Effectiveness of PD-(L)1 Inhibitors Alone or in Combination With Platinum-Doublet Chemotherapy in First-Line (1L) Non-Squamous Non-Small Cell Lung Cancer (nsq-NSCLC) With PD-L1–High Expression Using Real-World Data

Solange Peters,[1] Urania Dafni,[2] Maurice Pérol,[3] Enriqueta Felip,[4] Letizia Polito,[5] Navdeep Pal,[6] Thanh G.N. Ton,[6] David Merritt,[7] Stefanie Morris,[7] Rolf Stahel[8]

[1]Multidisciplinary Oncology, Centre Hospitalier Universitaire Vaudois – CHUV, Lausanne, Switzerland;
[2]ETOP Statistical Center, Frontier-Science Foundation—Hellas, Athens, Greece; [3]Medical Oncology, Centre Leon Berard, Lyon, France;
[4]Medical Oncology Service (Lung Cancer Unit), Vall d'Hebron University Hospital, Barcelona, Spain;
[5]Product Development Personalized Healthcare, F. Hoffmann-La Roche Ltd, Basel, Switzerland;
[6]Product Development Personalized Healthcare, Genentech, Inc., South San Francisco, CA, USA;
[7]Product Development Medical Affairs, F. Hoffmann-La Roche Ltd, Basel, Switzerland;
[8]European Thoracic Oncology Platform (ETOP), Berne, Switzerland.

Background

- Anti–PD-(L)1 cancer immunotherapy alone (CIT-mono) or in combination with platinum-based doublet chemotherapy (CIT-chemo) are 1L standards of care for metastatic NSCLC[1,2]
  - Tumour PD-L1 expression level, histology and clinical scenario are used to determine treatment regimens
- Among patients with PD-L1–high expression (TPS ≥50%), the impact of additional determinants potentially associated with a greater benefit from CIT-mono or CIT-chemo remains hypothetical
- This retrospective cohort study using the nationwide Flatiron Health (FH) electronic health record (EHR)–derived de-identified US database evaluates clinical outcomes using CIT-mono vs CIT-chemo in high PD-L1–expressing NSCLC

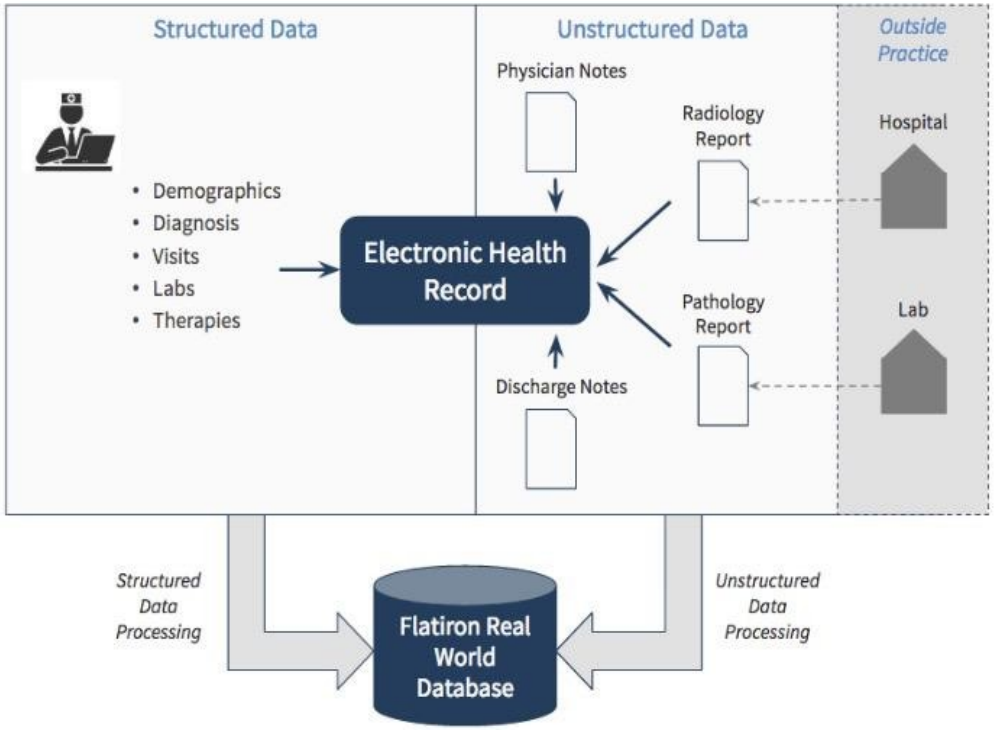
TPS, tumour proportion score.

1. Planchard D, et al. Ann Oncol 2018;29(Suppl 4):iv192-iv237. 2. NCCN. V4.2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 15 March 2021.

Data source

- This retrospective observational study used the US nationwide FH EHR–derived database[1,2]
  - Additional data were abstracted, including date of metastatic diagnosis, sites of metastases and confirmation of treatment discontinuation date
- During the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care)

Flatiron Health database components

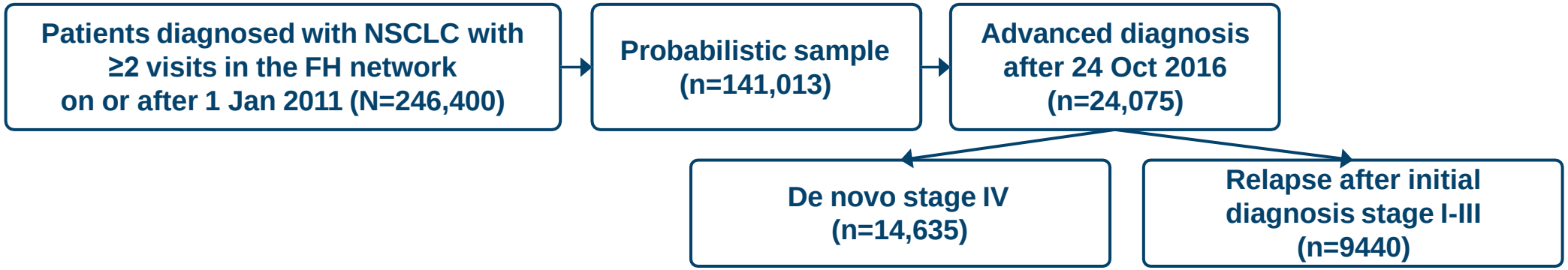


1. Ma X, et al. medRxiv. https://doi.org/10.1101/2020.03.16.20037143. Accessed 19 March 2021. 2. Birnbaum B, et al. arXiv. https://arxiv.org/abs/2001.09765. Accessed 21 March 2021.

