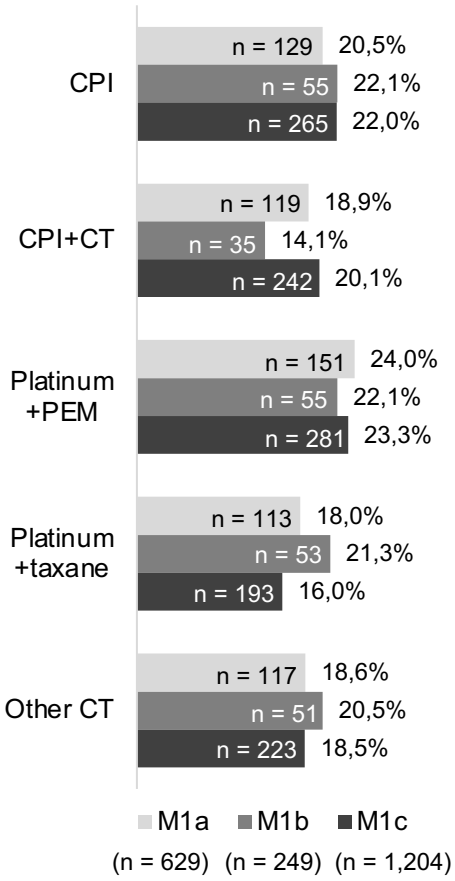


Number at risk

Low-risk group	1731	784	368	250	194	130	73	41	23	11	3
High-risk group	336	99	36	20	15	12	8	5	2	0	

Figure 5

First-line Registry-OS and first-line PFS in patients with advanced NSCLC by IVa and IVb stage according to recent IALSC staging system (**A** and **B**), for the amalgamated low-risk group (consisting of stage M1a, M1b non-liver and M1c 1-3 organ sites without liver) and the high-risk group (consisting of M1b liver, M1c 1-3organ sites with liver and M1c with ≥4 organ sites) (**C** and **D**). Analysis is based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. **Abbreviations**: CI, confidence interval; PFS, progression-free survival; OS, overall survival.

