NSCLC avanzato: quali novità nel 2018?
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Nivolumab: esperienze italiane nel carcinoma polmonare avanzato

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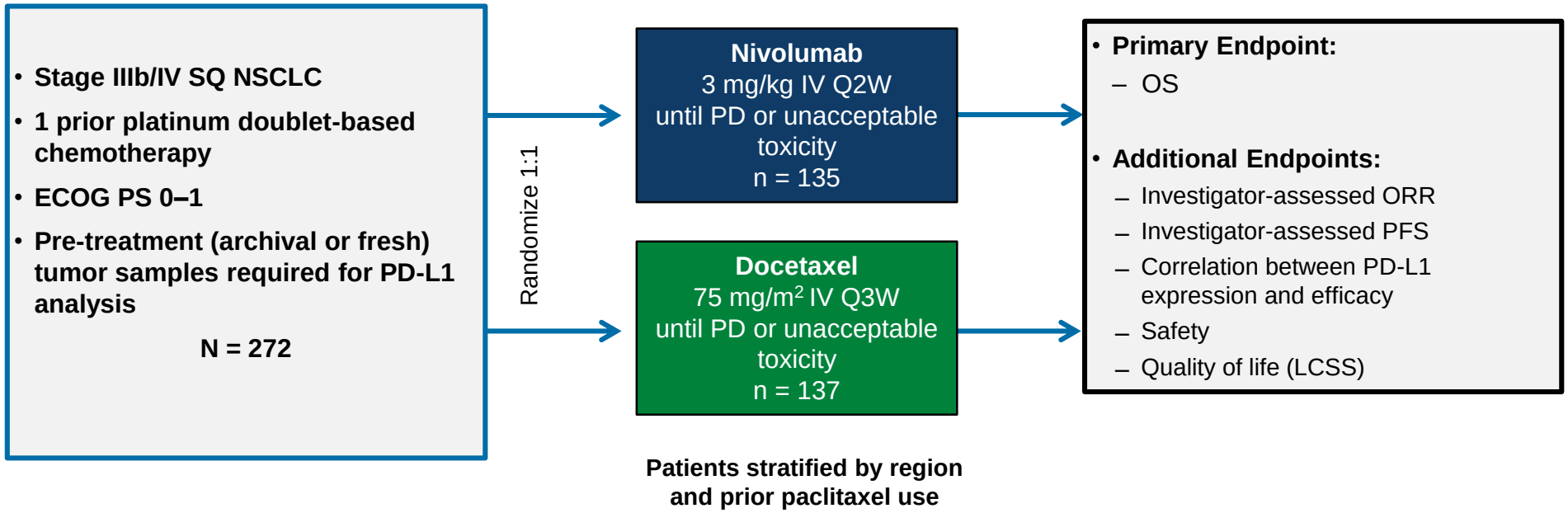
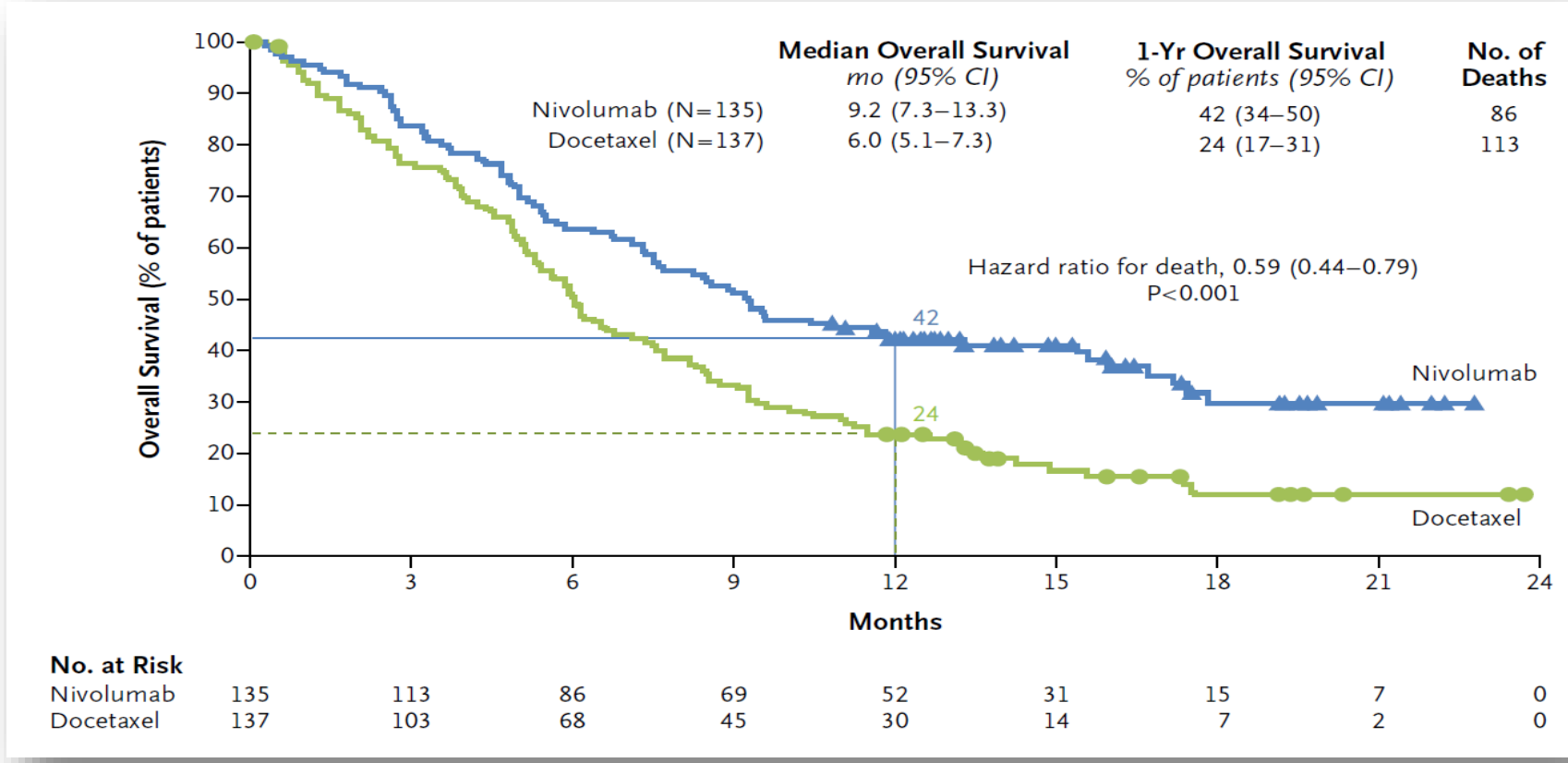
CheckMate 017 (NCT01642004) study design



- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was *P* <0.03

Spigel DR , ASCO 2015

CheckMate 017: Overall Survival



Brahmer J, NEJM 2015

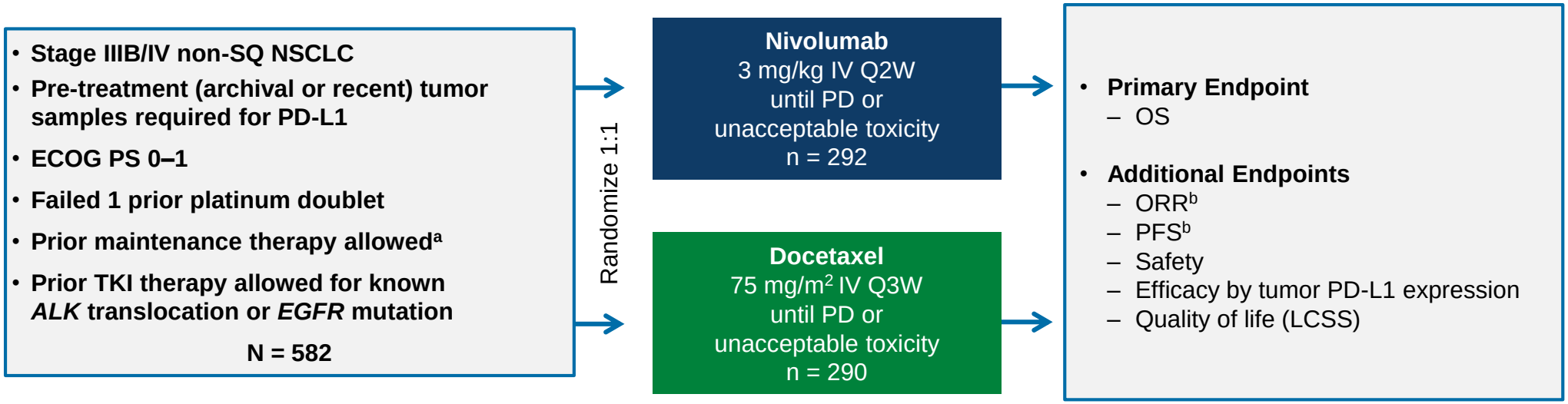
CheckMate 017: treatment-related AEs reported in at least 5% of patients and safety summary