Methods

- This was a retrospective cohort study using the nationwide Flatiron Health Electronic Health Record-derived deidentified US database.
- Patients with metastatic Nsq-NSCLC with high PD-L1 expression initiating 1L CIT-mono or CIT chemo between 24 Oct 2016 and 28 Feb 2019 were followed until study end (28 Feb 2020).
- Overall survival (OS) and real-world progression-free survival (rwPFS) were compaired using Kaplan-Meier methodology.
- Hazard ratios (HR) were adjusted (aHR) for differences in baseline characteristics.

Cohort attrition



Attrition step	De novo stage IV NSCLC	Initial diagnosis stage I-III NSCLC
Receipt of CIT-mono or CIT-combo[a]	5168	2125
Relevant line of therapy started before 28 Feb 2019	3132	1271
Normal laboratory values	2756	1104
ECOG performance status, 0-1	1508	642
PD-L1 ≥1%	975	379
No evidence of ALK, EGFR, ROS1, BRAF	930	352
No structured activity gap	905	347
Evidence of metastatic diagnosis	905	253
Random sample	774	–
Confirmed receipt of treatment in 1L	764	191
Non-squamous histology	594	134
PD-L1 ≥50%	428	92

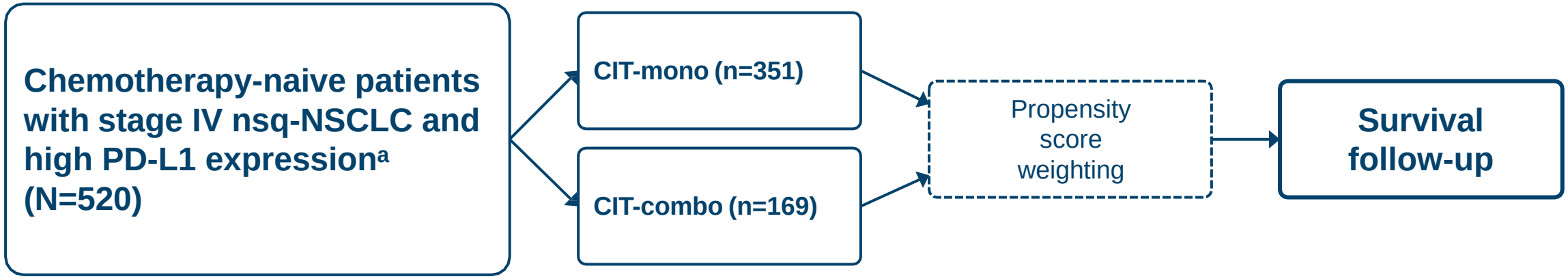
N=520

[a] CIT-combo included platinum-doublet therapy without bevacizumab; patients participating in a clinical trial were excluded.

ECOG, Eastern Cooperative Oncology Group.

Study design

- Primary outcome was overall survival (OS) among treatment initiators[1]
- Secondary endpoints included real-world progression-free survival (rwPFS) using a clinician-anchored approach supported by radiology report data[2]
- Subgroup analyses were conducted to evaluate the influence of brain metastases, liver metastases and smoking history



[a] PD-L1–high expression defined as TPS ≥50% by local test. Assay type was balanced between CIT-mono (86% 22C3) and CIT-combo (85% 22C3); remaining patients in each group had "Other/Unknown" assay.

1. Curtis MD, et al. Health Serv Res 2018;53(6):4460-76. 2. Griffith SD, et al. Adv Ther 2019;36(8):2122-36.

Statistical considerations

- Treatment duration was computed as time to treatment discontinuation
- Time-to-event Kaplan-Meier analyses were used to estimate median survival, rwPFS and treatment duration with corresponding 95% CIs
- To reduce indication bias, in the absence of randomization, a propensity score was estimated by regressing treatment assignment (CIT-mono vs CIT-chemo) on key prognostic factors (age, sex, race, smoking history, ECOG performance status, metastatic type,[a] brain metastases, liver metastases and time to treatment initiation)
  - The propensity score was applied via inverse probability treatment weighting methodology
  - Graphical display of the propensity score assessed the distribution before and after weighting

[a] Defined as de novo stage IV or recurrent disease.

Patient characteristics (PD-L1 high)

Characteristic, n (%)	CIT-mono (n=351)	CIT-chemo (n=169)
Age group, years		
< 65	109 (31)	77 (46)
65-74	112 (32)	58 (34)
≥75	130 (37)	34 (20)
Sex, female	183 (52)	75 (44)
Region		
Midwest	69 (20)	24 (14)
Northeast	74 (21)	29 (17)
South	159 (45)	92 (54)
West	40 (11)	20 (12)
Smoking status		
Former or current	317 (90)	153 (91)
No history	34 (10)	16 (9)
ECOG performance status		
0	138 (39)	77 (46)
1	213 (61)	92 (54)
Metastases		
Brain	91 (26)	50 (30)
Liver	43 (12)	28 (17)
Metastatic type		
De novo stage IV	271 (77)	157 (93)
Recurrent disease	80 (23)	12 (7)
PD-L1 testing assay		
22C3	302 (86)	144 (85)
Other/unknown	49 (14)	25 (15)