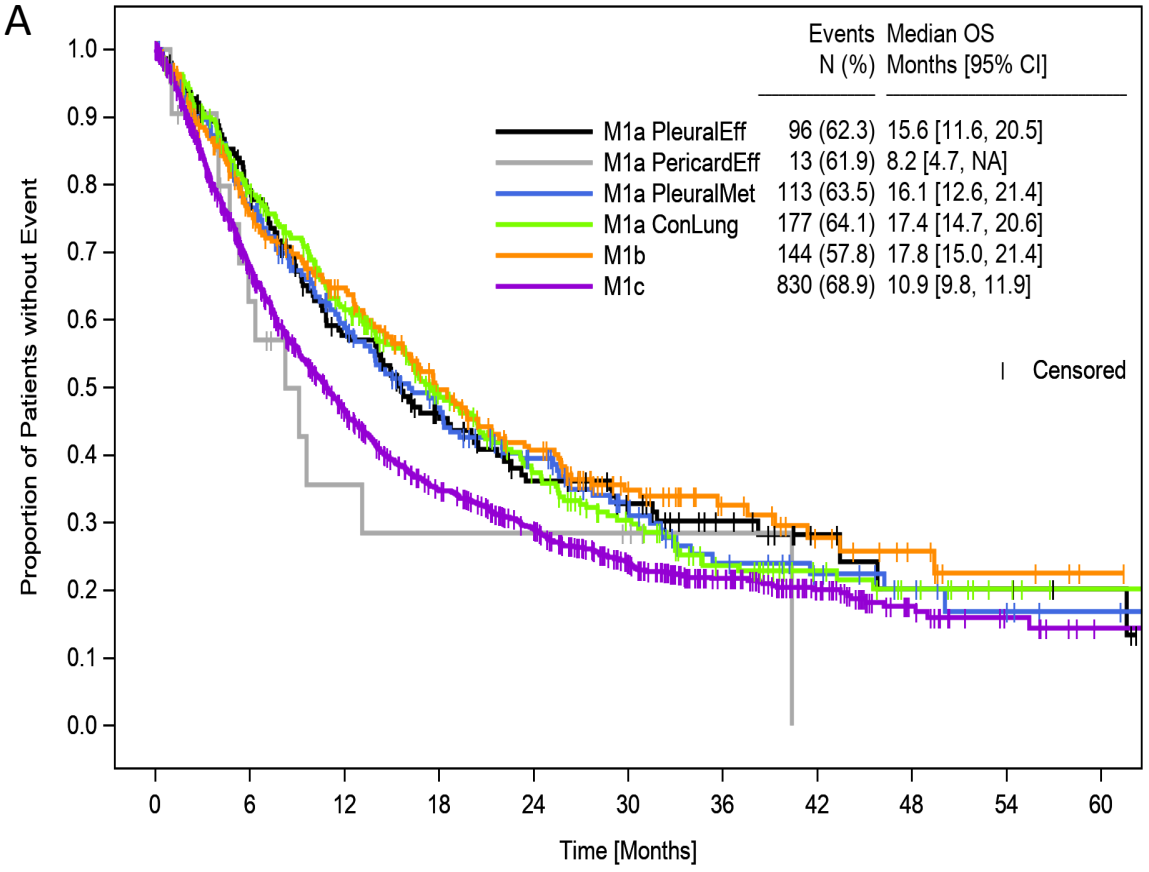

CPI
n = 129
20,5%
n = 55
22,1%
n = 265
22,0%
CPI+CT
n = 119
18,9%
n = 35
14,1%
n = 242
20,1%
Platinum +PEM
n = 151
24,0%
n = 55
22,1%
n = 281
23,3%
Platinum +taxane
n = 113
18,0%
n = 53
21,3%
n = 193
16,0%
Other CT
n = 117
18,6%
n = 51
20,5%
n = 223
18,5%
M1a
M1b
M1c
(n = 629)
(n = 249)
(n = 1,204)

Supplement Figure 1

Top first-line treatment regimens for patients with M1a, M1b and M1c stage (outcome sample). Checkpoint inhibitors: pembrolizumab, atezolizumab, or nivolumab; platinum agents: carboplatin or cisplatin; taxanes: nab-paclitaxel or paclitaxel.

Abbreviations: CPI, checkpoint inhibitor; CT, chemotherapy; PEM, pemetrexed.