	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–5[a]	Any Grade	Grade 3–5
Treatment-related AEs, %	58	7	86	57
Treatment-related AEs leading to discontinuation, %	3[b]	2	10[c]	7
Treatment-related deaths, %	0		2[d]	

Brahmer J, NEJM 2015; Spigel DR , ASCO 2015

CheckMate 057 (NCT01673867) study design



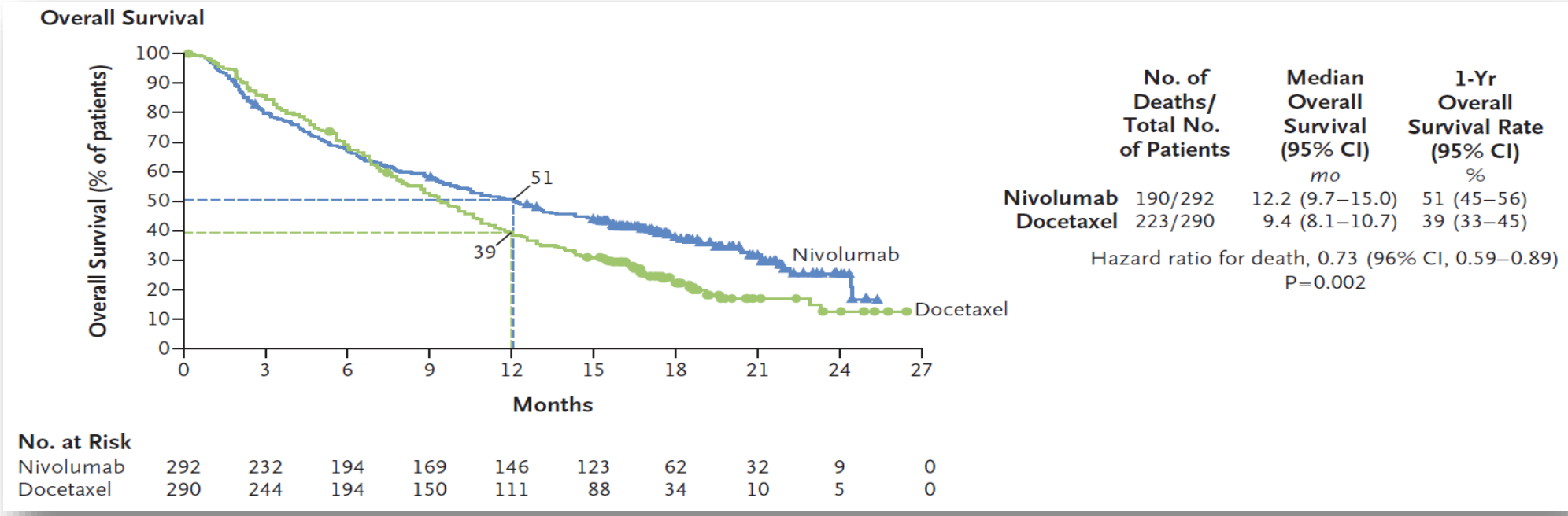
Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

Paz-Ares L , ASCO 2015

CheckMate 057: Overall Survival



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

Borghaei H , NEJM 2015

CheckMate 057: treatment-related AEs reported in at least 5% of patients and safety summary

Event	Nivolumab (N = 287)		Docetaxel (N = 268)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	199 (69)	30 (10)	236 (88)	144 (54)
Fatigue	46 (16)	3 (1)	78 (29)	13 (5)
Nausea	34 (12)	2 (1)	70 (26)	2 (1)
Decreased appetite	30 (10)	0	42 (16)	3 (1)
Asthenia	29 (10)	1 (<1)	47 (18)	6 (2)
Diarrhea	22 (8)	2 (1)	62 (23)	3 (1)
Peripheral edema	8 (3)	0	28 (10)	1 (<1)
Myalgia	7 (2)	1 (<1)	30 (11)	0
Anemia	6 (2)	1 (<1)	53 (20)	7 (3)
Alopecia	1 (<1)	0	67 (25)	0
Neutropenia	1 (<1)	0	83 (31)	73 (27)
Febrile neutropenia	0	0	27 (10)	26 (10)
Leukopenia	0	0	27 (10)	22 (8)

	Nivolumab (n = 287)		Docetaxel (n = 268)	
Median number of doses received (range)	6 (1, 52)		4 (1, 23)	
Relative dose intensity, ≥90%	83		66	
Patients continuing treatment, %	15		0	
Patients who received subsequent systemic therapy, %	42		50	
	Any Grade	Grade 3–4[a]	Any Grade	Grade 3–4[a]
Treatment-related AEs, %	69	10	88	54
Treatment-related SAEs, %	7	5	20	18
Treatment-related AEs leading to discontinuation, %	5	4	15	7
Treatment-related deaths, %	0[b]		<1[c]	

Borghaei H , NEJM 2015; Paz-Ares L , ASCO 2015

Inclusion and Exclusion Criteria

KEY INCLUSION CRITERIA:

- Patients with histologically- or cytologically-documented Stage IIIB/Stage IV non-squamous cell NSCLC
  Note: Enrollees must not be eligible for another clinical study with -nivolumab.
  A fresh biopsy is not required to take part in this program.
- Subjects must have experienced disease progression or recurrence during or after at least one systemic chemotherapy for advanced or metastatic disease.
- ECOG Performance Status ≤ 2
- Eligible if CNS metastasis is treated and patients have neurologically returned to baseline for at least 2 weeks prior to first dose and either be off corticosteroids or on a stable dose or decreasing dose of ≤ 10 mg daily prednisone (or equivalent)

KEY EXCLUSION CRITERIA:

- ECOG PS ≥ 3
- CNS metastases (untreated and/or symptomatic)
- Carcinomatous meningitis
- Corticosteroids > 10 mg prednisolone/day (or equivalent)
- Prior treatment with anti-PD-1, anti-PD-L-1, anti-PD-L2, anti-CT137 or anti-CTLA antibody, including ipilimumab or any other drugs specifically targeting T cell costimulation or checkpoint pathways
- Any Autoimmune disease, that required immunosoppressive therapy

EAP-S: methods and patients characteristics

- Nivolumab was provided upon physician request to patients aged ≥18 years who had relapsed after ≥1 prior systemic treatment for stage IIIB/IV SQ NSCLC.
  - Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≤24 months.
- Patients were monitored for AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0.
- Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were evaluated.
- From April 2015 to September 2015, 371 patients with SQ NSCLC. participated in the EAP at 96 centers in Italy and received ≥1 dose of nivolumab
- Patients received a median of 6 doses (range: 1–22) of nivolumab, with a median follow-up of 7.1 months (range: 0.1–16.4).

Crinò L, WCLC 2016

EAP-S: patients characteristics

Characteristic	N = 371
Gender, n (%)	
Male	298 (80)
Female	73 (20)
Median age, years (range)	68 (31–91)
≥75, n (%)	70 (19)
Smoking status, n (%)	
Smoker	83 (22)
Former smoker	225 (61)
Never smoker	31 (8)
Unknown	32 (9)
ECOG PS, n (%)	
0	134 (36)
1	215 (58)
2	22 (6)
Metastasis site, n (%)	
CNS	37 (10)
Liver	63 (17)
Bone	120 (32)
Number of prior therapies, n (%)	
1	162 (44)
2	120 (32)
3	68 (18)
≥4	21 (6)

Crinò L, WCLC 2016, Brahmer J, NEJM 2015

Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy.*

Characteristic	Nivolumab (N = 135)	Docetaxel (N = 137)	Total (N = 272)
Age — yr			
Median	62	64	63
Range	39–85	42–84	39–85
Age category — no. (%)			
<65 yr	79 (59)	73 (53)	152 (56)
≥65 to <75 yr	45 (33)	46 (34)	91 (33)
≥75 yr	11 (8)	18 (13)	29 (11)
Sex — no. (%)			
Male	111 (82)	97 (71)	208 (76)
Female	24 (18)	40 (29)	64 (24)
Race — no. (%)†			
White	122 (90)	130 (95)	252 (93)
Black	6 (4)	2 (1)	8 (3)
Asian	4 (3)	2 (1)	6 (2)
Other	1 (1)	2 (1)	3 (1)
Not reported	2 (1)	1 (1)	3 (1)
Disease stage — no. (%)			
IIIB	29 (21)	24 (18)	53 (19)
IV	105 (78)	112 (82)	217 (80)
Not reported	1 (1)	1 (1)	2 (1)
ECOG performance-status score — no. (%)‡			
0	27 (20)	37 (27)	64 (24)
1	106 (79)	100 (73)	206 (76)
Not reported	2 (1)	0	2 (1)
Central nervous system metastasis — no. (%)			
Yes	9 (7)	8 (6)	17 (6)
No	126 (93)	129 (94)	255 (94)
Smoking status — no. (%)			
Current or former smoker	121 (90)	129 (94)	250 (92)
Never smoked	10 (7)	7 (5)	17 (6)
Unknown	4 (3)	1 (1)	5 (2)
Geographic region — no. (%)			
United States or Canada	43 (32)	43 (31)	86 (32)
Europe	77 (57)	78 (57)	155 (57)
Rest of world§	15 (11)	16 (12)	31 (11)
Other systemic cancer therapy — no. (%)¶			
Bevacizumab	1 (1)	1 (1)	2 (1)
Cetuximab	0	2 (1)	2 (1)
Etoposide	17 (13)	11 (8)	28 (10)
Fluorouracil	1 (1)	0	1 (<1)
Gemcitabine	60 (44)	71 (52)	131 (48)
Paclitaxel	46 (34)	46 (34)	92 (34)
Pemetrexed	3 (2)	3 (2)	6 (2)
Vinorelbine	20 (15)	24 (18)	44 (16)