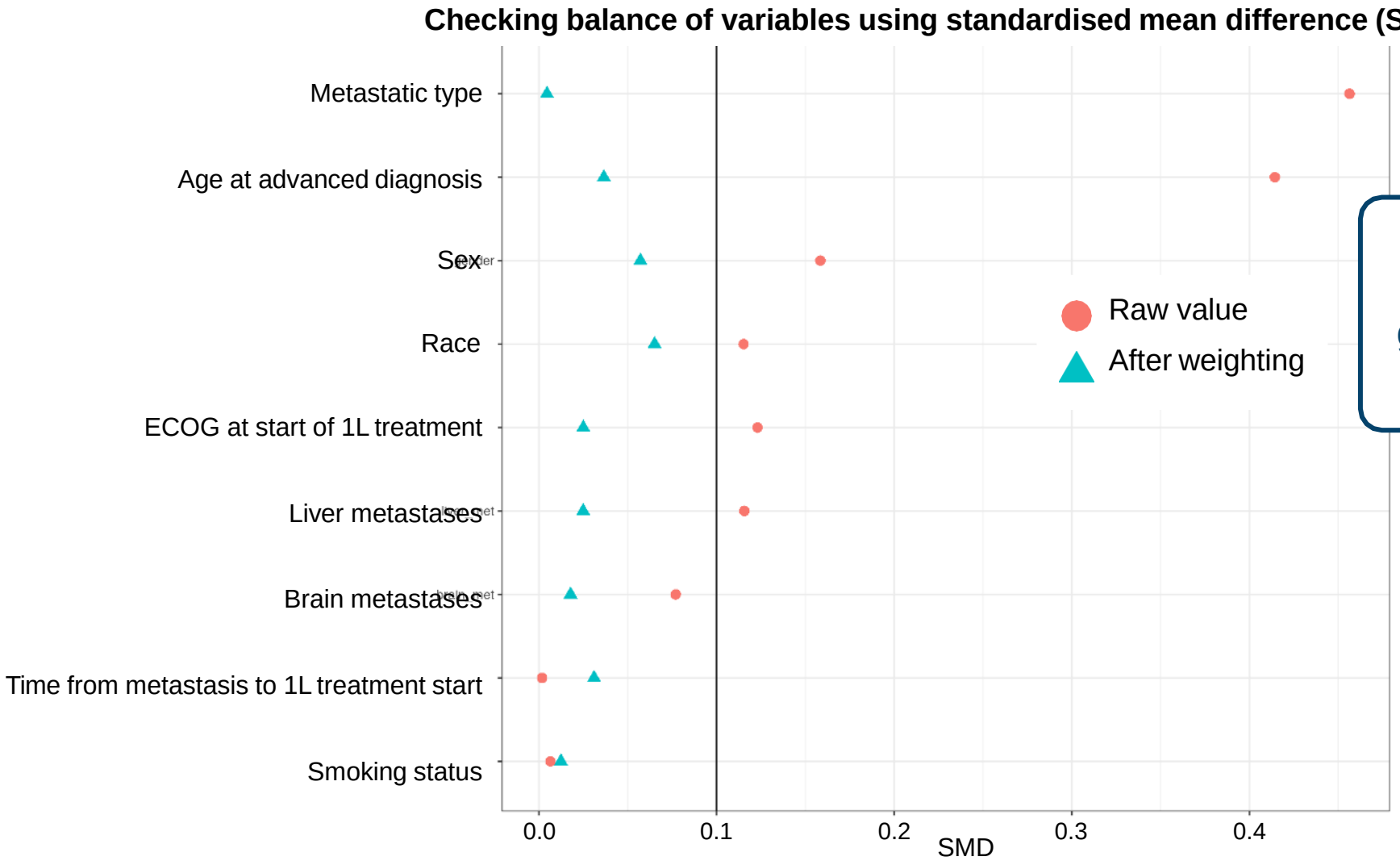
Treatment characteristics

	Patients with PD-L1–high expression[a]	
Characteristic	**CIT-mono (n=351)**	**CIT-chemo (n=169)**
Prior chemotherapy, past 6 months[b] n (%)	8 (2)	0
Time from metastasis diagnosis, median (IQR), months	1.10 (0.76-1.60)	0.92 (0.69-1.40)
Treatments, n (%)		
Pembrolizumab	347 (99)	–
Atezolizumab	4 (1)	–
Carboplatin + pembrolizumab + pemetrexed	–	163 (96)
Carboplatin + pembrolizumab + paclitaxel	–	3 (2)
Cisplatin + pembrolizumab + pemetrexed	–	2 (1)
Carboplatin + pembrolizumab + paclitaxel + pemetrexed	–	1 (1)

IQR, interquartile range.

[a] PD-L1–high expression defined as TPS ≥50%. [b] Treatment received in the locally-advanced setting in the last 6 months prior to index date.

Propensity score weighting: OS and rwPFS



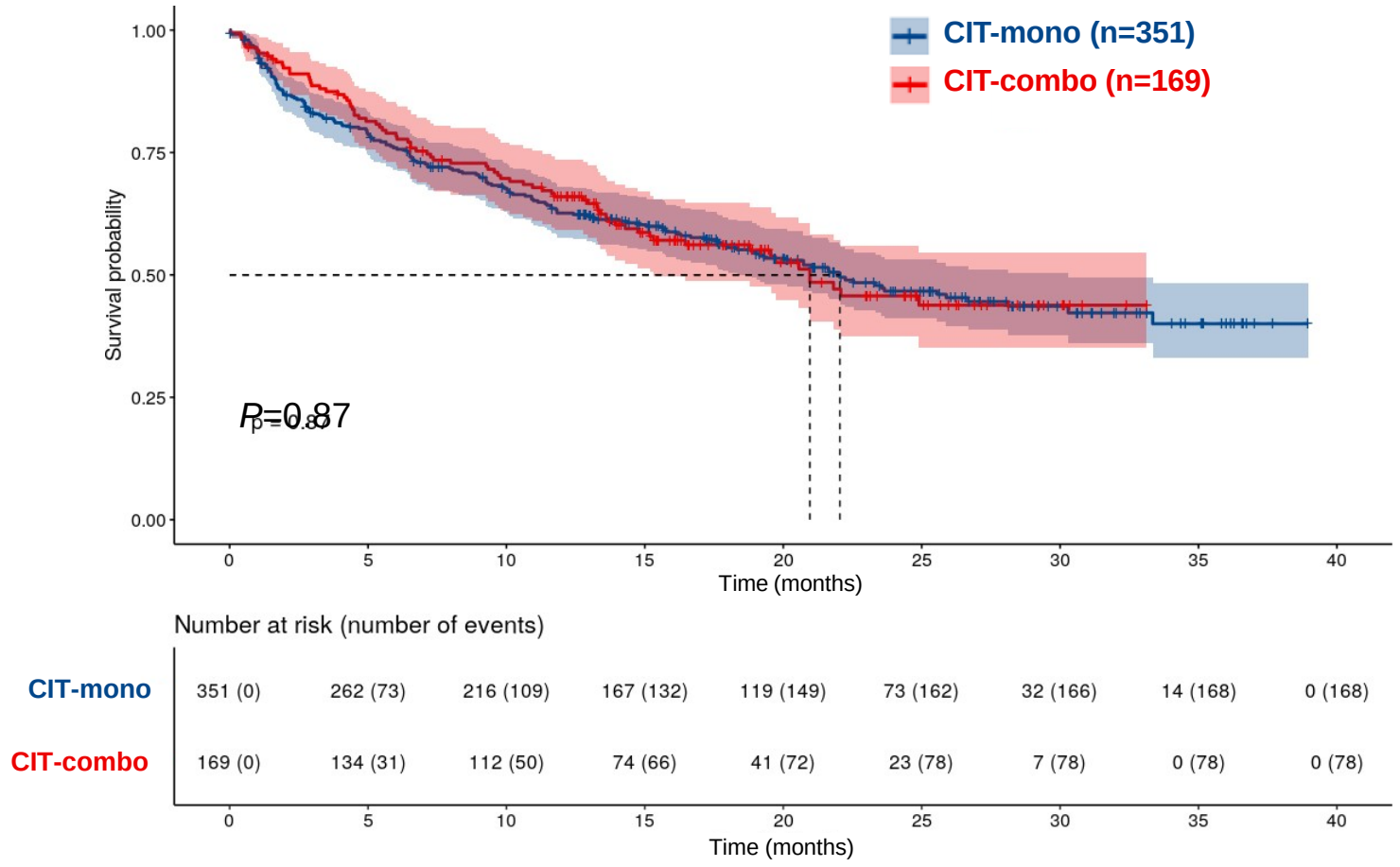
The observed imbalance between groups was corrected (all SMD <0.1)

