ASCO Update
Lungen Karzinom

PD Dr. G Chakupurakal

Praxis Klinik für Hämatologie-Onkologie, Koblenz

26.06.2019

Was ist Neu

- Neoadjuvante Therapie
- Adjuvante Therapie
  - Chemotherapie
  - EGFR TKI
- Radiochemotherapie in nicht operable NSCLC
- VEGF Inhibitoren als Erhaltung
- EGFR TKI und Chemotherapie
- Immuntherapie

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Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): interim analysis and biomarker data from a multicenter study (LCMC3)

David J. Kwiatkowski,[1] Valerie Rusch,[2] Jamie Chaft,[2] Bruce Johnson,[3] Alan Nicholas,[4] Ignacio Wistuba,[5] Robert Merritt,[6] Jay M. Lee,[7] Paul Bunn,[8] Yan Tang,[1] See Phan,[4] Saiama N. Waqar,[9] Alexander Patterson,[9] Eric Haura,[10] Eric M. Toloza,[10] Karen L. Reckamp,[11] Dan Raz,[11] Katja Schulze,[4] Ann Johnson,[4] David P. Carbone[6]

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PRESENTED BY: David Kwiatkowski, MD, PhD
Presented By David Harpole at 2019 ASCO Annual Meeting

Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): clinical and correlative results from the NEOSTAR study

Tina Cascone[1], William N. William Jr.[1], Annikka Weissferdt[2], Heather Lin[3], Cheuk H. Leung[3], Brett W. Carter[4], Frank V. Fossella[1], Frank E. Mott[1], Vassiliki A. Papadimitrakopoulou[1], George Blumenschein Jr.[1], Xiuning Le[1], Lorenzo Federico[5], Edwin R. Parra[6], Chantale Bernatchez[5], Ignacio I. Wistuba[6], Ara A. Vaporciyan[7], Don L. Gibbons[1], Stephen G. Swisher[7], John V. Heymach[1], Boris Sepesi[7]

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Additional contributors: Cara Haymaker[5,6], Junya Fushimoto[6], Jianjun Zhang[1,8], Alexandre Reuben[1], Jun Lin[8], Regina Chen[8]

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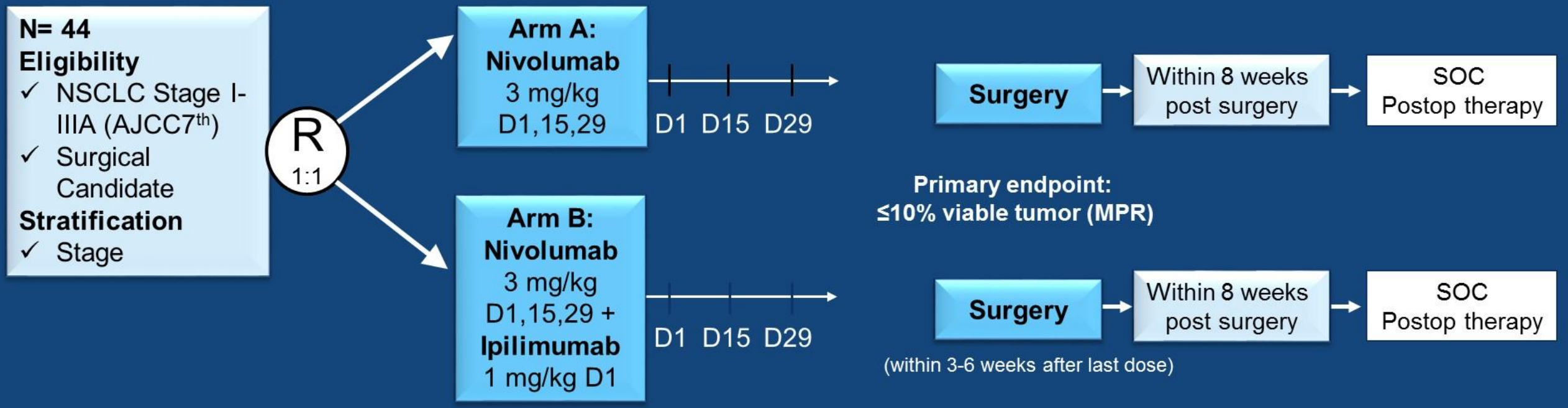
NEOSTAR: phase II study of induction checkpoint blockade for untreated stage I-IIIA NSCLC amenable for surgical resection



PI: Cascone
Co-PI: Sepesi
NCT03158129

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Summary of Neoadjuvant Immunotherapy Studies

	N resected	Stage	Drug(s)	Cycles	MPR	RECIST ORR
LCMC3	84	IB-IIIB	Atezo	2	18% (10-28)	7%
NEOSTAR						
Arm A	23	IA-IIIA	Nivo	3	17% (5-39)	22%
Arm B	21	IA-IIIA	Nivo/Ipi	3	33% (15-57)	19%
Forde et al[1]	20	IB-IIIA	Nivo	2	45% (23-68)	10%
Historical Control						
Chaft et al[2]	41	IB-IIIA	Cisplatin/Docetaxel/Bev	4	27% (15-43)	45%
Immunotherapy + chemotherapy						
NADIM[3]	30	IIIA	Nivo/Carbo/Paclitaxel	3	80% (61-92)	70%
Shu et al.[4]	11	IB-IIIA	Atezo/Carbo/Nab-Paclitaxel	2	64% (32-88)	73%

[1]Forde et al. *NEJM* 2018 [2]Chaft et al. *JTO* 2013 [3]Provencio et al. WCLC 2018 #OA01.05 [4]Shu et al. ASCO 2018 #8532

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LCMC3 and NEOSTAR Clinical Summary

Strengths

- 18-33% MPR rates
- Relatively low toxicity (G3+ 6-11%)
- Low progression rates (≤5%)
- High resection rates (~90%)
- Collection of valuable biospecimens

Limitations

- Relatively small # of patients
- MPR rates lower than chemo+immunotherapy combos
- MPR has not been validated as surrogate for survival
- Need longer follow-up for survival results

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Randomized phase III study of pemetrexed/cisplatin versus vinorelbine/cisplatin for completely resected non-squamous non-small-cell lung cancer: the JIPANG study

Hirotsugu Kenmotsu[1], Nobuyuki Yamamoto[2], Takeharu Yamanaka[3], Katsuo Yoshiya[4], Toshiaki Takahashi[1], Tsuyoshi Ueno[5], Koichi Goto[6], Haruko Daga[7], Norihiko Ikeda[8], Kenji Sugio[9], Takashi Seto[10], Shinichi Toyooka[11], Hiroshi Date[12], Tetsuya Mitsudomi[13], Isamu Okamoto[14], Kohei Yokoi[15], Hideo Saka[16], Hiroaki Okamoto[17], Yuichi Takiguchi[18], Masahiro Tsuboi[6]

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JIPANG: Study Design

KEY ELIGILITY

- Completely resected non-Sq NSCLC
- Pathological stage II-IIIA (7th TNM)
- ECOG PS 0-1
- Age 20-75 years
- Lobectomy or pneumonectomy with resection of N2 lymph nodes within 3–8 weeks

N=804

RANDOMIZED

1:1

Vinorelbine (25 mg/m^2, days 1, 8)
+Cisplatin (80 mg/m^2, day 1)
every 3 weeks, up to 4 cycles

Pemetrexed (500 mg/m^2, day 1)
+Cisplatin (75 mg/m^2, day 1)
every 3 weeks, up to 4 cycles

ENDPOINTS

- Primary
  - Recurrence-free survival
- Secondary
  - Overall survival
  - Rate of treatment completion
  - Toxicity

Stratification factors:

- Gender (female vs. male)
- Age (<70 years vs. ≥70 years)
- Pathological stage (II vs. IIIA)
- *EGFR* mutation (mutant vs. wild)
- Institution

UMIN000006737; https://www.umin.ac.jp/
jRCTs041180023; https://jrct.niph.go.jp/

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Statistical considerations

- Primary endpoint: Recurrence-free survival (RFS)
  - Target RFS HR 0.755, assumption of 3-year RFS 50% vs. 58%.
  - Approximately 420 RFS events (disease recurrence or death) required to achieve 90% power of the log-rank test at a one-sided significance level of 5% (planned sample size: 800).
  - Although the primary endpoint was OS at first, a protocol amendment during the study changed it to RFS, based on a meta-analysis showing the surrogacy of DFS for OS in post-operative adjuvant chemotherapy for NSCLC (Lancet Oncol 2013; 14: 619-626).

- Secondary endpoints:
  - Overall survival, rate of treatment completion, toxicity

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Baseline characteristics

		VNR+CDDP		PEM+CDDP	
		N=395	(%)	N=389	(%)
Gender	Male	235	(59.5)	227	(58.4)
	Female	160	(40.5)	162	(41.6)
Age, median	（Range），years	65	(33 - 75)	64	(28 - 75)
ECOG-PS	0	306	(77.5)	295	(75.8)
	1	89	(22.5)	94	(24.2)
Histology	Adenocarcinoma	379	(95.9)	373	(95.9)
	Other	16	(4.1)	16	(4.1)
EGFR mutations	Positive	95	(24.1)	97	(24.9)
	Wild type	300	(75.9)	292	(75.1)

ECOG-PS, Eastern Cooperative Oncology Group performance status

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Surgical characteristics

		VNR+CDDP		PEM+CDDP	
		N=395	(%)	N=389	(%)
Surgery	Lobectomy	324	(82.0)	329	(84.6)
	Complex lobectomy or other	62	(15.7)	57	(14.6)
	Pneumonectomy	9	(2.3)	3	(0.8)
Pathological stage	IIA T1N1	42	(10.6)	49	(12.6)
(7th TNM classification)	IIA T2aN1, T2bN0	88	(22.3)	82	(21.1)
	IIB T2bN1	8	(2.0)	9	(2.3)
	IIB T3N0	49	(12.4)	43	(11.1)
	IIIA T1N2	67	(17.0)	51	(13.1)
	IIIA T2N2	104	(26.3)	99	(25.4)
	IIIA T3N1-2	28	(7.1)	47	(12.1)
	IIIA T4N0-1	9	(2.3)	9	(2.3)
Time from surgery, median	（Range）, days	42	(22 - 58)	43	(36 - 55)

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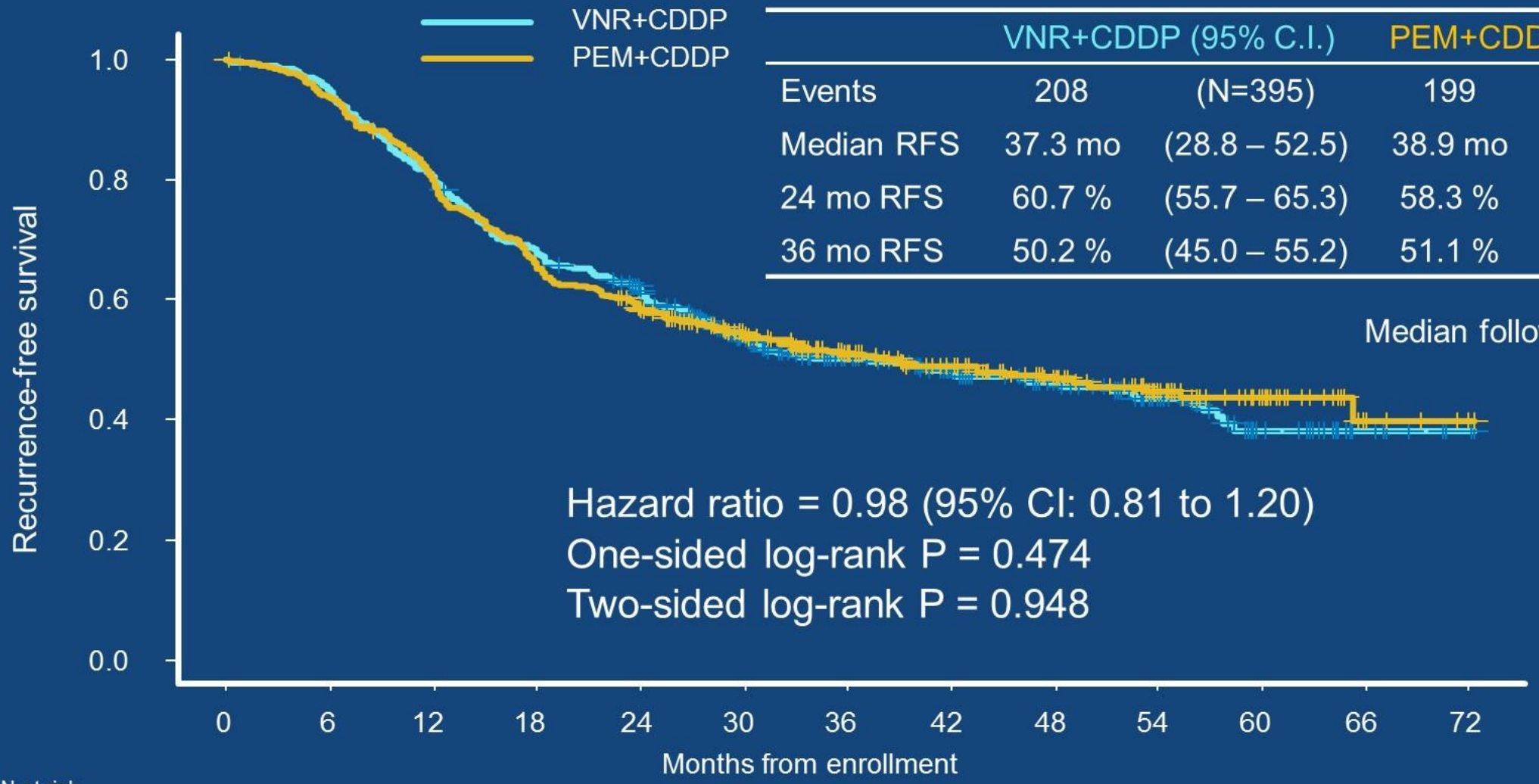
Primary endpoint: RFS, assessed by investigators



	VNR+CDDP (95% C.I.)		PEM+CDDP (95% C.I.)	
Events	208	(N=395)	199	(N=389)
Median RFS	37.3 mo	(28.8 – 52.5)	38.9 mo	(28.7 – 55.3)
24 mo RFS	60.7 %	(55.7 – 65.3)	58.3 %	(53.2 – 63.0)
36 mo RFS	50.2 %	(45.0 – 55.2)	51.1 %	(45.8 – 56.0)

Median follow up; 45.2 mo

Hazard ratio = 0.98 (95% CI: 0.81 to 1.20)
One-sided log-rank P = 0.474
Two-sided log-rank P = 0.948

N at risk													
VNR+CDDP	395	372	314	267	227	175	136	104	79	52	25	9	3
PEM+CDDP	389	363	305	253	220	175	136	108	76	53	30	7	1

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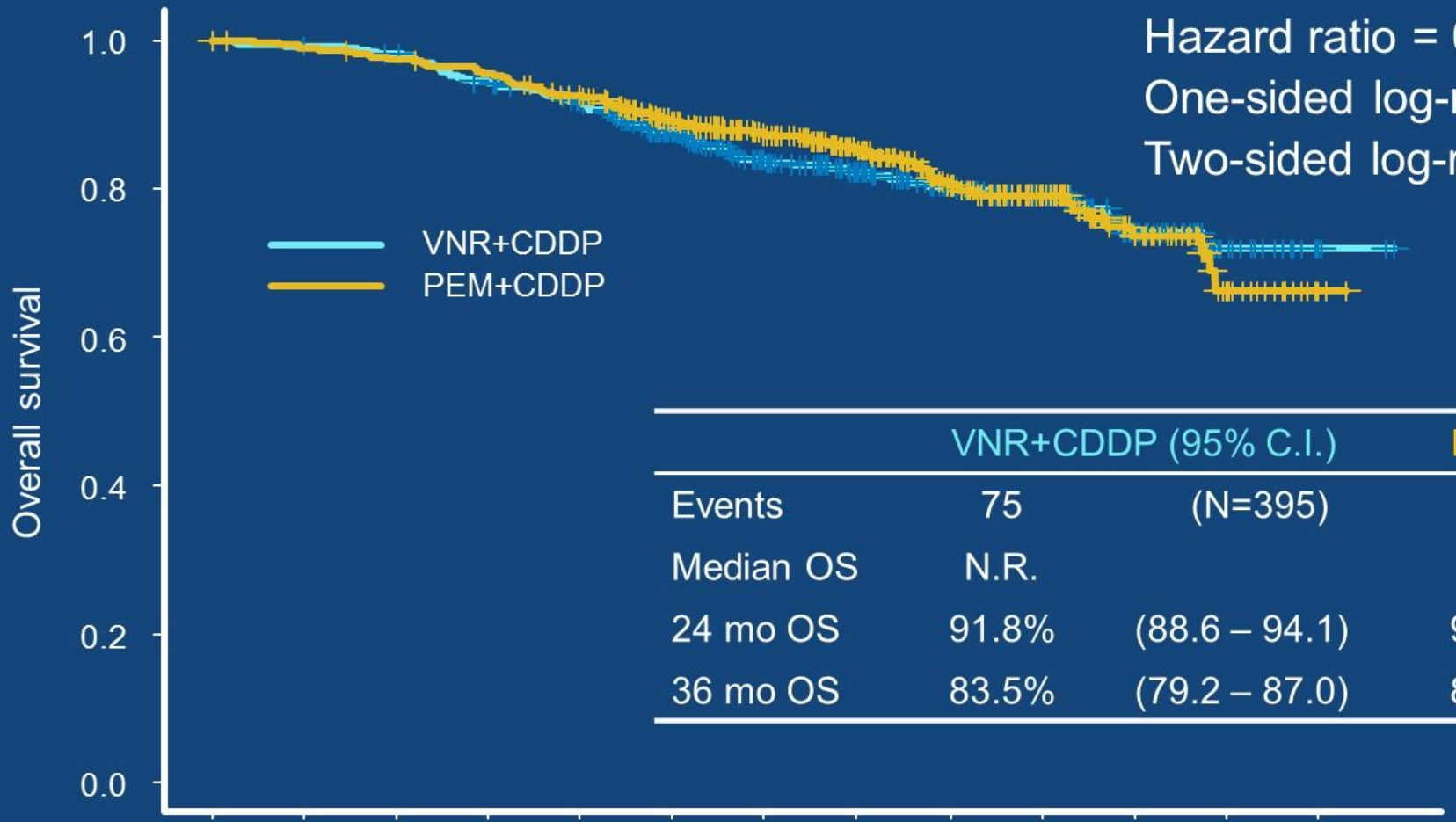
Overall survival



Hazard ratio = 0.98 (95% CI: 0.71 to 1.35)
One-sided log-rank P = 0.434
Two-sided log-rank P = 0.868

Median follow up; 45.2 mo

	VNR+CDDP (95% C.I.)		PEM+CDDP (95% C.I.)	
Events	75	(N=395)	71	(N=389)
Median OS	N.R.		N.R.	
24 mo OS	91.8%	(88.6 – 94.1)	92.5%	(89.3 – 94.7)
36 mo OS	83.5%	(79.2 – 87.0)	87.2%	(83.8 – 90.2)

N at risk

VNR+CDDP	395	391	386	367	348	292	232	187	144	101	58	20	5
PEM+CDDP	389	383	376	368	349	298	237	193	134	98	56	22	4

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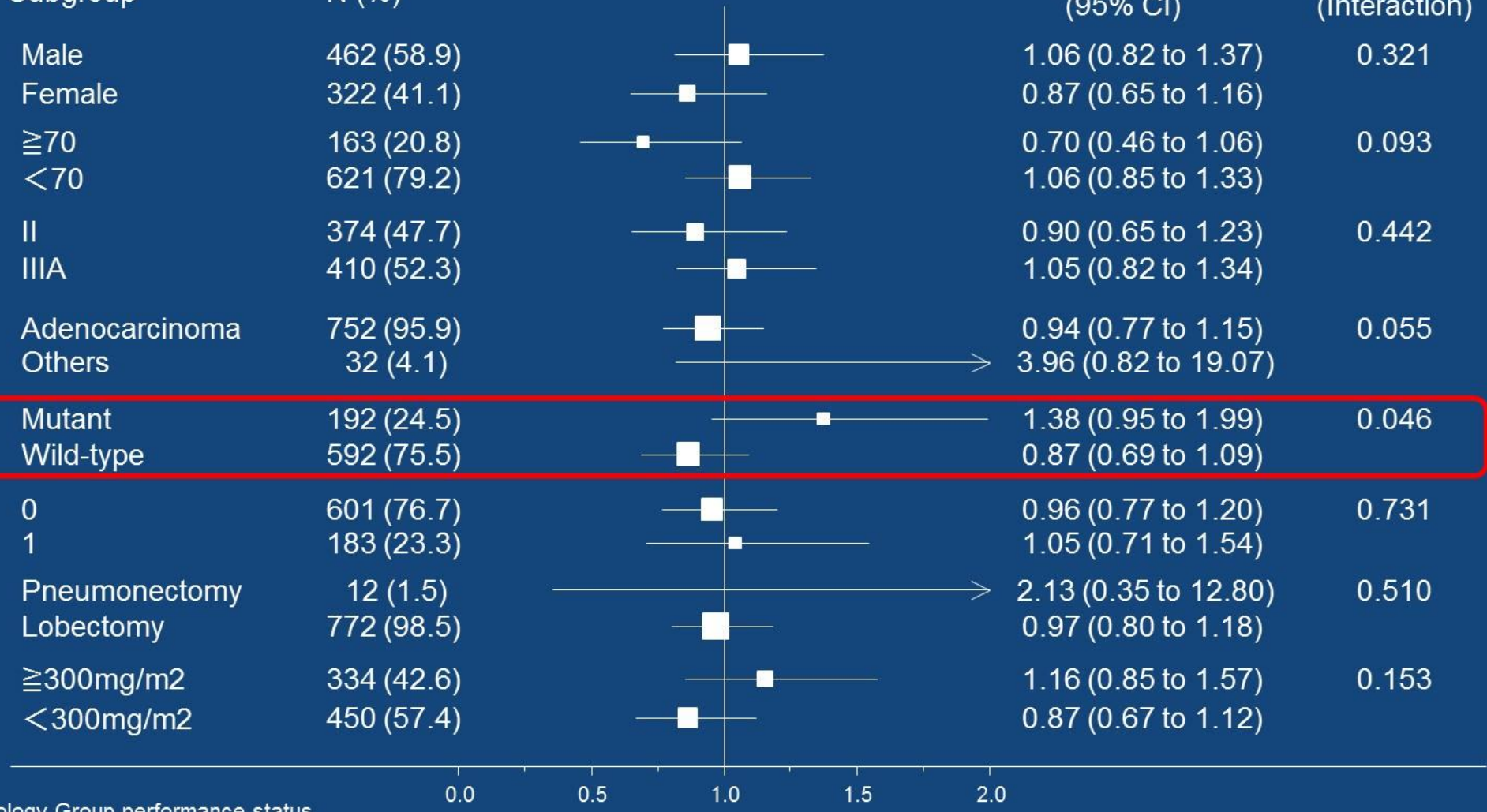
RFS: subgroup analysis

Subgroup		N (%)	Hazard ratio (95% CI)	P-value (Interaction)
Gender	Male	462 (58.9)	1.06 (0.82 to 1.37)	0.321
	Female	322 (41.1)	0.87 (0.65 to 1.16)	
Age	≧70	163 (20.8)	0.70 (0.46 to 1.06)	0.093
	＜70	621 (79.2)	1.06 (0.85 to 1.33)	
Pathological stage	II	374 (47.7)	0.90 (0.65 to 1.23)	0.442
	IIIA	410 (52.3)	1.05 (0.82 to 1.34)	
Histology	Adenocarcinoma	752 (95.9)	0.94 (0.77 to 1.15)	0.055
	Others	32 (4.1)	3.96 (0.82 to 19.07)	
EGFR mutation	Mutant	192 (24.5)	1.38 (0.95 to 1.99)	0.046
	Wild-type	592 (75.5)	0.87 (0.69 to 1.09)	
ECOG PS	0	601 (76.7)	0.96 (0.77 to 1.20)	0.731
	1	183 (23.3)	1.05 (0.71 to 1.54)	
Surgery	Pneumonectomy	12 (1.5)	2.13 (0.35 to 12.80)	0.510
	Lobectomy	772 (98.5)	0.97 (0.80 to 1.18)	
CDI/cisplatin	≧300mg/m2	334 (42.6)	1.16 (0.85 to 1.57)	0.153
	＜300mg/m2	450 (57.4)	0.87 (0.67 to 1.12)	



ECOG-PS, Eastern Cooperative Oncology Group performance status
CDI, Cumulative Dose Intensity

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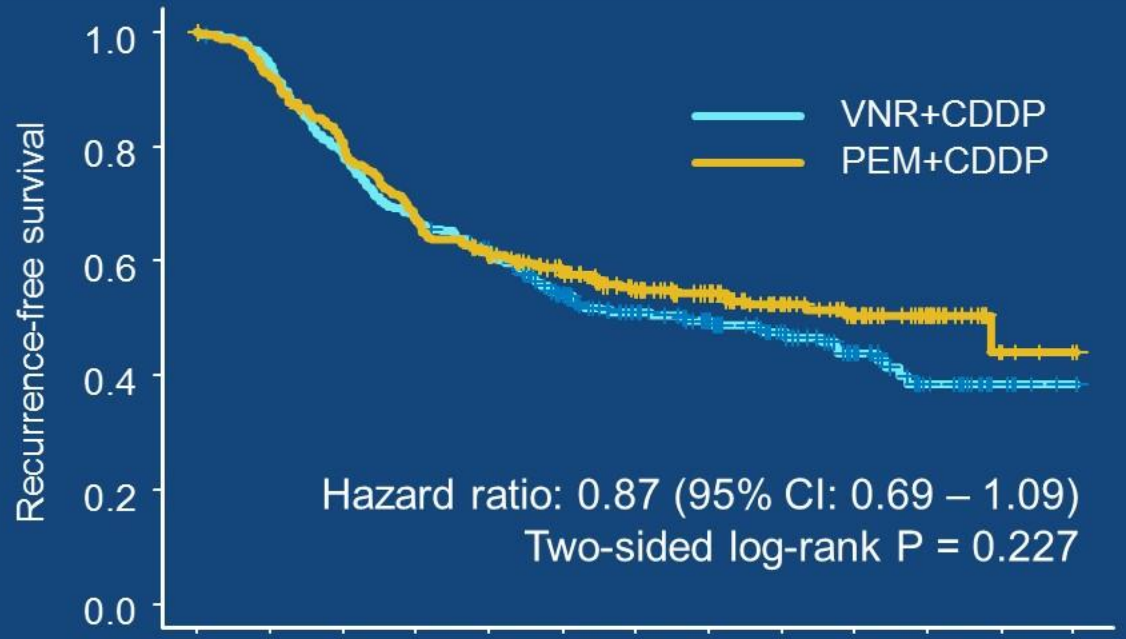
RFS by *EGFR* mutation status

EGFR mt: wild

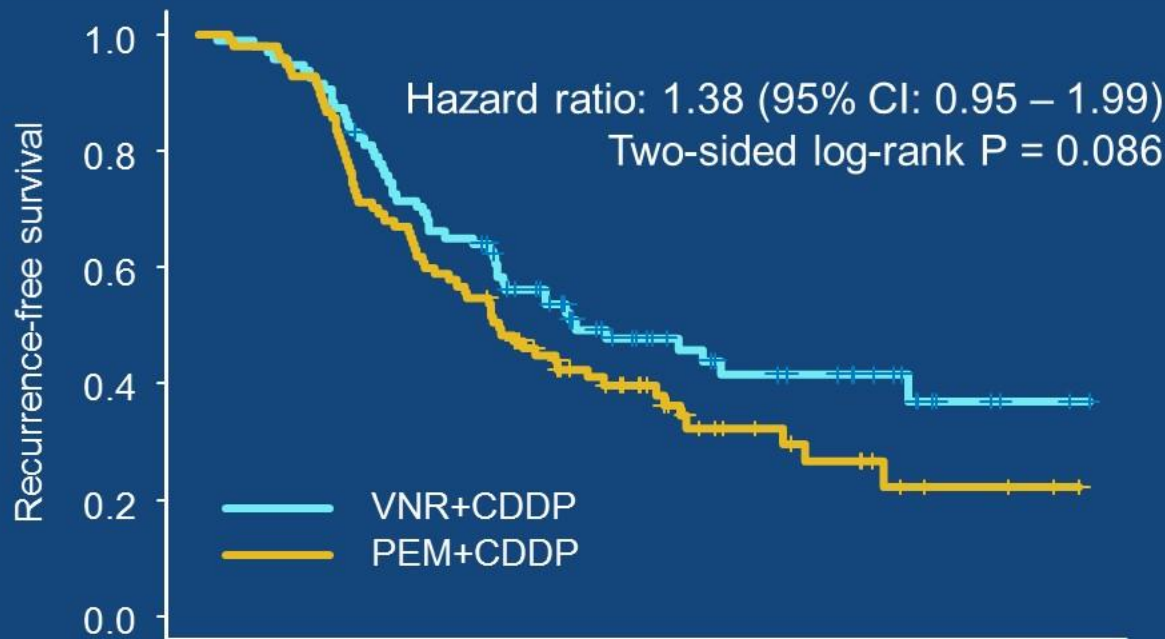
	VNR+CDDP (95% C.I.)		PEM+CDDP (95% C.I.)	
Events	157	(N=300)	135	(N=292)
Median RFS	39.9 mo	(28.2 – 56.0)	65.2 mo	(33.1 – NA)



N at risk													
VNR+CDDP	300	281	233	201	174	140	109	85	63	40	21	7	2
PEM+CDDP	292	268	230	193	172	144	112	94	66	46	27	5	1

EGFR mt: positive

	VNR+CDDP (95% C.I.)		PEM+CDDP (95% C.I.)	
Events	51	(N=95)	64	(N=97)
Median RFS	30.4 mo	(23.9 – 57.3)	24.1 mo	(18.2 – 32.7)



N at risk													
VNR+CDDP	95	91	81	66	53	35	27	19	16	12	4	2	1
PEM+CDDP	97	95	75	60	48	31	24	14	10	7	3	2	

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Rate of treatment completion

	VNR+CDDP		PEM+CDDP	
	N=395	(%)	N=389	(%)
Treatment complete (4 cycles)	287	(72.7)	342	(87.9)
Treatment incomplete (< 4 cycles)	108	(27.3)	47	(12.1)

*p<0.001 (chi-square test)

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Safety overview

	VNR+CDDP		PEM+CDDP	
	N=396	(%)	N=392	(%)
Treatment-related AEs	396	(100)	391	(99.7)
Serious AEs	47	(11.9)	19	(4.8)
Grade 3-5*	354	(89.4)	186	(47.4)
Hematological AEs*	324	(81.8)	97	(24.7)
Non-hematological AEs	135	(34.1)	122	(31.1)
Led to death	1	(0.3)	1	(0.3)
Led to discontinuation*	93	(23.5)	37	(9.5)

AEs; adverse events
*in eligible population

*p<0.001 (chi-square test)

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Conclusion

- The JIPANG study is the first phase III study to evaluate pemetrexed plus cisplatin as postoperative adjuvant chemotherapy.
- Although this study did not show the superiority of pemetrexed plus cisplatin in RFS, this regimen had a similar efficacy to vinorelbine plus cisplatin for patients with resected non-Sq NSCLC.
- Pemetrexed plus cisplatin had milder toxicities and better tolerability as adjuvant chemotherapy, compared with vinorelbine plus cisplatin.
- These data suggest that pemetrexed plus cisplatin can be an option for post-operative adjuvant chemotherapy in pathological stage II-IIIA non-Sq NSCLC, especially for *EGFR* wild-type non-sq NSCLC.

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Adjuvant chemotherapy for pathological stage I non-small cell lung cancer with high-risk factors for recurrence: A multicenter study.

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Background

- The role of adjuvant chemotherapy for pathological stage I non-small cell lung cancer (NSCLC) is controversial.

- The purpose of this study was to investigate the effect of adjuvant chemotherapy for pathological stage I NSCLC with high-risk factors for recurrence.

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Methods

- Prospectively collected data from 1,278 patients with pathological stage I (8th edition) NSCLC undergoing lobectomy were retrospectively analyzed.
- High-risk factors for recurrence were determined by multivariable Cox proportional hazards model for recurrence-free survival (RFS).
- RFS, overall survival (OS), and cancer-specific survival (CSS) were compared between patients who received adjuvant chemotherapy and those who did not.