EAP-S: Overall Response Rate (ORR)

Tumor Assessment

•The best ORR was 18%, and the best DCR was 47% among 364 evaluable patients.
–66 patients were treated beyond RECIST v1.1-defined progression
•23 (35%) of 66 patients obtained a non-conventional benefit (PR=6; SD=17)

EAP

Response	First tumor assessment (N = 371)	Best response (N = 371)
ORR, n (%)	51 (14)	67 (18)
DCR, n (%)	151 (41)	175 (47)
Overall response, n (%)		
CR	1 (<1)	4 (1)
PR	50 (13)	63 (17)
SD	100 (27)	108 (29)
PD	212 (57)	189 (51)
Not determined	8 (2)	7 (2)

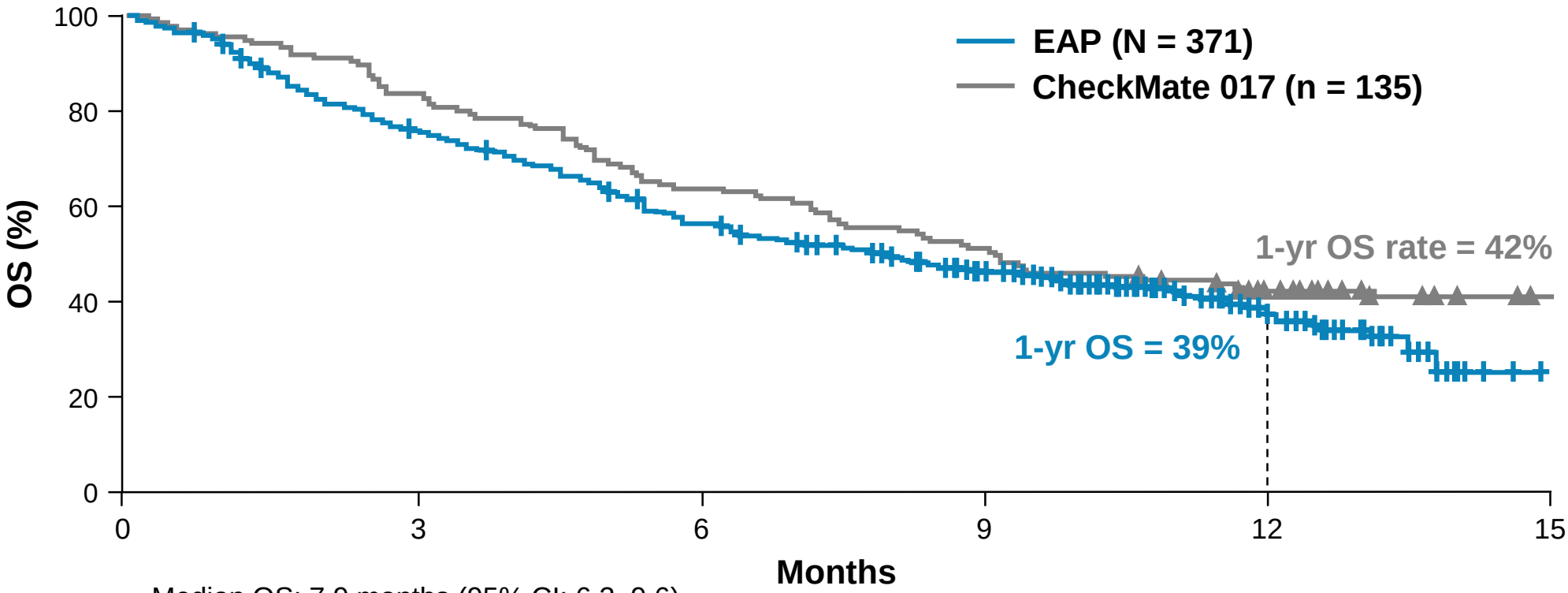
PD = progressive disease

CheckMate 017

	Nivolumab n = 135	Docetaxel n = 137
ORR, % (95% CI)	**20** (14, 28)	**9** (5, 15)
***P*-value[a]**	**0.0083**	
Best overall response, %		
Complete response	1[b]	0
Partial response	19	9
Stable disease	29	34
Progressive disease	41	35
Unable to determine	10	22
Median DOR,[c] mo (range)	NR (2.9, 21+)	8.4 (1.4+, 15+)
Median time to response,[c] mo (range)	2.2 (1.6, 12)	2.1 (1.8, 9.5)

Crinò L, WCLC 2016, Brahmer J, NEJM 2015

EAP-S: Overall Survival



- Median OS: 7.9 months (95% CI: 6.2, 9.6)
- Median follow-up = 7 months

Crinò L, WCLC 2016, Brahmer J, NEJM 2015

EAP-S: safety and patient discontinuation

Grade 3–4 AEs considered to be treatment-related were reported in 6% of patients
The most frequent treatment-related grade 3–4 AEs were diarrhea, increased transaminases, and rash (1% each)

EAP

All treatment-related AEs	Patients, n (%)	
	Any grade	Grade 3-4
Total	109 (29)	21 (6)
General		
Fatigue/Asthenia	24 (6)	2 (1)
Pyrexia	10 (3)	0
Lack of appetite/anorexia	9 (2)	0
Skin and mucosal	42 (11)	5 (1)
Rash	31 (8)	3 (1)
Gastrointestinal	27 (7)	4 (1)
Diarrhea	18 (5)	4 (1)
Pain	19 (5)	3 (1)
Endocrine	16 (4)	1 (<1)
Hypothyroidism	10 (3)	0
Hyperthyroidism	5 (1)	1 (<1)
Respiratory/Pulmonary	12 (3)	4 (1)
Pneumonitis	3 (1)	1 (<1)
Hematologic	10 (3)	1 (<1)
Anemia	9 (2)	1 (<1)
Hepatic/Pancreatic	8 (2)	4 (1)
Increased transaminases	6 (1)	4 (1)
Increased lipase/amylase	2 (1)	0

CheckMate 017

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

Crinò L, WCLC 2016, Brahmer J, NEJM 2015

EAP-S: conclusions

- This EAP represents extensive real-world experience with nivolumab in patients with previously treated, advanced SQ NSCLC.
- The 12-month OS rate was 39%, similar to that observed in the CheckMate 017 trial (42%).
- The safety profile of nivolumab was consistent with that reported in the CheckMate 017 trial.
- By confirming the prognostic role of known factors, the multivariate analysis reinforces the validity of this data collection.
- These preliminary EAP data provide insights into real-world experience with nivolumab and seem to confirm data from pivotal trials.

EAP-NS: methods and patients characteristics

- Nivolumab was provided upon physician request to patients aged ≥18 years who had relapsed after ≥1 prior systemic treatment for stage IIIB/IV non-SQ NSCLC.
  - Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≤24 months.
- Patients were monitored for AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0.
- Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were evaluated.
- From May 2015 to December 2016, 1,588 patients with non-SQ NSCLC. participated in the EAP at 153 centers in Italy and received ≥1 dose of nivolumab
- Patients received a median of 7 doses (range: 1–55) of nivolumab, with a median follow-up of 8.1 months (range: 0.1–27.4).

Grossi F, WCLC/AIOM 2017

EAP-NS: patients characteristics

EAP

Characteristic	All patients (N = 1588)
Male, n (%)	1029 (65)
Median age, years (range)	66 (27–89)
Smoking status, n (%)	
Smoker	360 (23)
Former smoker	765 (48)
Never-smoker	305 (19)
Unknown	158 (10)
ECOG PS, n (%)	
0	648 (41)
1	815 (51)
2	108 (7)
Unknown	17 (1)
Metastatic site, n (%)	
CNS	409 (26)
Liver	327 (21)
Bone	626 (39)
Number of prior therapies, n (%)	
1	378 (24)
2	562 (35)
3	332 (21)
≥4	307 (19)
Unknown	9 (1)

CheckMate 057

	Nivolumab (n = 292)	Docetaxel (n = 290)
Male, %	**52**	58
Median age, years (range)	**61 (37, 84)**	64 (21, 85)
≥75 years, %	7	8
Smoking status, %		
Current/former smoker	79	78
Never smoker	20	21
ECOG PS,[a] %		
0	**29**	33
1	**71**	67
Number of prior systemic regimens,[b,c] %		
1	**88**	89
2	**12**	11
EGFR-positive mutation status, %	15	13
ALK-positive translocation status, %	4	3

Grossi F, WCLC/AIOM 2017; Borghaei H, NEJM 2015

EAP-NS: Overall Response Rate (ORR)

Tumor Assessment

- The ORR was 18%, comprising 12 (<1%) patients with a CR and 278 (18%) patients with a PR.
- The DCR was 44%.