Primary outcome: overall survival

Unadjusted analysis

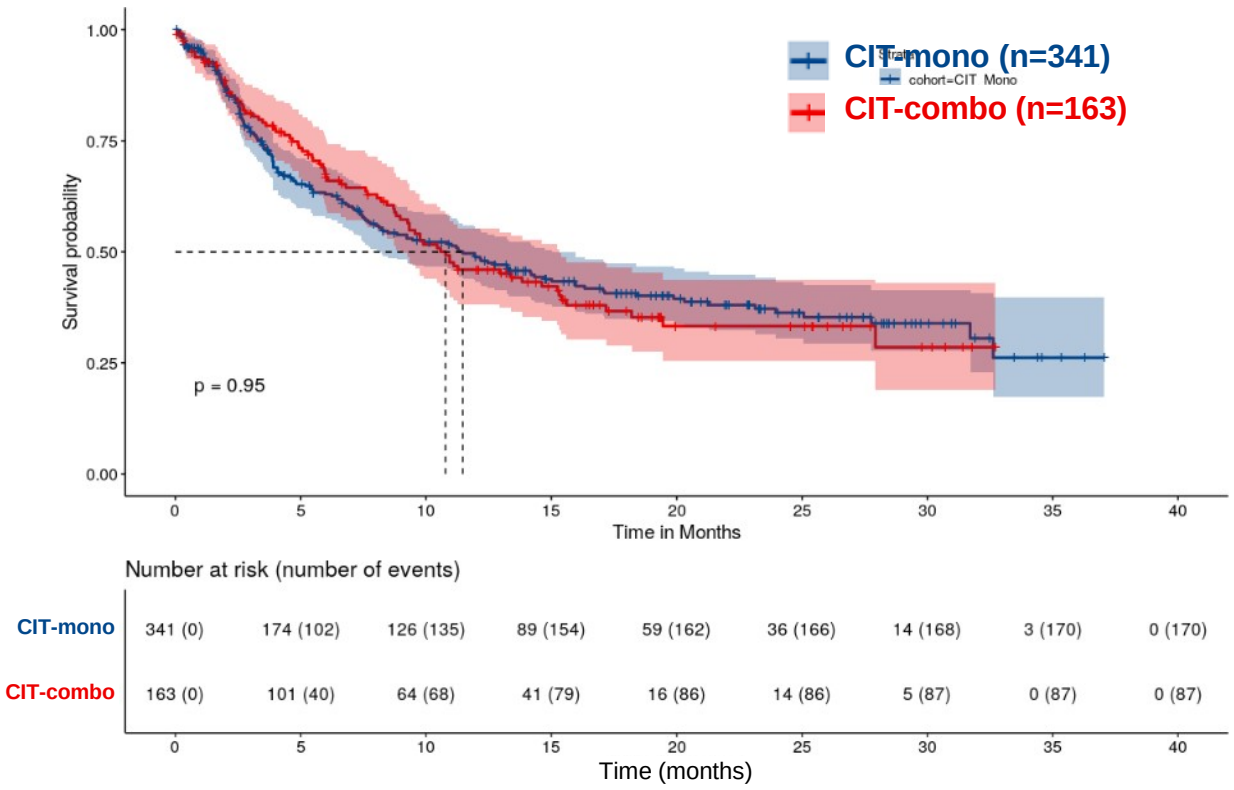
	CIT-mono (n=351)	CIT-combo (n=169)
Events, n (%)	168 (49)	78 (46)
OS, mo Median (95% CI)	22.05 (18.33, 30.29)	20.96 (15.31, NA)
Follow-up, mo Median (IQR)	23.46 (15.74, 28.71)	19.92 (14.92, 26.25)

CIT-combo vs CIT-mono (reference)	Hazard ratio (95% CI)	*P* value
Unadjusted analysis	0.98 (0.75, 1.28)	0.868
Adjusted analysis	1.03 (0.77, 1.39)	0.833

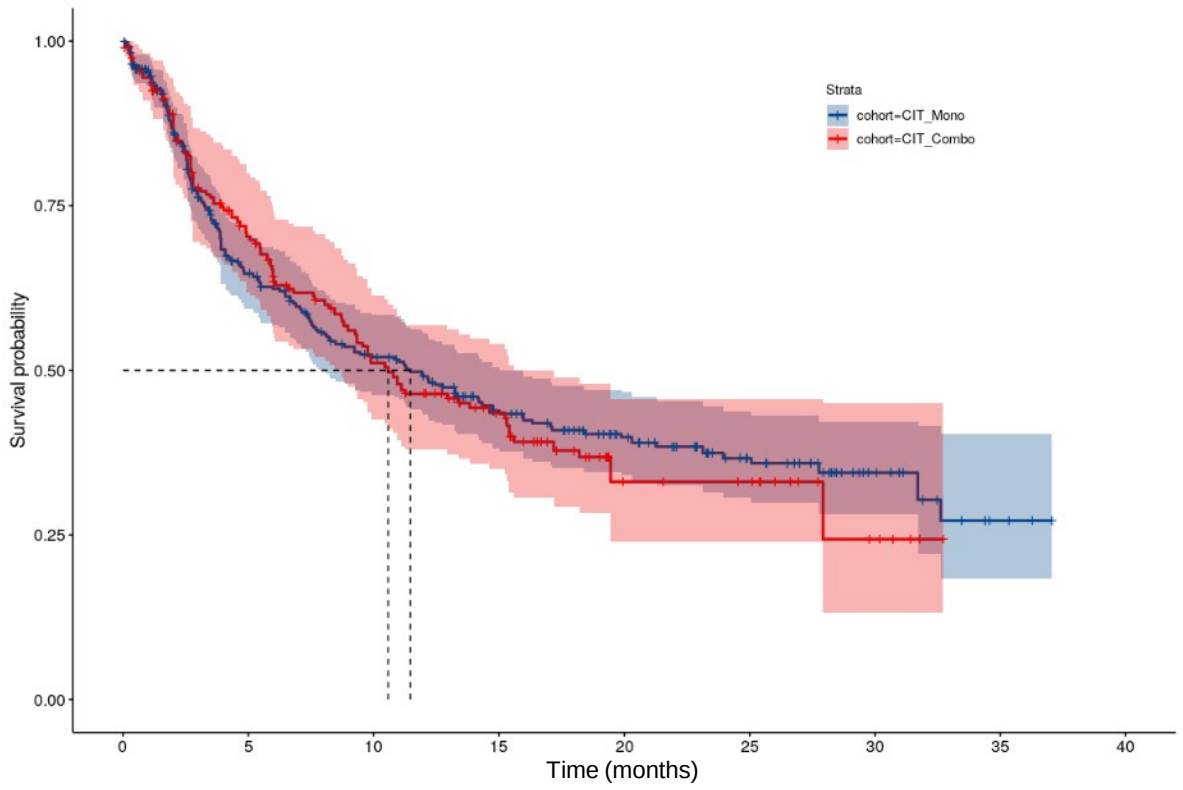


Secondary outcome: rwPFS

Unadjusted analysis[a]