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Patients characteristics

		n = 1,278
Age, y (IQR)		69 (63-75)
Gender	Male	661 (51.7%)
Histology	Adenocarcinoma	1069 (83.6%)
	Squamous cell carcinoma	141 (11.0%)
	Others	68 (5.3%)
Invasive component size, cm (IQR)		1.6 (0.9-2.45)
Lymphatic permeation		220 (17.2%)
Vascular invasion		329 (25.7%)
Visceral pleural invasion		216 (16.9%)
Stage	IA	973 (76.1%)
	IB	305 (23.9%)
Adjuvant chemotherapy		305 (23.9%)

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Chemotherapy regimen (n = 305)

Platinum doublets (n = 114, 37.4%)

Monotherapy (n = 191, 62.6%)

- Tegafur-uracil (UFT) (n = 157)
- Tegafur-gimeracil-oteracil (S-1) (n = 24)
- Others (n = 10)

} Oral fluoropyrimidines

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Multivariable Cox analysis for RFS

Variables	HR	95% CI	P value
Age (> 70 y)	2.14	1.50–3.09	<0.0001
Gender (Female)	0.71	0.48–1.05	0.089
Invasive component size (> 2 cm)	1.60	1.09–2.36	0.016
Histology (Adenocarcinoma)	0.92	0.62–1.40	0.698
Lymphatic permeation	1.67	1.13–2.43	0.008
Vascular invasion	2.78	1.84–4.22	<0.0001
Visceral pleural invasion	1.81	1.22–2.68	0.003

High-risk group (n = 641)
Invasive component size > 2 cm
or
Lymphatic permeation
or
Vascular invasion
or
Visceral pleural invasion

Low-risk group (n = 637)
Invasive component size ≤ 2 cm
and
No lymphatic permeation
and
No vascular invasion
and
No visceral pleural invasion

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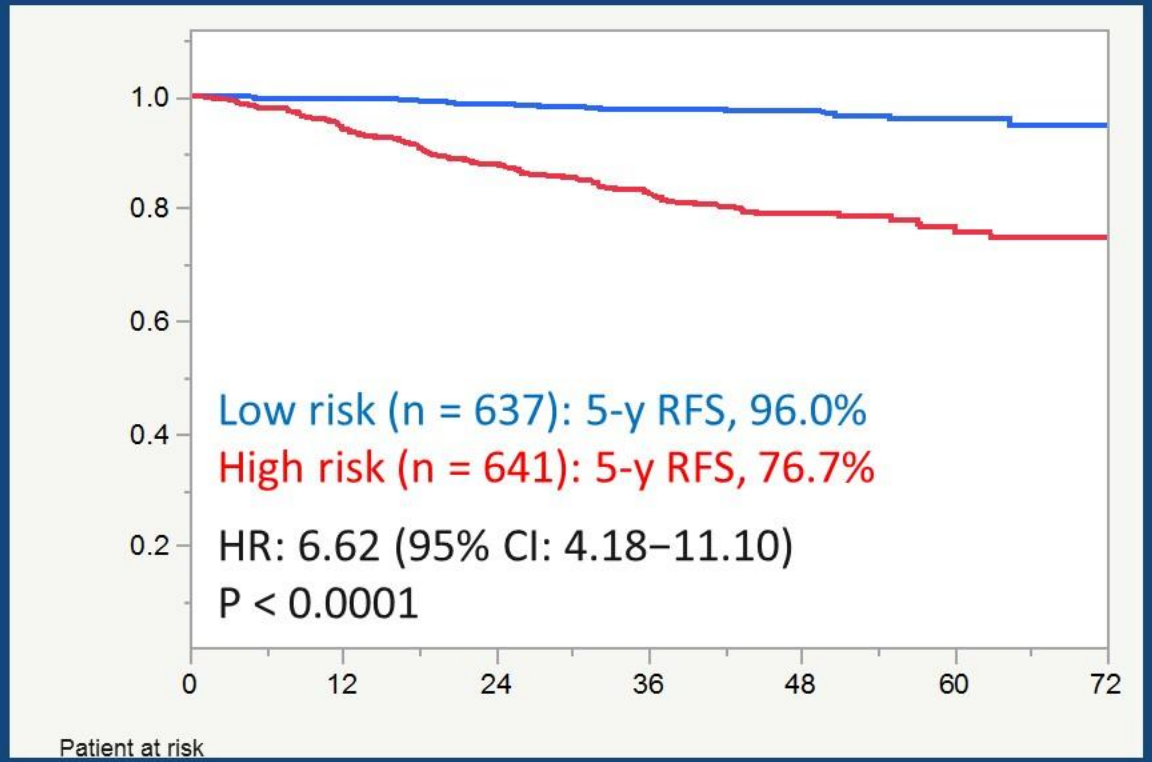
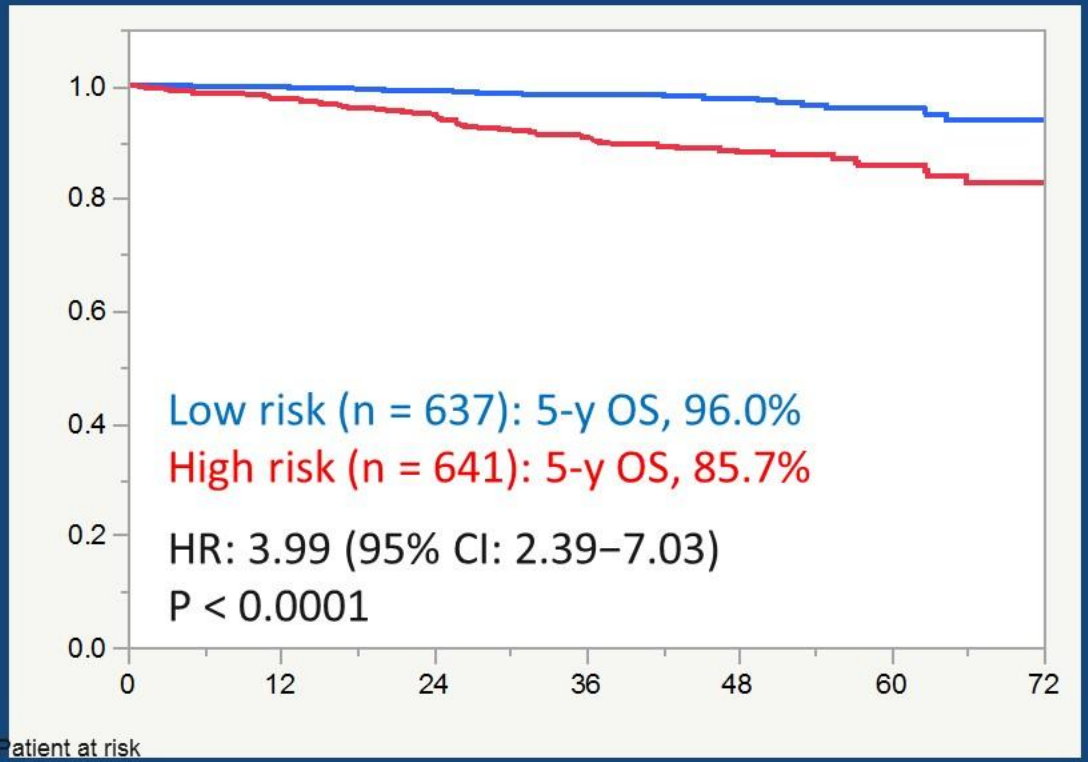
RFS



OS



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Patients characteristics (High-risk group)

Variables	Observation (n = 419)	Adjuvant chemotherapy (n = 222)	P value
Age, y (IQR)	71 (65-77)	67 (62-71.3)	< 0.001
Gender (Female)	156 (37.2%)	94 (42.3%)	0.21
Invasive component size, cm (IQR)	2.4 (1.8-3.0)	2.5 (2.0-3.1)	0.21
Histology (Adenocarcinoma)	287 (68.5%)	178 (80.2%)	0.002
Lymphatic permeation	139 (33.2%)	81 (36.5%)	0.40
Vascular invasion	218 (52.0%)	111 (50.0%)	0.63
Visceral pleural invasion	120 (28.6%)	96 (43.2%)	0.0002

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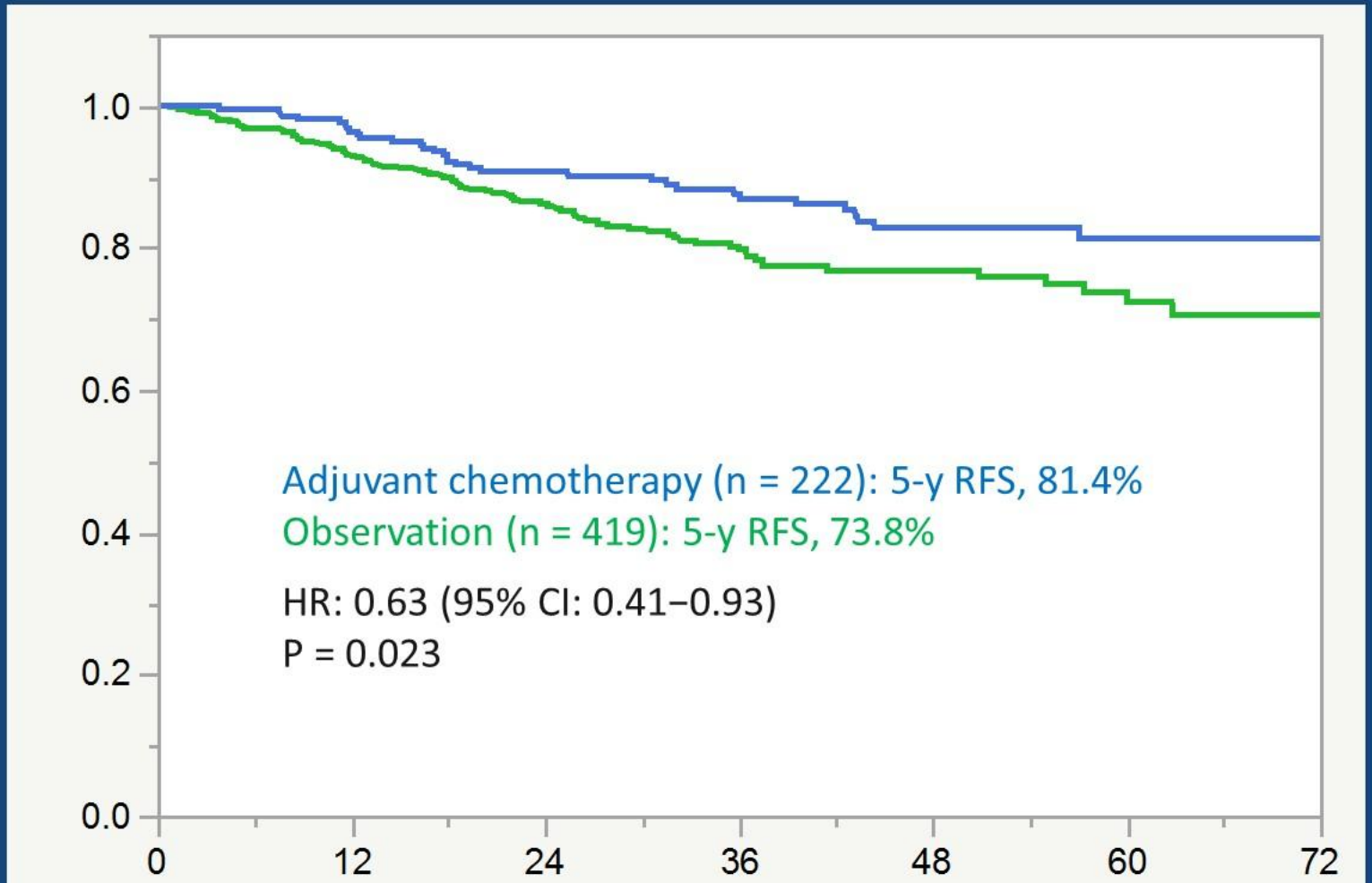
RFS (High risk group)



Patient at risk							
ACT	222	214	171	135	83	52	25
No ACT	419	381	273	182	117	55	17

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Comparison between platinum doublets and monotherapy

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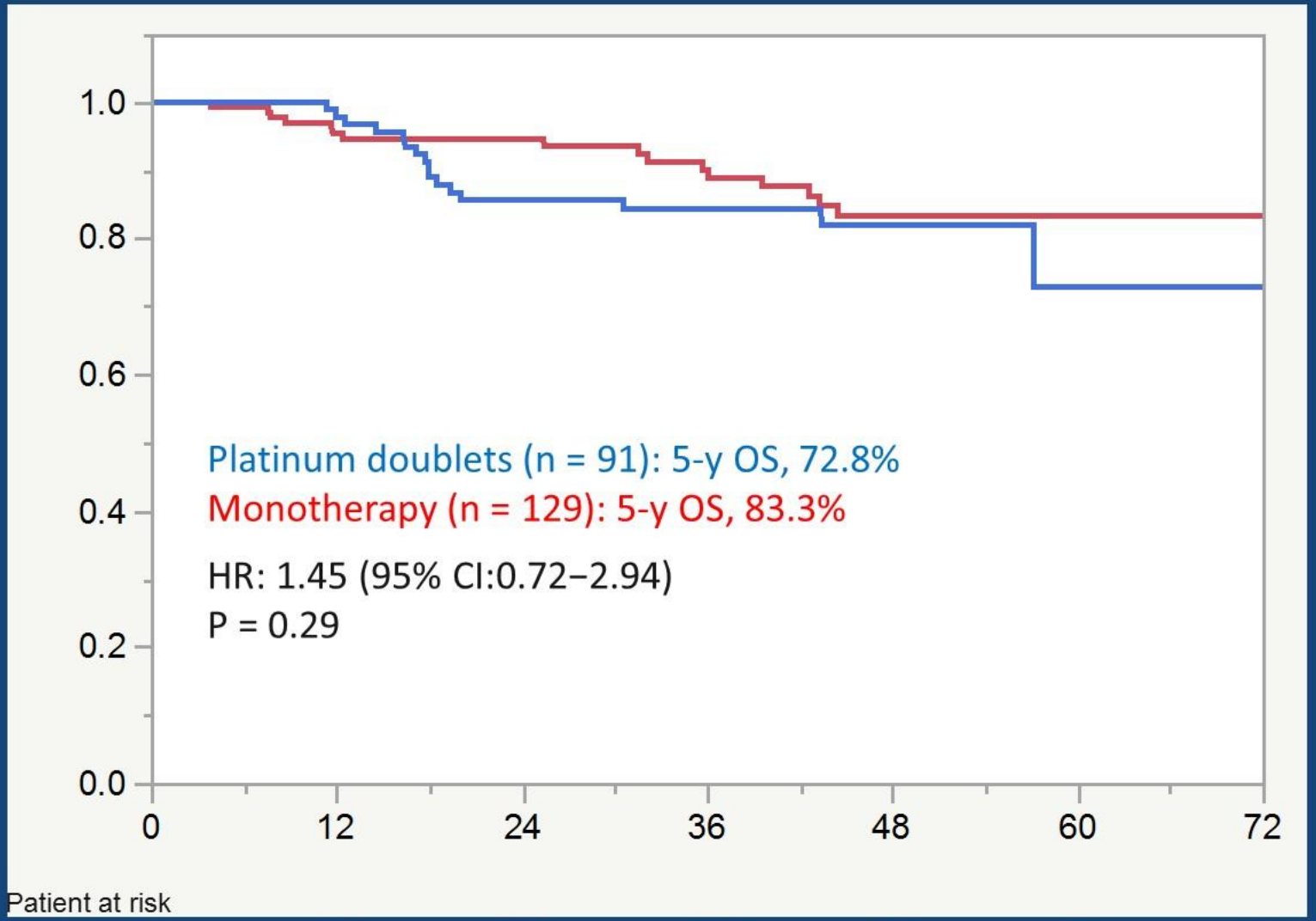
RFS (High risk group)



Patient at risk

Doublet	91	90	72	57	25	7	3
Mono	129	123	98	77	57	44	22

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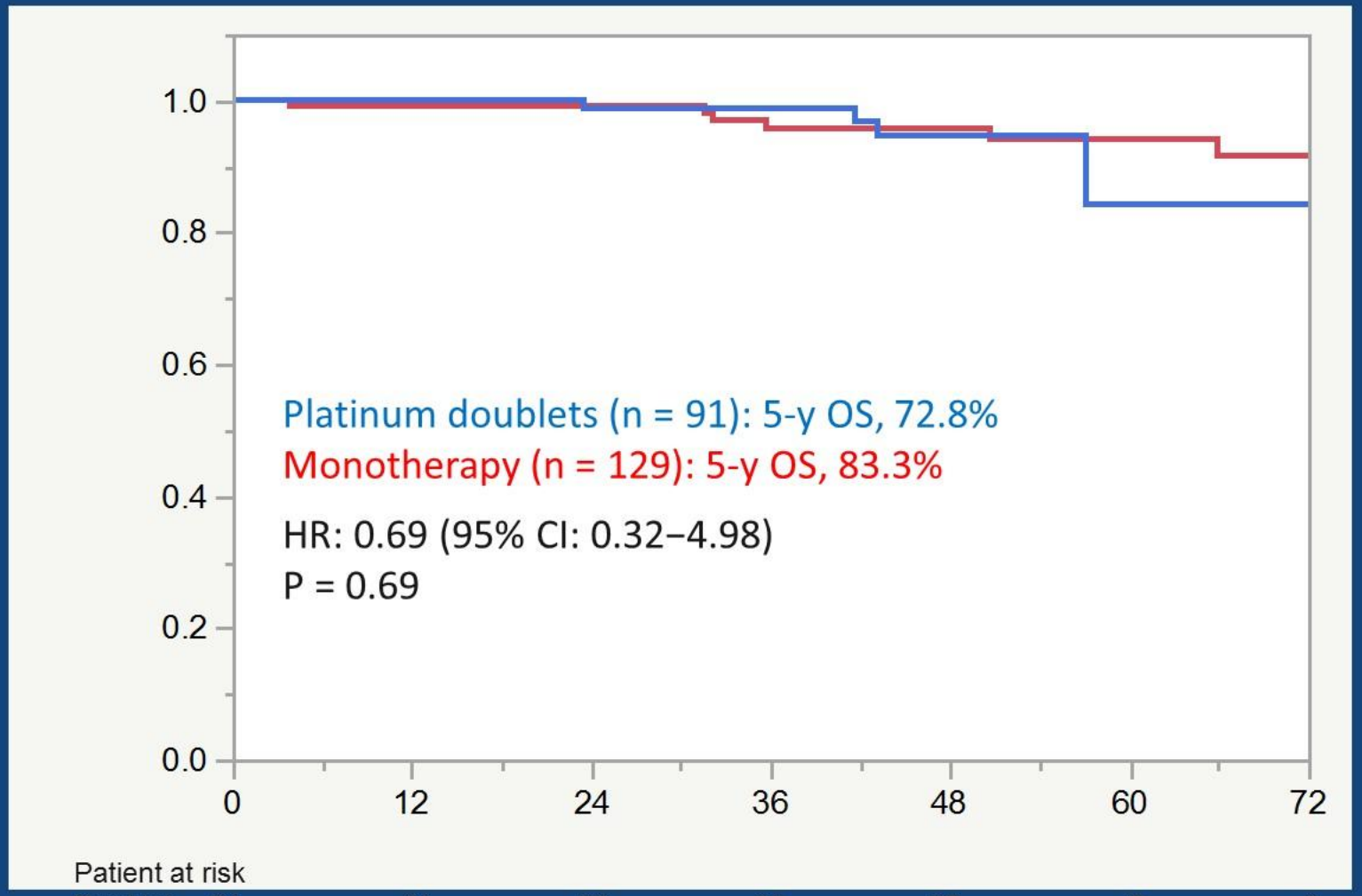
OS (High risk group)



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Summary and Conclusions

- Patients with invasive component size of >2 cm, Lymphatic permeation, vascular invasion, or VPI are at high risk for recurrence in p-stage I NSCLC.
- Adjuvant chemotherapy may improve survival in patients with high-risk p-stage I NSCLC.
- Platinum doublets did not improve the survival compared with monotherapy in patients with high-risk p-stage I NSCLC.

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Was ist Neu

- Neoadjuvante Therapie
- **Adjuvante Therapie**
  - Chemotherapie
  - **EGFR TKI**
- Radiochemotherapie in nicht operable NSCLC
- VEGF Inhibitoren als Erhaltung
- EGFR TKI und Chemotherapie
- Immuntherapie

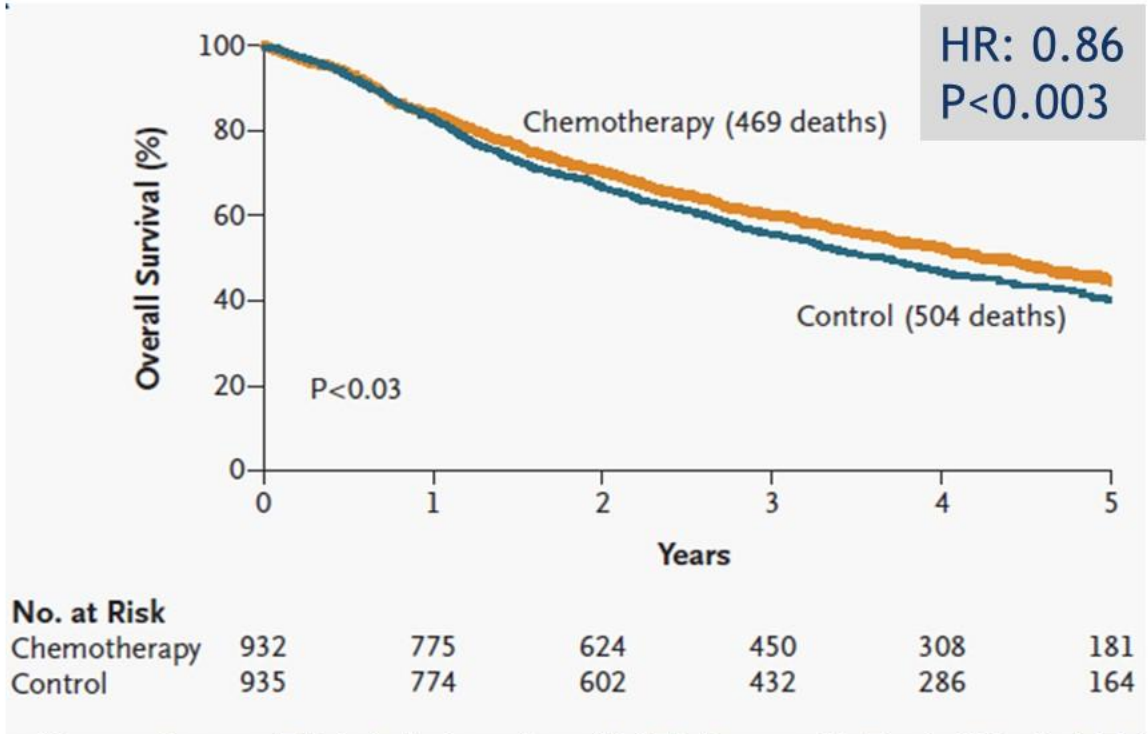
Adjuvant chemo prolongs OS and reduces likelihood of recurrence at 5 years by ~5%: The IALT study

Stage I-III NSCLC
Post resection
No prior tx
N=1867

R

Adjuvant chemo 3-4 cycles
cisplatin + vinca or etoposide

Observation



The International Lung Cancer Trial Collaborative (IALT) Group; N Engl J Med, 2004

- Not built upon our current molecular marker assessment or treatment approaches in the metastatic setting
- Precedent in other tumor types that targeted adjuvant therapy improves survival

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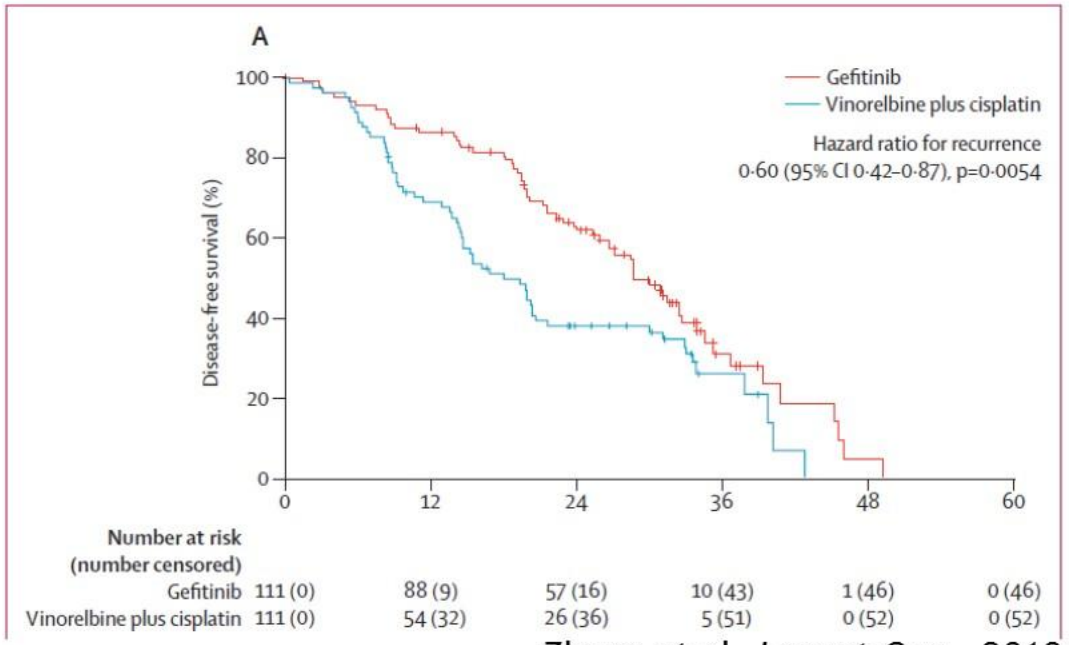
ADJUVANT Trial (CTONG1104): Randomized gefitinib vs vinorelbine/cisplatin



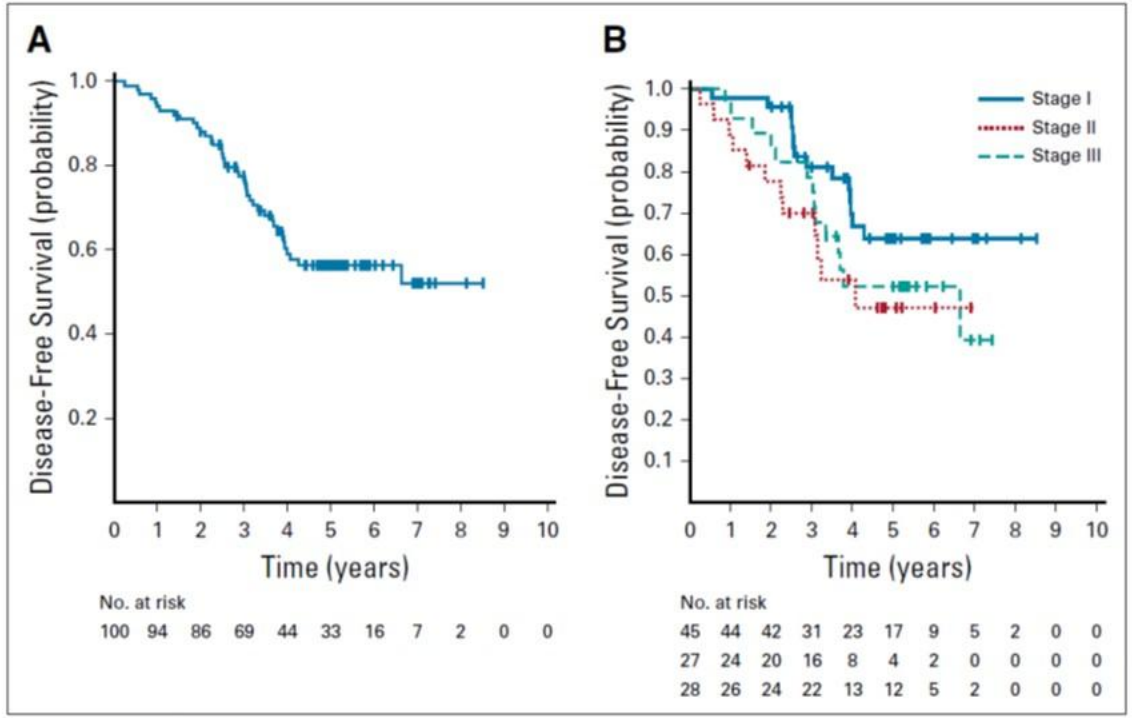
Zhong et al, *Lancet Onc.*, 2018

Stage II-IIIA
Planned 2 years of gefitinib

79% received gefitinib for 1 year
68% for more than 18 months

Result: Delayed recurrence, median DFS: 28.7 vs. 18 mos.

SELECT Study: Phase II of adjuvant erlotinib in EGFR mutant NSCLC



Pennell et al, *JCO*, 2019

Stage I-IIIA
After standard adjuvant chemo/XRT
~2 years of erlotinib (69% completed at least 22 mos)

40% dose reduction to 100 mg
16% needed second dose reduction to 50 mg
Result: Delayed recurrence, median DFS not reached.
2 year DFS 88%.

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EGFR Inhibitors as Adjuvant Therapy for EGFR Mutation Positive NSCLC

Wenjie Tang, Xiaolin Li, Xindong Sun, Jinming Yu*, Peng Xie*

Shandong Cancer Hospital and Institute, China

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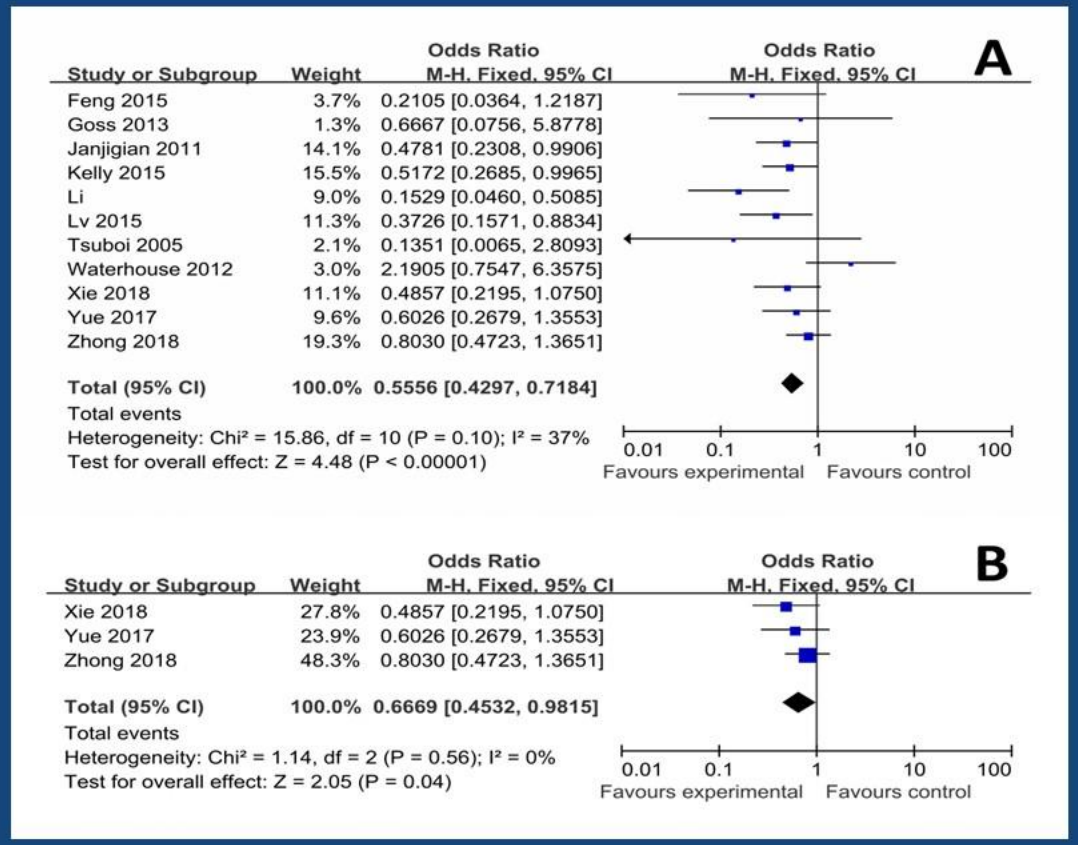
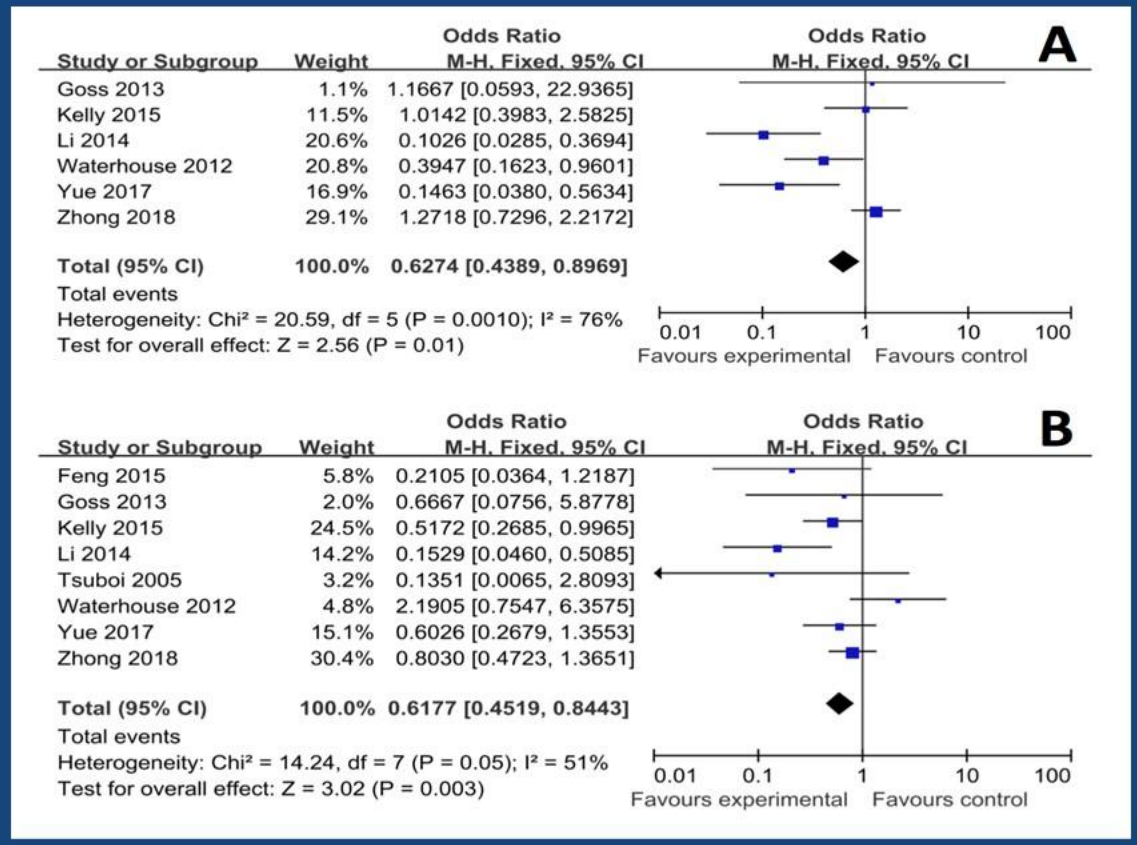
Meta-analysis of 11 identified trials of adjuvant EGFR TKI Regimens



Forest plot of DFS when comparing TKIs VS no TKIs (A), TKIs VS chemo (B)



Forest plot of OS (A) and DFS (B) when retrospective studies were excluded

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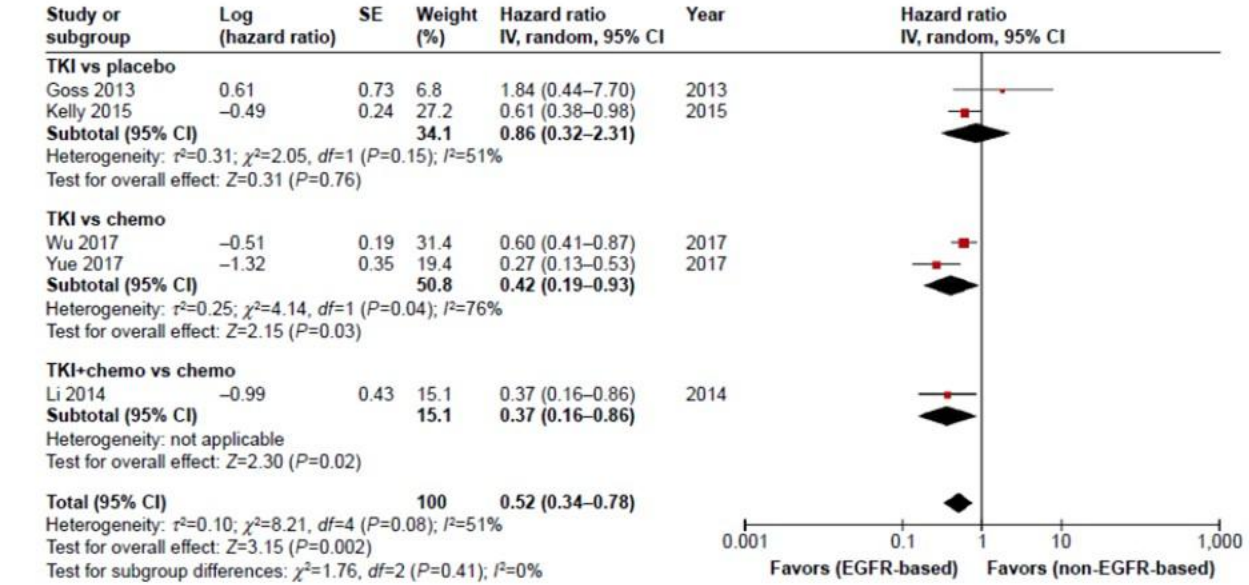
Authors:The role of EGFR inhibitors as adjuvant therapy for EGFR mutation positive non-small cell lung cancer.