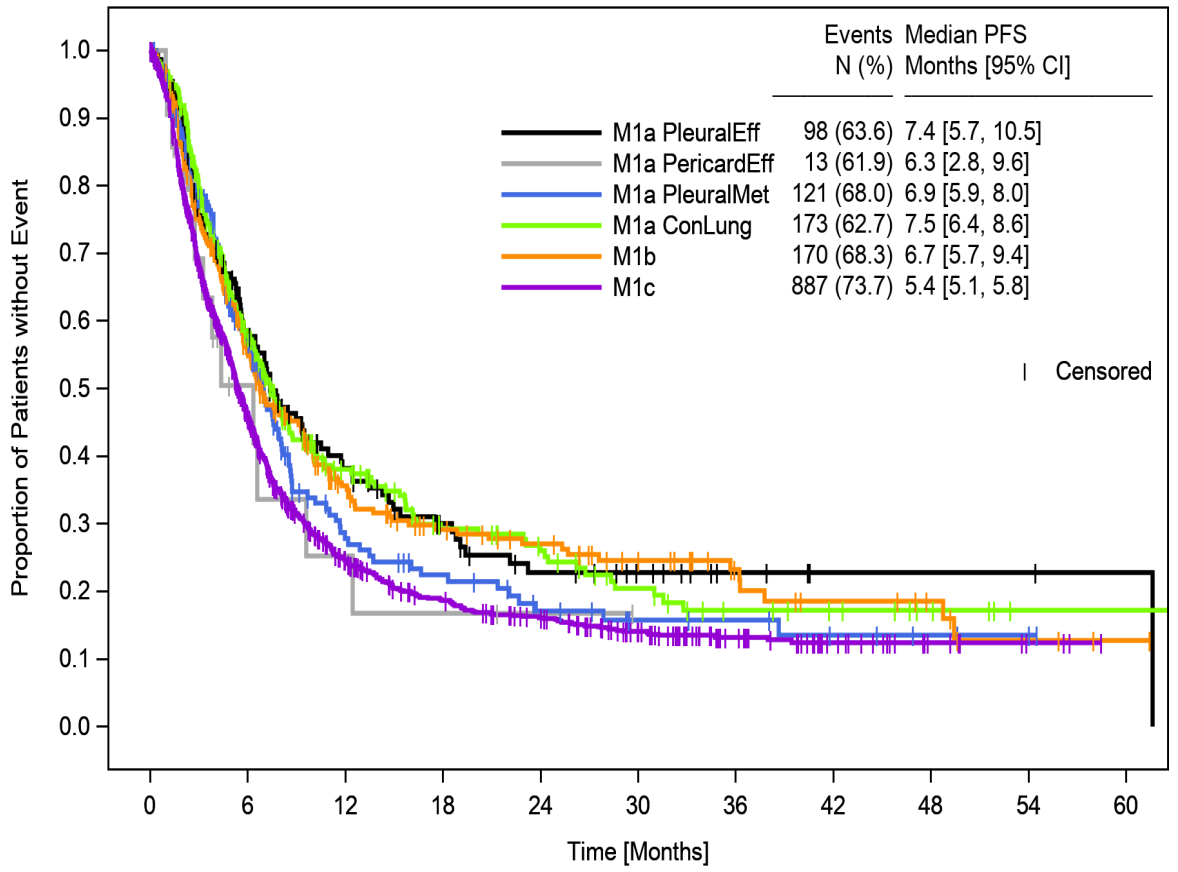
A



Number at risk

M1a PleuralEff	154	115	78	53	37	28	17	8	5	5	3
M1a PericardEff	21	11	5	4	4	3	1	0			
M1a PleuralMet	178	129	89	65	47	32	19	13	8	5	2
M1a ConLung	276	202	149	104	74	49	30	18	12	5	2
M1b	249	172	134	93	69	40	23	15	9	4	1
M1c	1204	743	474	326	250	165	100	55	23	10	2

B



Number at risk

M1a PleuralEff	154	75	40	26	17	12	6	2	2	2	1
M1a PericardEff	21	6	3	2	1	0					
M1a PleuralMet	178	85	32	23	15	9	8	5	3	2	0
M1a ConLung	276	131	64	39	31	20	12	9	5	1	1
M1b	249	123	64	44	36	26	15	10	7	3	1
M1c	1204	469	205	138	110	75	40	20	8	3	0

Supplement Figure 2

First-line Registry-OS and first-line PFS in patients with advanced NSCLC by different variations of M1a or M1b or M1c (**A** and **B**). Analysis is based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019.

Abbreviations: CI, confidence interval; PFS, progression-free survival; OS, overall survival.

A

Cox proportional hazards model

Variable		Hazard Ratio (95% CI)	HR	95% CI	p
Age group					
>=65 years vs <65 years	n=688 vs n=656		0.92	0.79-1.07	0.275
BMI group					
20-25 vs <20	n=573 vs n=176		1.03	0.82-1.28	0.819
25-30 vs <20	n=414 vs n=176		0.90	0.71-1.13	0.358
>=30 vs <20	n=181 vs n=176		0.92	0.70-1.21	0.544
Sex					
Male vs female	n=823 vs n=521		1.28	1.11-1.49	<0.001***
ECOG Performance Status					
1 vs 0	n=845 vs n=499		1.39	1.20-1.61	<0.001***
Charlson score					
1-2 vs 0	n=475 vs n=747		0.99	0.85-1.16	0.939
3-4 vs 0	n=96 vs n=747		0.89	0.67-1.19	0.423
>=5 vs 0	n=26 vs n=747		0.91	0.53-1.57	0.737
Smoking status					
Current smoker vs Never smoker	n=422 vs n=100		0.88	0.66-1.17	0.383
Ex-smoker vs Never smoker	n=724 vs n=100		0.96	0.73-1.25	0.753
Unknown/Missing vs Never smoker	n=98 vs n=100		0.96	0.67-1.37	0.817
Histology					
Non-squamous vs Squamous	n=1024 vs n=320		0.88	0.74-1.04	0.124
T status					
T2 vs T1	n=250 vs n=134		1.37	1.03-1.84	0.033*
T3 vs T1	n=238 vs n=134		1.49	1.11-2.00	0.008**
T4 vs T1	n=569 vs n=134		1.48	1.13-1.94	0.004**
TX vs T1	n=153 vs n=134		1.18	0.83-1.67	0.356
N status					
N1 vs N0	n=120 vs n=170		1.08	0.78-1.48	0.649
N2 vs N0	n=420 vs n=170		1.48	1.16-1.89	0.002**
N3 vs N0	n=465 vs n=170		1.28	1.00-1.63	0.049*
NX vs N0	n=169 vs n=170		1.37	1.00-1.87	0.052
M status					
M1b vs M1a	n=147 vs n=411		0.83	0.64-1.08	0.161
M1c vs M1a	n=786 vs n=411		1.24	1.06-1.45	0.009**