Adjusted analysis



CIT-combo vs CIT-mono (reference)	Hazard ratio (95% CI)	*P* value
Unadjusted analysis	1.01 (0.78, 1.05)	
Adjusted analysis	1.04 (0.78, 1.37)	

Group	Patients	Events, n (%)	Median rwPFS (95% CI), mo
CIT-mono	351	170 (48)	11.5 (8.12, 15.01)
CIT-combo	169	87 (52)	10.8 (8.97, 15.31)

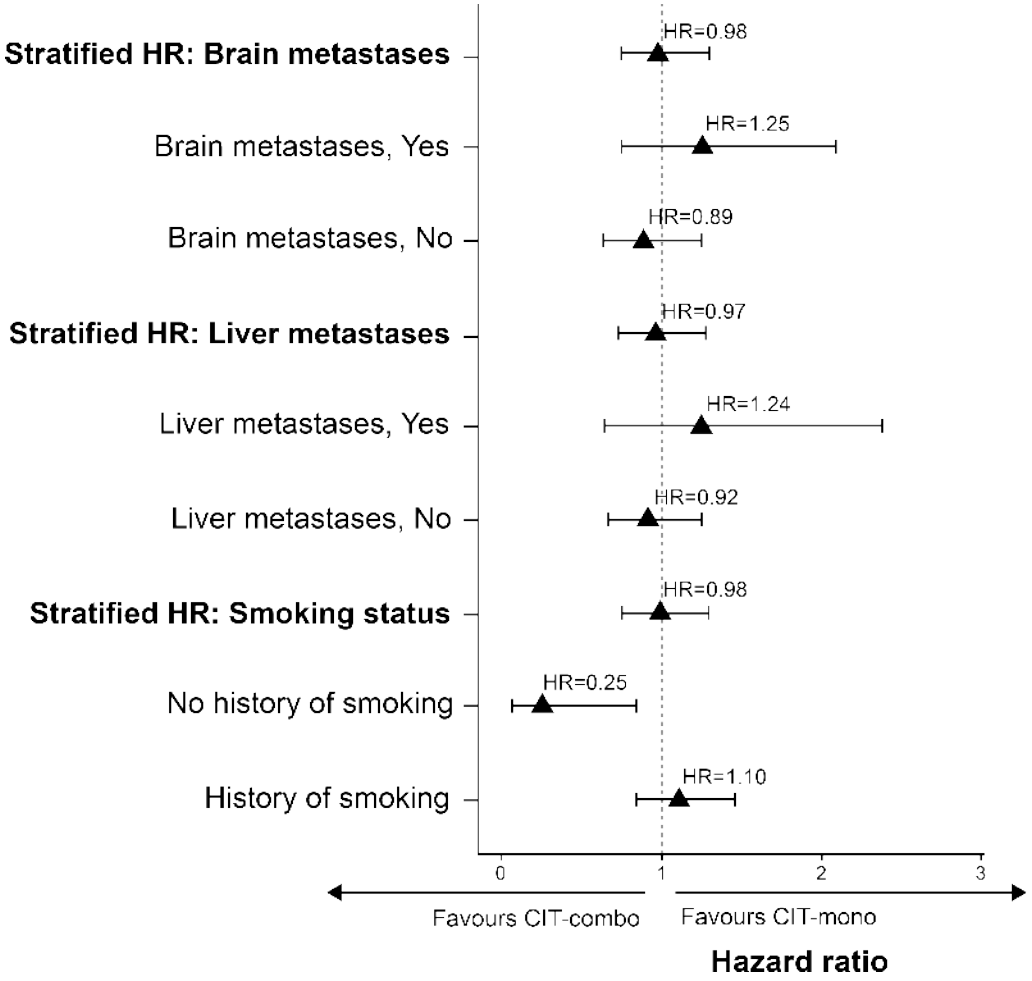
[a] Proportional hazards assumption is violated in the unadjusted model (Schoenfeld residual test).

The propensity score model included metastatic type, age, race, ECOG performance status score, brain metastases, smoking status, sex, liver metastases, time to 1L treatment start.