Peng Xie, Wenjie Tang, Xiaolin Li, Xindong Sun, Jinming Yu; Department of Radiaiton Oncology, Shandong Cancer Hospital and Institute, Jinan, China; Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, China; Department of Radiation Oncology, Shandong Tumor Hospital and Institute, Jinan, China; Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to...

Abstract Disclosures

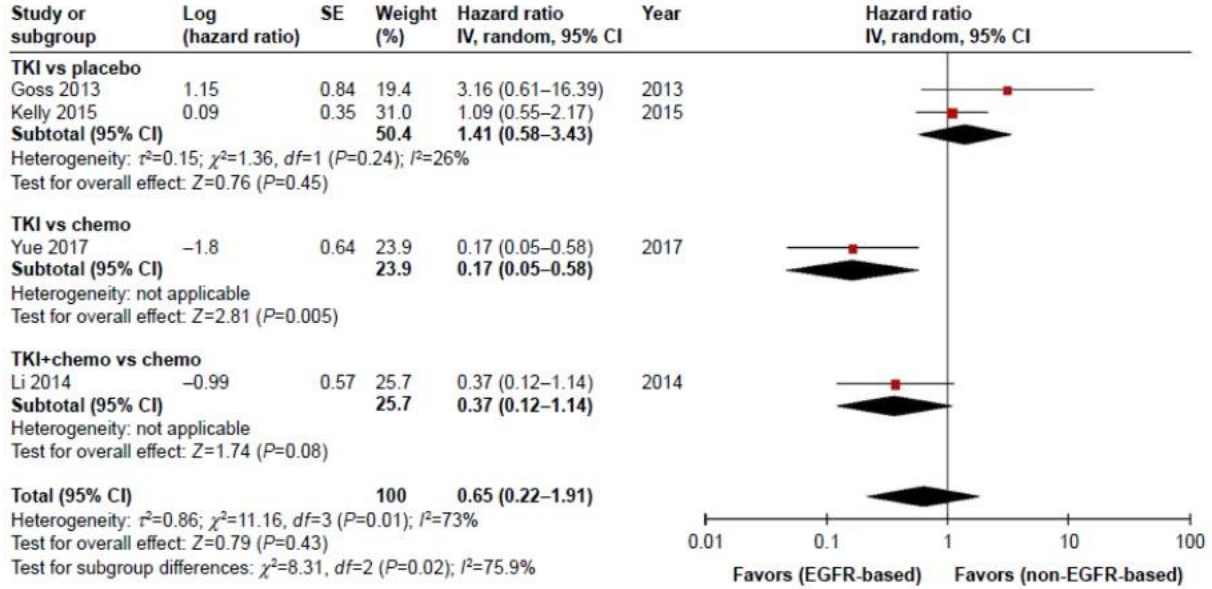
Background: Cisplatin-based chemotherapy as adjuvant therapy for resected NSCLC has reached its plateau, and was limited by high risk of recurrence and significant toxicities. The clinical value of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in resected non-small cell lung cancer (NSCLC) harboring EGFR mutations remains controversial. In this study, we performed a meta-analysis to evaluate the role of EGFR inhibitors as adjuvant therapy for targeted patients. **Methods:** Studies were identified via an electronic search on Pubmed, EMBASE, ISI Web of Science, ScienceDirect, SpringerLink, The Cochrane library and so on. Pooled odds ratio (OR) for disease-free survival (DFS) and overall survival (OS) were calculated for meta-analysis. Registration number: PROSPERO (CRD42018093144). **Results:** There were 11 trials (1,152 resected NSCLC patients with EGFR sensitive mutations) in this meta-analysis. Results showed that adjuvant treatment with EGFR-TKIs can prolong both OS and DFS when compared to treatment without TKIs as adjuvant therapy (OS: OR, 0.63; 95% CI, 0.46 to 0.87, P = 0.004; heterogeneity I^2= 61%, P = 0.008; DFS: OR, 0.56; 95% CI, 0.43 to 0.72, P < 0.00001; heterogeneity I^2= 37%, P = 0.1). Results of predefined subgroup analyses in this meta-analysis **suggested a greater DFS with EGFR-TKI mono compared with chemotherapy, whereas the OS benefit failed to show a similar difference between the two arms** (p = 0.3). And we also find that treatment with EGFR-TKI plus chemotherapy was associated with significantly longer DFS as well as OS than chemotherapy mono in patients with completely resected EGFR-mutant NSCLC (DFS: OR, 0.48; 95%CI, 0.34-0.68; P < 0.00001; heterogeneity I^2= 15%, P = 0.29; OS: OR, 0.50; 95% CI, 0.31-0.78; P = 0.003; heterogeneity I^2 = 57%, P = 0.05). And less grade 3 or higher AEs were observed in the TKIs group (OR, 0.22; 95% CI, 0.14 to 0.37, P < 0.00001; heterogeneity I^2= 22%, P = 0.28). **Conclusions:** Adjuvant EGFR-TKIs may be a potential treatment option compared to adjuvant chemotherapy in completed resected patients with EGFR mutation-positive NSCLC. This project was supported by the National Natural Science Foundation of China (Grant No. 81502667), Key Research and Development Plan of Shandong, China (Grant No. 2016GSF201167).

Similar results reported in another recent meta-analysis



Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Year
TKI vs placebo					
Goss 2013	0.61	0.73	6.8	1.84 (0.44–7.70)	2013
Kelly 2015	–0.49	0.24	27.2	0.61 (0.38–0.98)	2015
Subtotal (95% CI)			**34.1**	**0.86 (0.32–2.31)**	
Heterogeneity: τ^2=0.31; χ^2=2.05, *df*=1 (*P*=0.15); I^2=51%					
Test for overall effect: *Z*=0.31 (*P*=0.76)					
TKI vs chemo					
Wu 2017	–0.51	0.19	31.4	0.60 (0.41–0.87)	2017
Yue 2017	–1.32	0.35	19.4	0.27 (0.13–0.53)	2017
Subtotal (95% CI)			**50.8**	**0.42 (0.19–0.93)**	
Heterogeneity: τ^2=0.25; χ^2=4.14, *df*=1 (*P*=0.04); I^2=76%					
Test for overall effect: *Z*=2.15 (*P*=0.03)					
TKI+chemo vs chemo					
Li 2014	–0.99	0.43	15.1	0.37 (0.16–0.86)	2014
Subtotal (95% CI)			**15.1**	**0.37 (0.16–0.86)**	
Heterogeneity: not applicable					
Test for overall effect: *Z*=2.30 (*P*=0.02)					
Total (95% CI)			**100**	**0.52 (0.34–0.78)**	
Heterogeneity: τ^2=0.10; χ^2=8.21, *df*=4 (*P*=0.08); I^2=51%					
Test for overall effect: *Z*=3.15 (*P*=0.002)					
Test for subgroup differences: χ^2=1.76, *df*=2 (*P*=0.41); I^2=0%					

Figure 2 Forest plot of hazard ratio for disease-free survival of resected non-small-cell lung cancer with EGFR mutations.
Abbreviations: chemo, chemotherapy; SE, standard error; TKI, tyrosine kinase inhibitor.



Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Year
TKI vs placebo					
Goss 2013	1.15	0.84	19.4	3.16 (0.61–16.39)	2013
Kelly 2015	0.09	0.35	31.0	1.09 (0.55–2.17)	2015
Subtotal (95% CI)			**50.4**	**1.41 (0.58–3.43)**	
Heterogeneity: τ^2=0.15; χ^2=1.36, *df*=1 (*P*=0.24); I^2=26%					
Test for overall effect: *Z*=0.76 (*P*=0.45)					
TKI vs chemo					
Yue 2017	–1.8	0.64	23.9	0.17 (0.05–0.58)	2017
Subtotal (95% CI)			**23.9**	**0.17 (0.05–0.58)**	
Heterogeneity: not applicable					
Test for overall effect: *Z*=2.81 (*P*=0.005)					
TKI+chemo vs chemo					
Li 2014	–0.99	0.57	25.7	0.37 (0.12–1.14)	2014
Subtotal (95% CI)			**25.7**	**0.37 (0.12–1.14)**	
Heterogeneity: not applicable					
Test for overall effect: *Z*=1.74 (*P*=0.08)					
Total (95% CI)			**100**	**0.65 (0.22–1.91)**	
Heterogeneity: τ^2=0.86; χ^2=11.16, *df*=3 (*P*=0.01); I^2=73%					
Test for overall effect: *Z*=0.79 (*P*=0.43)					
Test for subgroup differences: χ^2=8.31, *df*=2 (*P*=0.02); I^2=75.9%					

Figure 3 Forest plot of hazard ratio for OS of resected non-small-cell lung cancer with EGFR mutations.
Abbreviations: chemo, chemotherapy; OS, overall survival; SE, standard error; TKI, tyrosine kinase inhibitor.

Wu et al., *OncoTargets and Therapy*, 2018

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Randomized phase II study of adjuvant afatinib for 3 months versus 2 years in patients with resected stage I-III *EGFR* mutant NSCLC

Jamie E. Chaft[1], Daniel B. Costa[2], Alona Muzikansky[3], Joseph B. Shrager, Michael Lanuti[4], James Huang[1], Kavitha J. Ramchandran[4], Deepa Rangachari[2], Mark Huberman[2], Zofia Piotrowska[3], Mark G. Kris[1], C. Jerry Azzoli[3], Lecia Sequist[3], Joel W. Neal[4]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Beth Israel Deaconess, Boston, MD; [3]Massacheusettes General Hospital, Boston, MA; [4]Stanford Cancer Institute, Stanford, CA

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Study schema

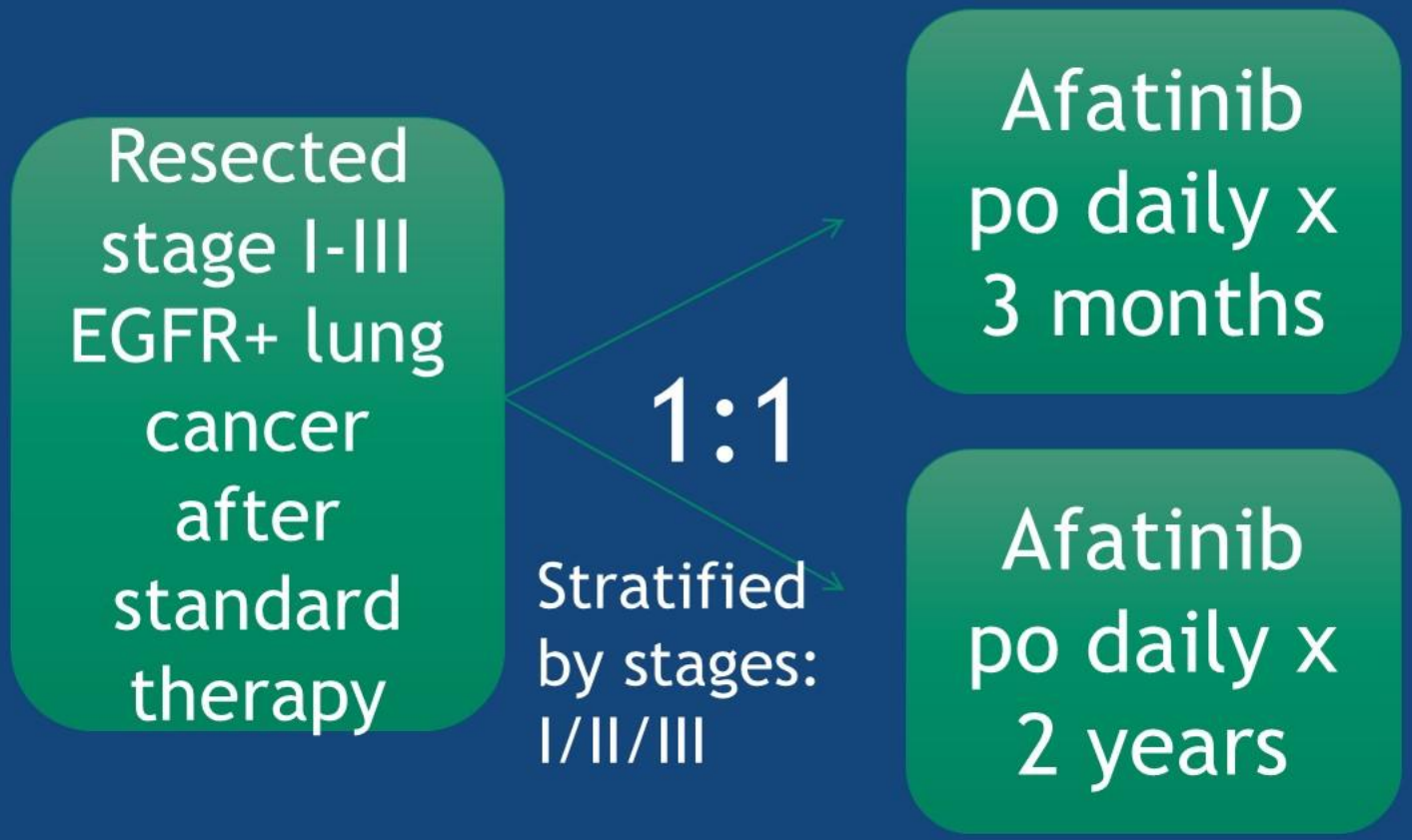
Resected stage I-III EGFR+ lung cancer after standard therapy

1:1

Stratified by stages: I/II/III

Afatinib po daily x 3 months

Afatinib po daily x 2 years



- After completion of standard adjuvant therapy, randomized to 3-months or 2-years of afatinib
- Afatinib was administered in 28 day cycles at **30 mg po daily, with optional increase to 40 mg** after cycle 1
- Chest CT was performed every 6 months for 3 years and then annually

Statistics: The primary endpoint was 2 year Disease Free Survival. The planned sample size of 30 patients per arm had a power of 82.5% to detect a 26% difference between recurrence proportions with a one-sided α=0.1. **The study closed after limited accrual of 46 pts.**

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Patients	3-month N=24	2-year N=22
Male	9	6
Female	15	16
Race		
White	7	9
Black	1	2
Asian	9	6
Mixed/Unknown	7	12
Former/current smoker	10	8
Never smoker	14	14
Stage (7th Edition)		
IA	2	3
IB	6	8
IIA	5	6
IIB	3	0
IIIA	8	5
EGFR Exon 19 del	11	10
EGFR Exon 21 L858R	17	16
Other sensitizing EGFR mutation	6	6
No prior therapy	12	12
Adjuvant/Neoadjuvant	12	10
Radiation	4	5

Toxicity & Compliance

	3-month	2-year
Median # cycles	3 cycles	17 cycles
Range	0-3 cycles	1-26 cycles
Completed treatment	92%	50%
Discontinued due to toxicity	4%	18%
Recurrence	0%	9%
Withdrew consent/other	4%	23%

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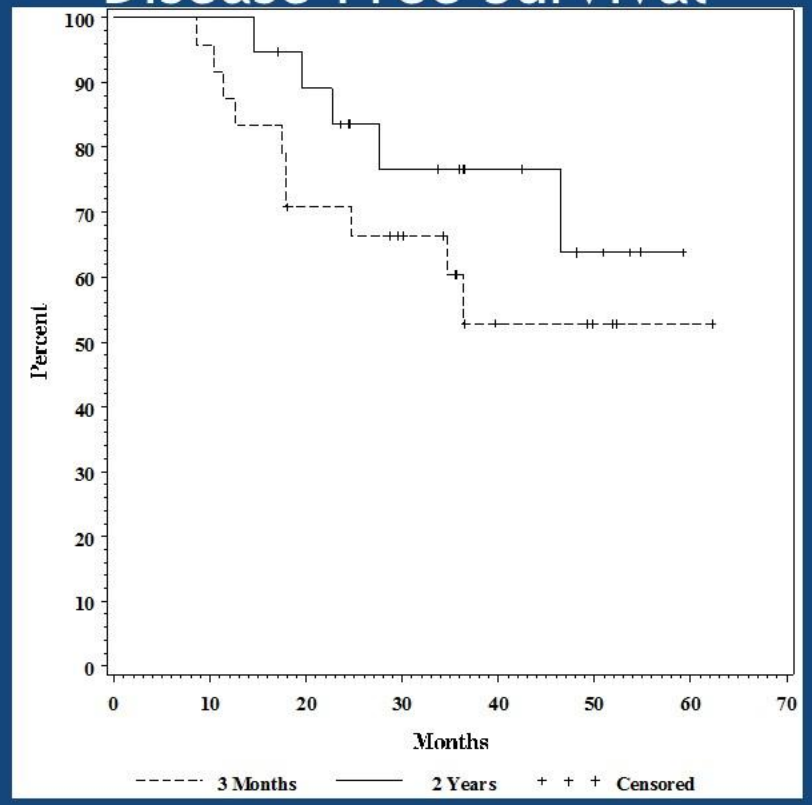
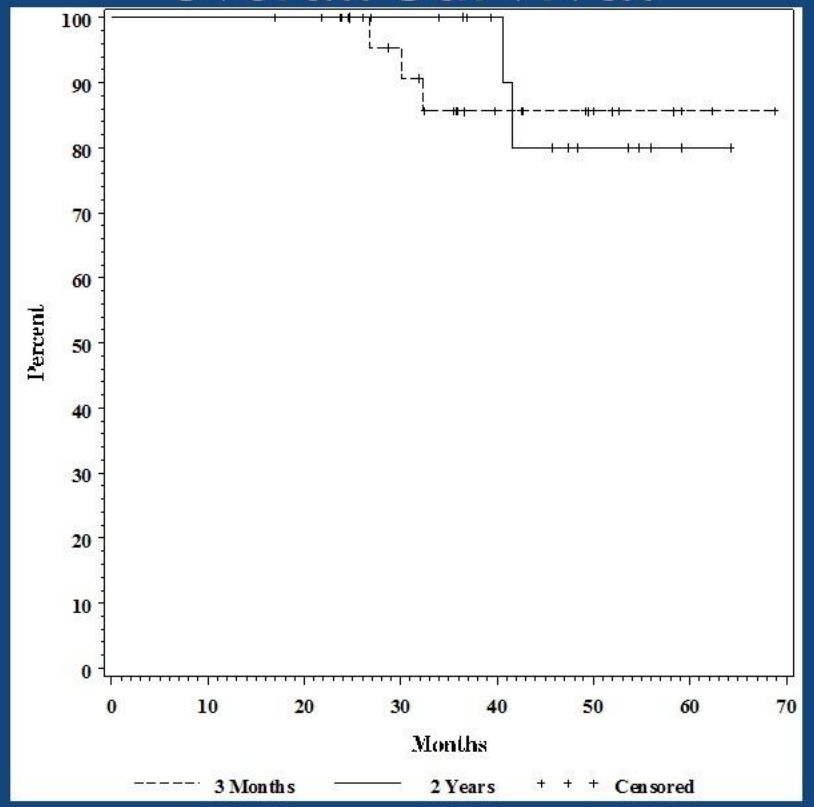
Outcomes

Disease Free Survival



Overall Survival



- Median follow-up ≥ 38 months
- 2-year DFS 71% in the 3-month arm and 85% in the 2-year arm, but did not meet the primary endpoint
- Median DFS and OS have not been reached

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Take Home Points:

1. EGFR TKI's do not cure patients with metastatic disease, but delay overt recurrence
2. TKI therapy after standard adjuvant chemotherapy/radiation appears to provide better long-term outcomes than TKI therapy alone
3. Compliance and toxicity are an issue with long-term therapies
   - Will better tolerated drugs, like osimertinib, give a different outcome? Pending ADAURA trial (NCT02511106)
   - Or will biomarkers help select patients—efforts like ALCHEMIST (NCT02193282) should address
4. Do not have an answer about the "optimum" length of treatment

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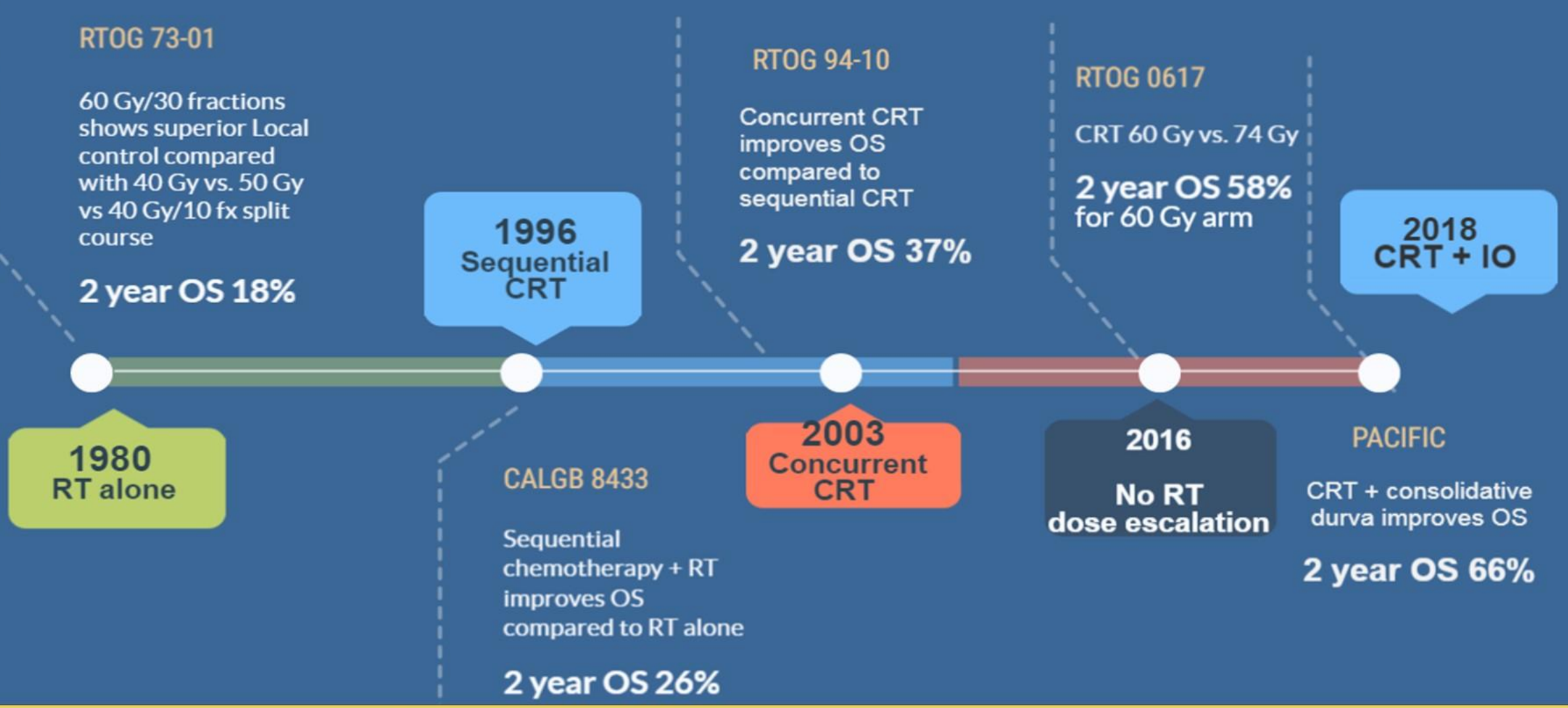
Was ist Neu

- Neoadjuvante Therapie
- Adjuvante Therapie
  - Chemotherapie
  - EGFR TKI
- **Radiochemotherapie in nicht operable NSCLC**
- VEGF Inhibitoren als Erhaltung
- EGFR TKI und Chemotherapie
- Immuntherapie
- Resistance Mutationen

Evolution of
Treatment for Unresectable Stage III NSCLC



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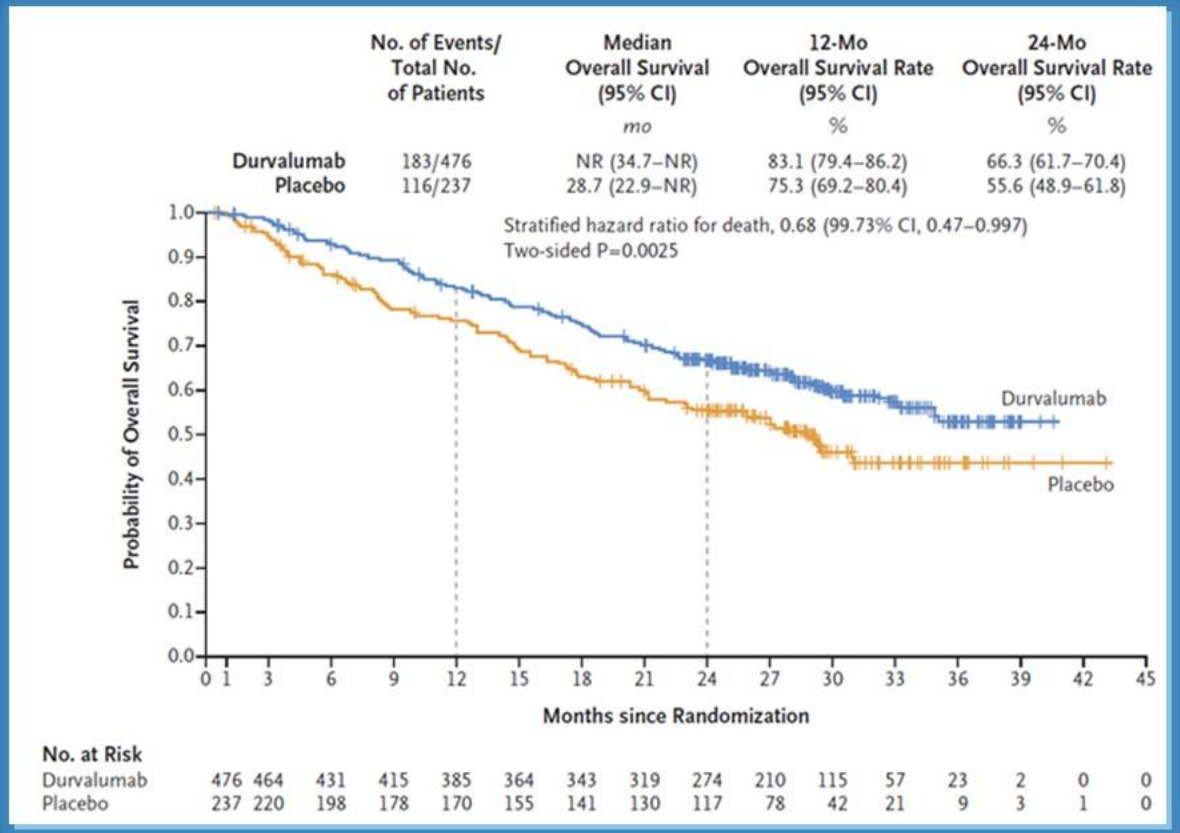
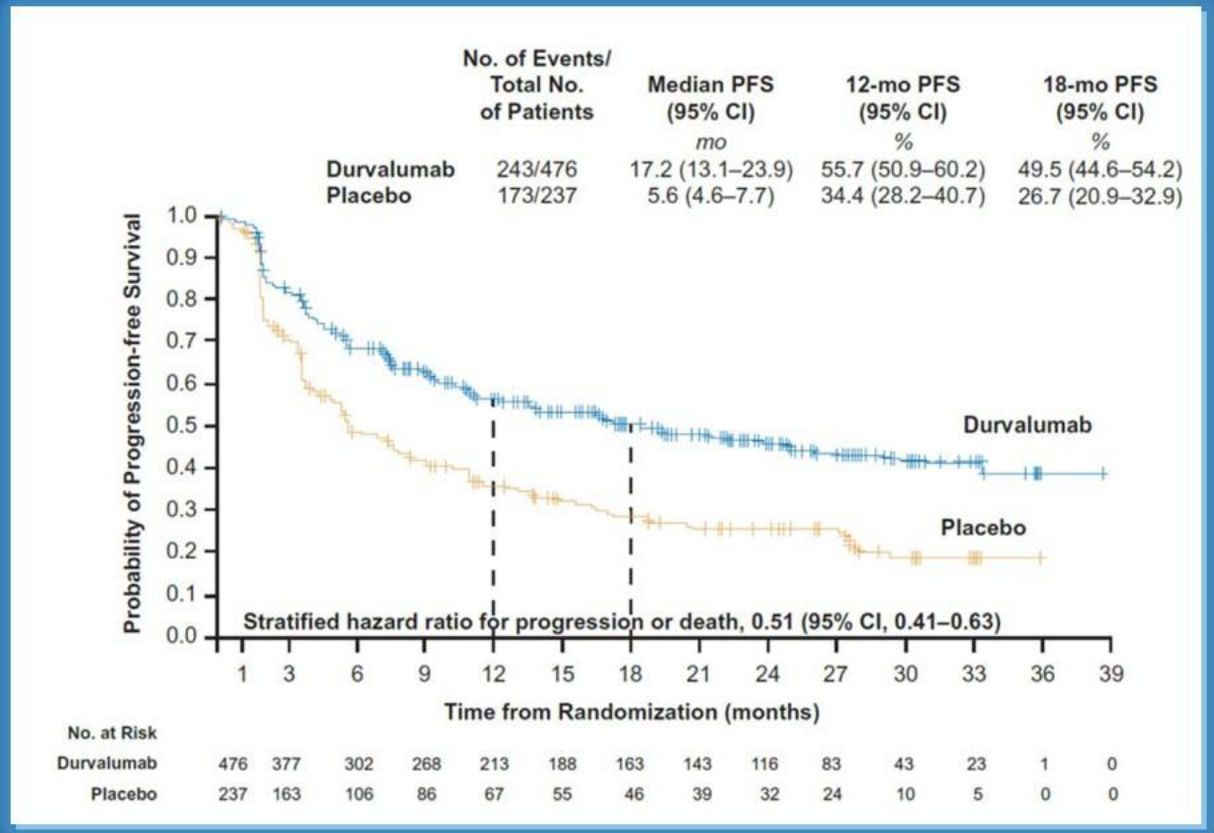
New Standard of Care in Stage III NSCLC: Durvalumab Improves OS and PFS





Antonia et al, NEJM 2018

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Abstract 8511 (270715)

Prospective phase I multi-institutional trial of PD-1 blockade with pembrolizumab during concurrent chemoradiation for locally advanced, unresectable non-small cell lung cancer

Authors: **Salma K. Jabbour**, Abigail T. Berman, Roy H. Decker, Yong Lin, Steven J. Feigenberg, Scott N. Gettinger, Charu Aggarwal, Corey J. Langer, Charles B. Simone II, Jeffrey D. Bradley, Joseph Aisner, Jyoti Malhotra