EAP

Response	All patients (N = 1588)
ORR, n (%)	290 (18)
DCR, (%)	704 (44)
Best overall response, n (%)	
CR	12 (<1)
PR	278 (18)
SD	414 (26)
PD	688 (43)
Early Death	130 (8)
Not determined	66 (4)

PD = progressive disease

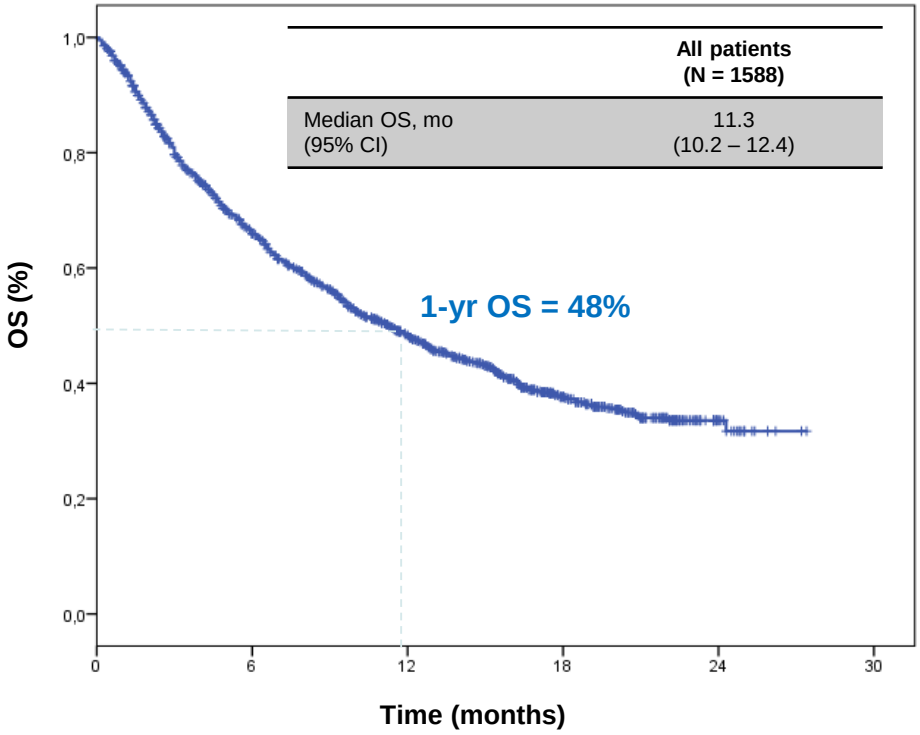
CheckMate 057

	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR (95% CI)	19%(15, 24)	12% (9, 17)
Best overall response, %		
Complete response	1	<1
Partial response	18	12
Stable disease	25	42
Progressive disease	44	29
Unable to determine	11	16

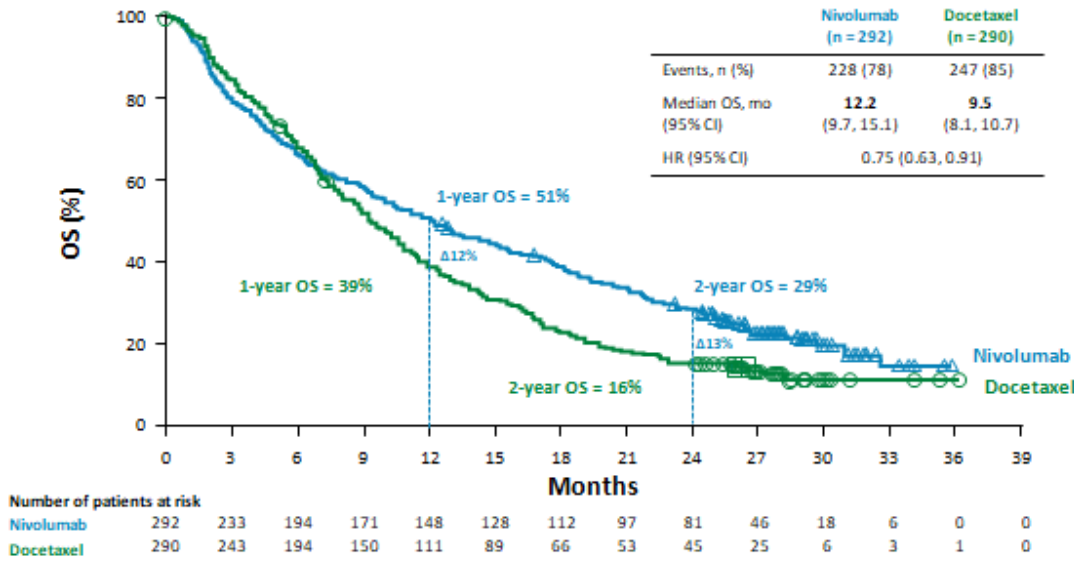
Grossi F, WCLC/AIOM 2017; Borghaei H, NEJM 2015

EAP-NS: Overall Survival (OS)

EAP



CheckMate 057



Grossi F, WCLC/AIOM 2017; Borghaei H, NEJM 2015

EAP-NS: safety and patient discontinuation

- Any grade and grade 3-4 treatment related adverse events (TRAEs) occurred in 523 (33%) and 102 (6%) respectively
- The most frequent grade 3-4 TRAEs (≥1%) were fatigue/asthenia and dyspnea
- Adverse events were managed using protocol defined toxicity management algorithms
- No treatment-related deaths were reported

EAP

Discontinuations	All patients (N = 1588)
Discontinued treatment, n (%)	1300 (82)
Reason for discontinuation, n (%)	954 (73)
PD	130 (10)
Death	101 (8)
AEs or serious AEs	65 (5)
Treatment-related AEs	115 (9)
Other	

CheckMate 057

	Nivolumab (n = 287)		Docetaxel (n = 268)	
Median number of doses received (range)	6 (1, 52)		4 (1, 23)	
Relative dose intensity, ≥90%	83		66	
Patients continuing treatment, %	15		0	
Patients who received subsequent systemic therapy, %	42		50	
	Any Grade	Grade 3–4[a]	Any Grade	Grade 3–4[a]
Treatment-related AEs, %	69	10	88	54
Treatment-related SAEs, %	7	5	20	18
Treatment-related AEs leading to discontinuation, %	5	4	15	7
Treatment-related deaths, %	0[b]		<1[c]	

Grossi F, WCLC/AIOM 2017; Borghaei H, NEJM 2015

EAP-NS: conclusions

- This report represents the largest real-world analysis to date with nivolumab in previously treated patients with advanced non-SQ NSCLC.
- Survival and response observed with nivolumab in the Italian cohort of this EAP were similar to those observed in the nivolumab arm of the CheckMate 057 study.
- The safety profile of nivolumab seemed to be consistent with that reported in the CheckMate 057 trial.

EAP-S/NS: clinical activity in patients subgroup

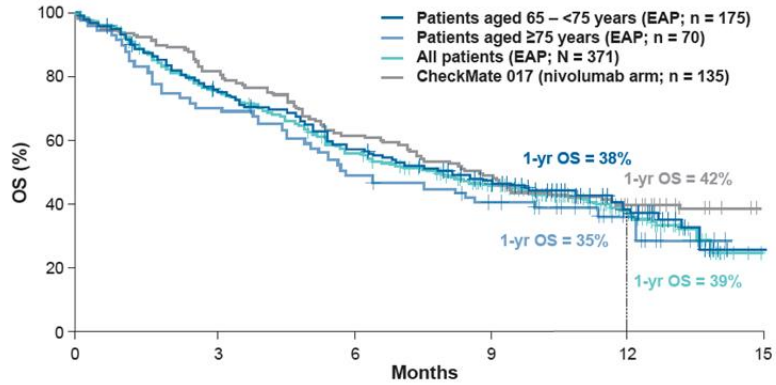
- Elderly patients
- Patients with brain metastases
- Never smokers and EGFR positive patients
- Patients exhibiting KRAS mutations
- Treatment beyond PD
- Bone metastasis