Planned subgroup analyses

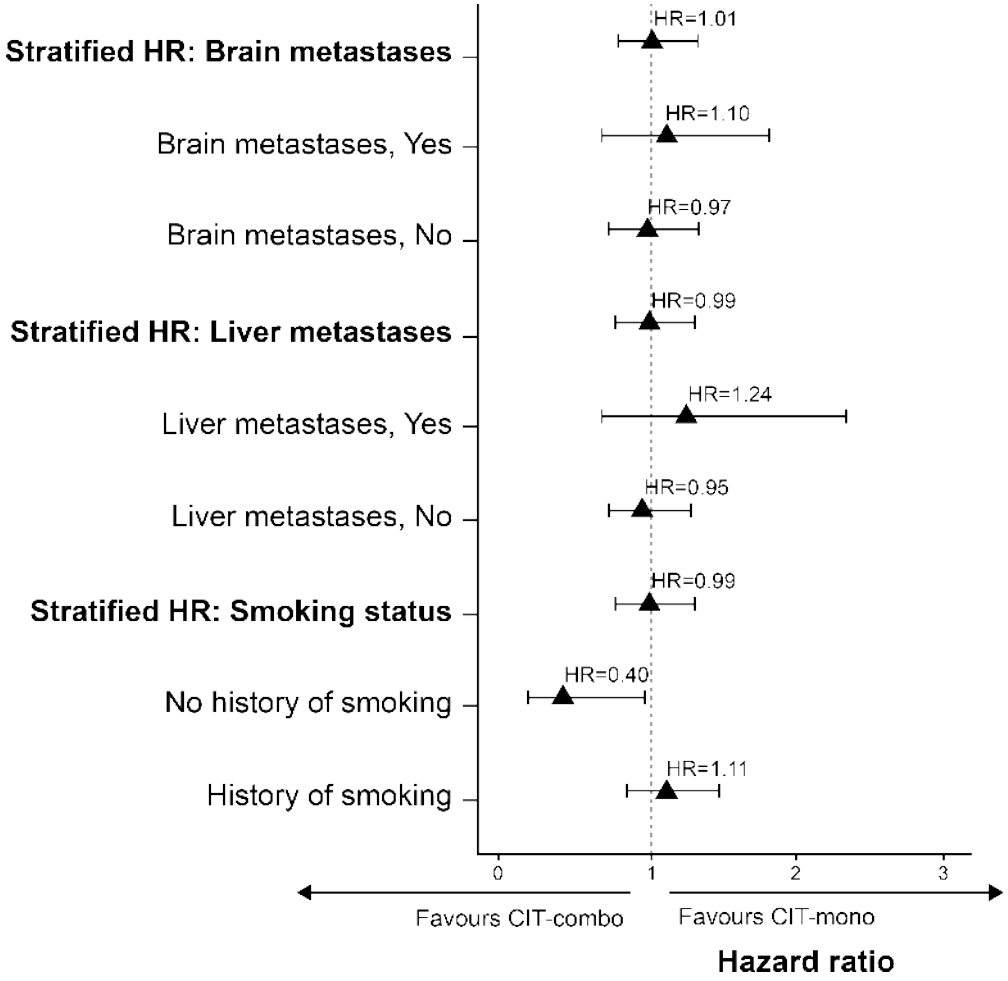
Overall survival

Unadjusted anlaysis



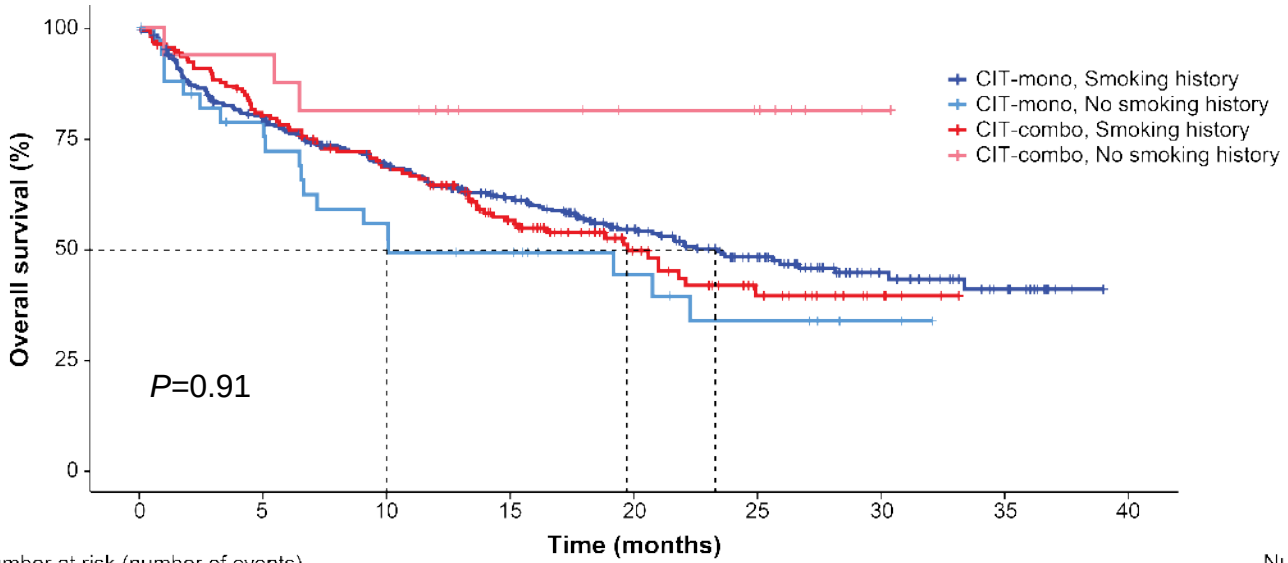
Real-world PFS

Unadjusted anlaysis



Subgroup analysis: smoking history

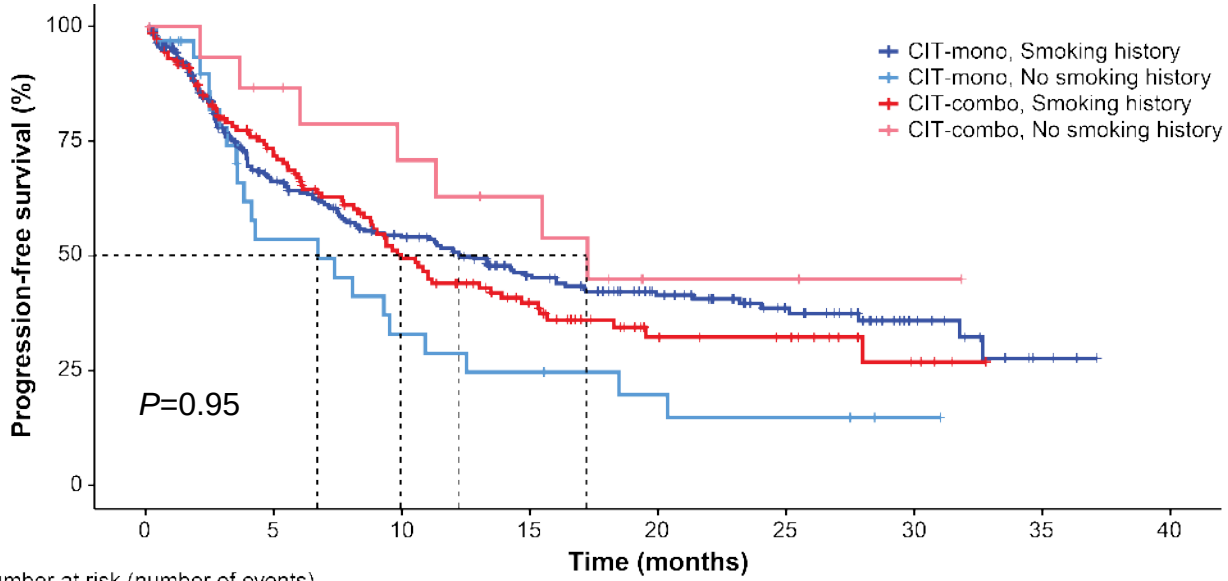
OS



Number at risk (number of events)

317 (0)	239 (65)	199 (95)	153 (116)	110 (132)	67 (143)	30 (147)	14 (149)	0 (149)
34 (0)	23 (8)	17 (14)	14 (16)	9 (17)	6 (19)	2 (19)	0 (19)	0 (19)
153 (0)	119 (30)	99 (47)	65 (63)	34 (69)	17 (75)	6 (75)	0 (75)	0 (75)
16 (0)	15 (1)	13 (3)	9 (3)	7 (3)	6 (3)	1 (3)	0 (3)	0 (3)

rwPFS



Number at risk (number of events)