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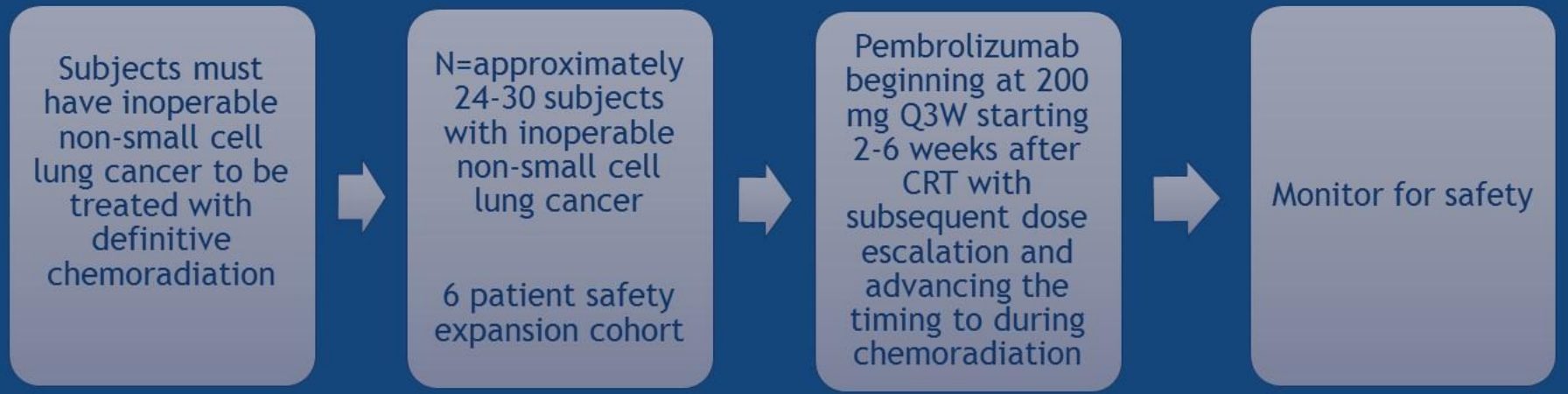
Study Design

- Multi-center Phase I clinical trial; 3+3 trial design
- Stage III NSCLC
- Evaluate the timing and dosing of pembrolizumab with concurrent chemoRT (carboplatin + paclitaxel weekly) and RT (60 Gy in 2 Gy/day).
- Pembrolizumab continued for up to 18 doses and delivered as monotherapy after CRT.
- Dose Limiting Toxicity (DLT) defined as Grade ≥4 Pneumonitis within 1 cycle of pembrolizumab (21 days)



Start of Pembrolizumab	Pembrolizumab Dose	Regimen
2-6 Weeks After CRT (Day 56-84)	100 mg Q3Weeks	-1
2-6 Weeks After CRT (Day 56-84)	200 mg Q3Weeks	1 *
2 Weeks Before End Of CRT (Day 28)	100 mg Q3Weeks	2
2 Weeks Before End Of CRT (Day 28)	200 mg Q3Weeks	3
At start of CRT (Day 0)	100 mg Q3Weeks	4
At start of CRT (Day 0)	200 mg Q3Weeks	5

*starting dose level

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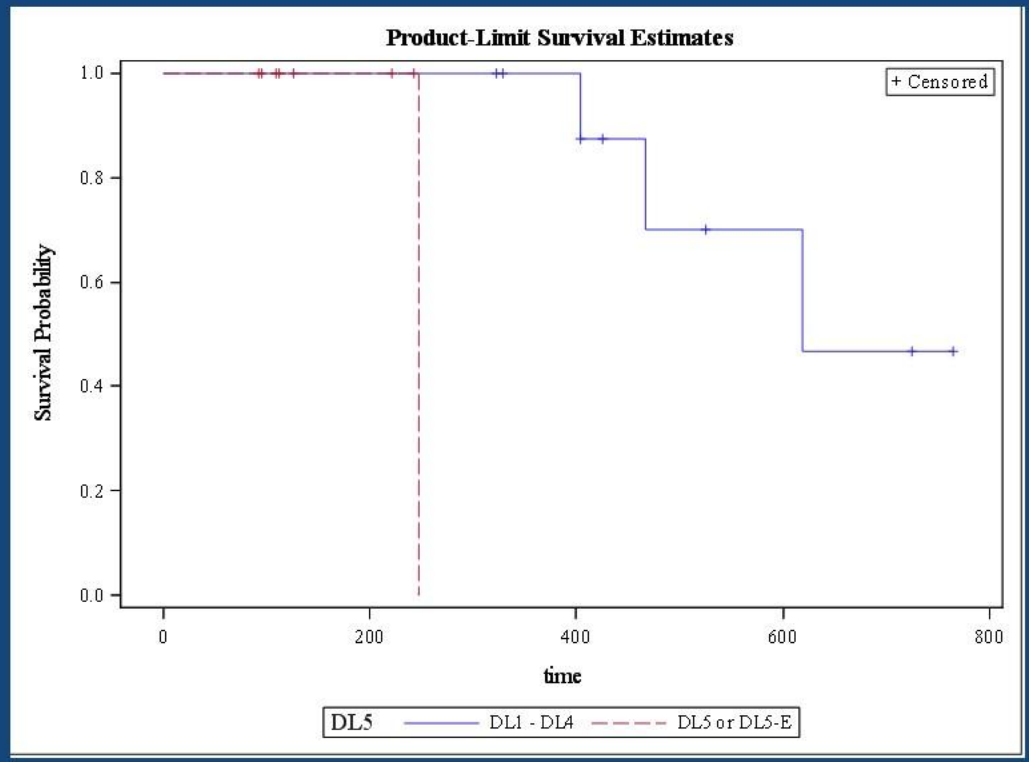
Results

- 23 subjects enrolled from 8/2016-11/2018
- Median age: 69 years (range 53-85), 52% women
- Stage IIIA: 22%, Stage IIIB: 78%
- No DLT upon completion of Regimen 5
- Grade ≥3 immune-related adverse events (irAE) occurred in 4 patients (18%)
- 2 subjects expired before receiving pembrolizumab



Kaplan-Meier Curve for PFS
Median PFS as for subjects with ≥ 2 cycles of pembrolizumab: 20.3 months (as of 2/2019)

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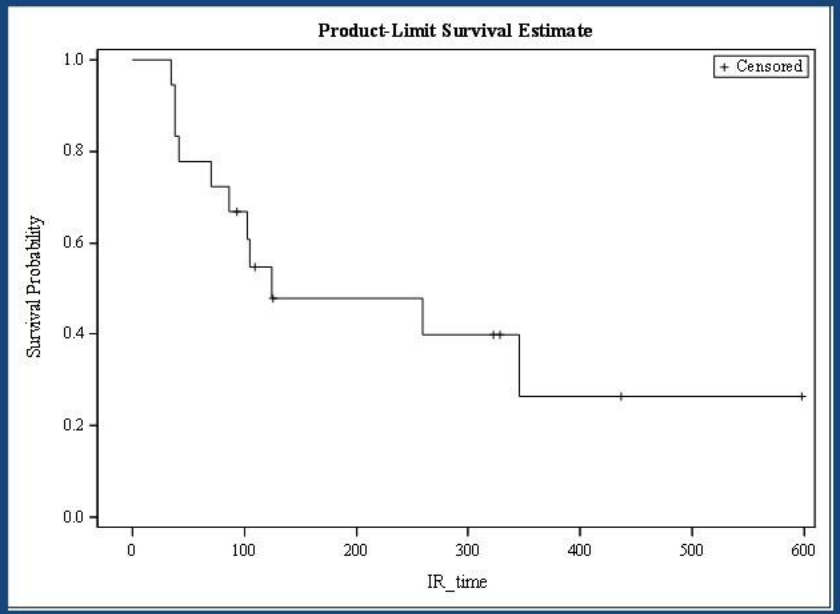
Results: Adverse Events

Event	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	Grade 5(n)
Pneumonitis	4 (Regimen 2 (1) and Dose Expansion (3))	1 (Regimen 2)		1 (Dose Expansion)
Nephritis	1 (Regimen 1)			
Thyroiditis	4 (Regimens 1,2,3,5)			
Transamanitis	1 (Regimen 2)			
Myositis	1 (Regimen 3)			
Hyperglycemia		1 (Regimen 5)		
Tracheoesophageal Fistula		1 (Regimen 5)		
Colovesical Fistula				1 (Regimen 1)



Median time to an immune-related event is 4.1 months (as of 2/2019)

In a Cox multivariable proportional hazard model for immune related event PDL1 H score is borderline significant (p=0.062) for immune-related events

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Abstract 8512 (270735)

Phase II trial combining atezolizumab concurrently with chemoradiation therapy in locally advanced non-small cell lung cancer

Authors: **Steven H. Lin**, Yan Lin, Isabel Mok, Jenean A. Young, See Phan, Alan Sandler, Vassiliki Papadimitrakopoulou, John Heymach, Anne S. Tsao

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Stage 1 (n=10)

Concurrent ChemoRadiation* → Consolidation Chemo** + **MPDL3280A** IV Q3weeks x 2 cycles → **MPDL3280A** IV Q3weeks for 1 year

If no concerning toxicities

Stage 2 (n=30)

Concurrent ChemoRadiation* + **MPDL3280A** IV Q3weeks → Consolidation Chemo** + **MPDL3280A** IV Q3weeks x 2 cycles → **MPDL3280A** IV Q3weeks for 1 year

*weekly carboplatin AUC 2 and paclitaxel 50 mg/m2 administered concurrent with thoracic radiation

**carboplatin AUC 6 and paclitaxel 200 mg/m2 IV Q 3 weeks for 2 cycles.

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Toxicity Summary

N=10	Part 1
All AEs	201
All Grade 3+ AEs	16
% pts developed any Grade 3+	6 of 10 (60%)
AEs leading to withdraw from tx	3 of 10 (30%)
% pts with immune-related Grade 3+ AEs	3 of 10 (30%)

Grade 2 AEs of special interest	Frequency
Dyspnea	4 of 10 (40%)
Pneumonitis	1 of 10 (10%)
Arthralgia	1 of 10 (10%)

Patients with Grade 3+ AEs	Frequency
Dyspnea (Grade 3)	1 of 10 (10%)
Arthralgia (Grade 3)	1 of 10 (10%)
Lung infection (Grade 5); Tracheoesophageal fistula (Grade 5)	1 of 10 (10%)

N=30	Part 2
All AEs	451
All Grade 3+ AEs	41
% pts developed any Grade 3+	20 of 30 (67%)
AEs leading to withdraw from tx	5 of 30 (17%)
% pts with immune-related Grade 3+ AEs	6 of 30 (20%)

Grade 2 AEs of special interest	Frequency
Nephritis	1 of 30 (3%)
Arthalgia	2 of 30 (7%)
Diarrhea	1 of 30 (3%)
Dyspnea	1 of 30 (3%)
Fatigue	1 of 30 (3%)
Hypothyroidism	1 of 30 (3%)
Pneumonitis	4 of 30 (13%)
Rash	5 of 30 (17%)

Patients with Grade 3+ AEs	Frequency
Diarrhea (Grade 3), Radiation pneumonitis (Grade 3)	1 of 30 (3%)
Nephritis (Grade 3), Fatigue (Grade 3)	1 of 30 (3%)
Fatigue (Grade 3)	2 of 30 (7%)
Heart failure (Grade 3)	1 of 30 (3%)
Respiratory failure NOS (Grade 4)	1 of 30 (3%)

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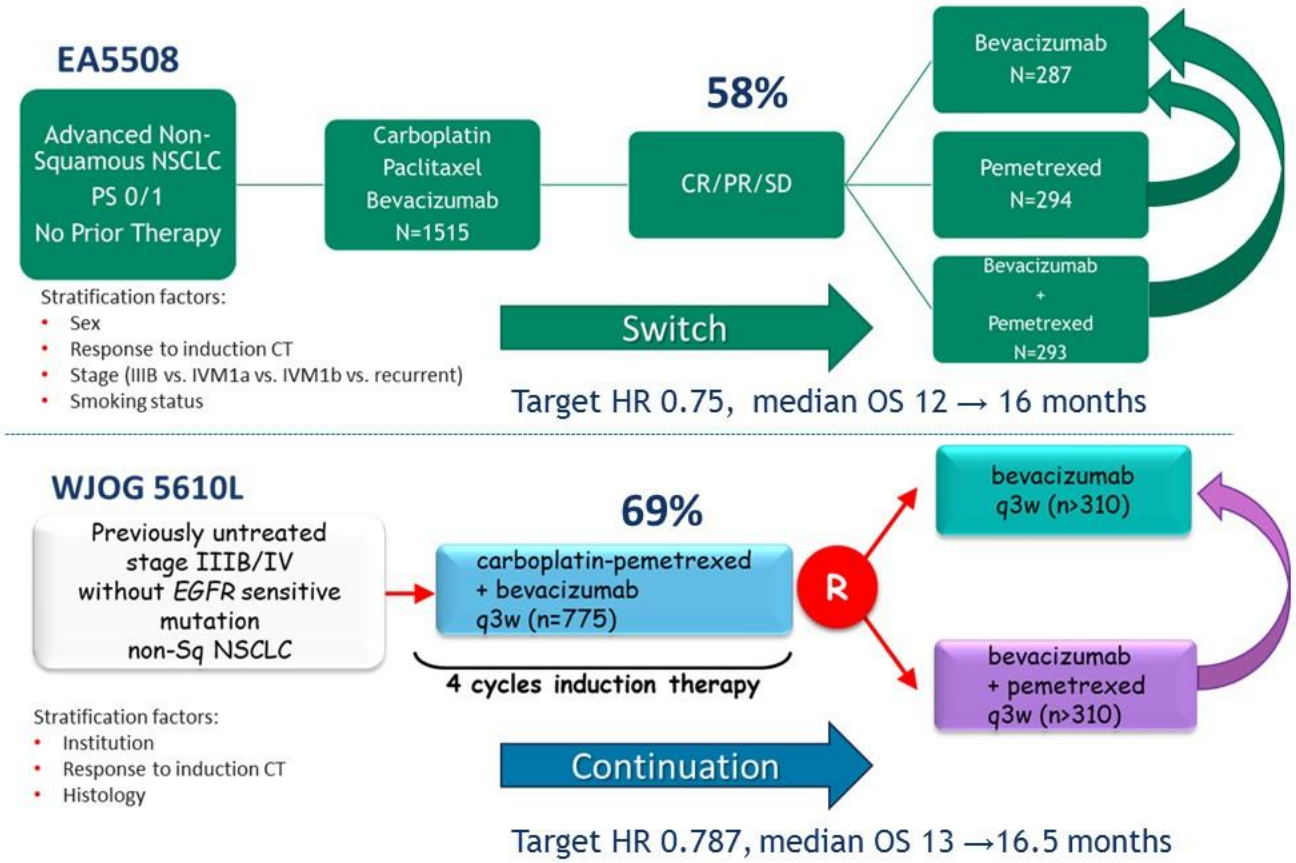
Was ist Neu

- Neoadjuvante Therapie
- Adjuvante Therapie
  - Chemotherapie
  - EGFR TKI
- Immuntherapie + Radiochemotherapie in nicht operable NSCLC
- **VEGF Inhibitoren als Erhaltung**
- EGFR TKI und Chemotherapie
- Immuntherapie

Which Maintenance Therapy After Induction Regimen Containing Bevacizumab?



Similarities

- Trials designed in 2009-2010
  - Before Paramount (pem continuation), Avaperl (pem + bev), Pointbreak
  - Before generalization of EGFR/ALK testing
  - Different perception of a relevant OS benefit
- Better prognosis for bev. eligible pts
- Same question: pem + bev *vs.* bev as maintenance treatment
- Primary endpoint: OS from randomization with an optimistic target HR (bevacizumab, not a placebo as control arm)

Differences for EA5508

- No testing for EGFR/ALK but stratification on smoking status
- Switch maintenance
- Additional comparison (pem *vs.* bev): split of α risk
- Lower proportion of patients randomized in the maintenance phase
- No recording of subsequent treatments (pem in the bev control arm?)

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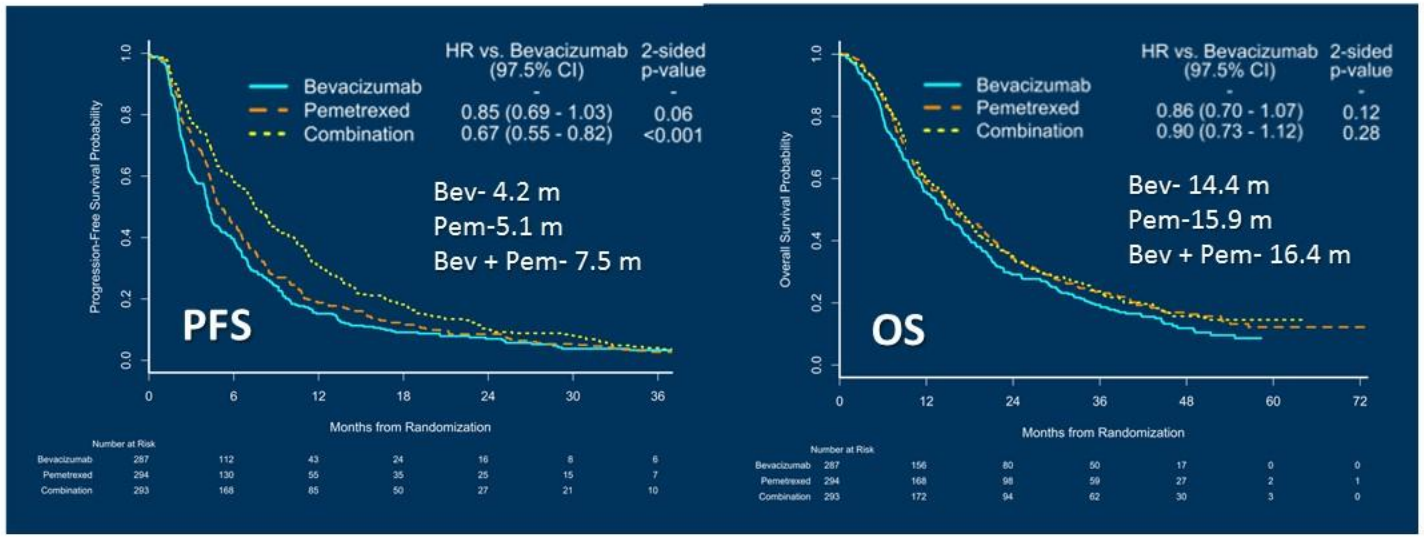
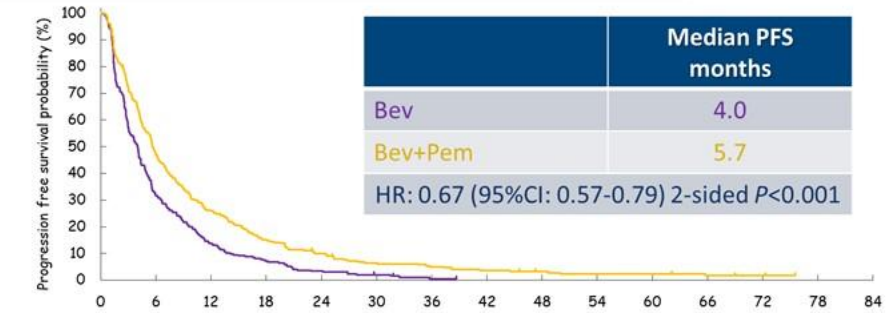
EA5508 *vs.* WJOG5610L

Maintenance phase	EA5508	WOG5610L
Oncogenic addiction	No testing, enrolled	No known common EGFR activating mutations
Female sex	**51%**	28%
Brain metastases	**15%**	5.5%
Never smokers	10%	**22%**
ORR to induction regimen	30%	**59.6%**
Median OS entire cohort (months)	**13.1**	**21.1**

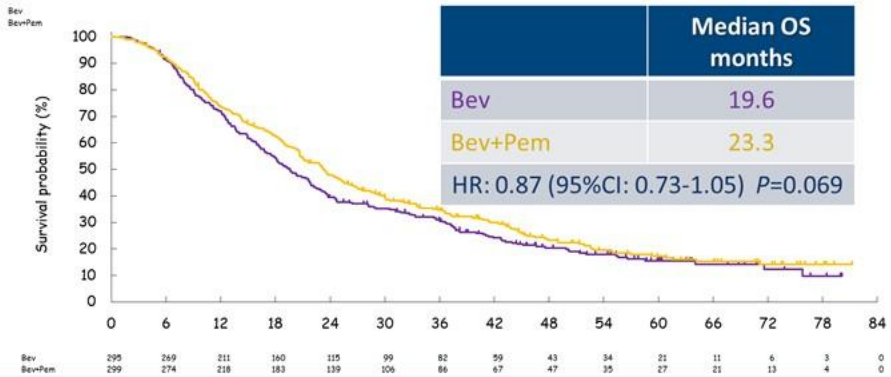


3 arms, Bonferroni correction for multiplicity, CI 97.5%

Multivariate OS analysis for pemetrexed *vs.* bevacizumab: HR 0.79, 97.5%CI: 0.62, 1.00, *P* = 0.02



	Median PFS months
Bev	4.0
Bev+Pem	5.7
HR: 0.67 (95%CI: 0.57-0.79) 2-sided *P*<0.001	



	Median OS months
Bev	19.6
Bev+Pem	23.3
HR: 0.87 (95%CI: 0.73-1.05) *P*=0.069	

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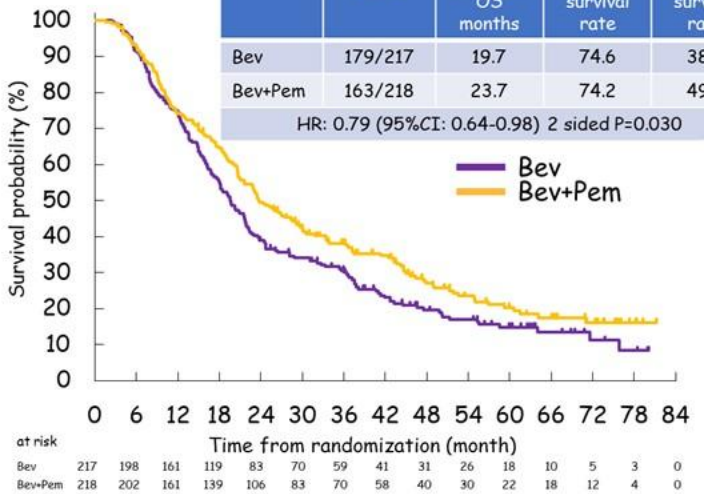
WJOG5610L: OS Subgroup Analysis

- No influence of response to induction therapy
- Trends favoring combination for younger age (< 70), wt EGFR and non smokers
  - Univariate analysis
  - No stratification on these factors
  - No adjustment for multiplicity, interaction test?

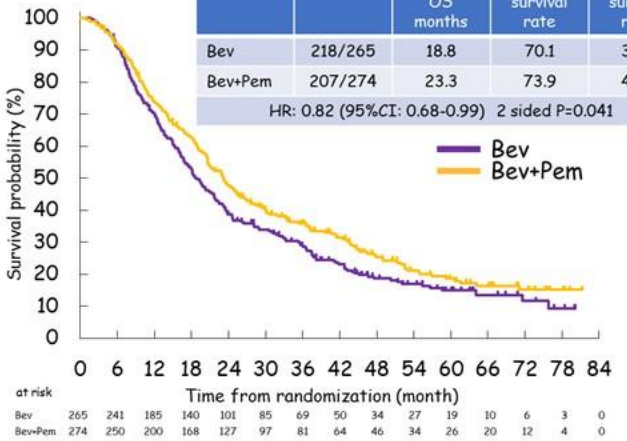
● <70 years old

	event	Median OS months	1 year survival rate	2years survival rate
Bev	179/217	19.7	74.6	38.9
Bev+Pem	163/218	23.7	74.2	49.5
HR: 0.79 (95%CI: 0.64-0.98) 2 sided P=0.030				



● wild-type *EGFR*

	event	Median OS months	1 year survival rate	2years survival rate
Bev	218/265	18.8	70.1	38.7
Bev+Pem	207/274	23.3	73.9	47.8
HR: 0.82 (95%CI: 0.68-0.99) 2 sided P=0.041				



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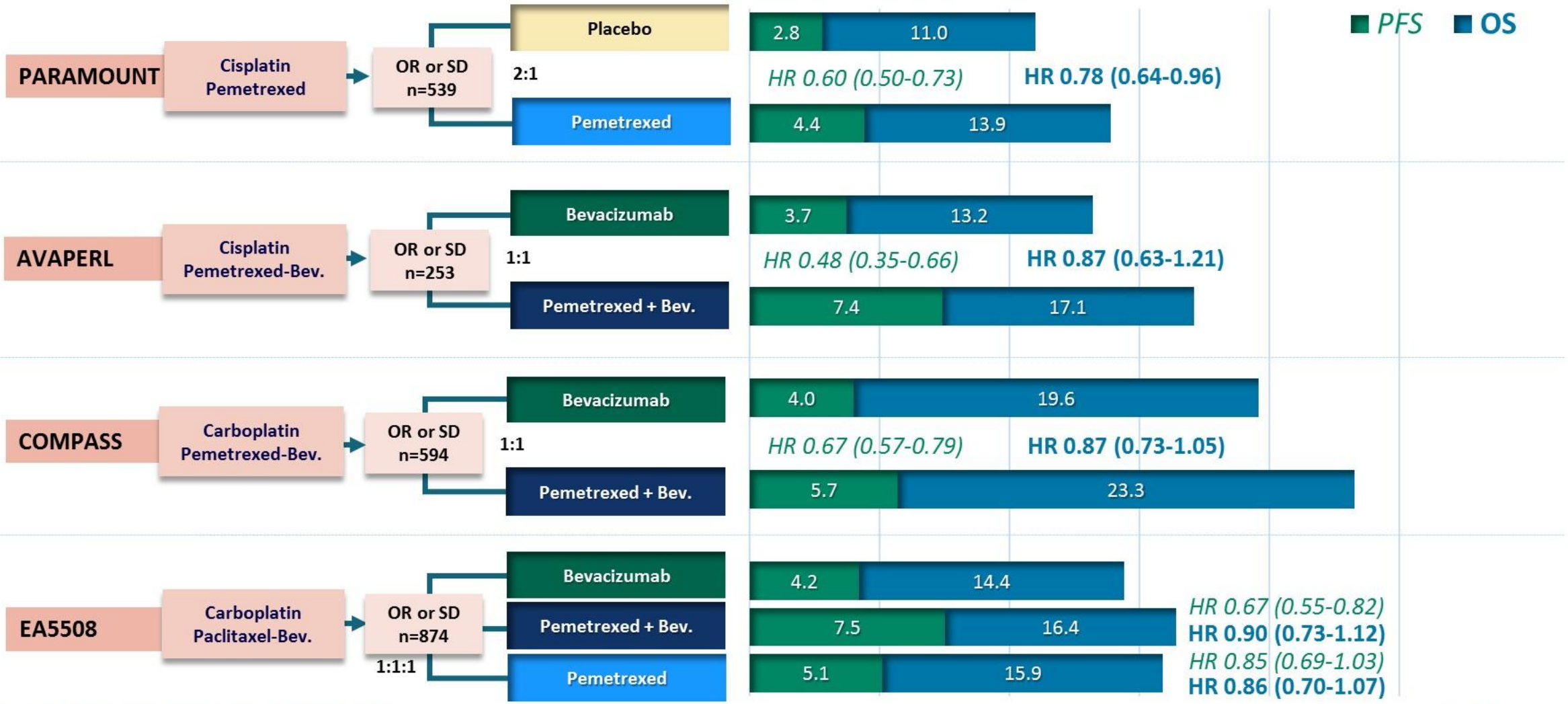
Which Maintenance After Induction Regimen Containing Bevacizumab?



Paz-Ares et al., J Clin Oncol 2013; Barlesi et al., Ann Oncol 2014;
Ramalingam et al., ASCO 2019; Seto et al., ASCO 2019

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Which Maintenance Therapy at the Era of Immunotherapy?

- Higher level of evidence for pemetrexed in non-squamous NSCLC
- Maintenance in clinical practice
  - Bevacizumab: acceptable after carboplatin-paclitaxel-bevacizumab, low toxicity level
  - Pemetrexed: preferred maintenance option after cis/carboplatin-pemetrexed
  - No clear evidence to use pemetrexed + bevacizumab instead of pemetrexed or bevacizumab
- Important part of chemo-ICIs combinations in non-squamous NSCLC, either with pemetrexed (+ pembrolizumab) or bevacizumab (+ atezolizumab)
  - Need for reassessment of the role of maintenance chemotherapy in this setting

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Was ist Neu

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  - Chemotherapie
  - EGFR TKI
- Radiochemotherapie in nicht operable NSCLC
- VEGF Inhibitoren als Erhaltung
- **EGFR TKI und Chemotherapie**
- Immuntherapie

Chemotherapy and Antiangiogenic Therapy in 2019: Who Needs It?

- RELAY: A multicenter, double-blind, randomized Phase 3 study of erlotinib in combination with ramucirumab or placebo in previously untreated patients with epidermal growth factor receptor mutation-positive metastatic NSCLC. K. Nakagawa *et al*. (#9000)
- Gefitinib versus gefitinib-pemetrexed-carboplatin in EGFR mutated lung cancer. V. Noronha *et al*. (#9001)

- *Can we use **cytotoxic chemotherapy** or **antiangiogenic therapy** to improve **frontline** treatment of **EGFR mutated NSCLC**?*

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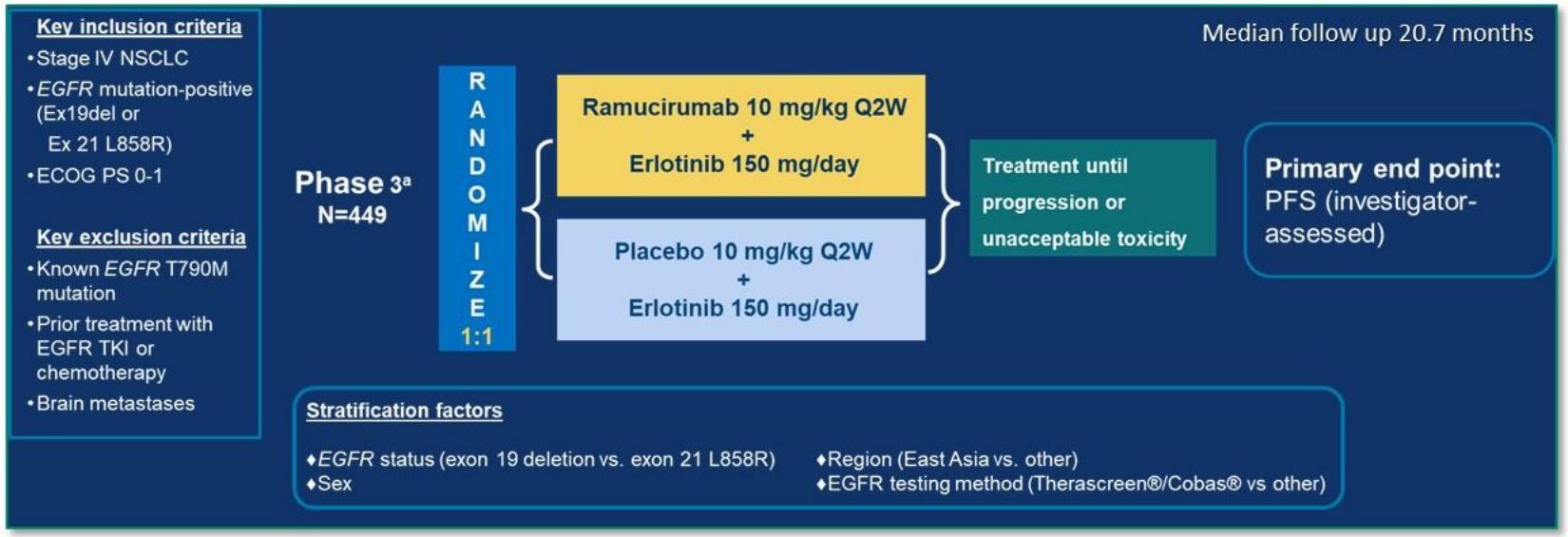
RELAY Phase III Trial



- Well designed, double-blinded, placebo-controlled phase III trial
- Reasonable (conservative?) target HR for PFS (primary endpoint): 0.71 (power 81%, α 5%)
- Brain metastases excluded as well as uncommon *EGFR* mutations
- 22% Caucasian pts
- 52% PS 0 pts, ex 19/ex 21: 55%/45%

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Tolerance of Erlotinib-Ramucirumab Combination

- Longer exposure to ramucirumab in *EGFR* mutants than in 2nd line with docetaxel
  - Median 11 months
  - **33%**/15% **ramucirumab**/placebo discontinuation rate (continuing on erlotinib)
  - 45% all grade hypertension with 24% grade 3
  - 2% grade 3 bleeding events
  - 34% proteinuria with 3% grade 3
  - No mention of thromboembolic events
- No worsening of erlotinib safety profile with the addition of ramucirumab

