



Multidisciplinary Tumour Board

How do we approach oligoprogressive disease?

Cycle 28 pemetrexed maintenance therapy and one enlarging adrenal gland



Filippo de Marinis

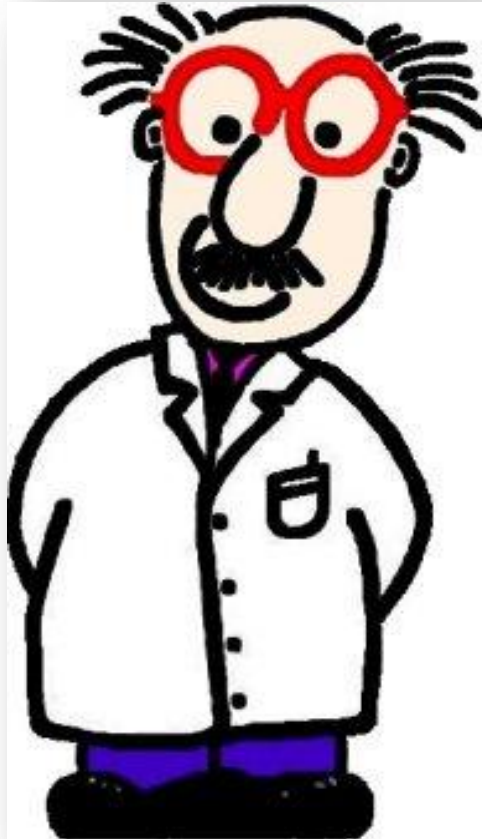
Thoracic Oncology Division, European Institute of Oncology, Milan, Italy

DISCLOSURE

- NO conflicts of interest
- NO grants, research supports, consultation fees or honoraria from ELI LILLY, in the last 5 ys.

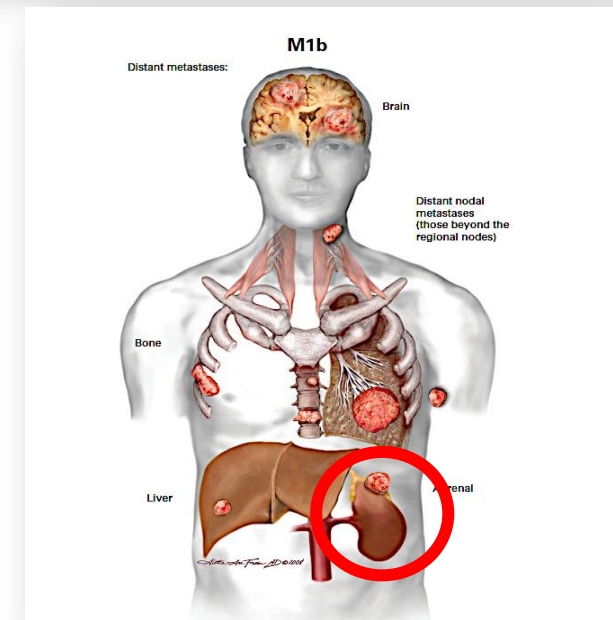
THE HYPOTHETICAL CASE REPORT

Cycle 28 pemetrexed maintenance therapy and one enlarging adrenal gland



- ✓ Adenocarcinoma
- ✓ Female
- ✓ Current smoker
- ✓ < 70 ys
- ✓ No concomitant diseases
- ✓ Metastatic cT2N2M1a (pleura)
- ✓ WT for EGFR/ALK
- ✓ PS 1
- ✓ Induction with Cisplatin/Pemetrexed
- ✓ Responder after 2 and stable after 4 cycles

- ✓ Stable Disease until 25th maintenance pem cycle
- ✓ Good tolerability/PS1
- ✓ Adrenal gland enlargement at 28th cycle with pain



DISTINCT COHORTS OF OLIGOMETASTATIC DISEASE

- 'oligometastases' = diagnosed with oligometastatic disease
- 'oligorecurrence' = relapsed oligometastatic disease
- 'oligoprogressive' = status after cytoreductive therapy