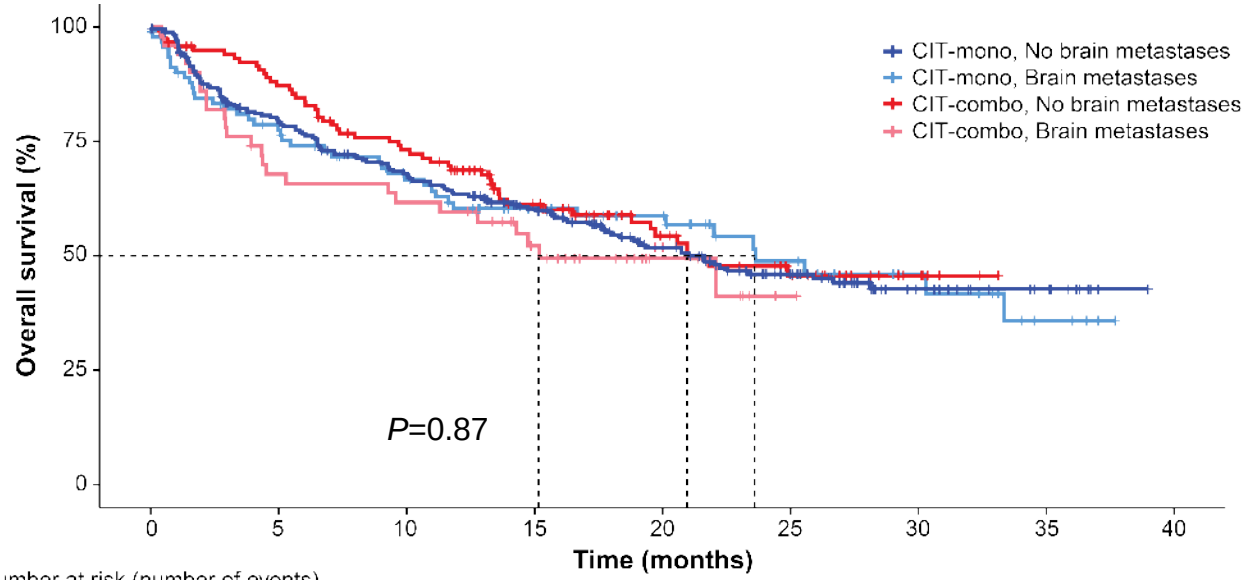
309 (0)	161 (90)	118 (118)	83 (135)	55 (142)	33 (145)	13 (147)	3 (149)	0 (149)
32 (0)	13 (12)	8 (17)	6 (19)	4 (20)	3 (21)	1 (21)	0 (21)	0 (21)
147 (0)	89 (38)	55 (64)	34 (74)	14 (79)	12 (79)	4 (80)	0 (80)	0 (80)
16 (0)	12 (2)	9 (4)	7 (5)	2 (7)	2 (7)	1 (7)	0 (7)	0 (7)

No smoking history stratum (n=50)
OS HR, 0.25 (95% CI: 0.07, 0.83)
interaction *P*=0.02

No smoking history stratum (n=50)
rwPFS HR, 0.40 (95% CI: 0.17, 0.95)
interaction *P*=0.04

Subgroup analysis: brain metastases

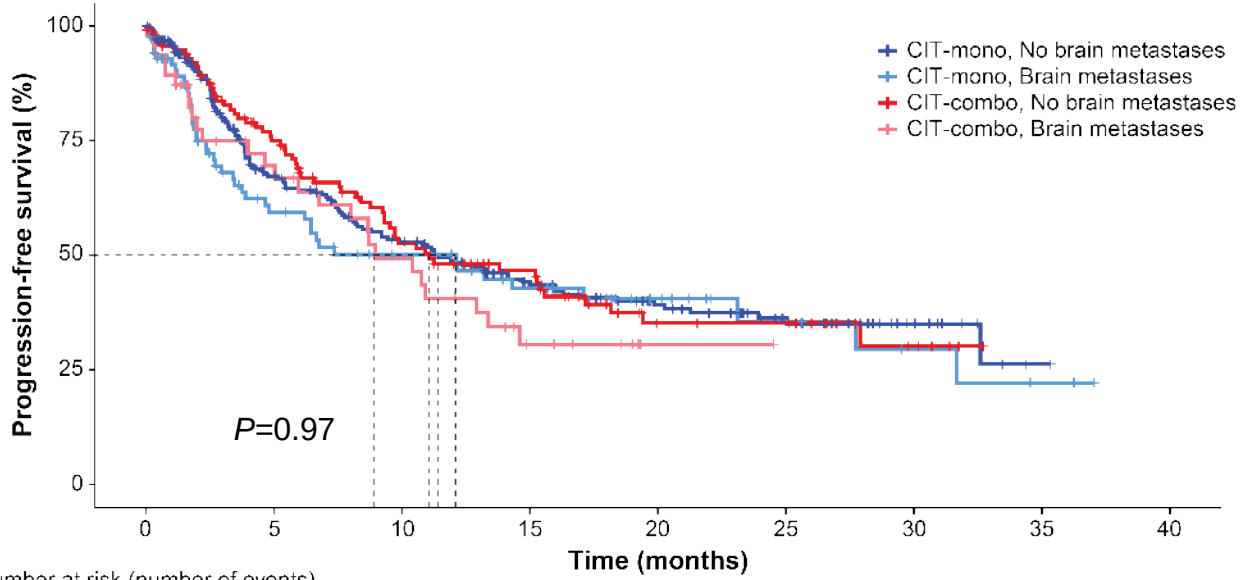
OS



Number at risk (number of events)

260 (0)	195 (53)	163 (80)	127 (98)	87 (114)	55 (123)	21 (126)	10 (126)	0 (126)
91 (0)	67 (20)	53 (29)	40 (34)	32 (35)	18 (39)	11 (40)	4 (42)	0 (42)
119 (0)	101 (15)	82 (31)	55 (43)	35 (48)	22 (53)	7 (53)	0 (53)	0 (53)
50 (0)	33 (16)	30 (19)	19 (23)	6 (24)	1 (25)	0 (25)	0 (25)	0 (25)