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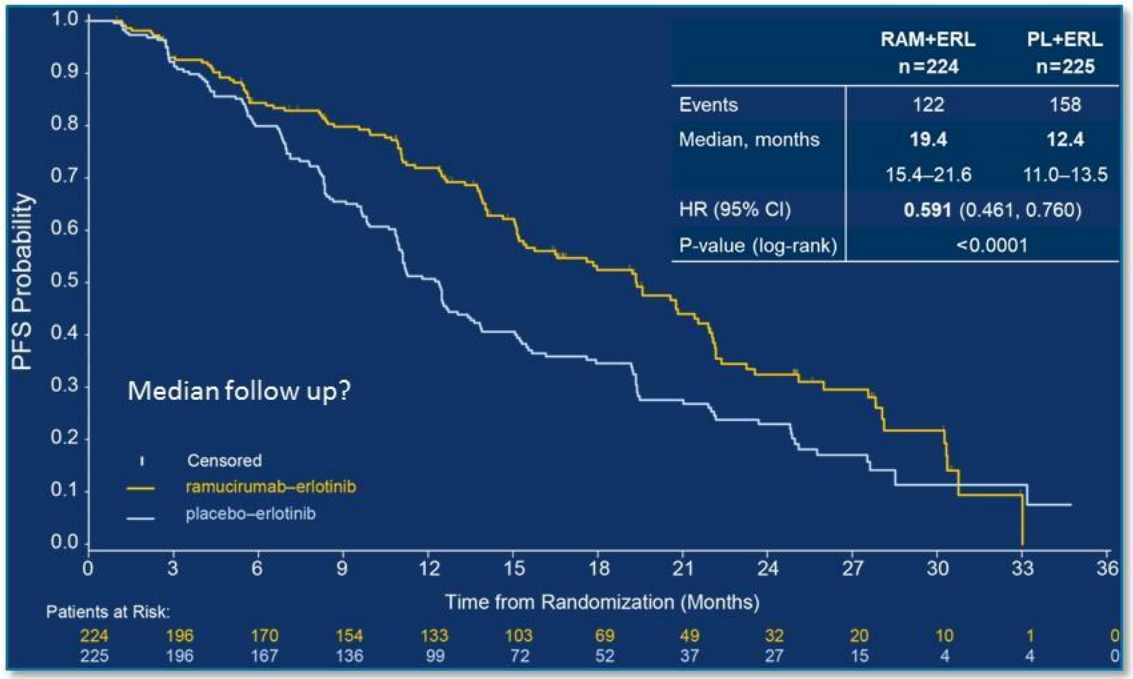
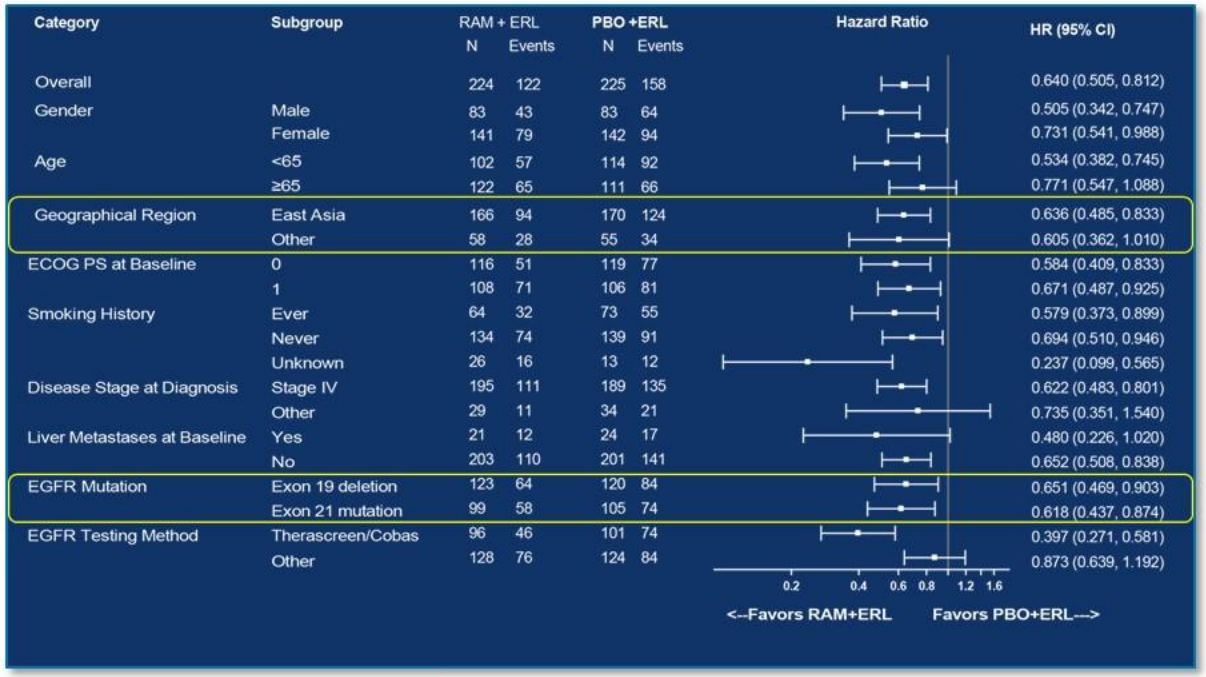
RELAY: Unambiguous PFS Improvement with Addition of Ramucirumab to Erlotinib



	RAM+ERL n=224	PL+ERL n=225
Events	122	158
Median, months	**19.4**	**12.4**
	15.4–21.6	11.0–13.5
HR (95% CI)	**0.591** (0.461, 0.760)	
P-value (log-rank)	<0.0001	



Category	Subgroup	RAM + ERL N	RAM + ERL Events	PBO +ERL N	PBO +ERL Events	HR (95% CI)
Overall		224	122	225	158	0.640 (0.505, 0.812)
Gender	Male	83	43	83	64	0.505 (0.342, 0.747)
	Female	141	79	142	94	0.731 (0.541, 0.988)
Age	<65	102	57	114	92	0.534 (0.382, 0.745)
	≥65	122	65	111	66	0.771 (0.547, 1.088)
Geographical Region	East Asia	166	94	170	124	0.636 (0.485, 0.833)
	Other	58	28	55	34	0.605 (0.362, 1.010)
ECOG PS at Baseline	0	116	51	119	77	0.584 (0.409, 0.833)
	1	108	71	106	81	0.671 (0.487, 0.925)
Smoking History	Ever	64	32	73	55	0.579 (0.373, 0.899)
	Never	134	74	139	91	0.694 (0.510, 0.946)
	Unknown	26	16	13	12	0.237 (0.099, 0.565)
Disease Stage at Diagnosis	Stage IV	195	111	189	135	0.622 (0.483, 0.801)
	Other	29	11	34	21	0.735 (0.351, 1.540)
Liver Metastases at Baseline	Yes	21	12	24	17	0.480 (0.226, 1.020)
	No	203	110	201	141	0.652 (0.508, 0.838)
EGFR Mutation	Exon 19 deletion	123	64	120	84	0.651 (0.469, 0.903)
	Exon 21 mutation	99	58	105	74	0.618 (0.437, 0.874)
EGFR Testing Method	Therascreen/Cobas	96	46	101	74	0.397 (0.271, 0.581)
	Other	128	76	124	84	0.873 (0.639, 1.192)

- Median PFS **19.4 months** (increase by 7 months)
- Consistent across all patients subgroups (ethnicity, ex. 19/ex. 21)
- Due to prolongation of response duration
- No information about depth of response

	RAM+ERL N=224	PL+ERL N=225
ORR, % (95% CI)	76 (71 – 82)	75 (69 – 80)
Median, months (95% CI)	18.0 (13.9 – 19.8)	11.1 (9.7 – 12.3)
HR (95% CI)	0.619 (0.477, 0.805)	

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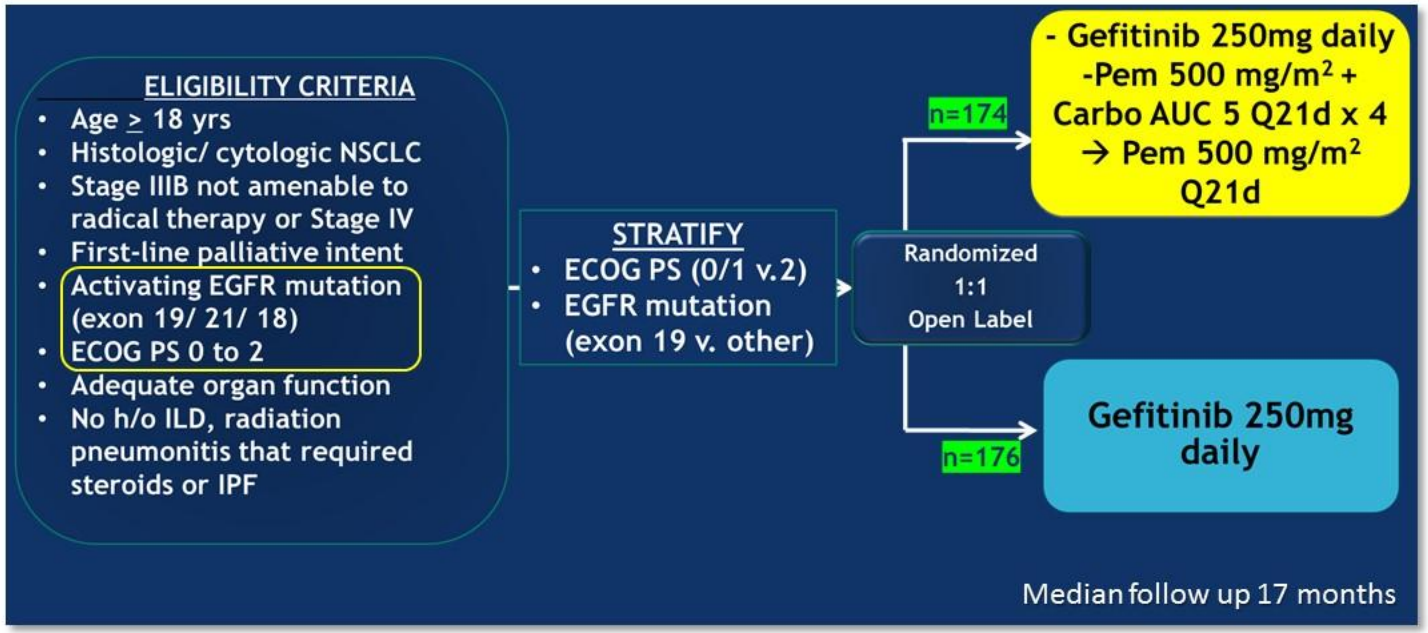
Gefitinib *vs*. Gefitinib-Pemetrexed-Carboplatin in *EGFR* Mutated Lung Cancer



- "Pragmatic" trial
  - Brain metastases allowed (majority with WBRT)
  - 21% PS 2, 2% PS 0
  - Investigators-assessed PFS as primary endpoint
    - Broad definition
    - Flexible schedule of assessment
  - PROs evaluation
- Reasonable expectation for PFS benefit (median PFS 10→15 months, HR 0.66)

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The Increase of Toxicity Must Be Taken into Consideration for Risk-Benefit Assessment of CT-TKI Combination

	Gef + C arm (n=164)	Gef arm (n=170)
Clinically relevant ≥ gr 3 toxicities	**50.6%**	**25.3%**
Pemetrexed discontinuation for toxicity	16.7%	-
Grade 3-4 neutropenia	16%	0
Febrile neutropenia	12%	0
Grade 3-4 anemia	19%	1%
Grade 2-4 diarrhea	32%	21%
Grade 2-3 fatigue grade 2-3	39%	21%
Grade 3-4 hypokalemia	8%	2%
Grade 2-4 nephrotoxicity	16%	2%

No significant increase of the gefitinib skin toxicity

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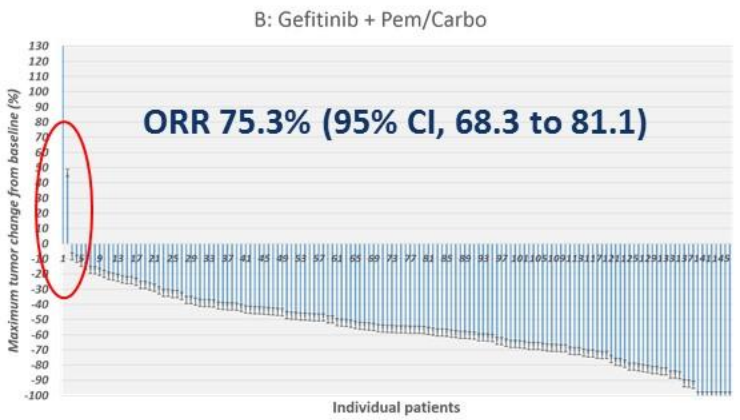
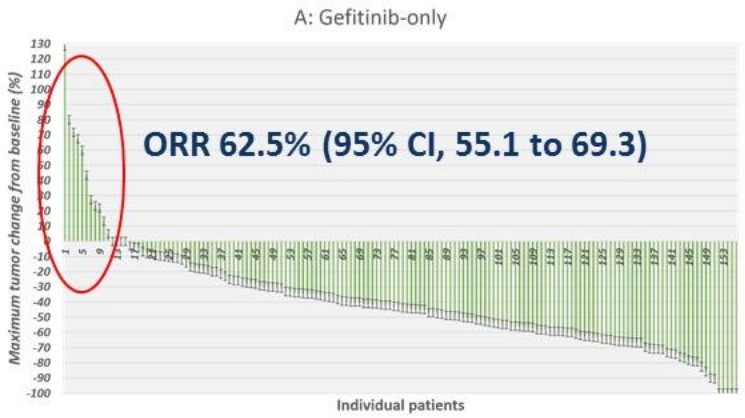
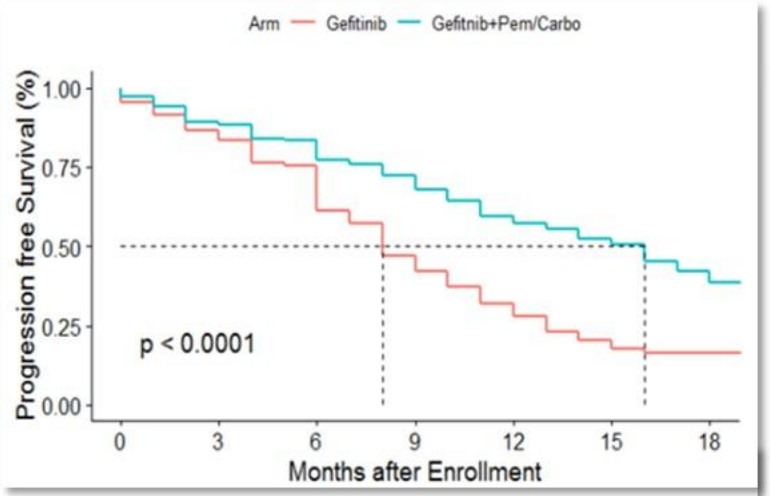
Response, PFS and OS Benefit with Upfront Chemotherapy Combined with Gefitinib

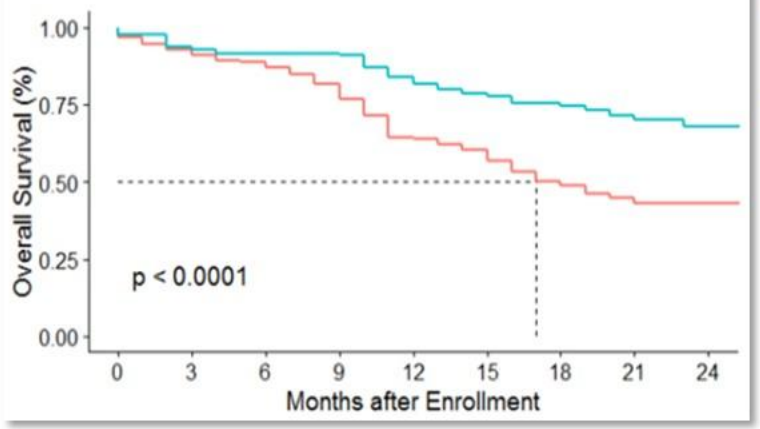




PFS



OS



- Impressive PFS benefit
  - Short median PFS in the control arm (21% PS 2 pts)
  - Improvement of ORR and depth of response
  - No information about DoR
  - No impact of mutation subtype
- No data about resistance mechanisms
- PFS benefit ➔ OS benefit: low rate of post-study treatments?
  - 24% Carbo-Pem in the G arm,
  - Osimertinib exposure: 11% G+C, 15% G

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Consistent Magnitude of Benefit with Combination of Chemotherapy and EGFR TKI

Trial	Treatment	N	PS 0/1/2 %	Exon 19/21 %	Brain mets %	ORR %	PFS Months	OS Months
NEJ009	Gefitinib	172	**62**/38/0	?	22	67.4	11.2	38.8
	Cb-Pem-G	170	**58**/42/0	?	30	84.0	**20.9**	**52.2**
							HR 0.49 *95%CI 0.39, 0.63*	***HR 0.70*** *95%CI 0.52, 0.93*
Noronha	Gefitinib	176	4/74/**22**	62/34	19	62.5	8	17
	Cb-Pem-G	174	1/79/**21**	62/35	17	75.3	**16**	**NR**
							HR 0.51 *95%CI 0.39, 0.66*	***HR 0.45*** *95%CI 0.31, 0.65*

Nakamura et al., ASCO 2018; Noronha et al., ASCO 2019

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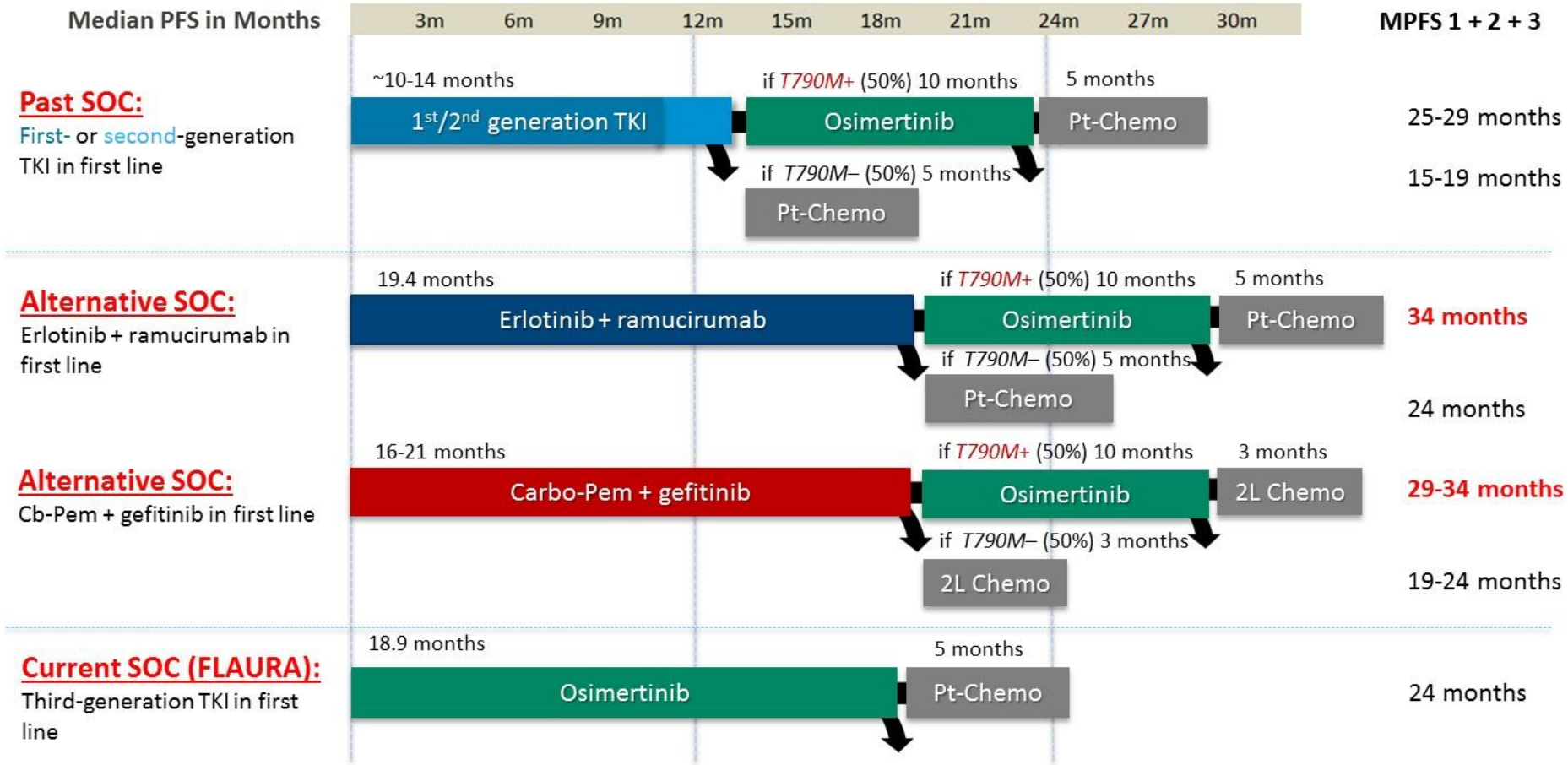
How to Integrate the Results of RELAY and Chemo + Gefitinib Trial in the Current Landscape of *EGFR* Mutant Treatment?

- **In the perspective of the whole treatment sequence**



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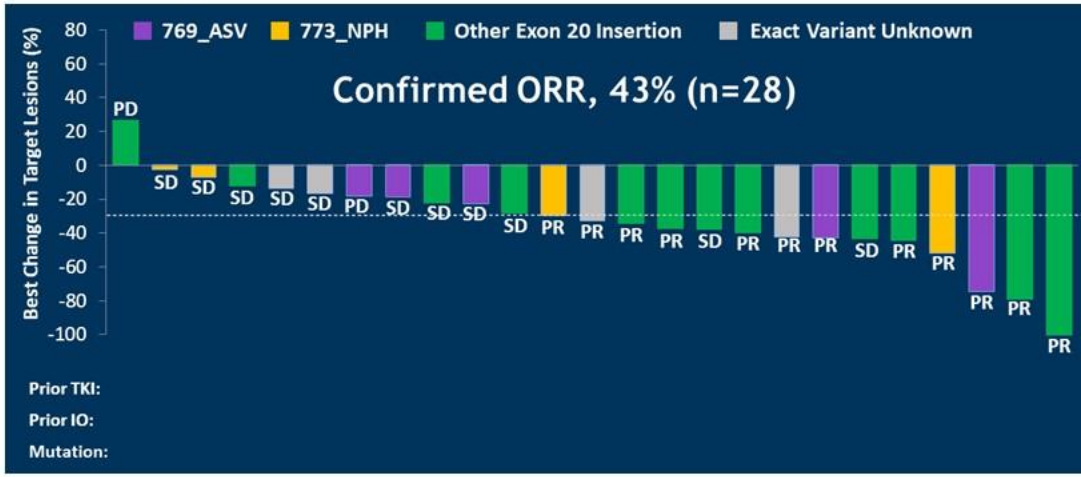
TAK788 – Encouraging activity profile in pts with advanced lung cancer harboring EGFR exon 20 insertion mutants

Activity observed:

- 43% confirmed ORR and 7.3-month median PFS in all patients, including those with baseline CNS metastases.
  - At R2PD dose of 160mg po QD
  - N= 28 patients
- Responses observed regardless of
  - Treatment history (prior chemo or CPI)
  - Which specific Exon 20 insertion variant
  - CNS involvement
- Activity against intracranial metastases
  - 3 of 12 pts (25%) with brain mets had objective responses.
- Most common AEs at 160mg QD
  - 96% had any AE; 63% had grade ≥ 3 AE
  - Diarrhea 85% any grade (18% grade ≥ 3)
  - Nausea 43% any grade
  - Rash 36% any grade
  - Vomiting 29% any grade



Exon 20 Insertion Variant	No. of Patients	No. of Confirmed Responders, n	Confirmed ORR
769_ASV	5	2	40%
773_NPH	4	2	50%
Exact variant unknown	4	2	50%
Other	15	6	40%

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Presented By Christine Lovly at 2019 ASCO Annual Meeting

Was ist Neu

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- Radiochemotherapie in nicht operable NSCLC
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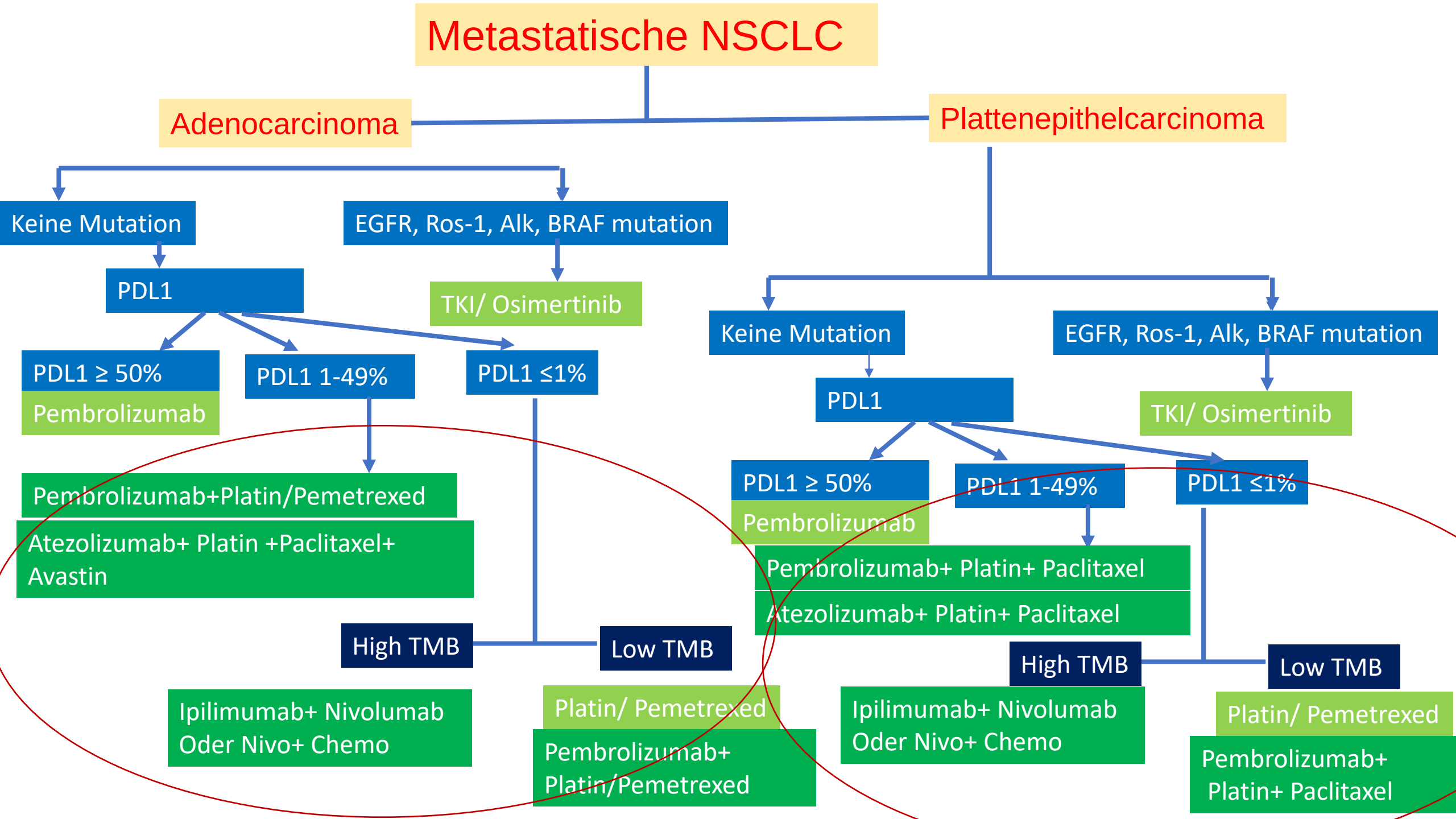
- VEGF Inhibitoren als Erhaltung
- **Immuntherapie**


Metastatische NSCLC
Adenocarcinoma
Plattenepithelcarcinoma
Keine Mutation
EGFR, Ros-1, Alk, BRAF mutation
PDL1
TKI/ Osimertinib
PDL1 ≥ 50%
Pembrolizumab
PDL1 1-49%
PDL1 ≤1%
Pembrolizumab+Platin/Pemetrexed
Atezolizumab+ Platin +Paclitaxel+ Avastin
High TMB
Low TMB
Ipilimumab+ Nivolumab Oder Nivo+ Chemo
Platin/ Pemetrexed
Pembrolizumab+ Platin/Pemetrexed
Keine Mutation
EGFR, Ros-1, Alk, BRAF mutation
PDL1
TKI/ Osimertinib
PDL1 ≥ 50%
Pembrolizumab
PDL1 1-49%
PDL1 ≤1%
Pembrolizumab+ Platin+ Paclitaxel
Atezolizumab+ Platin+ Paclitaxel
High TMB
Low TMB
Ipilimumab+ Nivolumab Oder Nivo+ Chemo
Platin/ Pemetrexed
Pembrolizumab+ Platin+ Paclitaxel

Parsing the Data for Checkpoint Inhibitors in 2019

- **Abstract LBA9015**: Five-year long-term overall survival for patients with advanced NSCLC treated with pembrolizumab: Results from KEYNOTE-001

- **Abstract 9014**: A phase III randomized study of nivolumab plus ipilimumab versus nivolumab for previously treated patients with stage IV squamous cell lung cancer and no matching biomarker (Lung-MAP Sub-Study S1400I, NCT02785952).

- **Abstract 9012**: IMpower150: Analysis of efficacy in patients with liver metastases

- **Abstract 9013**: KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC.

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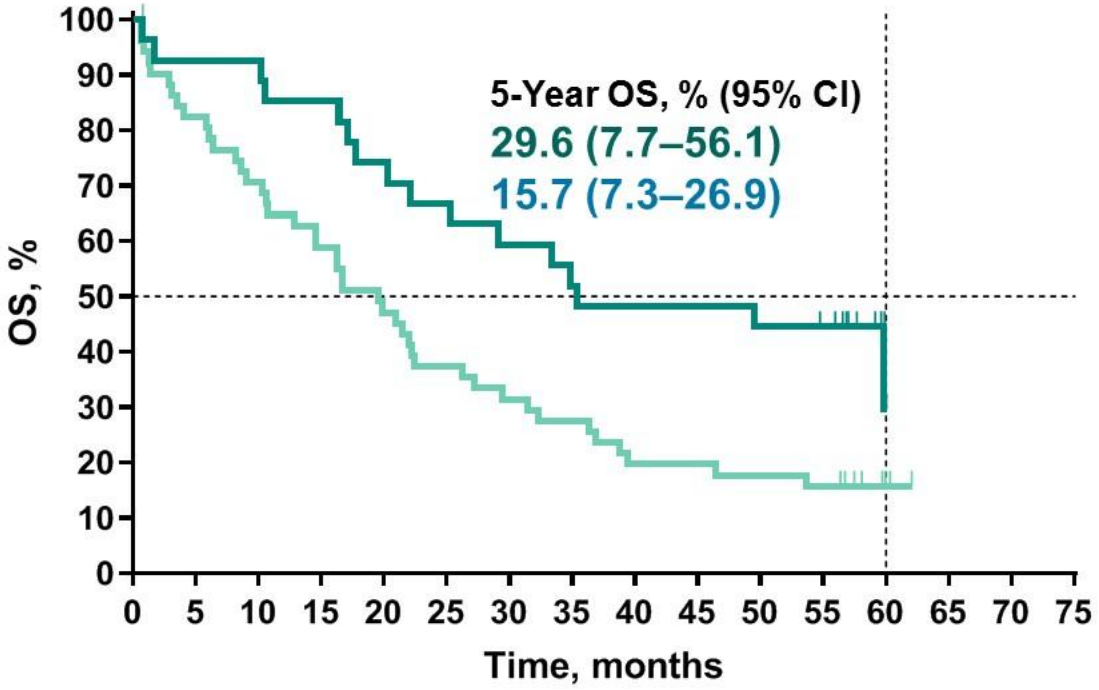
Abstract LBA9015: 5-year long-term overall survival for patients with advanced NSCLC treated with pembrolizumab

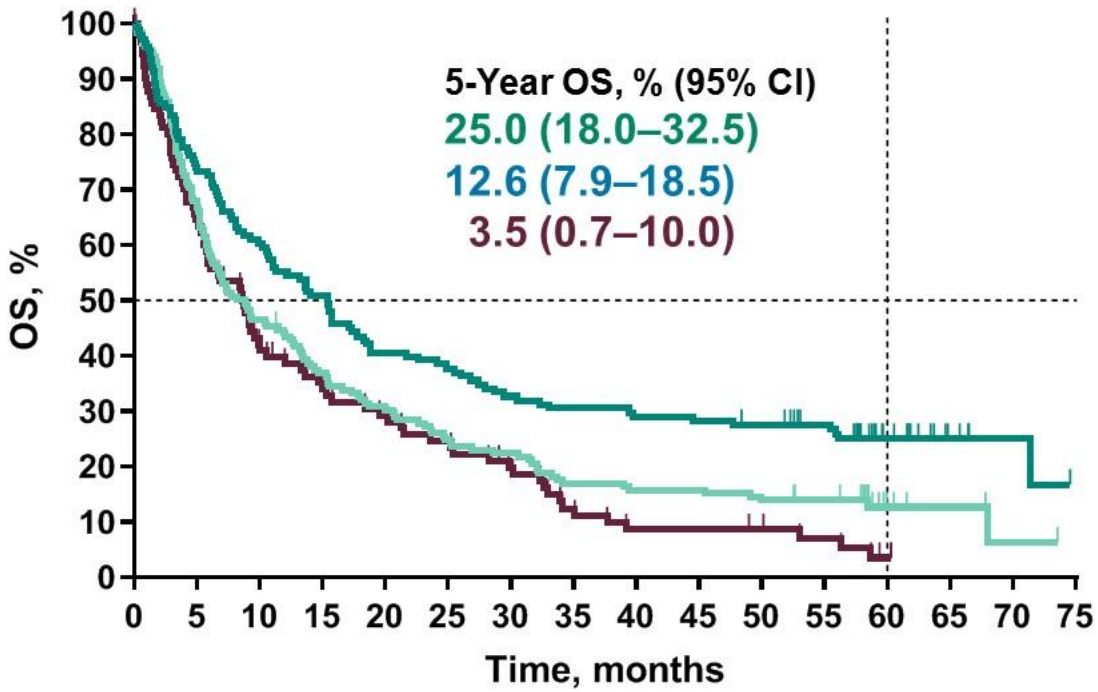
Treatment-Naive Patients

PD-L1 TPS	Events, n/N	Median (95% CI) OS, mo
TPS ≥50%	17/27	35.4 (20.3–63.5)
TPS 1%–49%	43/52	19.5 (10.7–26.3)