B

Cox proportional hazards model

Variable		Hazard Ratio (95% CI)	HR	95% CI	p
Age group					
>=65 years vs <65 years	n=83 vs n=64		1.18	0.70-2.01	0.530
BMI group					
20-25 vs <20	n=63 vs n=17		0.47	0.22-1.01	0.053
25-30 vs <20	n=44 vs n=17		0.42	0.18-0.96	0.039*
>=30 vs <20	n=23 vs n=17		0.42	0.16-1.06	0.066
Sex					
Male vs female	n=83 vs n=64		1.05	0.61-1.81	0.849
ECOG Performance Status					
1 vs 0	n=88 vs n=59		1.30	0.75-2.26	0.353
Charlson score					
1-2 vs 0	n=54 vs n=82		1.38	0.80-2.39	0.245
3-4 vs 0	n=10 vs n=82		1.67	0.60-4.66	0.330
>=5 vs 0	n=1 vs n=82		0.00	0.00-	0.987
Smoking status					
Current smoker vs Never smoker	n=43 vs n=6		0.66	0.18-2.48	0.542
Ex-smoker vs Never smoker	n=89 vs n=6		0.73	0.20-2.60	0.625
Unknown/Missing vs Never smoker	n=9 vs n=6		0.33	0.05-1.96	0.221
Histology					
Non-squamous vs Squamous	n=107 vs n=40		0.81	0.44-1.48	0.485
T status					
T2 vs T1	n=34 vs n=16		0.52	0.20-1.36	0.186
T3 vs T1	n=30 vs n=16		0.74	0.28-1.93	0.535
T4 vs T1	n=58 vs n=16		0.62	0.24-1.58	0.314
TX vs T1	n=9 vs n=16		0.21	0.05-0.90	0.036*
N status					
N1 vs N0	n=12 vs n=23		1.13	0.37-3.47	0.836
N2 vs N0	n=48 vs n=23		1.20	0.50-2.91	0.679
N3 vs N0	n=50 vs n=23		2.22	0.90-5.47	0.084
NX vs N0	n=14 vs n=23		3.29	1.06-10.18	0.039*
Selected organ sites					
Bone vs Other	n=31 vs n=31		2.35	1.11-4.98	0.026*
Brain vs Other	n=40 vs n=31		1.58	0.74-3.36	0.240
Gland vs Other	n=36 vs n=31		1.13	0.50-2.55	0.774
Liver vs Other	n=9 vs n=31		3.15	1.15-8.63	0.025*