EAP-S: elderly patients

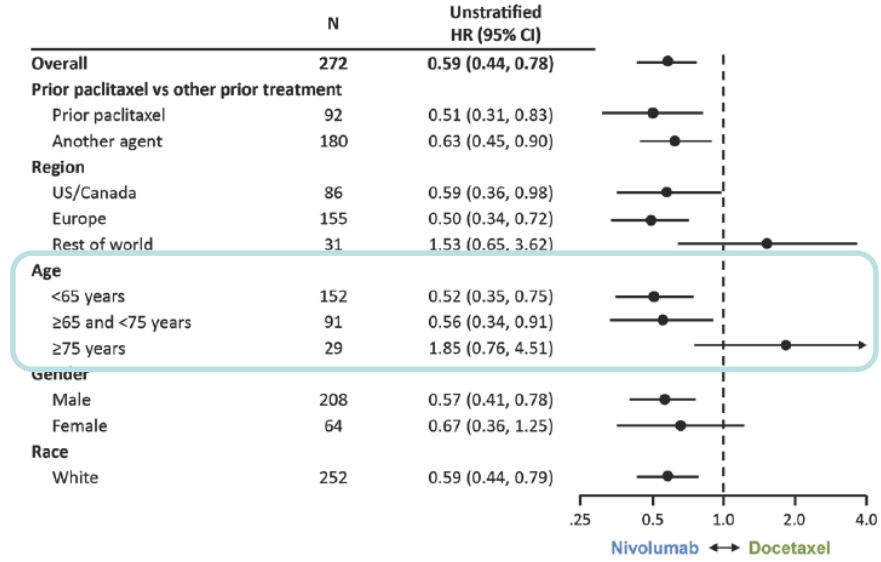
EAP

	Aged 65–<75 years (n = 175)	Aged ≥75 years (n = 70)	All patients (N = 371)
Objective response rate, n (%)	31 (18)	13 (19)	67 (18)
Disease control rate,[a] n (%)	83 (48)	30 (43)	175 (47)
Best response, n (%)			
Complete response	1 (1)	0	4 (1)
Partial response	30 (17)	13 (19)	63 (17)
Stable disease	52 (30)	17 (24)	108 (29)
Progressive disease	88 (50)	38 (54)	189 (51)
Could not be determined	4 (2)	2 (3)	7 (2)

[a]Defined as the combined rate of complete response, partial response, and stable disease.



CheckMate 017



CheckMate 171

	All patients (N = 809)	≥70 years (n = 279)
Median OS, months (95% CI)	9.9 (8.7, 13.1)	11.2 (7.6, NA)
3-month OS rate, % (95% CI)	81 (78, 83)	78 (73, 83)
6-month OS rate, % (95% CI)	67 (63, 70)	66 (59, 71)

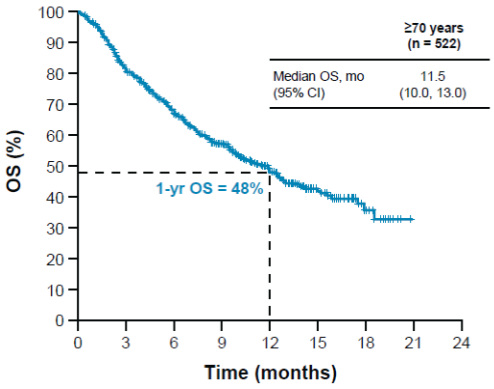
Grossi F, EJC 2018; Brahmer H, NEJM 2015
Popat S, ESMO 2017

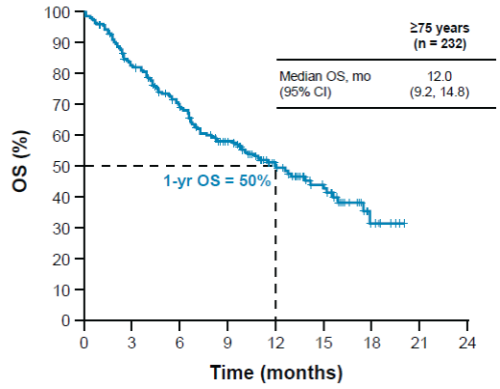
EAP-NS: elderly patients

EAP

Response	≥70 years (n = 522)	≥75 years (n = 232)	All patients (N = 1,588)
ORR, n (%)	108 (21)	58 (25)	290 (18)
DCR, n (%)	253 (48)	122 (53)	704 (44)
Overall response, n (%)			
CR	2 (<1)	0	10 (1)
PR	106 (20)	58 (25)	280 (18)
SD	145 (28)	64 (28)	414 (26)
PD	203 (39)	90 (39)	688 (43)
Death	41 (8)	11 (5)	130 (8)
Not determined	25 (5)	9 (4)	66 (4)

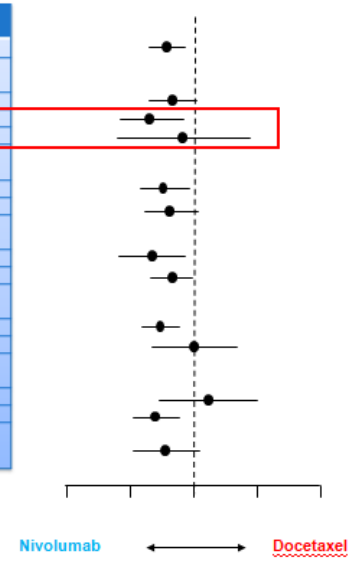
PD = progressive disease





CheckMate 057

	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)
EGFR Mutation Status		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.66 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)



CheckMate 171

	All patients (N = 809)	≥70 years (n = 279)
Median OS, months (95% CI)	9.9 (8.7, 13.1)	11.2 (7.6, NA)
3-month OS rate, % (95% CI)	81 (78, 83)	78 (73, 83)
6-month OS rate, % (95% CI)	67 (63, 70)	66 (59, 71)

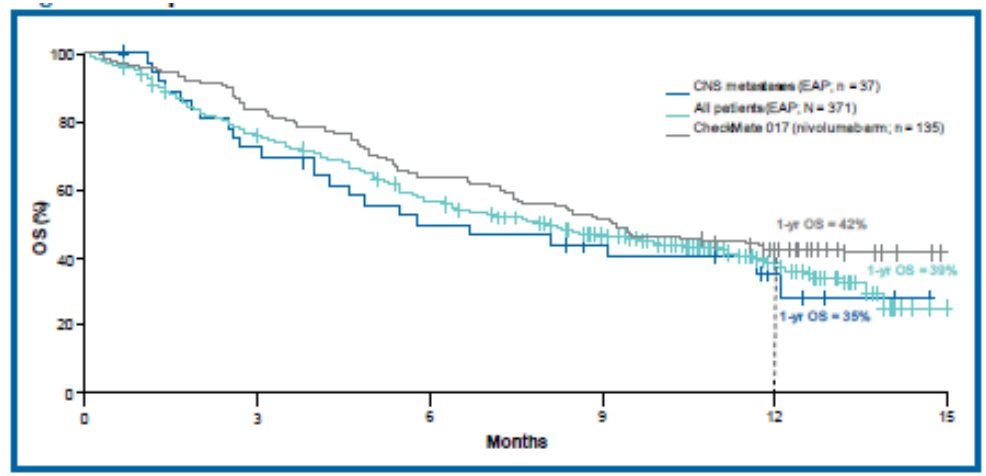
Migliorino R, ESMO 2017; Borghaei H, NEJM 2015
Popat S, ESMO 2017

EAP-S: patients with brain metastasis

- Patients with CNS metastases were eligible if the following criteria were met:
  - They had no neurologic symptoms related to metastatic CNS lesions occurring for ≥2 weeks before enrollment.
  - They did not need systemic corticosteroids or were on a stable or decreasing dose of ≤10 mg/day of prednisone or equivalent.
- 37(10%) patients had asymptomatic and controlled CNS metastases.
- Patients with CNS metastases received a median of 6 doses (range: 1–18) of nivolumab.
- 8 (22%) patients were receiving steroid therapy at baseline and 21 (57%) patients received concomitant radiotherapy.
- Median OS was 5.8 months for patients with CNS metastasis, compared with 7.9 months for all patients.
- The OS rate at 1 year was 35% for patients with CNS metastasis and 39% for all patients.