Previously Treated Patients

PD-L1 TPS	Events, n/N	Median (95% CI) OS, mo
TPS ≥50%	104/138	15.4 (10.6–18.8)
TPS 1%–49%	146/168	8.5 (6.0–12.6)
TPS <1%	83/90	8.6 (5.5–10.6)



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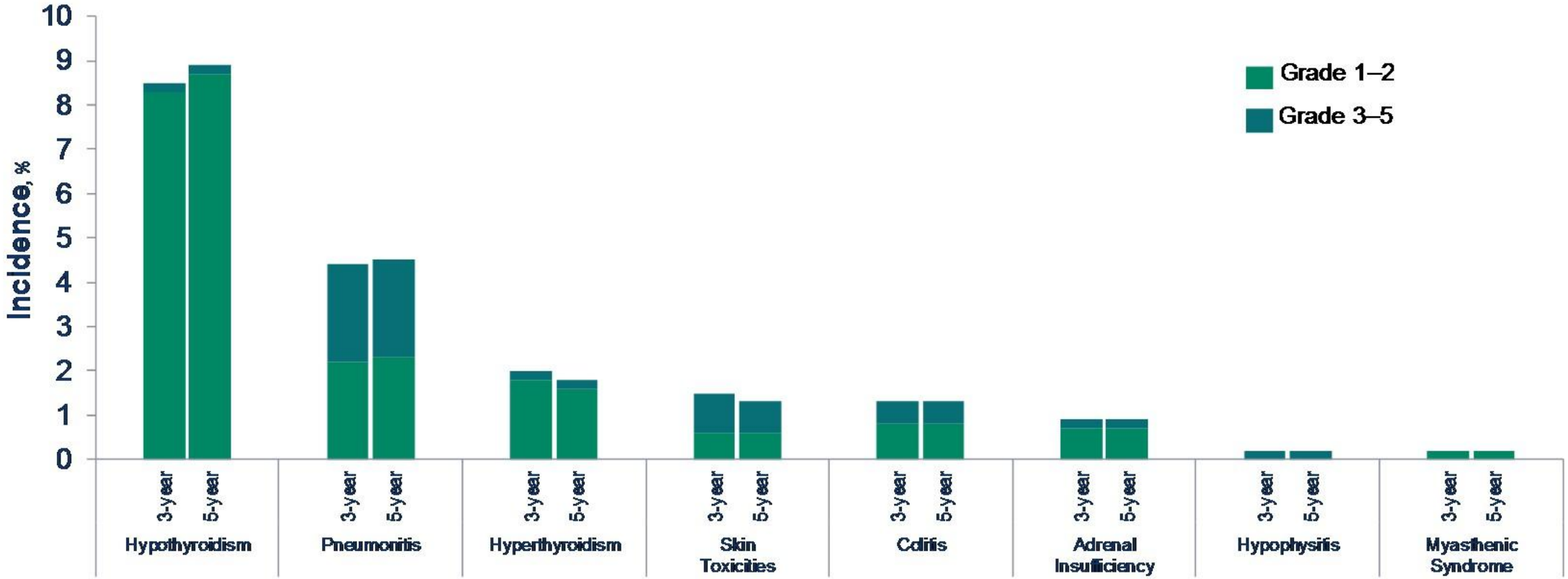
Presented By Kathryn Arbour at 2019 ASCO Annual Meeting

Abstract LBA9015: 5-year long-term overall survival for patients with advanced NSCLC treated with pembrolizumab: late toxicities

92 patients (17%) experienced an immune-mediated AE



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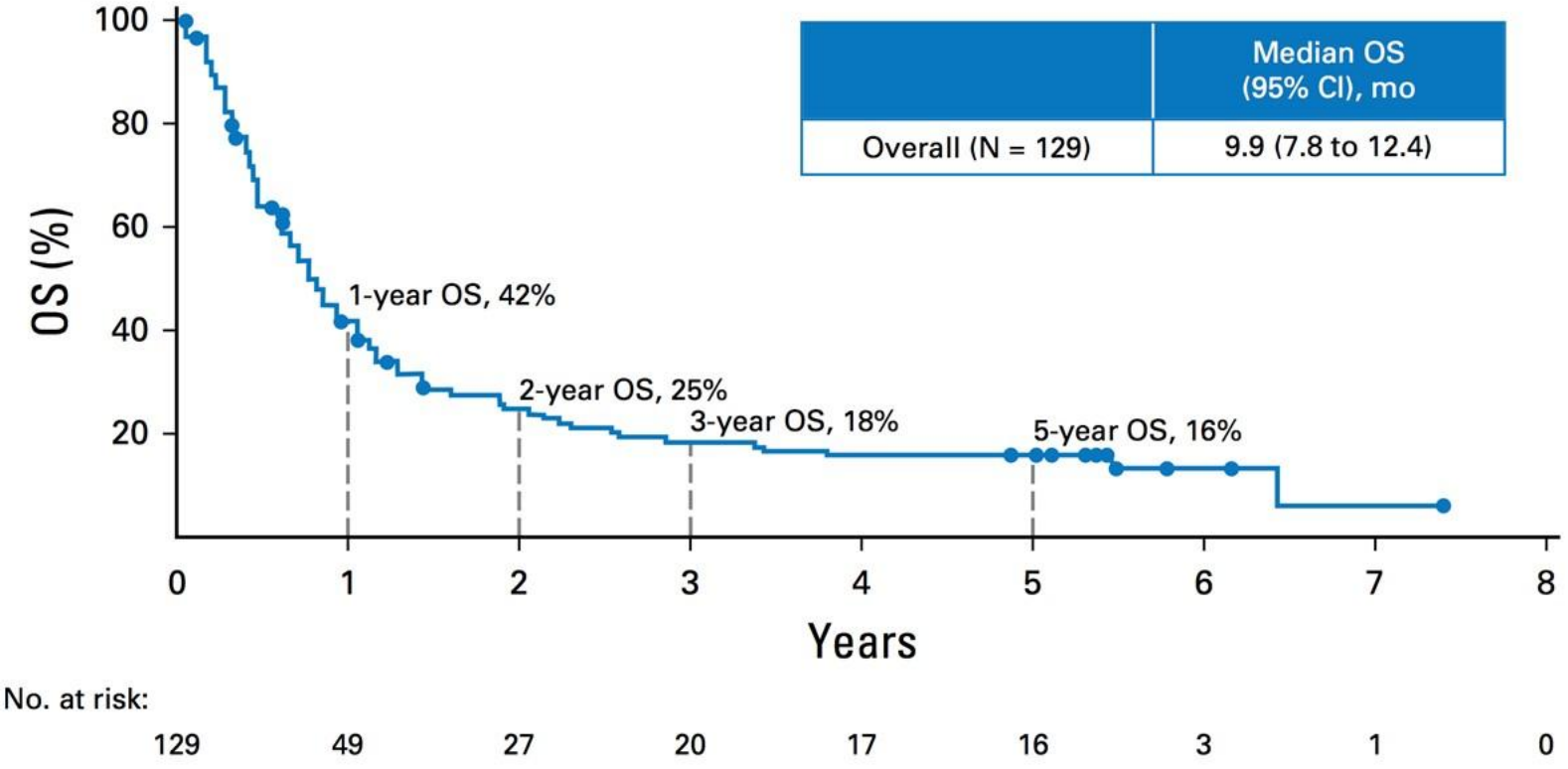
Nivolumab in previously treated patients: 5 year survival data

Overall Study Population (n=129)

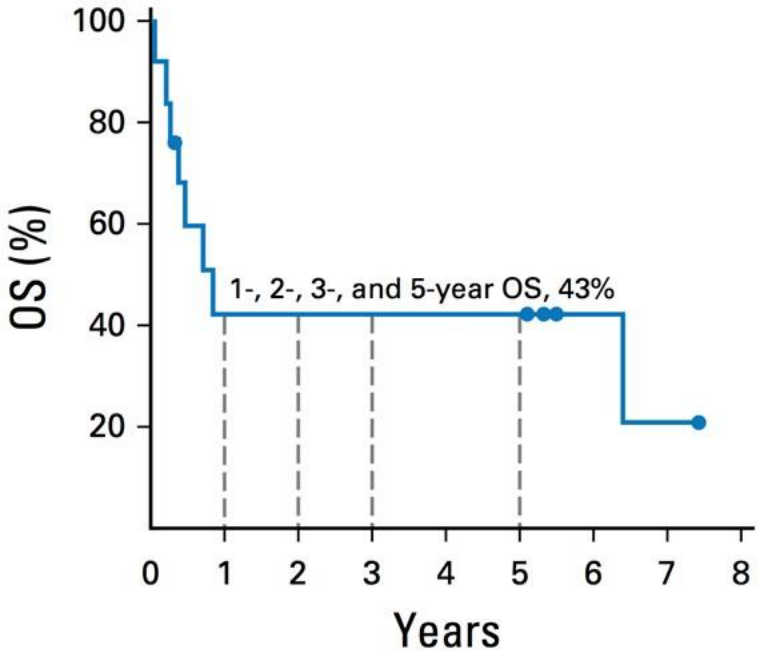


	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8 to 12.4)

No. at risk:

129	49	27	20	17	16	3	1	0

Patients with PD-L1 ≥50% (n=13)



No. at risk:

13	5	5	5	5	5	2	1	0

Gettinger et al. JCO. 2018

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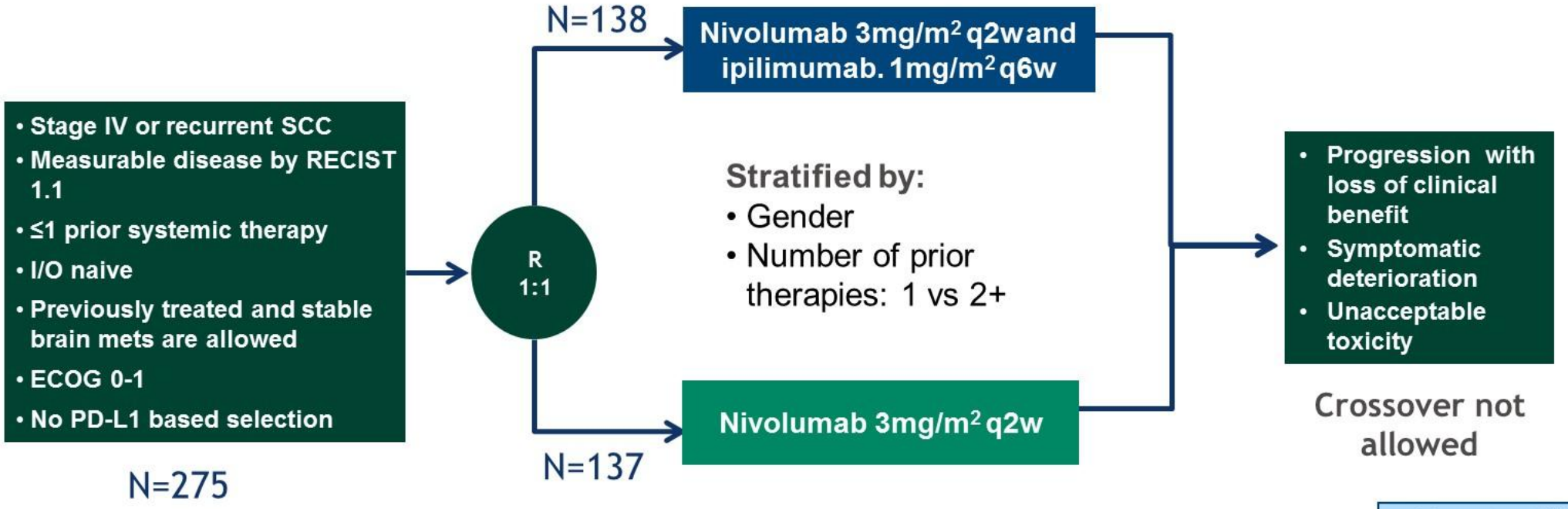
Abstract 9014: A phase III randomized study of nivo/ipi vs nivo for previously treated patients with Squamous Lung Cancer (Lung-MAP Sub-Study S1400I)



No stratification based on TMB and/or PD-L1

Primary Endpoint: Overall survival
Secondary Endpoints: investigator assessed PFS, ORR, toxicity
Correlatives: treatment effect (OS, PFS, ORR) by PD-L1 status (not required)

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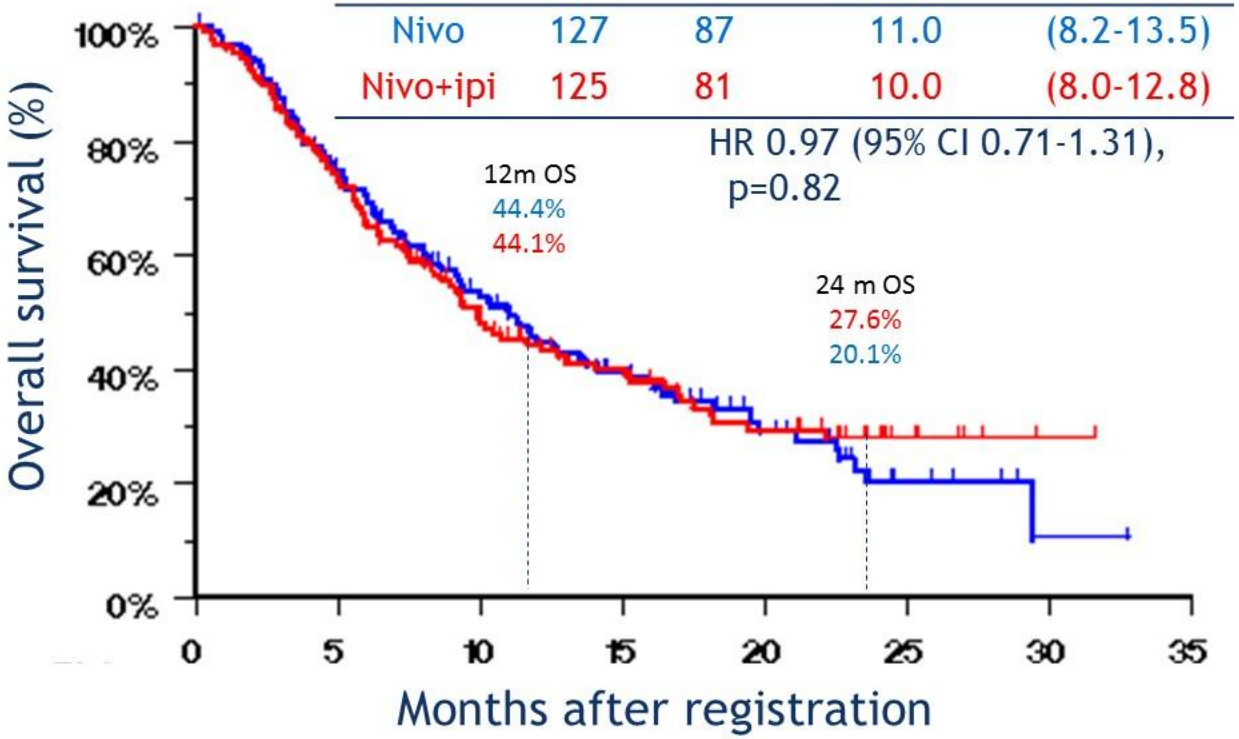
Abstract 9014: Lung MAP: Nivo vs Ipi/Nivo in previously treated squamous lung cancer: OS and PFS

Overall Survival

	N	Events	Median, month	96% CI
Nivo	127	87	11.0	(8.2-13.5)
Nivo+ipi	125	81	10.0	(8.0-12.8)

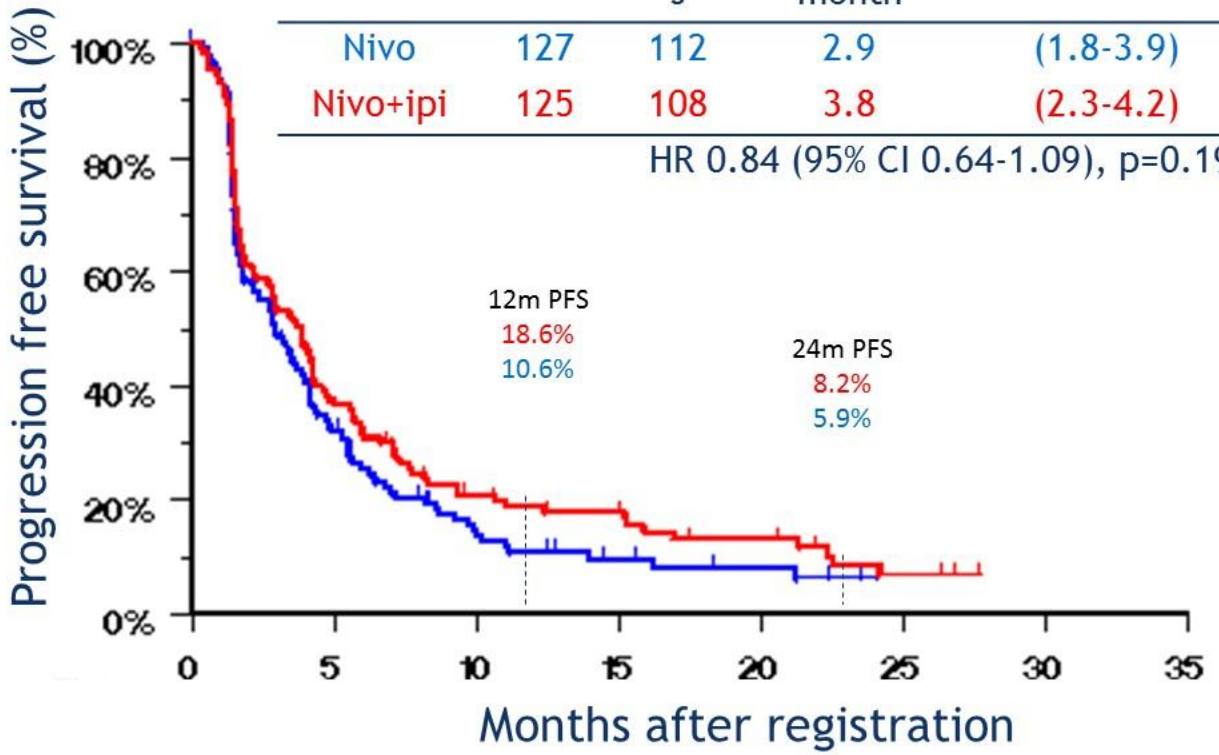
HR 0.97 (95% CI 0.71-1.31), p=0.82



Progression Free Survival

	N	Events	Median, month	96% CI
Nivo	127	112	2.9	(1.8-3.9)
Nivo+ipi	125	108	3.8	(2.3-4.2)

HR 0.84 (95% CI 0.64-1.09), p=0.19



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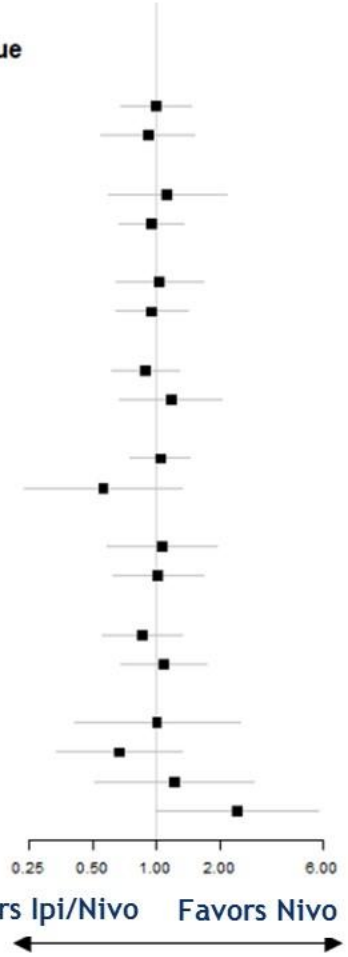
Abstract 9014: Lung MAP: Nivo vs Ipi/Nivo in previously treated squamous lung cancer: subgroup analyses

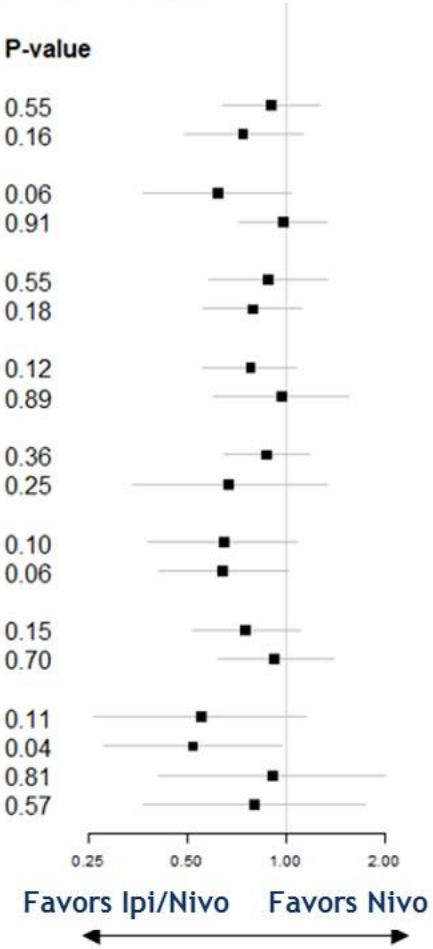
Overall Survival

	Nivo+Ipi Events/N	Nivo Events/N	HR (95% CI)	P-value
AGE				
Age 65+	52/77	53/76	0.99 (0.68,1.46)	0.97
Age Less than 65	29/48	34/51	0.91 (0.55,1.49)	0.70
PERFORMANCE STATUS				
Zubrod 0	20/36	18/35	1.12 (0.59,2.12)	0.73
Zubrod 1	61/89	69/92	0.95 (0.67,1.34)	0.77
SMOKING STATUS				
Current Smoker	30/48	38/54	1.03 (0.64,1.67)	0.90
Former/Never Smoker	51/77	49/73	0.94 (0.64,1.40)	0.77
SEX				
Male	55/83	63/86	0.88 (0.61,1.27)	0.50
Female	26/42	24/41	1.17 (0.67,2.03)	0.59
PRIOR THERAPY				
One Prior Line	72/106	72/105	1.04 (0.75,1.44)	0.84
Two+ Prior Lines	9/19	15/22	0.56 (0.24,1.32)	0.19
PD-L1				
PD-L1 5+	25/39	19/31	1.06 (0.58,1.92)	0.86
PD-L1 <5	25/37	46/54	1.01 (0.62,1.65)	0.97
TMB				
TMB 10+	40/66	42/62	0.86 (0.56,1.32)	0.48
TMB <10	35/50	38/53	1.08 (0.68,1.71)	0.74
TMB AND PD-L1				
TMB 10+ and PD-L1 5+	12/22	8/15	1.00 (0.41,2.45)	0.99
TMB 10+ and PD-L1 <5	14/24	22/25	0.67 (0.34,1.31)	0.24
TMB <10 and PD-L1 5+	11/14	10/14	1.21 (0.51,2.87)	0.67
TMB <10 and PD-L1 <5	9/10	21/25	2.40 (1.00,5.78)	0.05



Progression Free Survival

	Nivo+Ipi Events/N	Nivo Events/N	HR (95% CI)	P-value
AGE				
Age 65+	66/77	65/76	0.90 (0.64,1.27)	0.55
Age Less than 65	42/48	47/51	0.74 (0.49,1.13)	0.16
PERFORMANCE STATUS				
Zubrod 0	30/36	31/35	0.62 (0.37,1.03)	0.06
Zubrod 1	78/89	81/92	0.98 (0.72,1.34)	0.91
SMOKING STATUS				
Current Smoker	41/48	48/54	0.88 (0.58,1.34)	0.55
Former/Never Smoker	67/77	64/73	0.79 (0.56,1.12)	0.18
SEX				
Male	72/83	78/86	0.78 (0.56,1.07)	0.12
Female	36/42	34/41	0.97 (0.60,1.55)	0.89
PRIOR THERAPY				
One Prior Line	93/106	91/105	0.87 (0.65,1.17)	0.36
Two+ Prior Lines	15/19	21/22	0.67 (0.34,1.33)	0.25
PD-L1				
PD-L1 5+	31/39	29/31	0.65 (0.38,1.08)	0.10
PD-L1 <5	31/37	51/54	0.64 (0.41,1.01)	0.06
TMB				
TMB 10+	54/66	54/62	0.75 (0.52,1.10)	0.15
TMB <10	46/50	48/53	0.92 (0.62,1.39)	0.70
TMB AND PD-L1				
TMB 10+ and PD-L1 5+	16/22	14/15	0.55 (0.26,1.15)	0.11
TMB 10+ and PD-L1 <5	19/24	24/25	0.52 (0.28,0.97)	0.04
TMB <10 and PD-L1 5+	13/14	13/14	0.91 (0.41,2.01)	0.81
TMB <10 and PD-L1 <5	9/10	23/25	0.80 (0.37,1.75)	0.57



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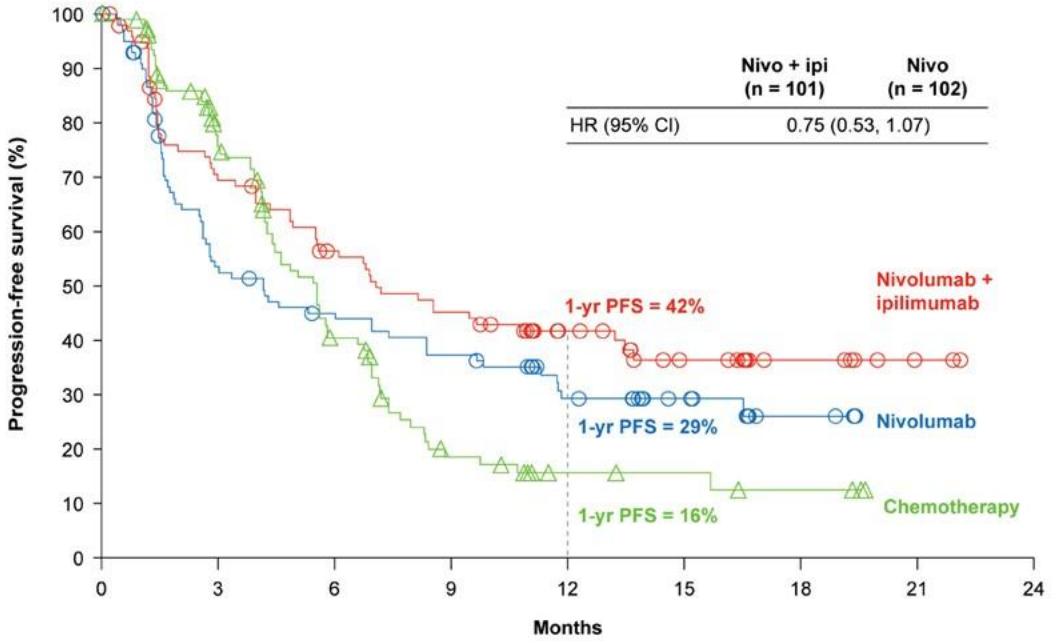
Rationale for PD-1 + CTLA-4 blockade in high TMB NSCLC

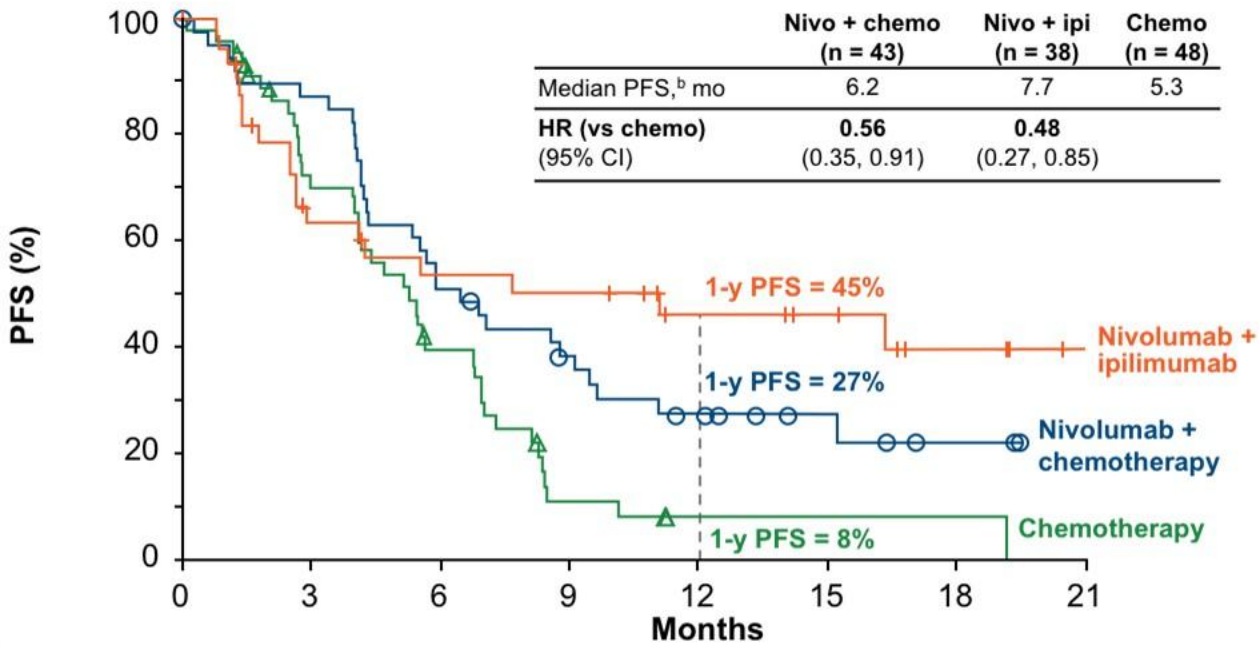
Checkmate-227: PFS With Nivo+Ipi vs Nivo vs Chemo in Patients With TMB ≥10 and PD-L1≥1%



HR for Ipi/Nivo vs Nivo = 0.75 (91% CI 53-1.07)

Hellmann et al. NEJM. 2018

Checkmate-227: PFS With Nivo+Ipi vs Nivo+chemo vs Chemo in Patients With TMB ≥10, PD-L1 <1%



Borghaei et al. ASCO 2018

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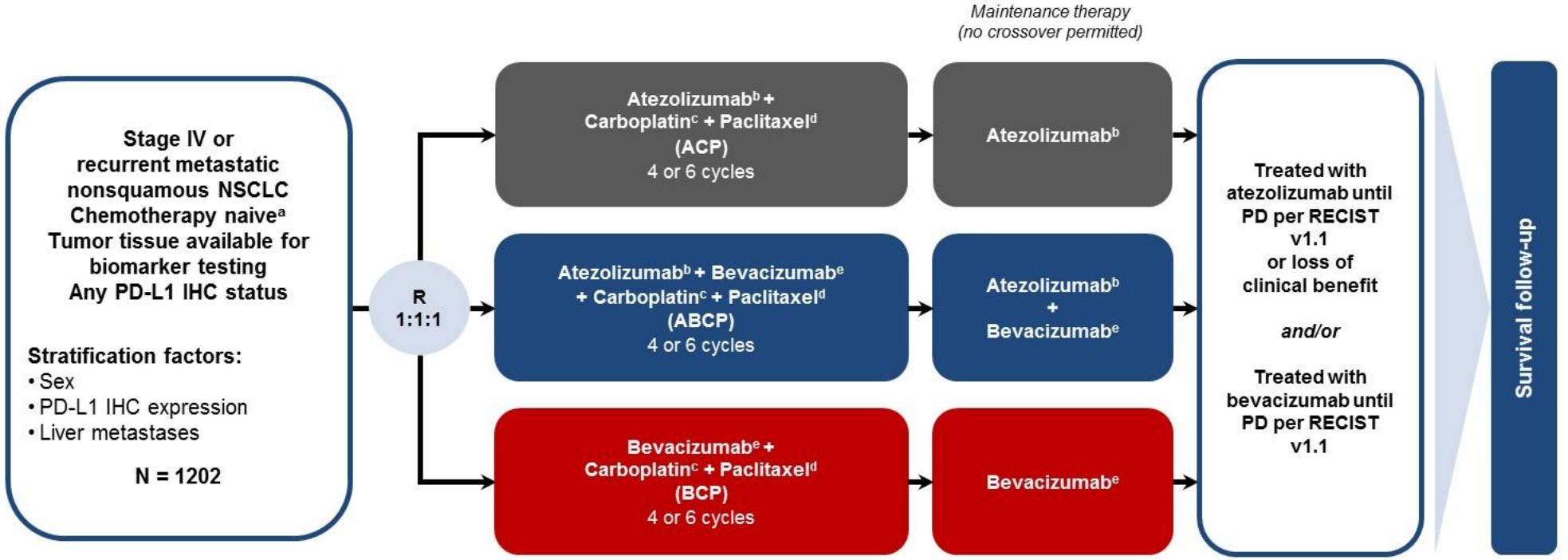
Abstract 9012: IMpower150: Analysis of efficacy in patients with liver metastases: Study Design



Co-primary objectives

- Investigator-assessed PFS in ITT-WT
- Investigator-assessed PFS in Teff-high WT
- OS in ITT-WT

This analysis explored: efficacy (PFS, OS, ORR, DOR) and safety of the ABCP regimen in patients with liver metastases at baseline

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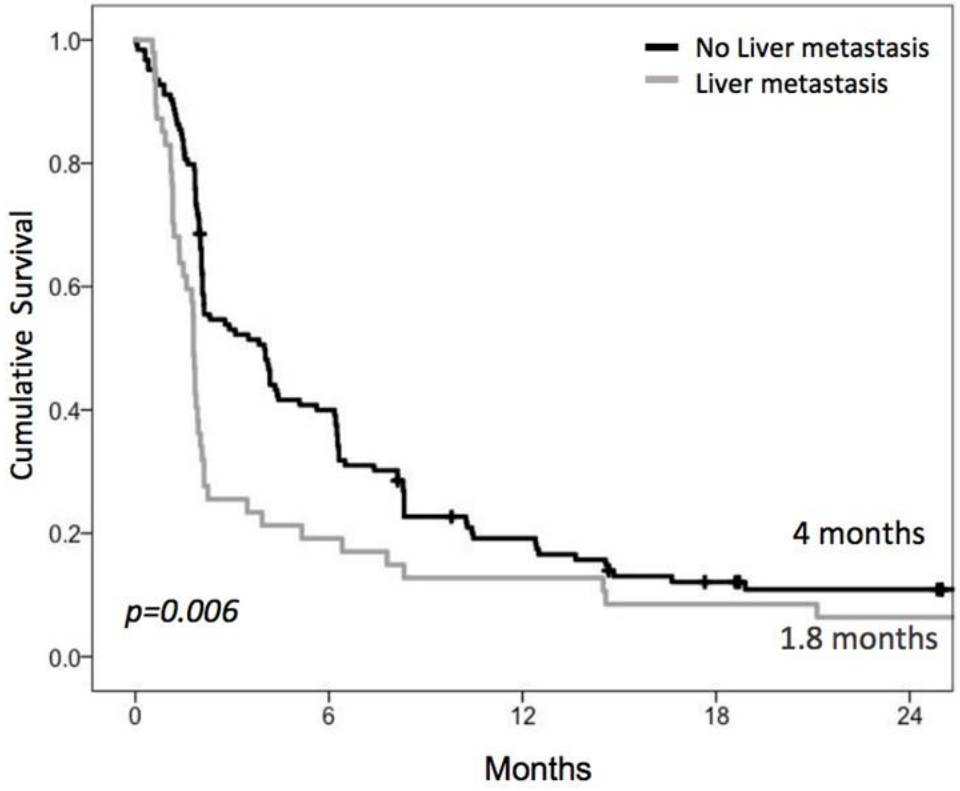
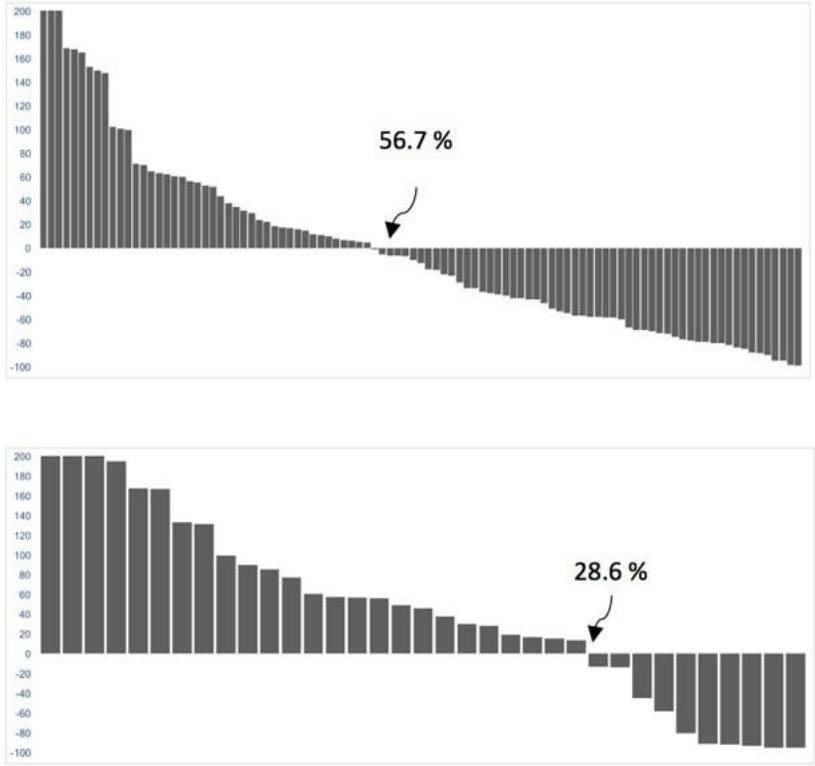
Are PD-1/L1 Inhibitors Effective in Patients with Liver Metastases?