Specific organ metastases and survival in metastatic non-small-cell lung cancer

TOMOHIRO TAMURA¹, KOICHI KURISHIMA², KENSUKE NAKAZAWA¹, KATSUNORI KAGOHASHI³, HIROICHI ISHIKAWA², HIROAKI SATOH³ and NOBUYUKI HIZAWA¹

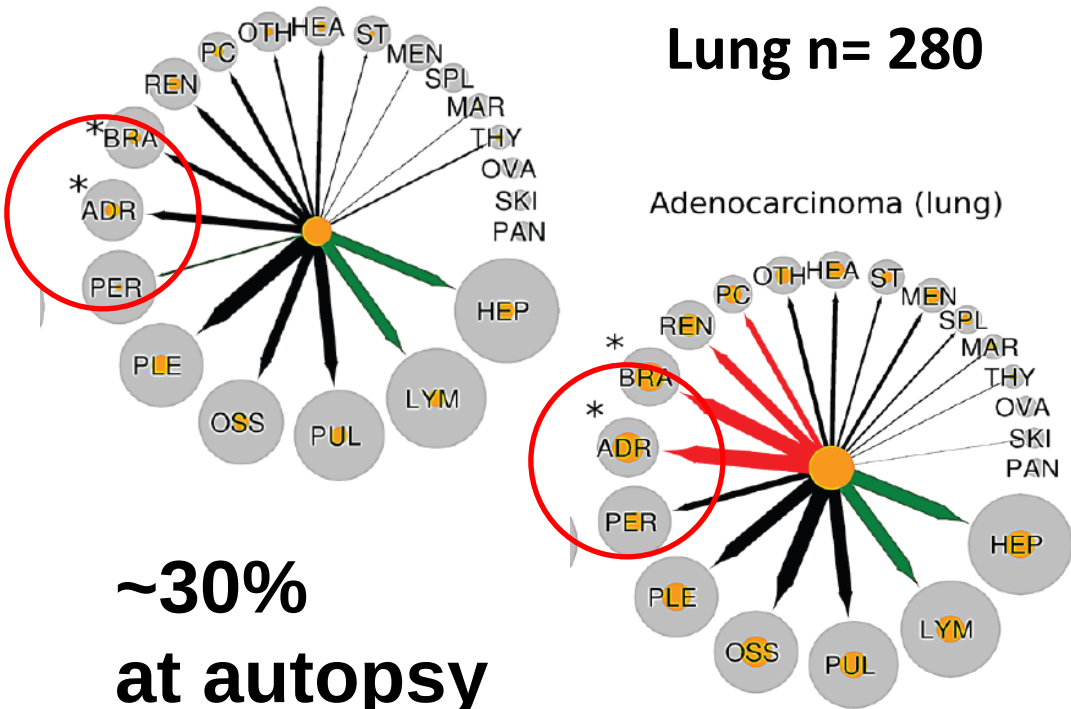
The landscape of metastatic progression patterns across major human cancers

Jan Budczies^{1,2,6,*}, Moritz von Winterfeld^{1,*}, Frederick Klauschen¹, Michael Bockmayr¹, Jochen K. Lennerz³, Carsten Denkert^{1,6}, Thomas Wolf^{4,6}, Arne Warth⁴, Manfred Dietel¹, Ioannis Anagnostopoulos¹, Wilko Weichert^{4,6,7}, Daniel Wittschieber⁵ and Albrecht Stenzinger⁴

Table I. Characteristics of 729 patients with metastatic non-small-cell lung cancer.

Characteristics	No. (%)
Metastatic site	
Pleural/pericardial fluid	283 (38.8%)
Bone	250 (34.3%)
Lungs	234 (32.1%)
Brain	207 (28.4%)
Adrenal glands	122 (16.7%)
Liver	98 (13.4%)
Extrathoracic lymph nodes	69 (9.5%)
Pleura	41 (5.6%)
Other ^a	40 (5.5%)

B Squamous cell carcinoma (lung)



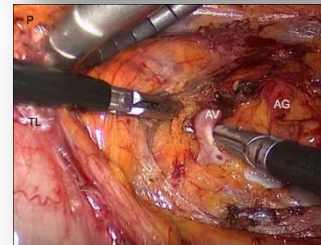
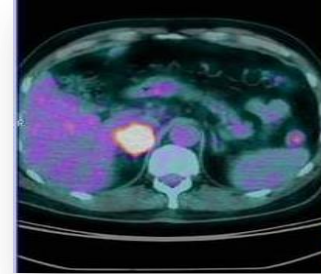
THREE «*CASES*» IN ONE !