Response	CNS metastases (n = 37)		All patients (N = 371)	
	First tumor assessment	Best response	First tumor assessment	Best response
ORR, n (%)	7 (19)	7 (19)	51 (14)	67 (18)
DCR, n (%)	18 (49)	18 (49)	151 (41)	175 (47)
Overall response, n (%)				
CR	0	1 (3)	1 (<1)	4 (1)
PR	7 (19)	6 (16)	50 (13)	63 (17)
SD	11 (30)	11 (30)	100 (27)	108 (29)
PD	19 (51)	19 (51)	212 (57)	189 (51)
Not determined	0	0	8 (2)	7 (2)

PD = progressive disease



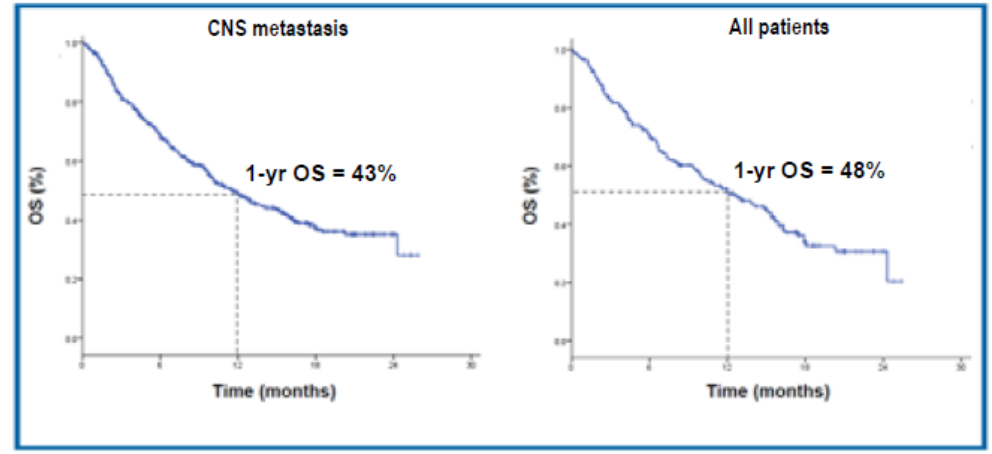
Cortinovis D, WCLC 2016

EAP-NS: patients with brain metastasis

- Patients with CNS metastases were eligible if the following criteria were met:
  - They had no neurologic symptoms related to metastatic CNS lesions occurring for ≥2 weeks before enrollment.
  - They did not need systemic corticosteroids or were on a stable or decreasing dose of ≤10 mg/day of prednisone or equivalent.
- 409 (26%) patients had asymptomatic and controlled CNS metastases.
- Patients with CNS metastases received a median of 7 doses (range: 1–54) of nivolumab.
- 117 (29%) patients were receiving steroid therapy at baseline and 74 (18%) patients received concomitant radiotherapy.
- Median OS was 8.6 months for patients with CNS metastasis, compared with 11.3 months for all patients.
- The OS rate at 1 year was 43% for patients with CNS metastasis and 48% for all patients.

Response, n (%)	CNS Metastasis (N = 409)	All patients (N = 1588)
ORR	68 (17)	290 (18)
DCR	164 (40)	704 (44)
Overall response		
CR	4 (1)	12 (<1)
PR	64 (16)	278 (18)
SD	96 (23)	414 (26)
PD	192 (47)	688 (43)
Death	35 (9)	130 (8)
Not determined	18 (4)	66 (4)

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease



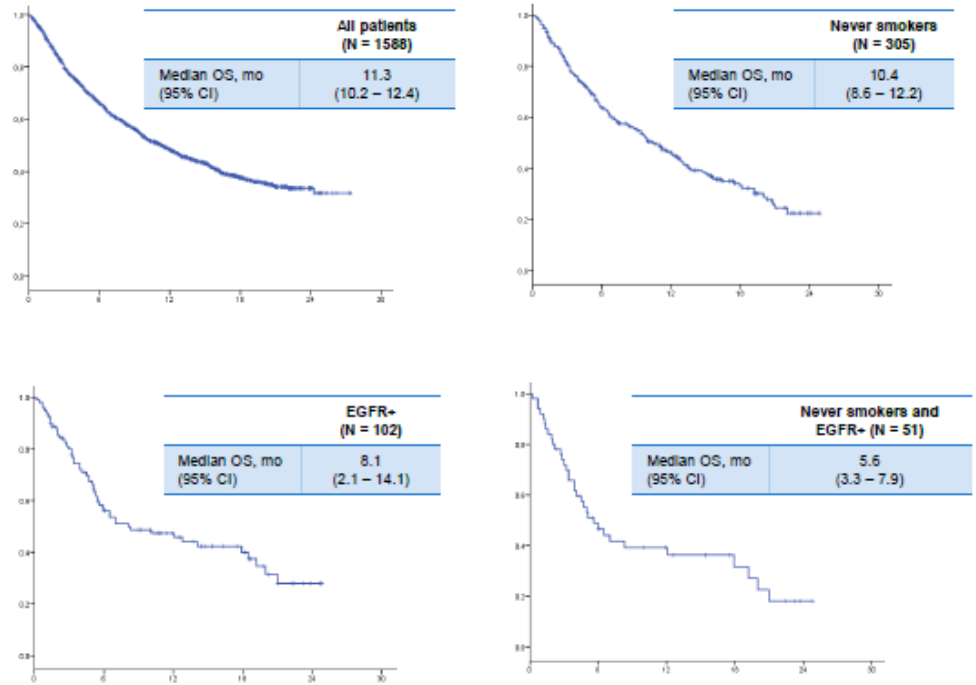
Median OS was 8.1 months for patients with CNS metastases and 11.0 months for all patients

Crinò L, WCLC 2017

EAP-NS: never smokers and EGFR+

Characteristic	Never-smoker (n = 305)	*EGFR*-positive (n = 102)	*EGFR*-positive never-smoker (n = 51)	All patients (N = 1,588)
Male, n (%)	137 (45)	44 (43)	18 (35)	1,029 (65)
Median age, years (range)	65 (29–87)	65 (40–83)	62 (40–81)	66 (27–89)
ECOG PS, n (%)				
0	123 (40)	42 (42)	14 (27)	648 (41)
1	162 (53)	52 (51)	32 (63)	815 (52)
2	19 (6)	7 (7)	5 (10)	108 (7)
Unknown	1 (<1)	1 (1)	0	17 (1)
Metastasis site, n (%)				
CNS	72 (24)	44 (43)	19 (37)	409 (26)
Bone	134 (44)	47 (46)	27 (53)	327 (21)
Liver	76 (25)	32 (31)	20 (40)	626 (39)
EGFR status, n (%)				
Mutant	51 (17)	102 (100)	51 (100)	102 (6)
Wild-type	236 (77)	–	–	1,293 (82)
Unknown	18 (6)	–	–	193 (12)
Previous EGFR TKI, n (%)				
1	96 (31)	72 (71)	38 (75)	383 (24)
>1	17 (6)	21 (21)	10 (20)	36 (2)

Garassino M, JTO 2018



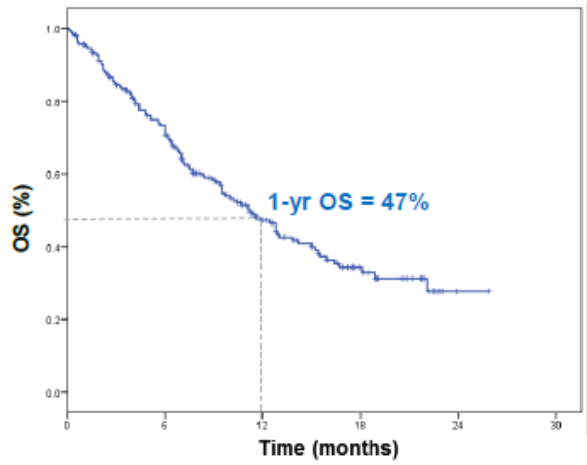
Tumor Assessment

- ORR was 9% in never-smokers, 9% in patients with an EGFR-positive tumor, 2% in never-smokers with an EGFR-positive tumor, and 18% in all patients
- DCR was 42% in never-smokers, 30% in patients with an EGFR-positive tumor, 22% in never-smokers with an EGFR-positive tumor, and 44% in all patients

EAP-NS: K-RAS mutated patients

Characteristic	KRAS mutation positive (n = 206)	All patients (N = 1588)
Male, n (%)	129 (63)	1029 (65)
Median age, years (range)	66 (36-87)	66 (27-89)
Smoking status, n (%)		
Smoker	45 (22)	360 (23)
Former smoker	119 (58)	765 (48)
Never-smoker	27 (13)	305 (19)
Unknown	15 (7)	158 (10)
ECOG PS, n (%)		
0	80 (39)	648 (41)
1	111 (54)	815 (51)
2	14 (7)	108 (7)
Unknown	1 (<1)	17 (1)
Metastasis site, n (%)		
CNS	60 (29)	409 (26)
Liver	35 (17)	327 (21)
Bone	91 (44)	626 (39)
Number of prior therapies, n (%)		
1	51 (25)	378 (24)
2	75 (36)	562 (35)
3	44 (21)	332 (21)
≥4	36 (18)	307 (19)
Unknown	0	9 (1)