C

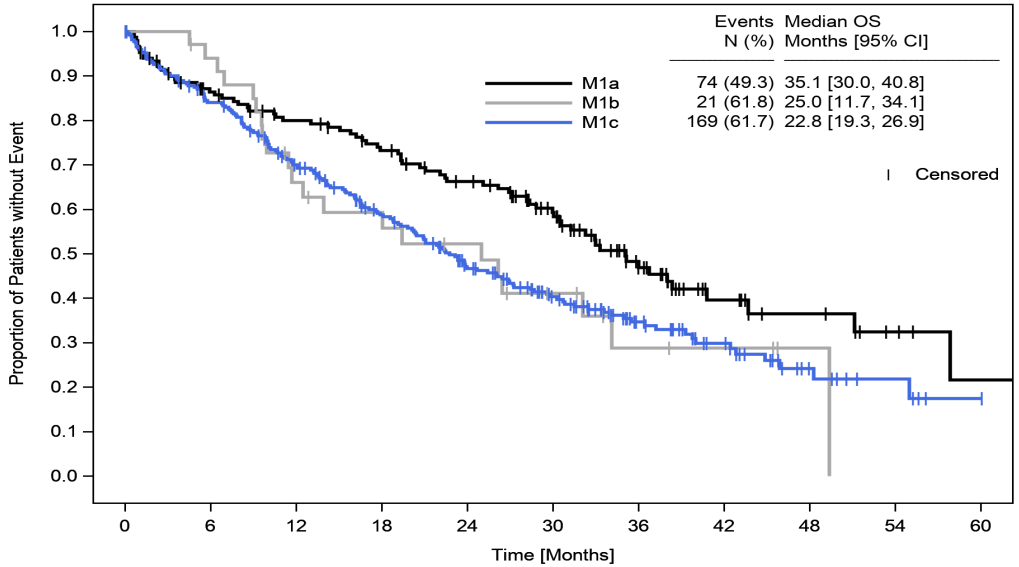
Cox proportional hazards model

Variable		Hazard Ratio (95% CI)	HR	95% CI	p
Age group					
>=65 years vs <65 years	n=357 vs n=429		0.92	0.76-1.12	0.398
BMI group					
20-25 vs <20	n=348 vs n=103		1.05	0.79-1.40	0.730
25-30 vs <20	n=244 vs n=103		0.89	0.65-1.20	0.434
>=30 vs <20	n=91 vs n=103		0.90	0.62-1.30	0.567
Sex					
Male vs female	n=477 vs n=309		1.29	1.07-1.56	0.007**
ECOG Performance Status					
1 vs 0	n=493 vs n=293		1.32	1.09-1.60	0.004**
Charlson score					
1-2 vs 0	n=255 vs n=468		0.88	0.72-1.08	0.213
3-4 vs 0	n=48 vs n=468		1.20	0.83-1.75	0.332
>=5 vs 0	n=15 vs n=468		1.75	0.95-3.24	0.074
Smoking status					
Current smoker vs Never smoker	n=270 vs n=54		0.85	0.59-1.23	0.392
Ex-smoker vs Never smoker	n=402 vs n=54		0.94	0.66-1.33	0.721
Unknown/Missing vs Never smoker	n=60 vs n=54		0.97	0.62-1.53	0.907
Histology					
Non-squamous vs Squamous	n=629 vs n=157		0.89	0.71-1.12	0.315
T status					
T2 vs T1	n=144 vs n=94		1.58	1.10-2.26	0.012*
T3 vs T1	n=138 vs n=94		1.72	1.20-2.46	0.003**
T4 vs T1	n=329 vs n=94		1.55	1.11-2.15	0.010**
TX vs T1	n=81 vs n=94		1.40	0.90-2.18	0.131
N status					
N1 vs N0	n=74 vs n=77		1.04	0.67-1.61	0.858
N2 vs N0	n=247 vs n=77		1.63	1.15-2.30	0.006**
N3 vs N0	n=299 vs n=77		1.27	0.90-1.78	0.178
NX vs N0	n=89 vs n=77		1.33	0.86-2.05	0.202
Number of metastatic organ sites (total)					
4+ vs 1-3 sites	n=81 vs n=705		1.78	1.35-2.34	<0.001***

Supplement Figure 3

Cox proportional hazards models for the subgroup of patients who received a checkpoint inhibitor (alone or in combination with chemotherapy) in the first or second line of therapy. Overall survival for (**A)** the whole subgroup sample (n=1,344), for (**B**) patients with M1b by selected organ sites (n=147) and for (**C**) patients with M1c by number of metastatic organ sites (n=786). Analyses are based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019. The parameters shown are an exhaustive list of co-variables used for the Cox proportional hazards models. * $p \leq 0{\cdot}05$, ** $p \leq 0{\cdot}01$, *** $p \leq 0{\cdot}001$. **Abbreviations**: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