**ADRENAL GLAND MET
TREATMENT**

ADRENAL GLAND ENLARGEMENT ISSUES....in this patient

- **IMAGING**
- **BIOPSY**
- **SURGERY**
- **SBRT**



^{18}F -FDG PET in Evaluation of Adrenal Lesions in Patients with Lung Cancer

TABLE 3

Results of Published ^{15}F -FDG PET Studies on Patients with Lung Cancer and Adrenal Lesions

Study	Year	Total no. of patients	No. of lung cancer patients	Sensitivity (%)	Specificity (%)	Accuracy (%)
Boland et al. (14)	1995	20	10	100	100	100
Erasmus et al. (16)	1997	27	27	100	80	94
Maurea et al. (15)	1999	27	—	100	93	96
Yun et al. (13)	2001	41	28	100	94	96
Gupta et al. (17)	2001	30	30	94	92	93
Present study	2004	94	94	93	90	92

TABLE 2

PET Findings and Final Diagnosis for 113 Adrenal Lesions

Biopsy/clinical follow-up finding	PET finding	
	Positive	Negative
Positive	67	5
Negative	4	37

CONCLUSION

^{18}F -FDG PET is an accurate, noninvasive technique for differentiating benign from metastatic adrenal lesions detected on CT or MRI in patients with lung cancer. In addition, PET has the advantage of assessing the primary cancer site and detecting other metastases. These results suggest the importance of ^{18}F -FDG PET in the management of these patients, especially since a solitary adrenal metastasis is considered to be treatable.

Role of endoscopic ultrasound fine-needle aspiration evaluating adrenal gland enlargement or mass



CONCLUSION: Adrenal gland EUS-FNA is safe, minimally invasive and a sensitive technique with significant impact in the management of adrenal gland mass or enlargement.

Treatment of oligometastatic NSCLC

In cases of solitary—histological proven—adrenal metastasis, prolonged survival after resection of adrenal and the primary tumor has been suggested in selected patients [II; B] [58].

58. Pfannschmidt J, Dienemann H. Surgical treatment of oligometastatic non-small cell lung cancer. *Lung Cancer* 2010; 69: 251–25

Laparoscopic Adrenalectomy for Solitary Adrenal Metastasis From Lung Cancer

Conclusion: The results obtained in this study, along with other published reports, support 4 criteria as operative indications for laparoscopic adrenalectomy in solitary adrenal metastasis from the lung: (1) the primary lung cancer is resected or can be cured by radical chemotherapy, (2) metastasis is limited to the adrenal gland only, (3) adrenal metastasis does not invade the surrounding organs, and (4) the size of the adrenal tumor does not exceed 10 cm.

STEREOTACTIC BODY RADIOTHERAPY FOR TREATMENT OF ADRENAL METASTASES

Table 1. Patient and disease characteristics

Characteristic	Value
Patients (<i>n</i>)	30
Gender (<i>n</i>)	
Male	14
Female	16
Age (y)	
Mean	61.8
Range	39.4–77.6
Primary site (<i>n</i>)	
Lung	20
Gastrointestinal	4
Breast	3
Head and neck	1
Melanoma	1
Unknown	1
Interval from primary diagnosis to adrenal metastases (mo)	
Median	8.4
Range	0–101.4
Unilateral adrenal metastases (<i>n</i>)	25
Left	14
Right	11
Bilateral adrenal metastases (<i>n</i>)	5