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status



Survival

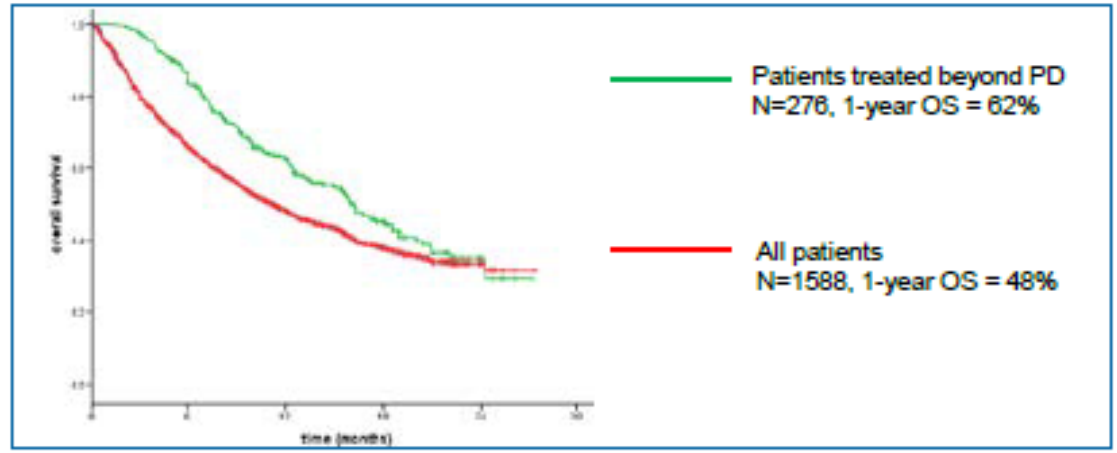
- Median OS was 11.2 months for patients with KRAS mutations and 11.3 months for all patients
- The OS rate at 1 year was 47% for patients with KRAS mutations and 48% for all patients

Response, n (%)	KRAS mutation positive (n = 206)	All patients (N = 1588)
ORR	41 (20)	290 (18)
DCR	96 (47)	704 (44)
Best overall response		
CR	2 (1)	12 (1)
PR	39 (19)	278 (18)
SD	55 (27)	414 (26)
PD	88 (43)	688 (43)
death	12 (6)	130 (8)
Not determined	10 (4)	66 (4)

Ardizzoni A, WCLC 2017

EAP-NS: treatment beyond PD

- Criteria for receiving nivolumab treatment beyond RECIST v1.1-defined initial progression included the following:
  - Investigator-assessedclinicalbenefit
  - Absence of rapid PD
  - Tolerance of nivolumab
  - Stable performance status
  - No delay of an imminent intervention to prevent serious complications of PD
- Of these 1588 patients, 1053 patients (66%) developed PD and 276 (26%) were treated beyond PD.

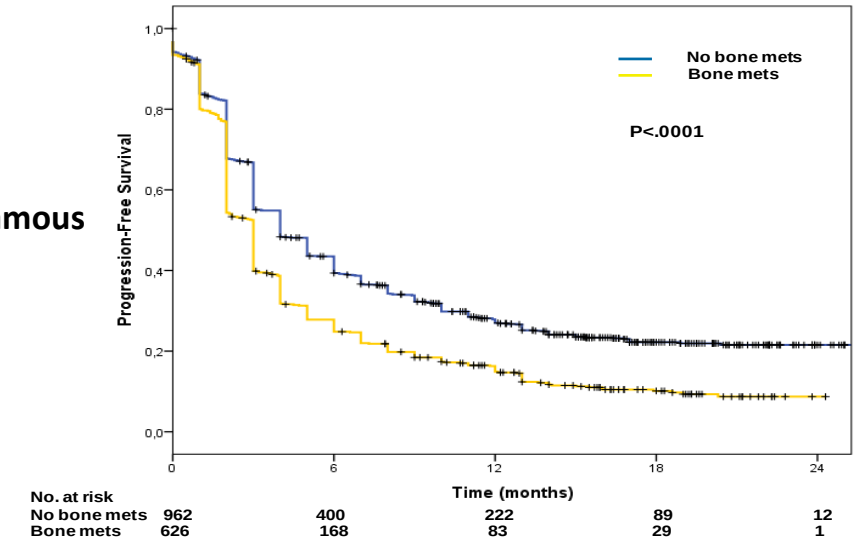


- Patients treated beyond PD received a median of 11 doses.
- Median OS was16.2 months for patients treated beyond PD and 11.3 months for all patients.

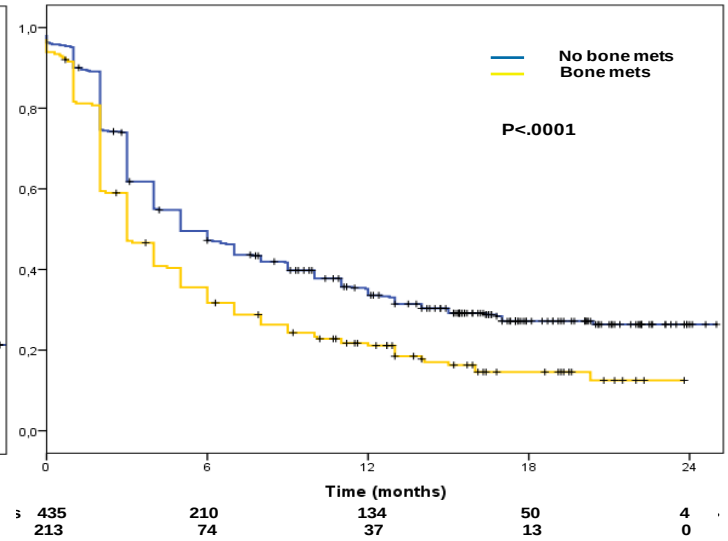
Cortesi E, WCLC 2017

Bone mets: PFS and OS in non-squamous cohort

A: PFS in all non squamous

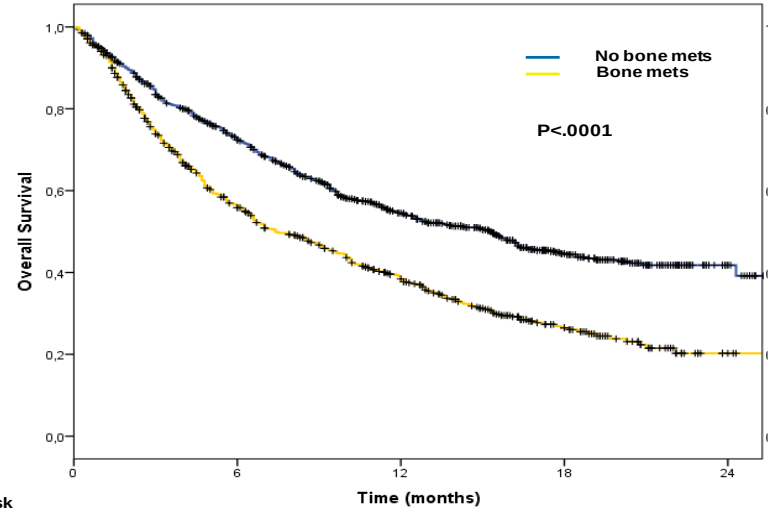


C: PFS in PS 0

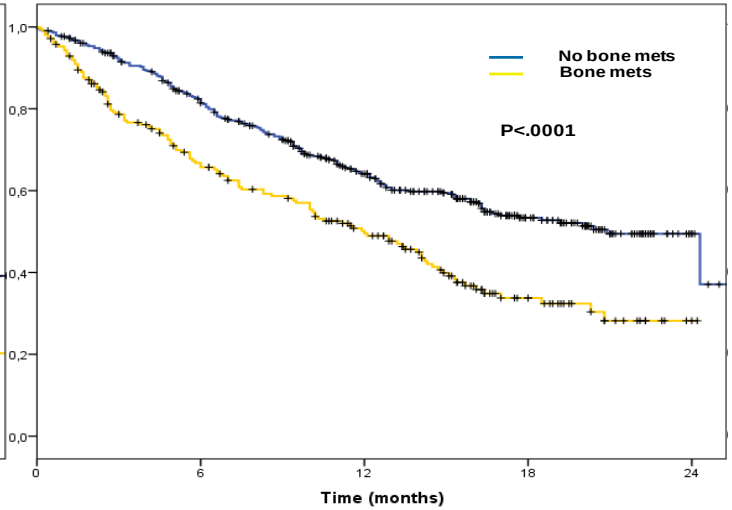


No. at risk										
No bone mets	962	400	222	89	12	435	210	134	50	4
Bone mets	626	168	83	29	1	213	74	37	13	0