PFS shorter in NSCLC patients with liver mets



Overall Response Rate Lower in Patients with Liver Mets



Tumeh et al. Cancer Immunology Research. May 2017

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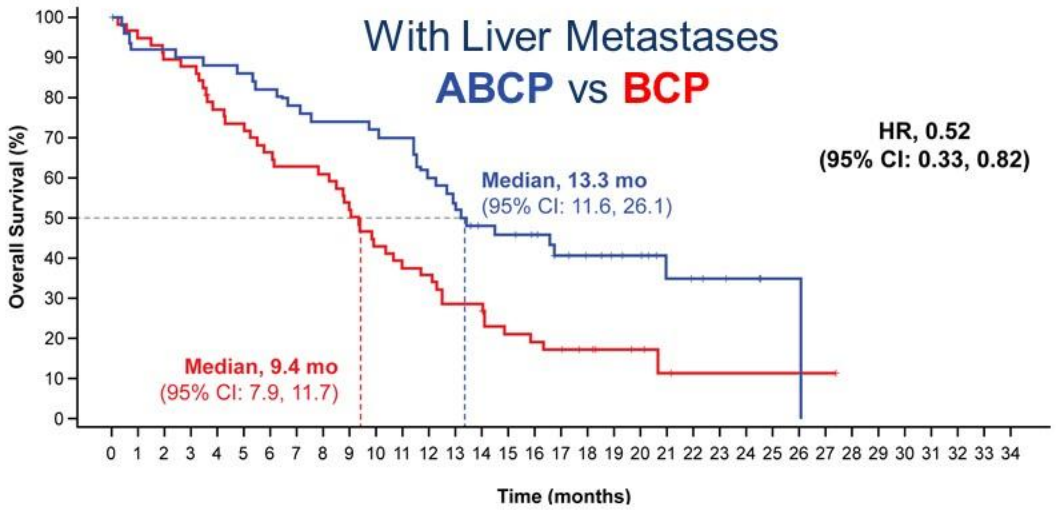
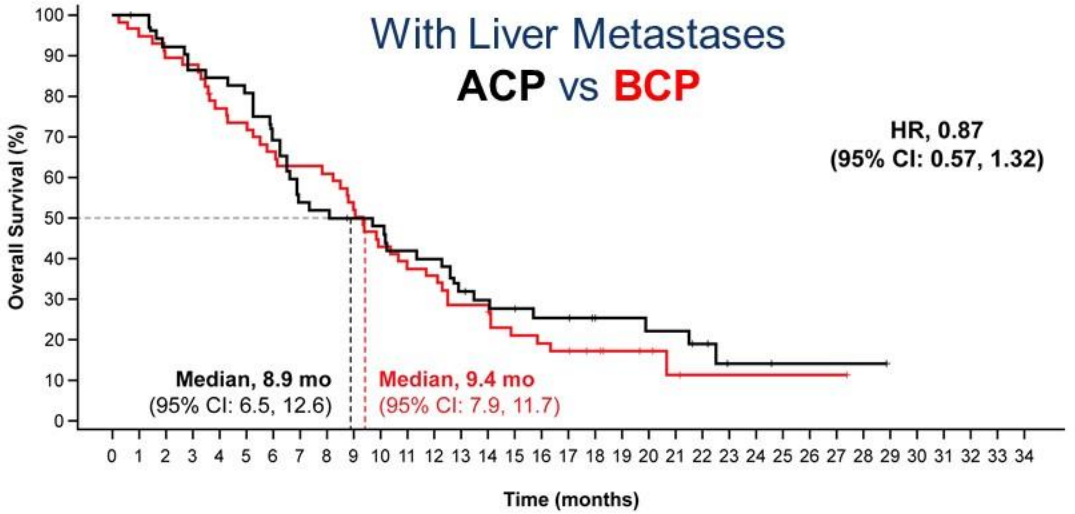
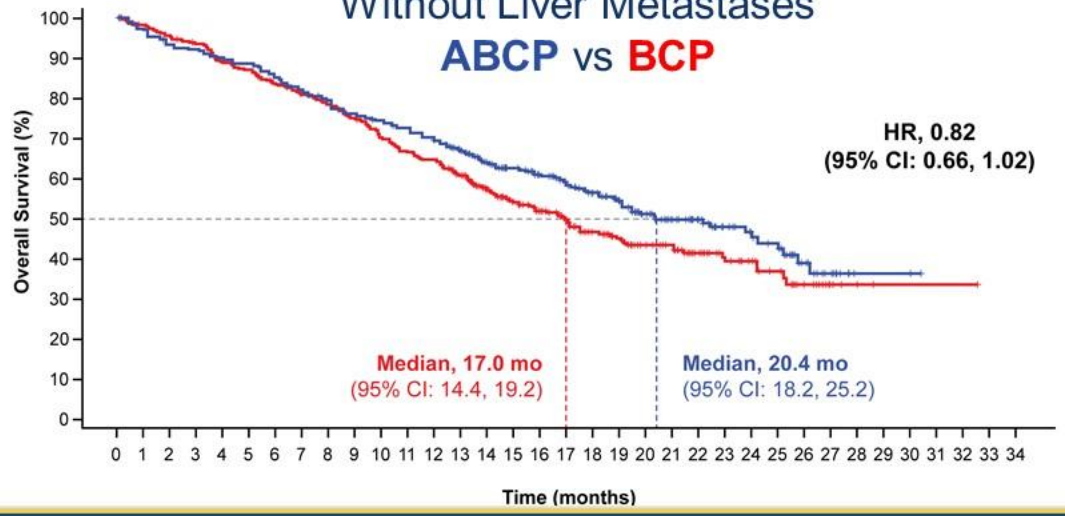
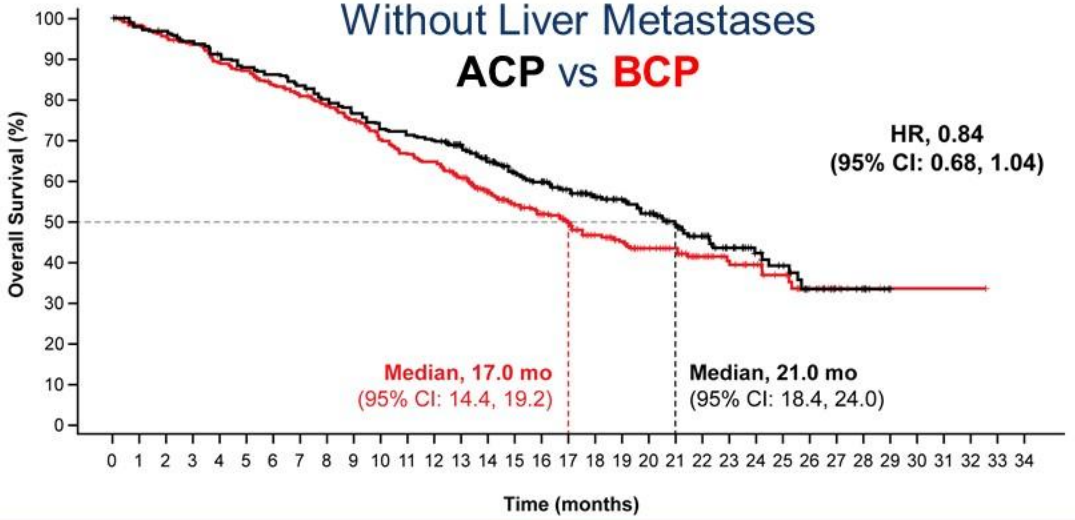
Abstract 9012: IMpower150: Analysis of efficacy in patients with liver metastases: Overall Survival









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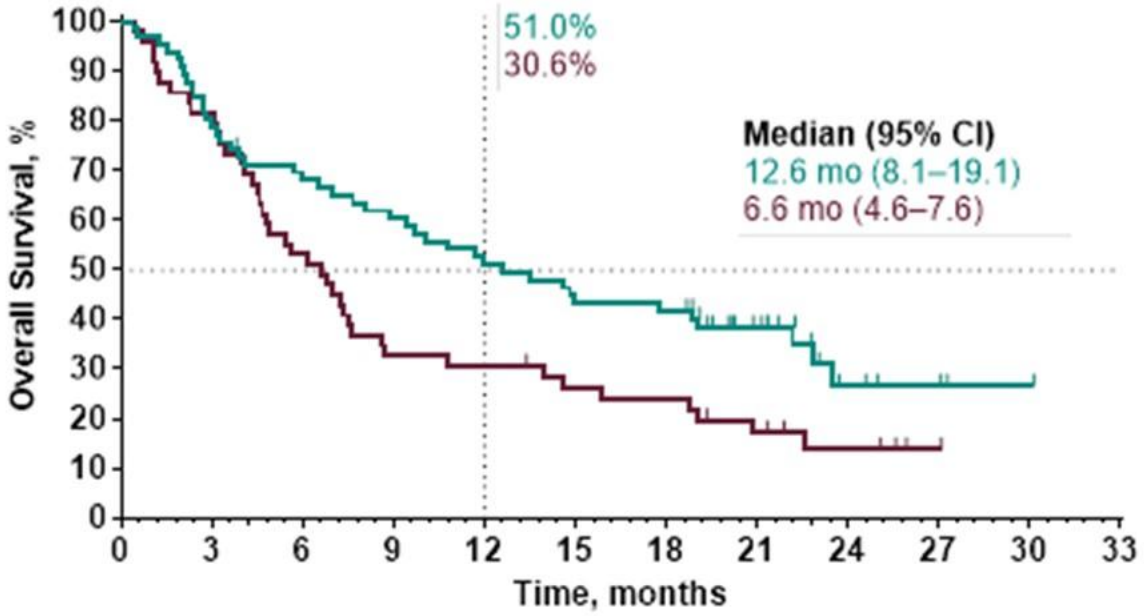
Potential impact of liver metastases in other IO clinical trials: KEYNOTE-189 subgroup analysis

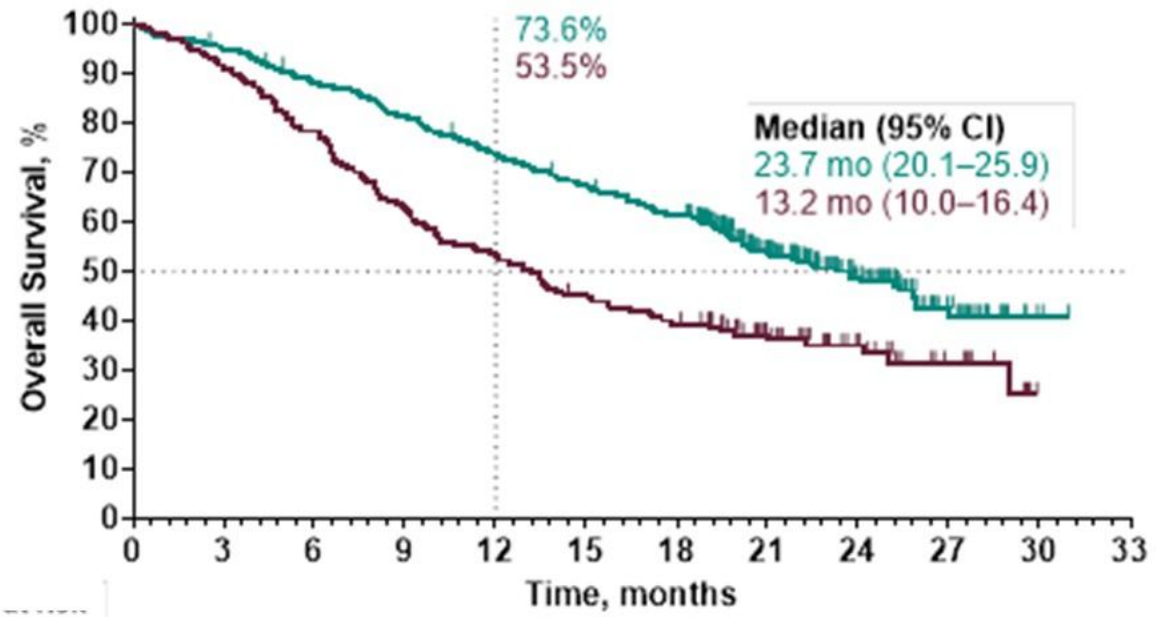
With Liver Metastases

	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	43 (65.2)	0.62 (0.39–0.98)
Placebo/Pem/Plat	41 (83.7)	



Without Liver Metastases

	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	170 (49.4)	0.58 (0.45–0.74)
Placebo/Pem/Plat	103 (65.6)	



Garassino et al. AACR. 2019

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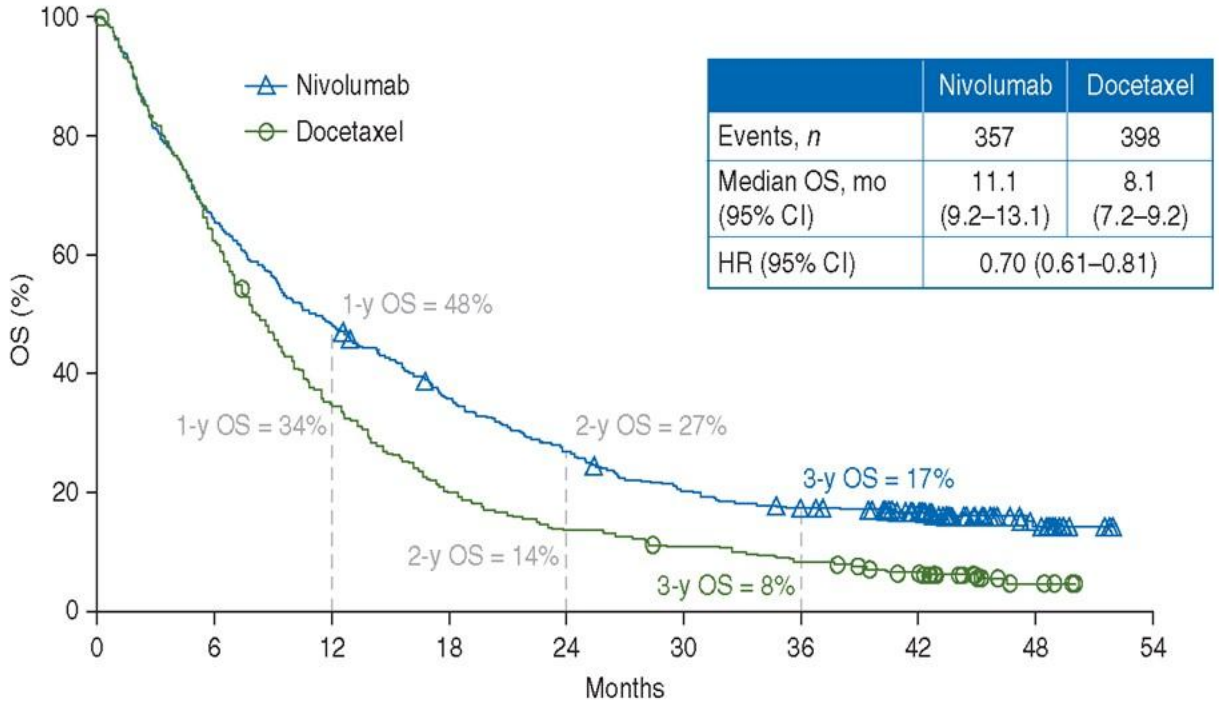
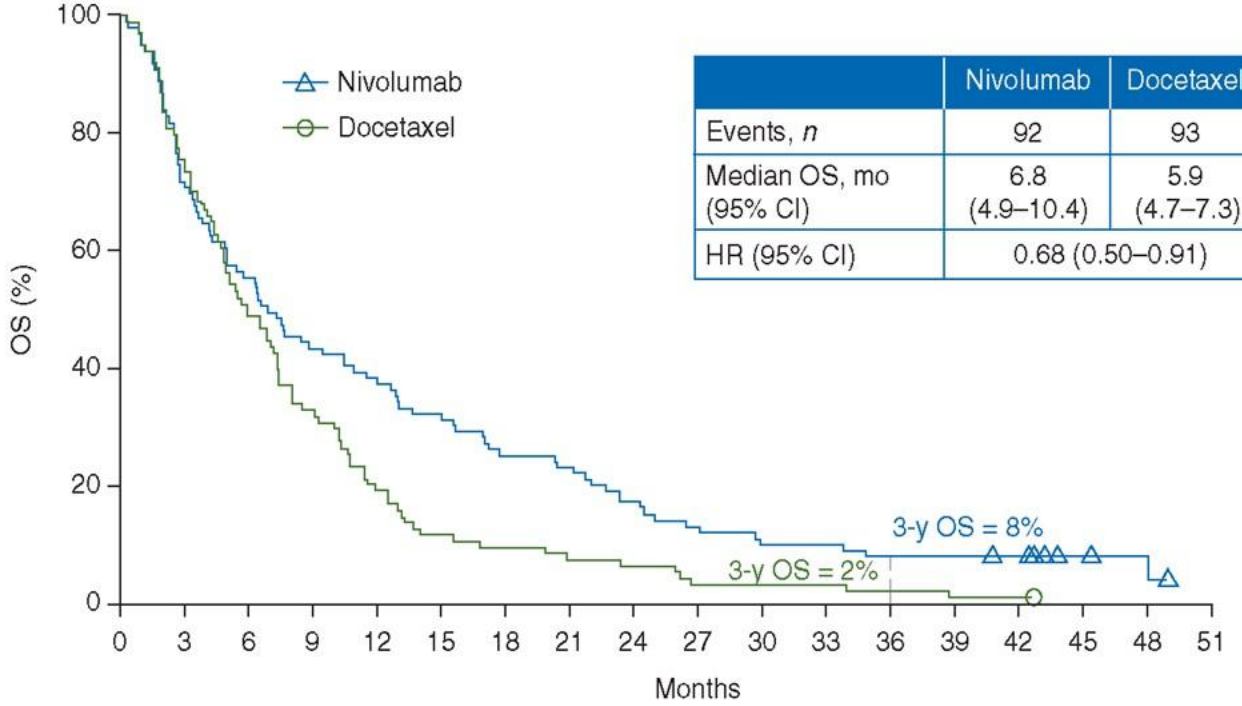
Potential impact of liver metastases in other IO clinical trials: nivolumab subgroup analysis

Overall Study Population



	Nivolumab	Docetaxel
Events, *n*	357	398
Median OS, mo (95% CI)	11.1 (9.2–13.1)	8.1 (7.2–9.2)
HR (95% CI)	0.70 (0.61–0.81)	

Patients with Liver Metastases



	Nivolumab	Docetaxel
Events, *n*	92	93
Median OS, mo (95% CI)	6.8 (4.9–10.4)	5.9 (4.7–7.3)
HR (95% CI)	0.68 (0.50–0.91)	

Vokes et al. Annals of Oncology. April 2018

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Abstract 9012: IMpower150: Analysis of efficacy in patients with liver metastases: Conclusions

- Presence of liver metastases is associated with a poor prognosis in patients with NSCLC
- Stratification in clinical trials based on presence of liver metastases is reasonable
- No clear evidence thus far in randomized trials that patients with liver mets should be treated differently than patients without liver mets

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Abstract 9013: KEYNOTE-189: Updated OS and progression after 2nd line of therapy (PFS2): Conclusions

- Updated analysis continues to show PFS and OS benefit in patients treated with pembro/plat/peme vs plat/peme
- Benefits seen across all PD-L1 subgroups
- 1/3 of patients died without having received 2nd line therapy

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Parsing the Data for Checkpoint Inhibitors in 2019: Take Home Message

- Durable responses continue to impress with PD-1 monotherapy
- Future trials for ipi/nivo vs nivo may be best focused on high TMB/low PD-L1 subset of patients
- Chemotherapy + PD-1/L1 inhibitor continues to be optimal first line therapy in patients with NSCLC PD-L1 <50%
  - →Benefits extend to patients with liver metastases
- 5 year overall survival rates are a realistic endpoint in patients with NSCLC

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Sonst noch was????

Efficacy and safety profile of Lurbinectedin in second-line SCLC patients: results from a phase II single-agent trial

Paz Ares L.[1];Trigo JM.[2]; Besse B.[3]; Moreno V.[4]; Lopez R.[5]; Sala MA.[6]; Ponce S.[1]; Fernandez C.[7]; Siguero M.[7]; Kahatt C.[7]; Zeaiter A.[7]; Zaman K.[8]; Boni V.[9]; Arrondeau J.[10]; Martinez M.[11]; Delord JP.[12]; Awada A.[13]; Kristeleit R.[14]; Olmedo ME.[15]; Subbiah V.[16]

Hospital Universitario Doce de Octubre, Madrid, Spain[1]; Hospital Universitario Virgen de la Victoria, Málaga, Spain[2]; Gustave Roussy Cancer Campus, Villejuif, France[3]; Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain[4]; Hospital Clínico Universitario de Santiago de Compostela, Santiago De Compostela, Spain[5]; Hospital Universitario de Basurto, Bilbao, Spain[6]; PharmaMar, Colmenar Viejo, Spain[7]; University Hospital CHUV, Lausanne, Switzerland[8]; START Madrid-CIOCC, Hospital Universitario Sanchinarro, Madrid, Spain[9]; Hôpital Cochin, Paris, France[10]; Complejo Hospitalario de Navarra, Pamplona, Spain[11]; Institut Claudius Regaud, Toulousse, France[12]; Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium[13]; UCL Cancer Institute, London, United Kingdom[14]; Hospital Universitario Ramón y Cajal , Madrid, Spain[15]; Md. Anderson Cancer Center, Houston, USA[16]

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PRESENTED BY: Dr. Luis Paz Ares

Presented By David Harpole at 2019 ASCO Annual Meeting

Disease background: SCLC – A high unmet medical need

- SCLC is an aggressive malignancy with dismal prognosis; the 5-year survival rate is less than 7%
- Topotecan is the only FDA-approved treatment in 20 years in 2L SCLC, for platinum-sensitive disease
  - The use of this drug is challenging due to its modest clinical benefit (ORR=5-24%; mOS=6-8 months) and significant hematological toxicity
- Recently, several new agents failed to demonstrate benefit in the 2L setting
- Lurbinectedin antitumor activity in SCLC was initially observed in a Phl/II study in combination with doxorubicin (ORR 37% and DoR 5.2 months)[1]
- SCLC is a transcription-addicted tumor[2]. Recently four molecular SCLC subtypes have been described, defined by differential expression of four key *transcription regulators*[3]

[1] Forster et al. P1.12-20. IASLC 2018
[2] Christensen et al. Cancer Cell 2014
[3] Rudin et al. Nature 2019

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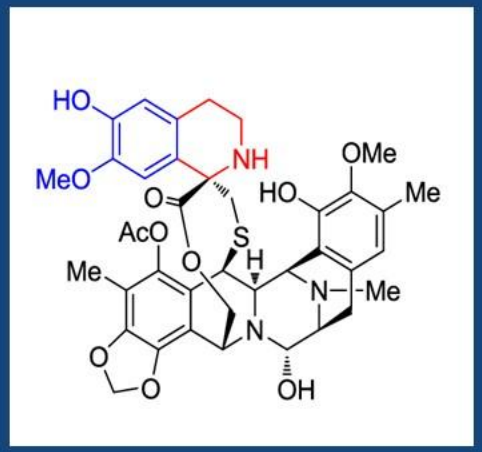
Lurbinectedin

Lurbinectedin is a synthetic analog of trabectedin

Natural marine-based tetrahydroisoquinoline antitumor agent

Inhibitor of activated transcription in preclinical studies

Signals of activity in SCLC with lurbinectedin/chemo combination phase 1 studies[1, 2]



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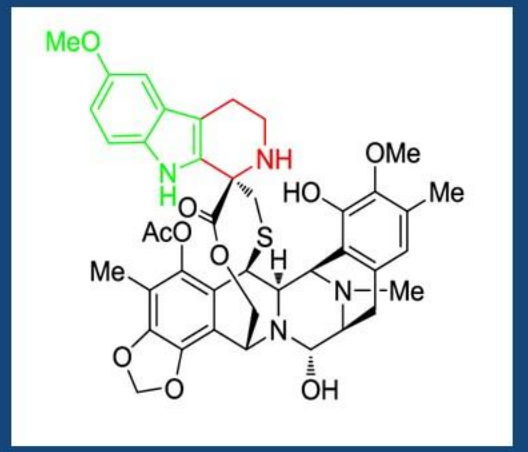

LURBINECTEDIN

[1]Calvo et al., Ann Oncol. 2017 Oct 1;28(10):2559-2566; [2]Olmedo et al., ESMO 2017.

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Lurbinectedin as Single Agent in SCLC: Phase II BASKET Trial

Primary Objective : ORR by RECIST v.1.1 (confirmed responses)

SCLC patients:

- One prior chemotherapy line
- Active CNS mets excluded
- PS 0-2

➢ **Lurbinectedin 3.2 mg/m², 1h iv, q3wk**

≥ 2 responses in first 15 patients*

Enroll up to 100 patients

* 5 confirmed response observed in the first 15 treated patients

Data cut-off: January 15th 2019

Statistical assumptions for SCLC cohort

Null hypothesis :
≤15% get a response
($p \leq 0.15$)

Alternative hypothesis:
≥30% get a response
($p \geq 0.30$)

Statistical power 95%

≥ 23% of confirmed responses needed to reject the null hypothesis

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Key points

This study met its primary endpoint

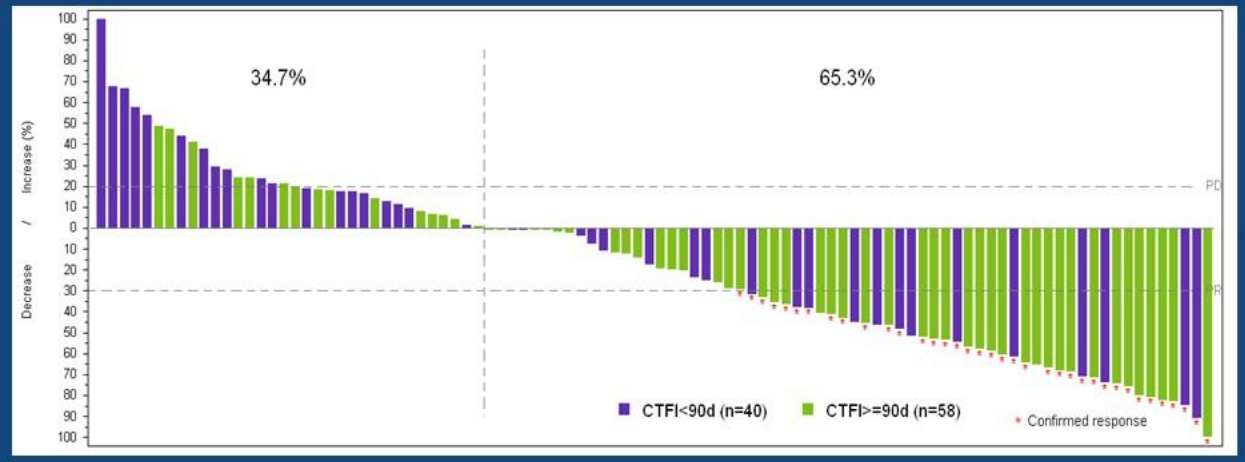
ORR 35.2%

Other efficacy endpoints:

mDOR 5.3 months

mPFS 3.9 months

mOS 9.3 months



How do these numbers compare to historical topotecan data?

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	Lurbinectedin (n=105)	Von Pawel 2014: Topotecan (n=213)[1]	Von Pawel 2014: Amrubicin (n=424)[1]	CheckMate 331: Chemotherapy (n=285)[2]	CheckMate 331: Nivolumab (n=284)[2]
ORR (%)	**35.2**	**16.9**	**31.1**	**16.5**	**13.7**
ORR sens (%)	45.0	23.1	40.9		
ORR res (%)	22.2	9.4	20.1		
mPFS	**3.9 m**	**3.5 m**	**4.1 m**	**3.8 m**	**1.4 m**
mPFS sens	4.6 m	4.3 m	5.5 m		
mPFS res	2.6 m	2.6 m	2.8 m		
mOS	**9.3 m** 95% CI 6.3-11.8	**7.8 m** 95% CI 6.6-8.5	**7.5 m** 95% CI 6.8-8.5	**8.4 m** 95% CI 7.0-10.0	**7.5 m** 95% CI 5.6-9.2
mOS sens	11.9 m	9.9 m	9.2 m	11.1 m	7.6 m
mOS res	5.0 m	6.2 m	5.7 m	5.7 m	7.0 m

✓ Efficacy appears comparable, if not superior, to historical studies.

[1]Von Pawel et al., JCO 2014: 32(35) 4012-2019; [2]Reck et al., ESMO IO 2018, abstract 489. Chemotherapy control arm was topotecan or amrubicin.