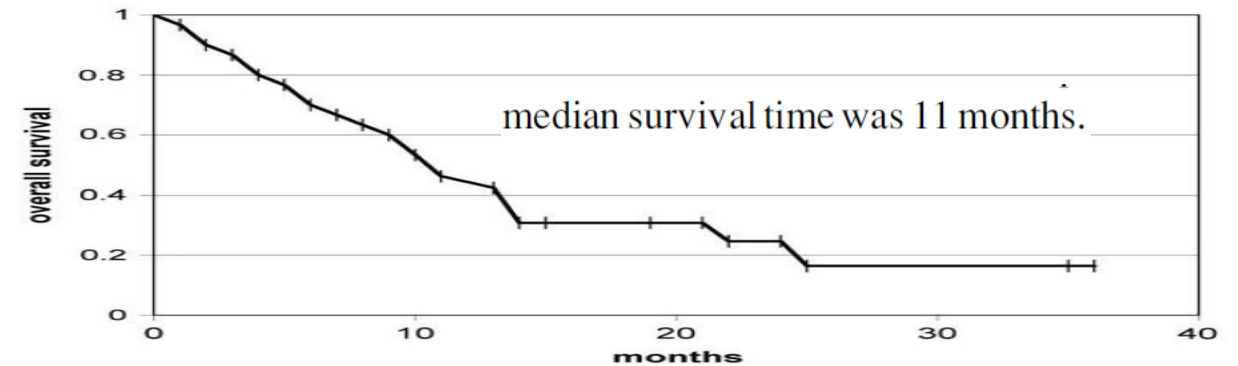


Fig. 1. Actuarial Kaplan-Meier overall survival of 30 patients treated with stereotactic body radiotherapy for adrenal metastasis.

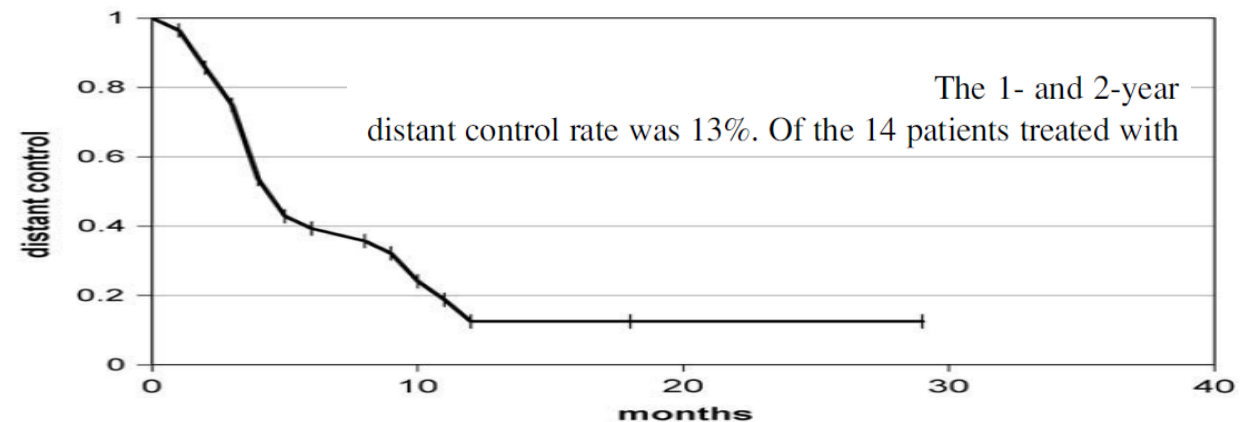


Fig. 2. Actuarial Kaplan-Meier distant control of 30 patients treated with stereotactic body radiotherapy for adrenal metastasis.

Review and Uses of Stereotactic Body Radiation Therapy for Oligometastases

FILIPPO ALONGI,^a STEFANO ARCANGELI,^a ANDREA RICCARDO FILIPPI,^b UMBERTO RICARDI,^b
MARTA SCORSETTI^a

Table 4. Summary of published trials of stereotactic body radiation therapy for adrenal metastases