rwPFS

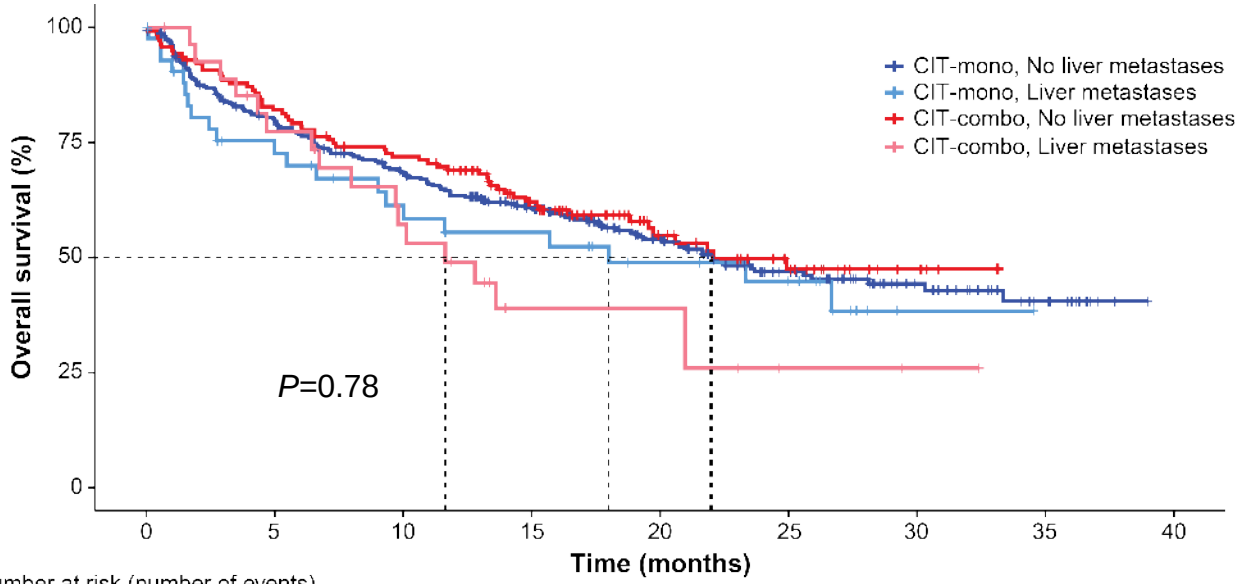


Number at risk (number of events)

255 (0)	134 (71)	97 (98)	67 (113)	46 (120)	29 (123)	10 (124)	1 (125)	0 (125)
86 (0)	40 (31)	29 (37)	22 (41)	13 (42)	7 (43)	4 (44)	2 (45)	0 (45)
116 (0)	76 (27)	47 (48)	34 (53)	15 (60)	14 (60)	5 (61)	0 (61)	0 (61)
47 (0)	25 (13)	17 (20)	7 (26)	1 (26)	0 (26)	0 (26)	0 (26)	0 (26)

Subgroup analysis: liver metastases

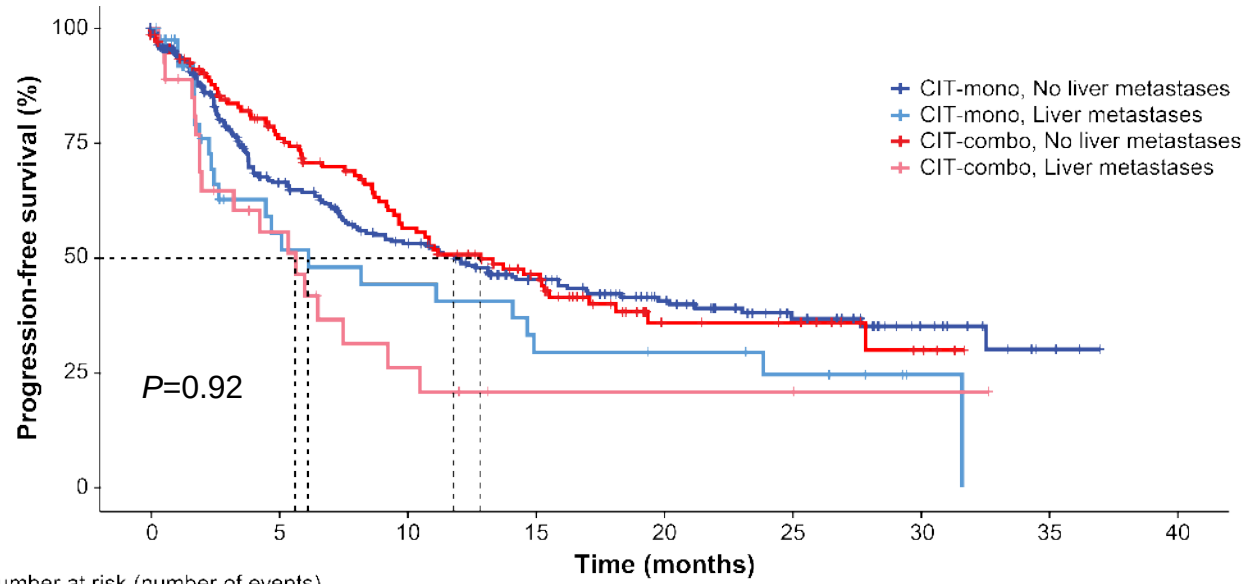
OS



Number at risk (number of events)

308 (0)	235 (62)	195 (94)	149 (115)	106 (130)	63 (142)	31 (145)	14 (147)	0 (147)
43 (0)	27 (11)	21 (15)	18 (17)	13 (19)	10 (20)	1 (21)	0 (21)	0 (21)
141 (0)	114 (25)	98 (39)	68 (51)	35 (57)	21 (61)	6 (61)	0 (61)	0 (61)
28 (0)	20 (6)	14 (11)	6 (15)	6 (15)	2 (17)	1 (17)	0 (17)	0 (17)

rwPFS



Number at risk (number of events)

300 (0)	159 (88)	114 (118)	80 (134)	52 (141)	31 (144)	13 (146)	3 (147)	0 (147)
41 (0)	15 (14)	12 (17)	9 (20)	7 (21)	5 (22)	1 (22)	0 (23)	0 (23)
136 (0)	89 (29)	59 (51)	39 (61)	14 (68)	12 (68)	4 (69)	0 (69)	0 (69)
27 (0)	12 (11)	5 (17)	2 (18)	2 (18)	2 (18)	1 (18)	0 (18)	0 (18)

Treatment follow-up

	PD-L1–high expression	
	CIT-mono (n=351)	**CIT-combo (n=169)**
Median follow-up (IQR), months	23.5 (15.7-28.7)	19.9 (14.9-26.3)
Median time to treatment discontinuation (95% CI), months[a]	8.5 (6.9, 11.0)	7.3 (5.5, 11.2)
Any subsequent treatment, n (%)	110 (31)	56 (33)
Subsequent CIT in any line, n (%)	51 (15)	13 (8)
Subsequent CIT in 2L treatment, n (%)	45 (13)	11 (7)

[a] Kaplan-Meier method (events: discontinuation confirmed by FH or death).

Conclusions

- Patients receiving CIT-mono for nsq-NSCLC are older and more frequently have recurrent disease than those treated with CIT-combo
- Median OS and rwPFS did not differ for patients with PD-L1–high nsq-NSCLC treated with CIT-mono or CIT-combo
- rwPFS in the CIT-mono arm showed a steeper decrease in the first months after D1C1 vs CIT-combo
  - This did not reflect an impact on long-term OS or rwPFS benefit
- CIT-mono performed significantly worse in the “no smoking history” stratum
  - Results in this group must be interpreted carefully due to the small sample size, multiple testing issues and lack of adjustment for baseline characteristics
- Sparing chemotherapy in 1L CIT treatment did not appear to impact survival outcomes, except potentially in patients with no smoking history

THANK YOU