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Presented By David Harpole at 2019 ASCO Annual Meeting

Abstract 8517

Randomized phase 2 study of maintenance pemetrexed (Pem) versus observation (Obs) for patients (pts) with malignant pleural mesothelioma (MPM) without progression after first-line chemotherapy: Cancer and Leukemia Group B (CALGB) 30901 (Alliance)

Arkadiusz Z. Dudek, Xiaofei F. Wang, Lin Gu, Tom Stinchcombe, Robert Arthur Kratzke, Everett E. Vokes, Hedy L. Kindler

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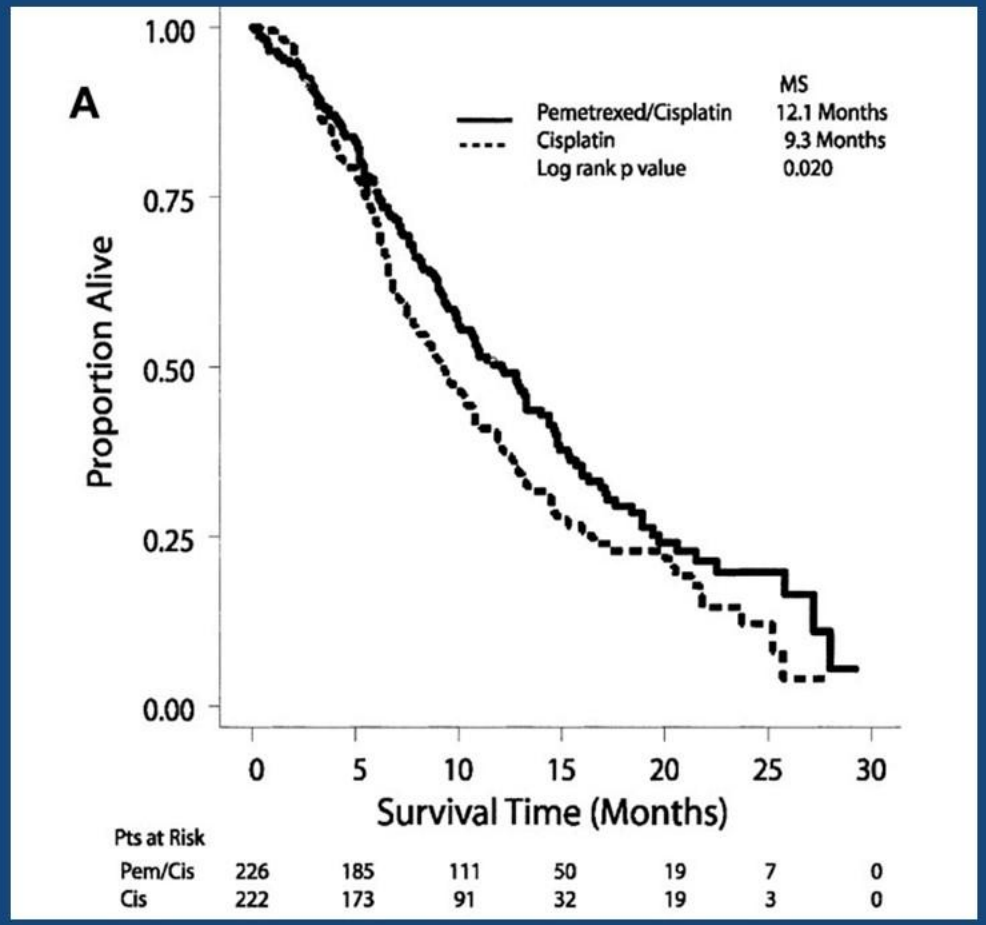
Presented By Aaron Mansfield at 2019 ASCO Annual Meeting

Cisplatin and pemetrexed

- Cisplatin and pemetrexed improved overall survival compared to cisplatin (HR 0.77)[1]
- Median of 6 cycles, range of 1-12 cycles administered
- Addition of bevacizumab to cisplatin and pemetrexed improves survival and is in NCCN guidelines but is not FDA approved[2]



1. Vogelzang et al *Journal of Clinical Oncology* 2003
2. Zalcman et al *Lancet* 2016

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Abstract 8517 - Dudek et al

- **Objective**: To determine if maintenance therapy with pemetrexed improves PFS in MPM patients who have at least stable disease after completion of first-line pemetrexed plus cisplatin or carboplatin

- Patients were treated initially with pemetrexed plus either cisplatin or carboplatin for 4-6 cycles at the discretion of the treating physician.
- Patients who achieved at least stable disease were randomized 1:1 to pemetrexed or observation
- Stratified by first-line regimen, histology and number of first-line cycles

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Abstract 8517 - Dudek et al

- 72 patients from 30 sites enrolled 12/2010 to 6/2016
- The study closed early due to slow accrual after 53 patients were randomized (initial goal was 63 patients).
- 49 eligible patients are included in the efficacy analysis
  - (27 pemetrexed, 22 observation)
- With 47 events observed at the time of final analysis, the trial has approximately 86% power to detect a 100% improvement in PFS (3 mo v 6 mo), corresponding to HR=0.5 as used in the original study design, at a 1-sided significance level of 0.01.

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	Observation (N=22)	Pemetrexed (N=27)	p value
Age at Randomization			0.3071[1]
Median (range)	70 (39-85)	70 (52-87)	
Gender			0.4492[2]
Male	15 (68.2%)	21 (77.8%)	
Race			0.4499[2]
White	21 (95.5%)	23 (85.2%)	
Black/African American	0 (0.0%)	1 (3.7%)	
Unknown	1 (4.5%)	3 (11.1%)	
Performance status			0.6471[2]
0	6 (27.3%)	9 (33.3%)	
1	16 (72.7%)	18 (66.7%)	
Histology			0.4026[2]
Biphasic	2 (9.1%)	6 (22.2%)	
Sarcomatoid	3 (13.6%)	2 (7.4%)	
Epithelial	17 (77.3%)	19 (70.4%)	
WBC			0.5957[1]
Median (range)	6.7 (4.1-12.5)	6.0 (2.9-15.9)	
Platelets			0.2933[1]
Median (range)	222 (48-759)	216 (101-599)	
First-line chemotherapy			0.9154[2]
Pemetrexed + Cisplatin	6 (27.3%)	7 (25.9%)	
Pemetrexed + Carboplatin	16 (72.7%)	20 (74.1%)	
Number of Cycles Administered			0.9441[2]
4	12 (54.5%)	16 (59.3%)	
5	1 (4.5%)	1 (3.7%)	
6	9 (40.9%)	10 (37.0%)	

[1]Unequal Variance T-Test [2]Chi-Square

Maintenance pemetrexed:
Median 4 cycles (range 1-33)
6/27 (22.2%) required dose modification

Grade 3/4 AE at least possibly related to pemetrexed

	Grade 3	Grade 4
Anemia	2 (8%)	0 (0%)
Lymphopenia	2 (8%)	0 (0%)
Neutropenia	0 (0%)	1 (4%)
Thrombocytopenia	1 (4%)	0 (0%)
Infection	2 (8%)	0 (0%)
Hyperglycemia	2 (8%)	0 (0%)
Fatigue	1 (4%)	0 (0%)
Hypernatremia	1 (4%)	0 (0%)

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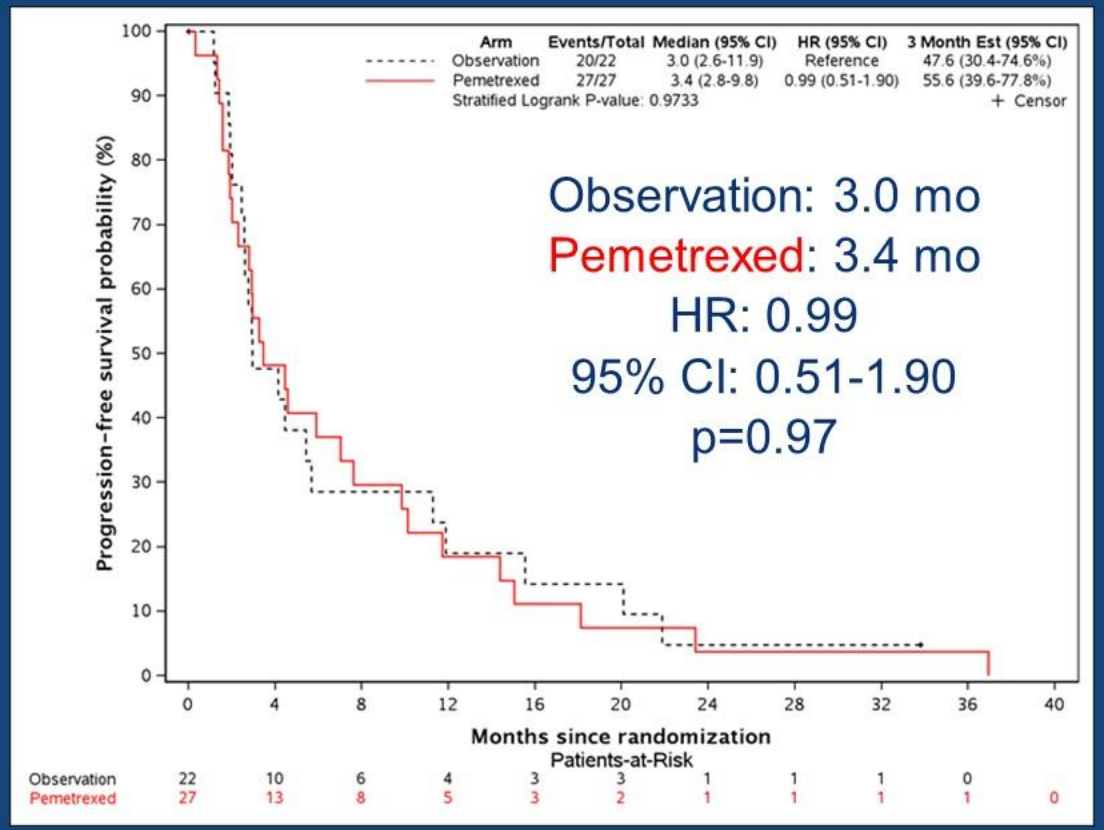
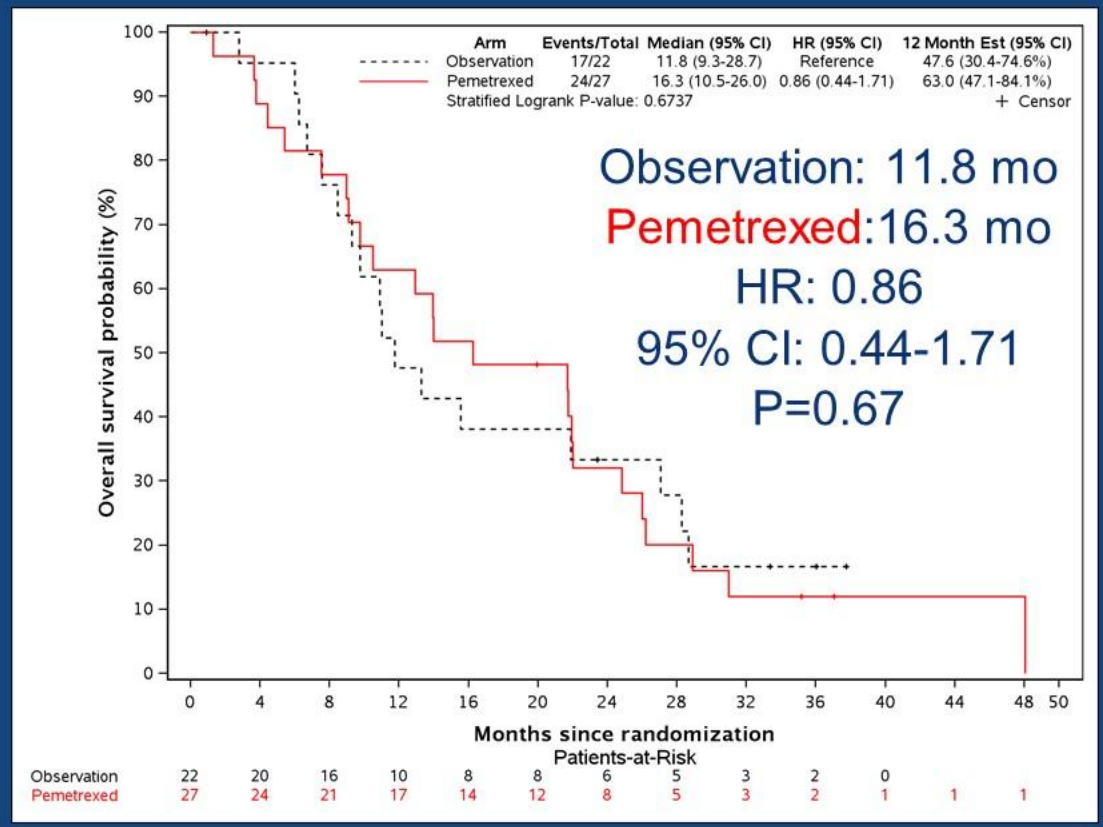
Abstract 8517 - Dudek et al

Progression free survival



Overall survival



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1

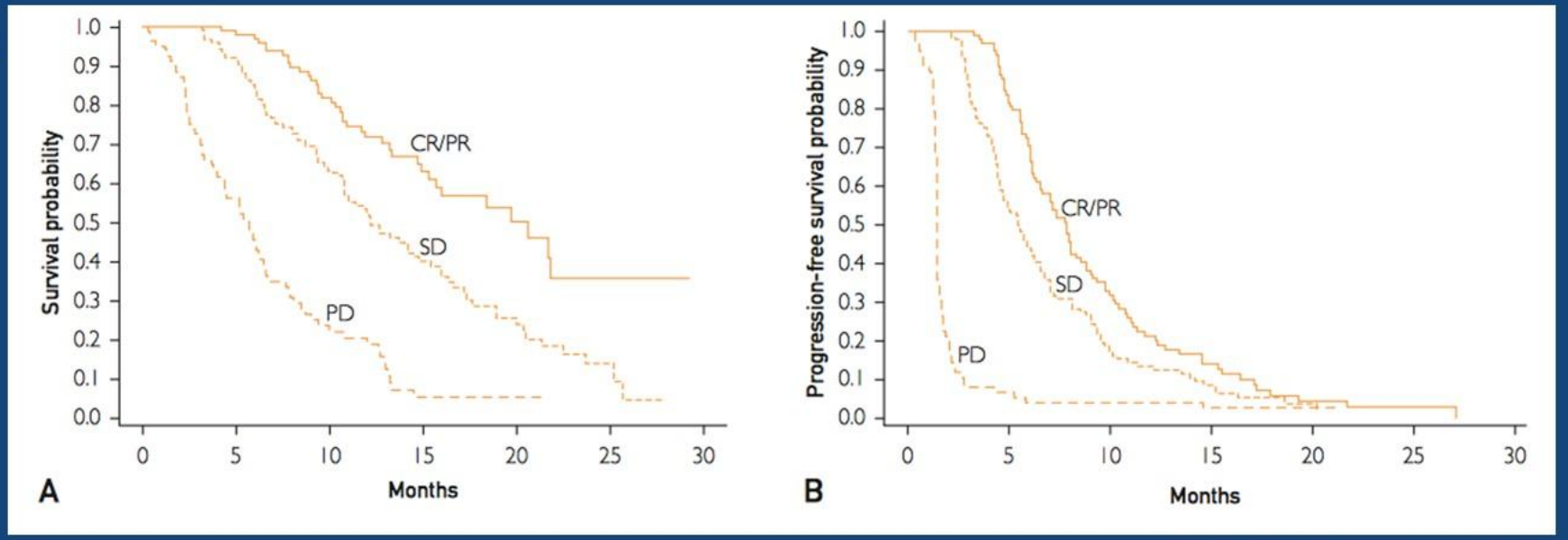
Best response to maintenance/observation

	Observation (N=21)	Pemetrexed (N=27)
Complete	0 (0%)	1 (3.7%)
Partial	0 (0%)	2 (7.4%)
Stable	14 (66.6%)	12 (44.4%)
Progression	6 (28.6%)	12 (44.4%)
Non CR/Non PD	1 (4.8%)	0 (0.0%)
Response rate (95% CI)	0 (0,0)	11.1 (2.4, 29.2)

† One patient's tumor response is unavailable due to withdrawal consent to all follow-up

* Fisher's exact test on response rate between two arms, two-sided: p =0.2423

2



1. Dudek et al Abstract 8517
2. Mansfield et al *Mayo Clinic Proceedings* 2018

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Abstract 8517 - Conclusions

- Trial was closed prematurely due to slow accrual
- These results are not supportive of the use of maintenance pemetrexed in mesothelioma
- Ongoing trials may change frontline approaches
  - Study of Nivolumab Combined With Ipilimumab Versus Pemetrexed and Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma Patients (CheckMate743 - NCT02899299)
  - Chemo-immuno approaches are in development (NCT03228537)

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Abstract 8518 – Hasegawa et al

A feasibility study of induction pemetrexed plus cisplatin followed by pleurectomy/decortication for malignant pleural mesothelioma (Japan Mesothelioma Interest Group 1101 Trial)

Seiki Hasegawa, Kohei Yokoi, Morihito Okada, Fumihiro Tanaka, Mototsugu Shimokawa, Takashi Daimon, Takashi Nakano

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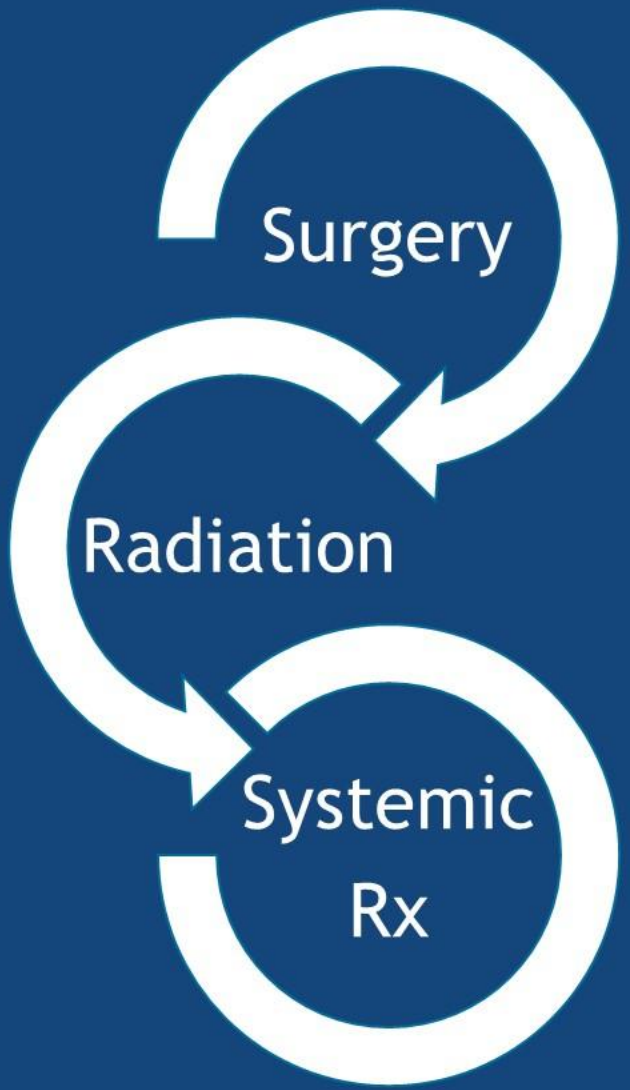

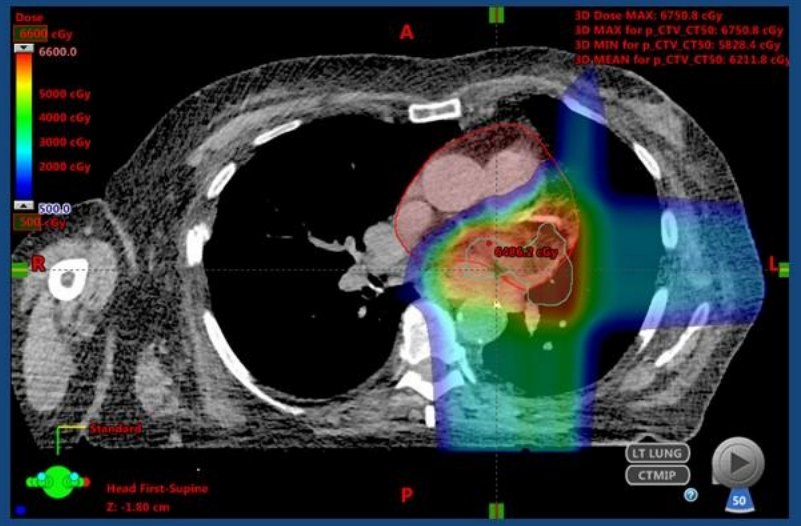

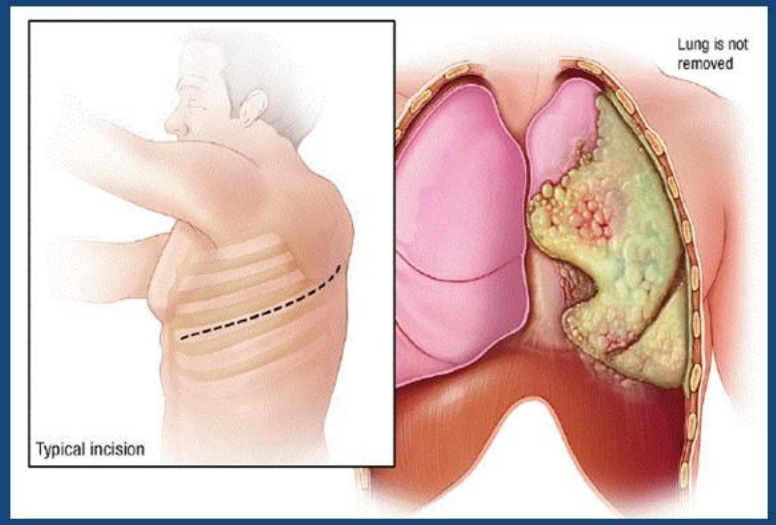

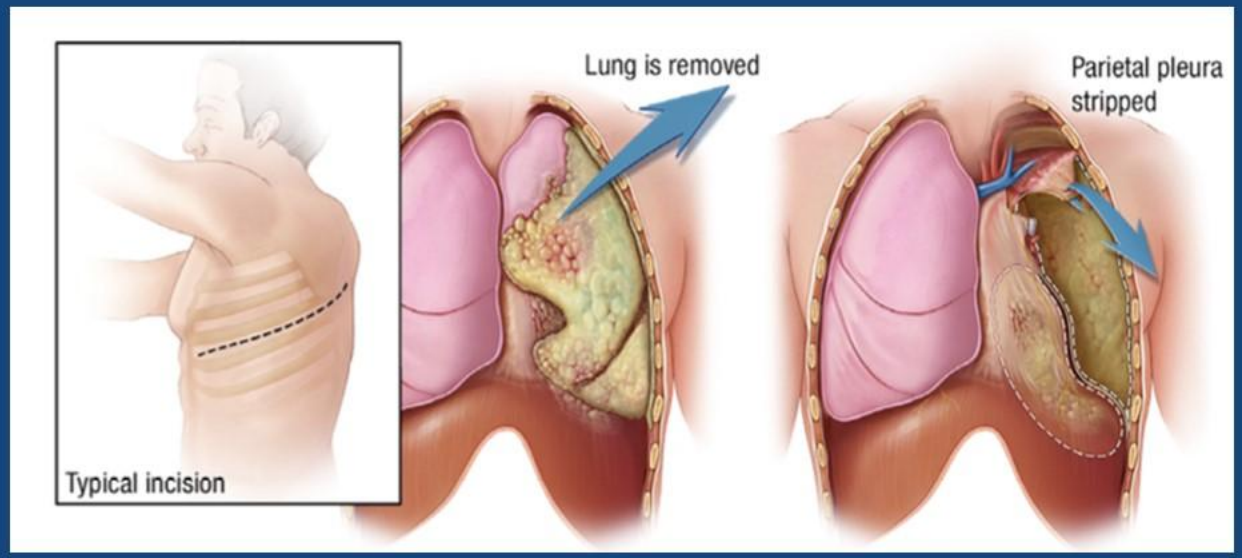

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Abstract 8518 – Hasegawa et al

Objective: Evaluate feasibility of multimodality therapy for patients with resectable mesothelioma

Primary endpoint: Macroscopic Complete Resection

Induction chemotherapy with cisplatin and pemetrexed for 3 cycles

Surgery (pleurectomy/decortication) within 42 days of completion of chemotherapy (conversion to EPP allowed)

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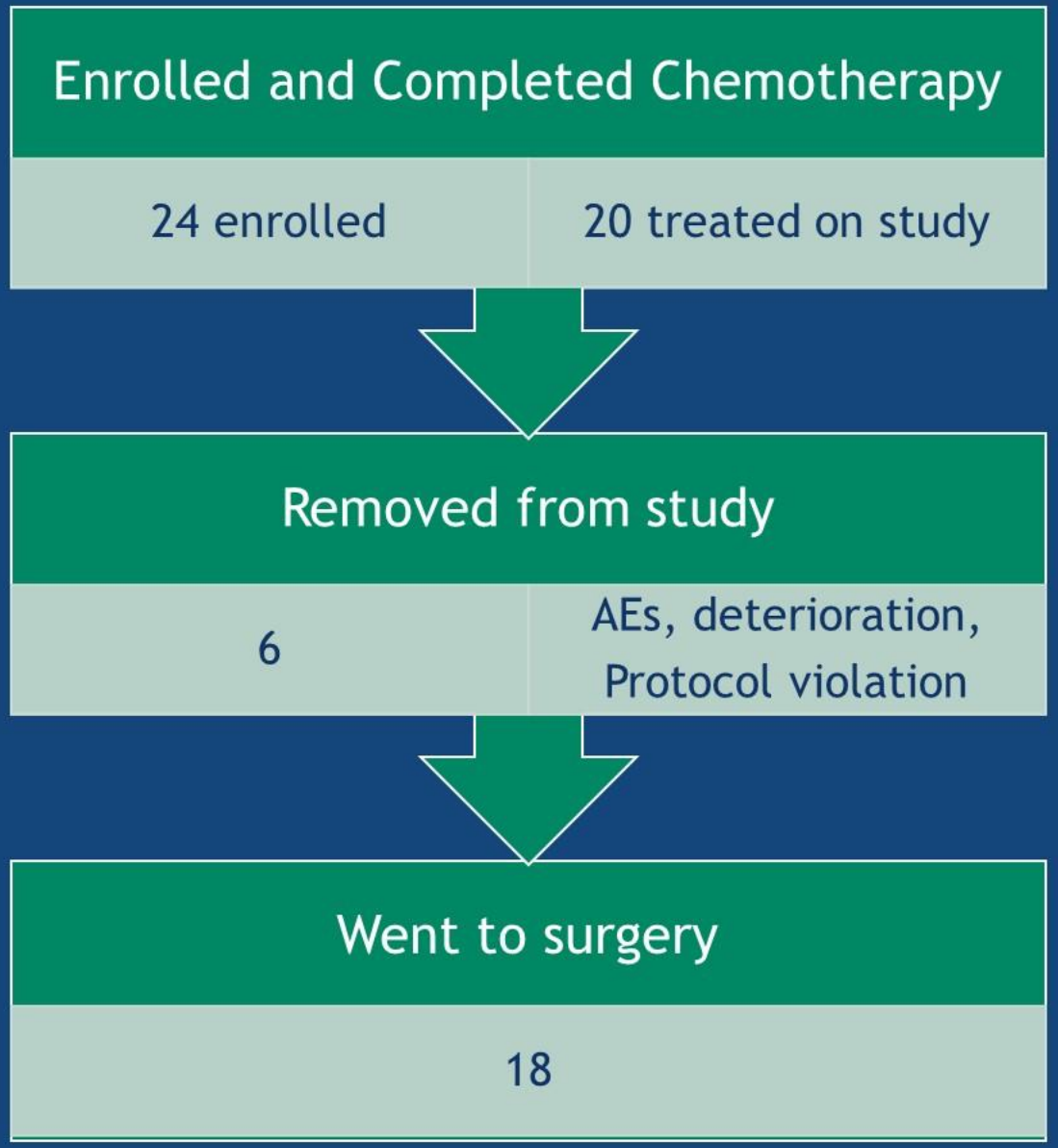
Abstract 8518

Table 1. Patient characteristics

Characteristics		No. of patient	(%)
Age	Median 67 (Range 48-74)		
Sex	Male	19	79.2
	Female	5	20.8
Location			
	Right	17	70.8
	Left	7	29.2
Histology			
	Epithelial	19	79.2
	Biphasic	4	16.7
	Sarcomatoid	0	0.0
	Desmoplastic	1	4.2
Performance Status			
	0	18	75.0
	1	6	25.0
IMIG Clinical stage (ver.7)			
	T1aN0M0	2	8.3
	T1bN0M0	7	29.2
	T2N0M0	9	37.5
	T2N1M0	2	8.3
	T3N0M0	3	12.5
	T3N2M0	1	4.2



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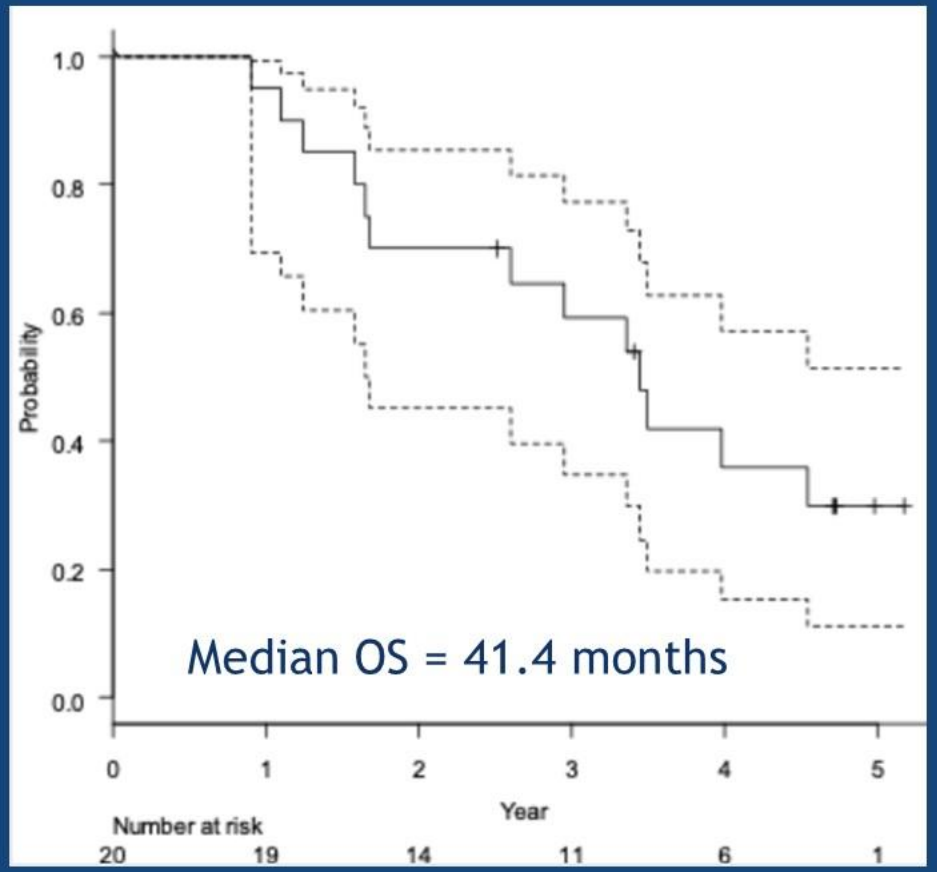
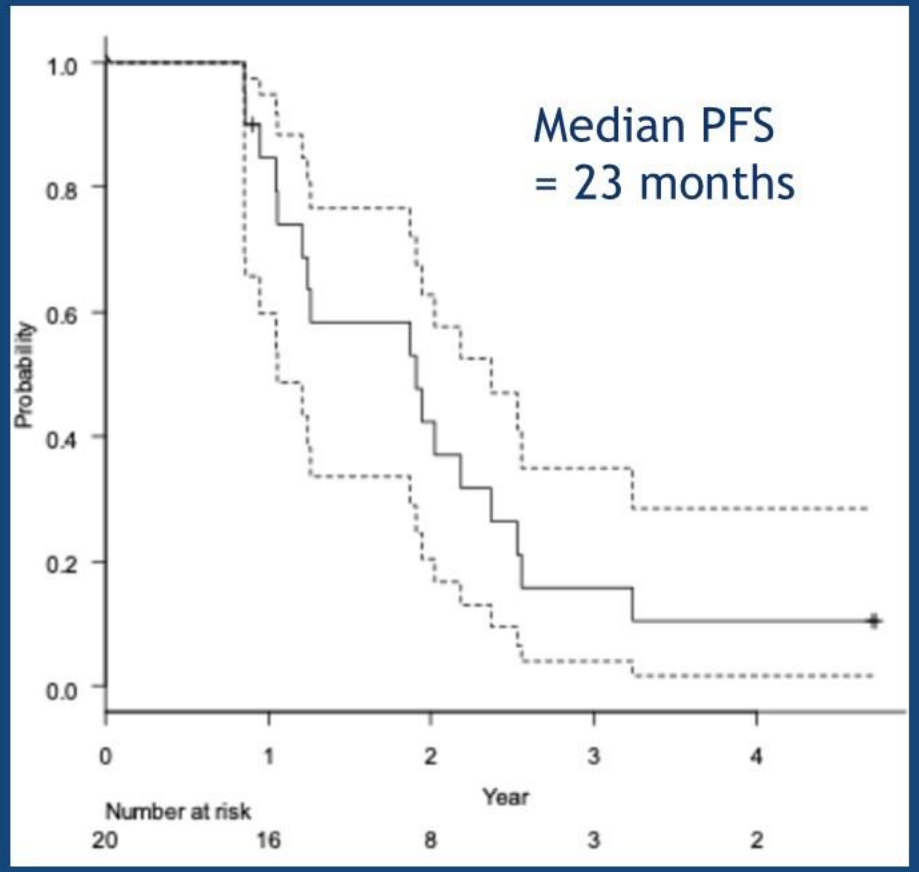
18/20 (90%) with macroscopic complete resection
18/24 (75%) enrolled who went to surgery
No treatment-related 30- or 90- day mortality





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Abstract 8518 – Conclusions

- Pre-operative/Neo-adjuvant chemotherapy is feasible for select patients
  - 25% of patients may no longer be eligible for surgery upon completion of chemo
  - This is similar to the rate of progressive disease with cisplatin/pemetrexed[1]
- Macroscopic Complete Resection achieved in all surgical patients
- Compared to prior experience for this same group, reduced peri-operative mortality than seen with extrapleural pneumonectomy
- Randomized trials are still needed to define optimal sequence of treatments and surgical approaches

1. Mansfield et al *Mayo Clinic Proceedings* 2018

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Fazit

- Cisplatin/Pemetrexed ist äquivalent zu Cisplatin/Vinorelbine als Adjuvante Chemotherapie
- Risikofaktoren in Frühstadium NSCLC
- EGFR TKI+ Chemotherapie verlängert nicht das DFS
- Immuntherapie
- Neue Targets und Therapien für Resistanzmutationen
- Neoadjuvante Chemotherapie hat eine Rolle im malignen Mesotheliom

THE
END