Study	<i>n</i> of patients	Median dose/ <i>n</i> of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Casamassima et al. [26]	48	36 Gy/3	16.2 (3–63)	1–2 yrs, 90%	1-yr, 39.7%; 2-yr, 14.5%	1 case of grade II adrenal insufficiency
Chawla et al. [24]	30	40 Gy/10	9.8 (3.2–28.3)	1-yr, 55%	1-yr, 44%; 2-yr, 25%	Mild grade 1 fatigue and nausea, “common”
Oshiro et al. [25]	19	45 Gy/10	11.5 (5.4–87.8)	Objective response rate, 68%	1-yr, 56%; 2-yr, 33%; 3-yr, 22%	1 grade 2 duodenal ulcer
Holy et al. [54]	18	20 Gy/5 or 40 Gy/8	21	Objective response rate, 77%	Median, 23 mos	–
Torok et al. [55]	7	16 Gy/1 or 27/3	14 (1–60)	1-yr, 63%	Median, 8 mos	–

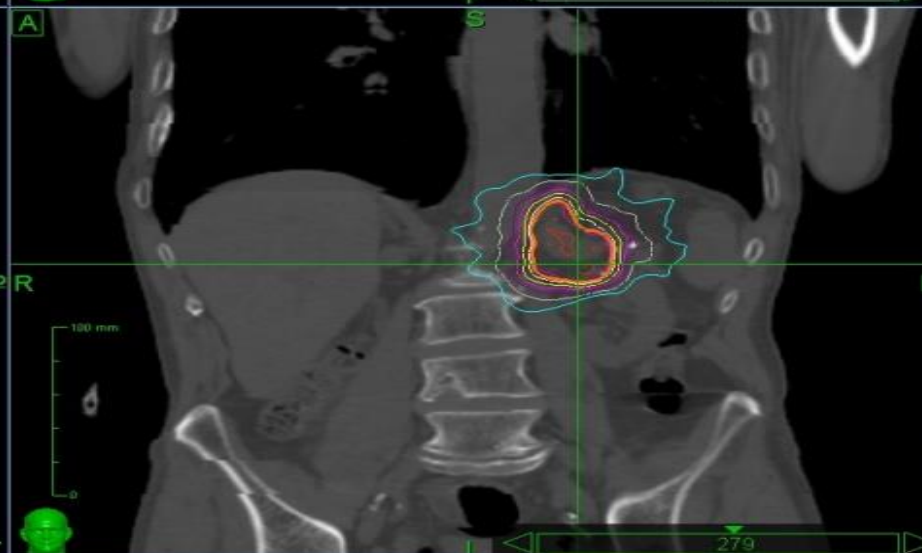
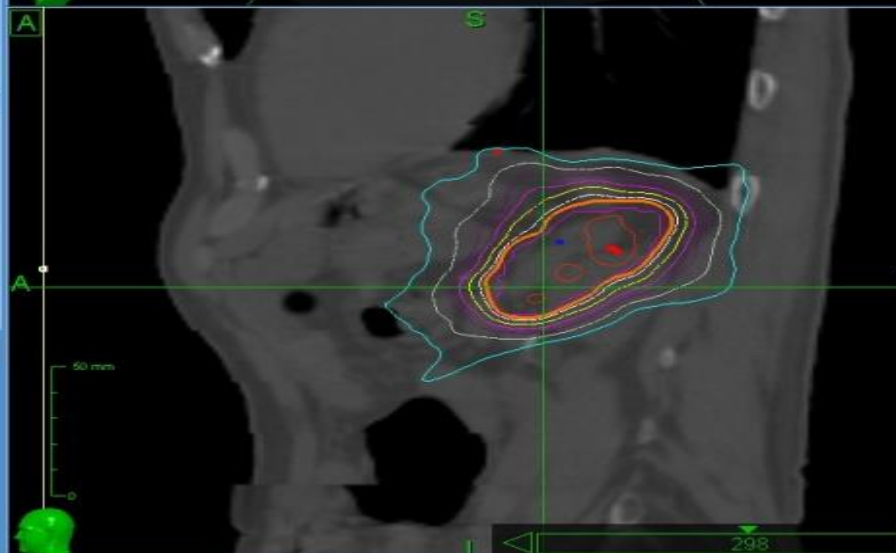
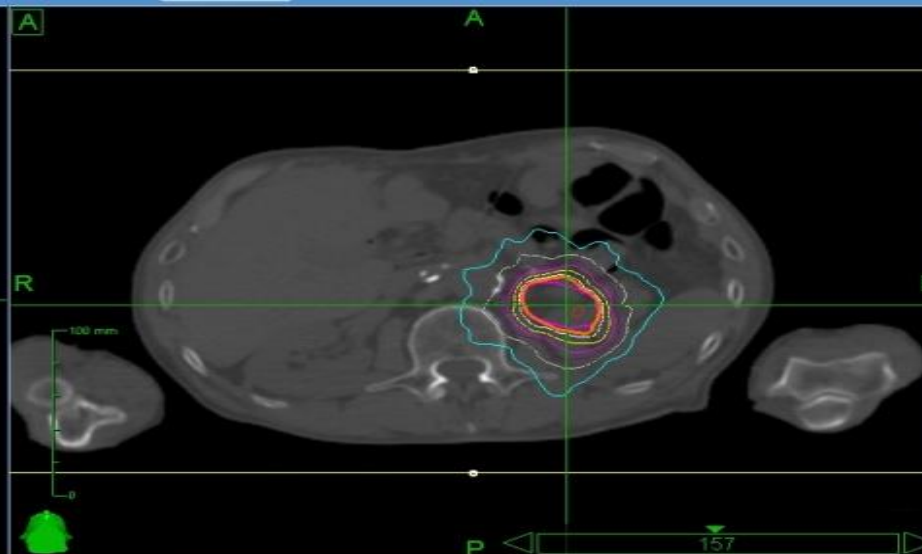
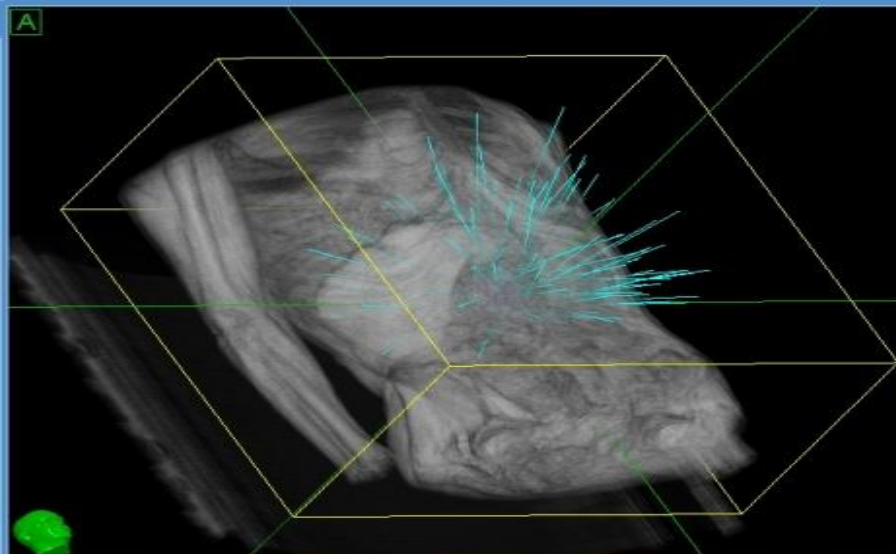
☐ Show Isocenters