B: OS in all non squamous



D: OS in PS 0

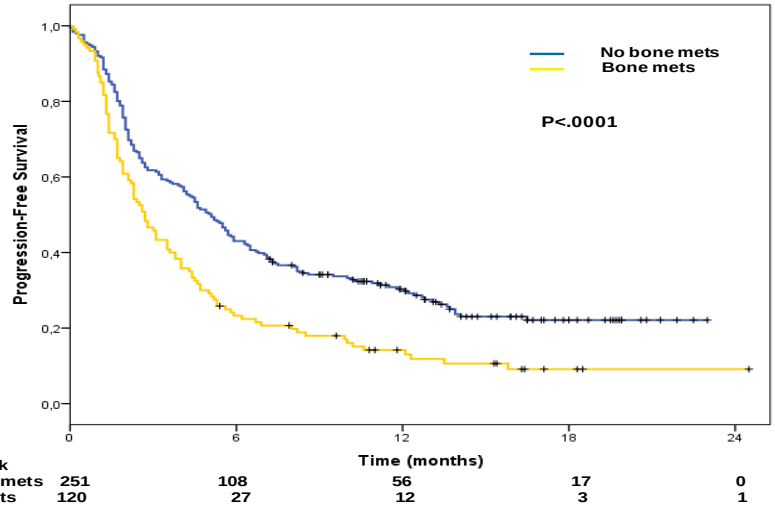


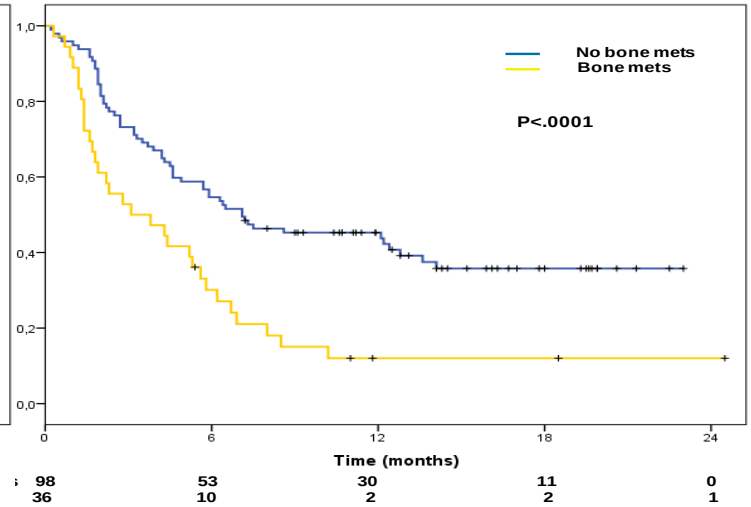
No. at risk										
No bone mets	962	628	374	159	19	435	330	216	92	7
Bone mets	626	303	168	62	4	213	127	82	27	2

Landi L, WCLC 2018

Bone mets: PFS and OS in non-squamous cohort

A: PFS in all squamous



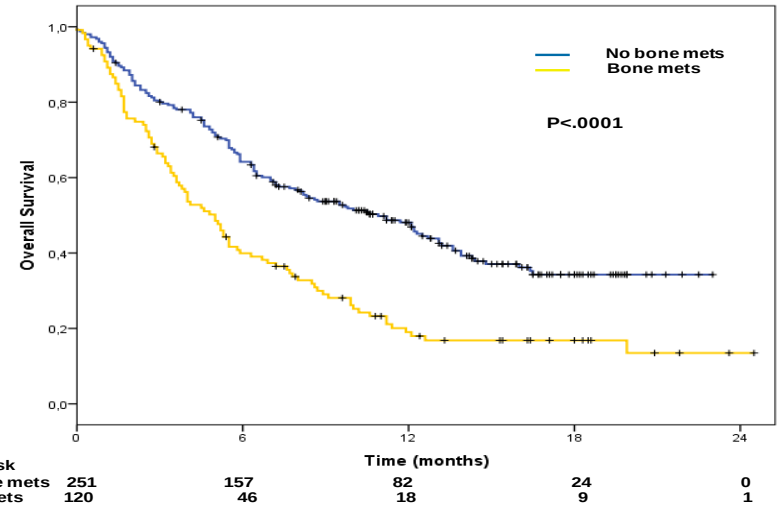


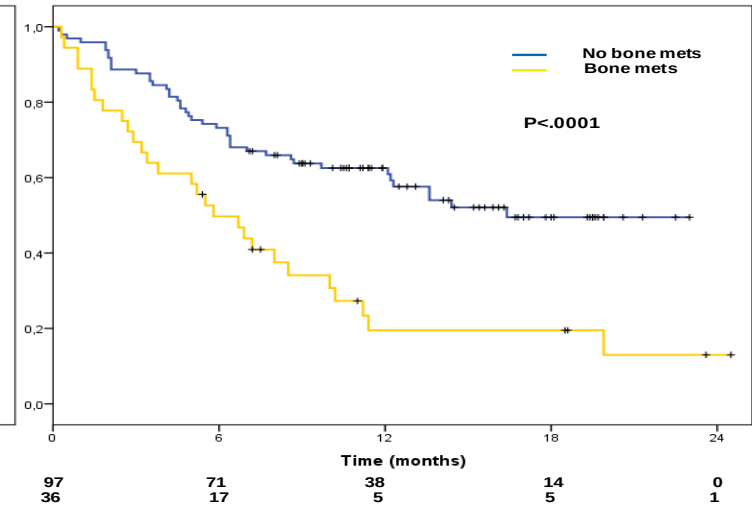
C: PFS in PS 0

No. at risk					
No bone mets	251	108	56	17	0
Bone mets	120	27	12	3	1

98	53	30	11	0
36	10	2	2	1

B: OS in all squamous





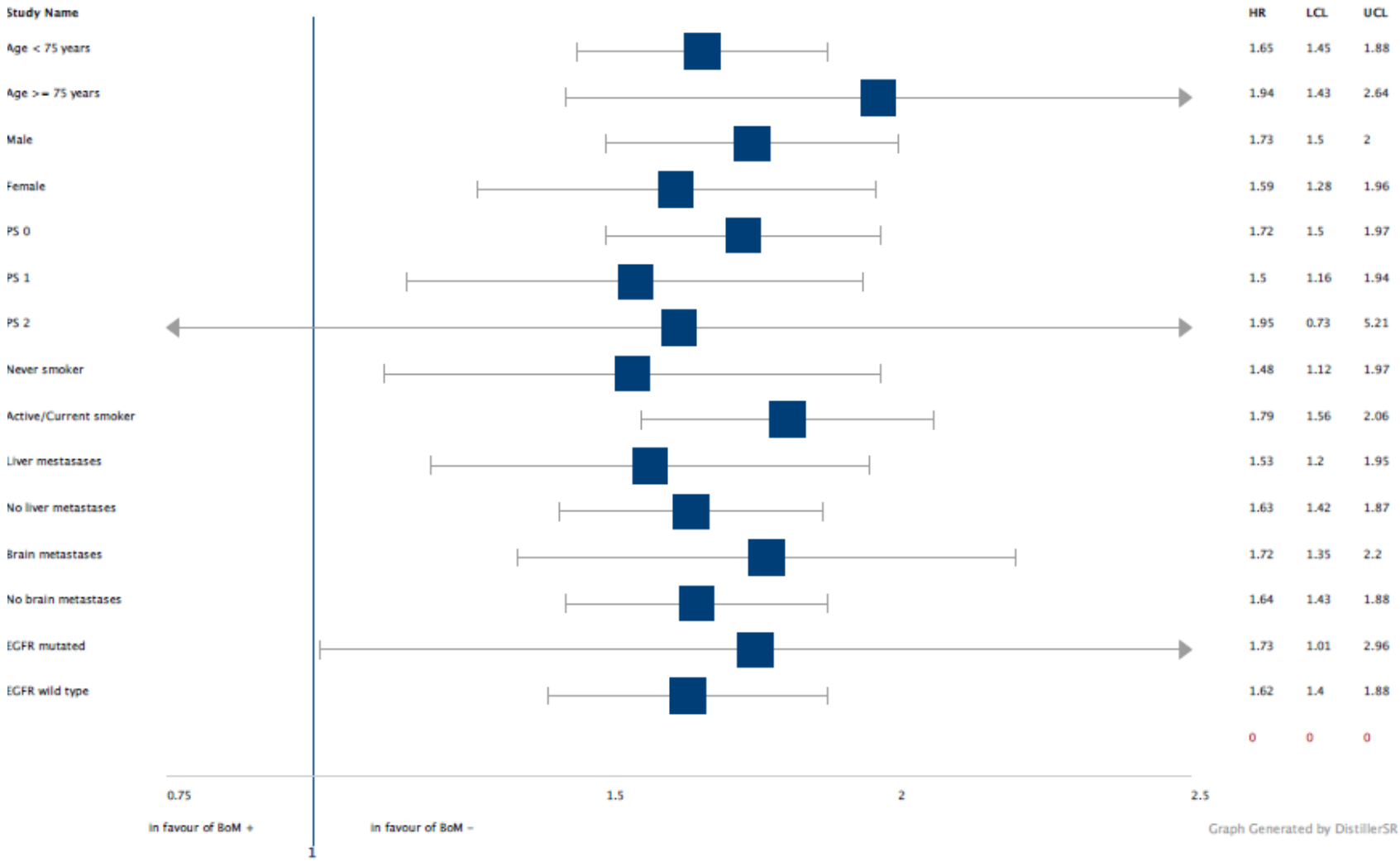
C: OS in PS 0

No. at risk					
No bone mets	251	157	82	24	0
Bone mets	120	46	18	9	1

97	71	38	14	0
36	17	5	5	1

Landi L, WCLC 2018

Forest plot for OS according to bone involvement



Landi L, WCLC 2018

Grazie per l'attenzione!

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