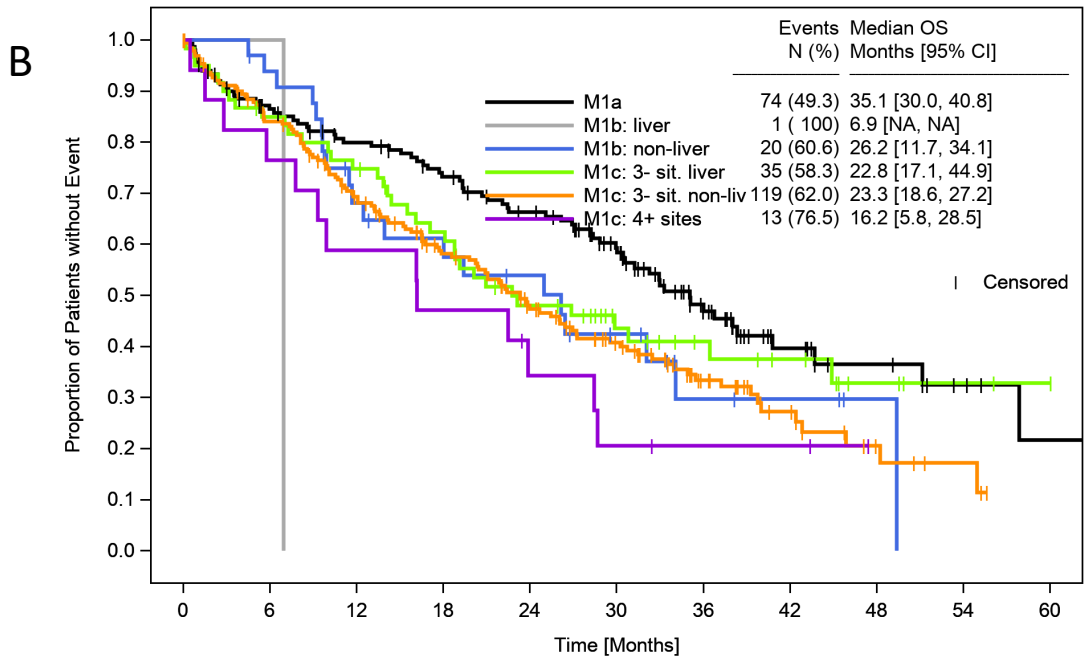
A



Number at risk

M1a	150	122	109	97	83	62	36	16	10	5	2
M1b	34	31	20	17	14	9	4	3	1	0	
M1c	274	224	180	140	103	73	42	26	10	5	1

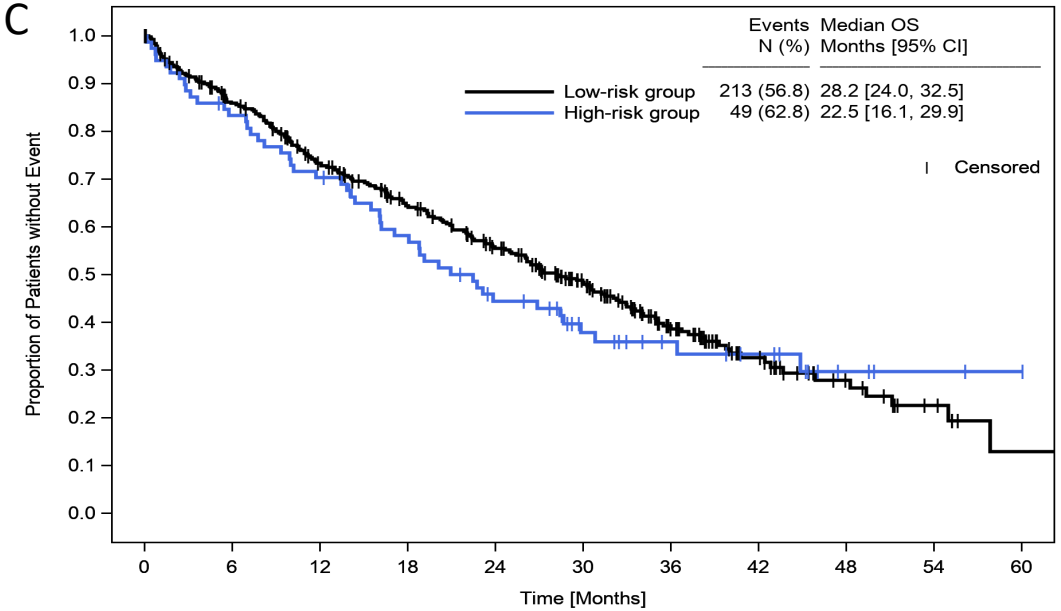
B



Number at risk

M1a	150	122	109	97	83	62	36	16	10	5	2
M1b: liver	1	1	0								
M1b: non-liver	33	30	20	17	14	9	4	3	1	0	
M1c: 3- sit. liver	60	50	44	35	26	17	12	9	4	2	1
M1c: 3- sit. non-liv	192	156	123	94	70	51	28	15	6	3	0
M1c: 4+ sites	17	13	10	8	5	3	2	2	0		

C



Number at risk

Low-risk group	375	308	252	208	167	122	68	34	17	8	2
High-risk group	78	64	54	43	31	20	14	11	4	2	1

Supplement Figure 4

First-line Registry-OS in patients with advanced NSCLC, whose tumours harbouring *a driver-mutation,* by M1a, M1b, M1c stage (**A**), by number of extrathoracic metastatic sites (for M1c) **(B)** and for the amalgamated low-risk and high-risk group **(C)** are given. Analysis is based on data of those patients who have been observed for at least 30 months, i.e. starting first-line treatment until June 30, 2019.

In **(B)** 5 patients could not be allocated to the specific subgroups because of partial missing data.

Abbreviations: CI, confidence interval; PFS, progression-free survival; OS, overall survival; 3- sit. liver, up to three metastatic sites including liver metastases; 3- sit. non-liv, up to three metastatic sites excluding liver metastases; 4+ sites, four and more metastatic sites;