Layouts

3D	DVH	3D	DVH
A	Dose	S	Dose
3D	DVH	3D	A
C	Dose	S	C

Standard Display

Plan
LesA_64n_102
06 Aug 2012, 04:23:47 PM
Rx
75%, 2000.00 cGy



X:298 Y:279 Z:157 Value:934

OUR CASE REPORT



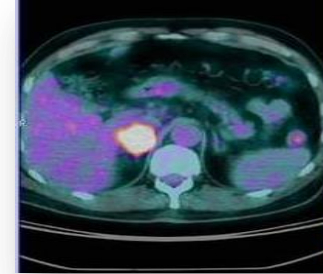
SBRT



ADRENAL GLAND ENLARGEMENT ISSUES....in this patient



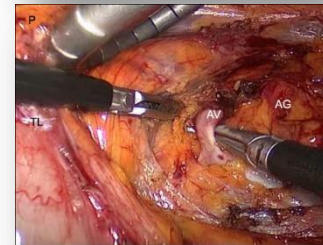
IMAGING



BIOPSY



SURGERY



SBRT



THREE «*CASES*» IN ONE !



**ADRENAL GLAND MET
TREATMENT**



Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

first-line treatment

- Pemetrexed-based combination chemotherapy represents a therapeutic option in patients with advanced non-squamous NSCLC based on the results of a recent meta-analysis that showed a slight but significant survival benefit compared with gemcitabine- or docetaxel-based combinations and of a pre-planned subgroup analysis of a large randomised phase III trial [II, A] [23, 24].

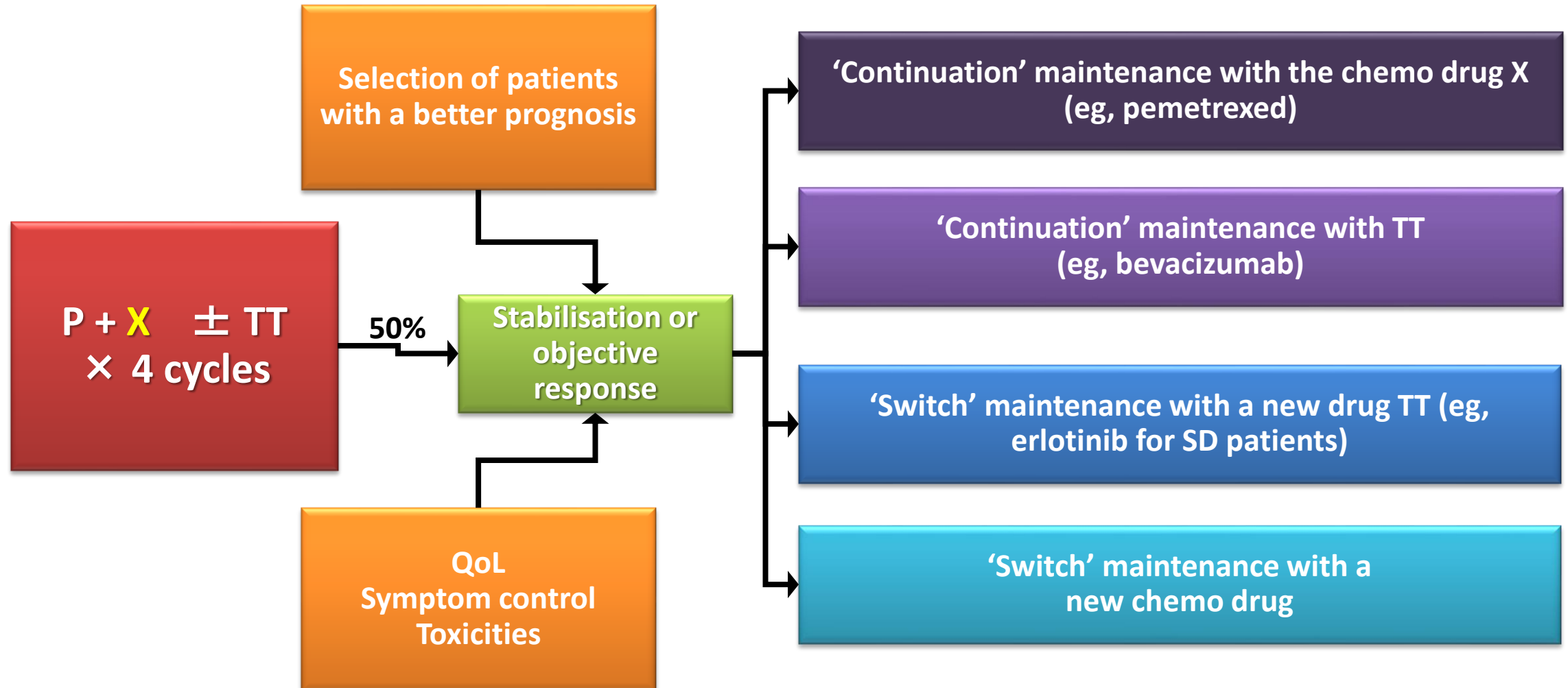
ESMO Guidelines Working Group*

23. Li M, Zhang Q, Fu P et al. Pemetrexed plus platinum as the first-line treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials. PLoS One 2012; 7: e37229.

24. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008; 26: 3543–3551.

MAINTENANCE THERAPY

Continuation vs Switch

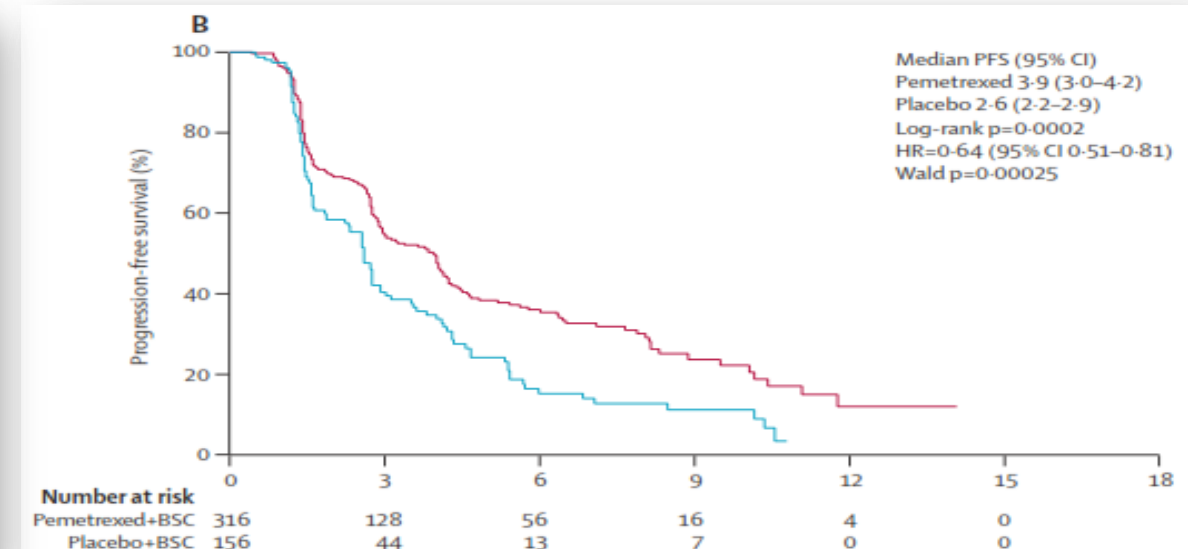
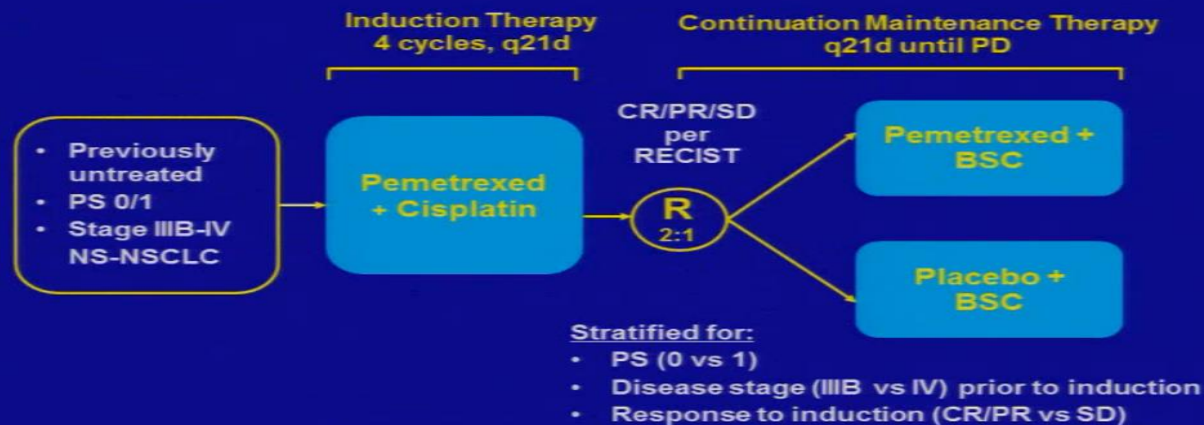


Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

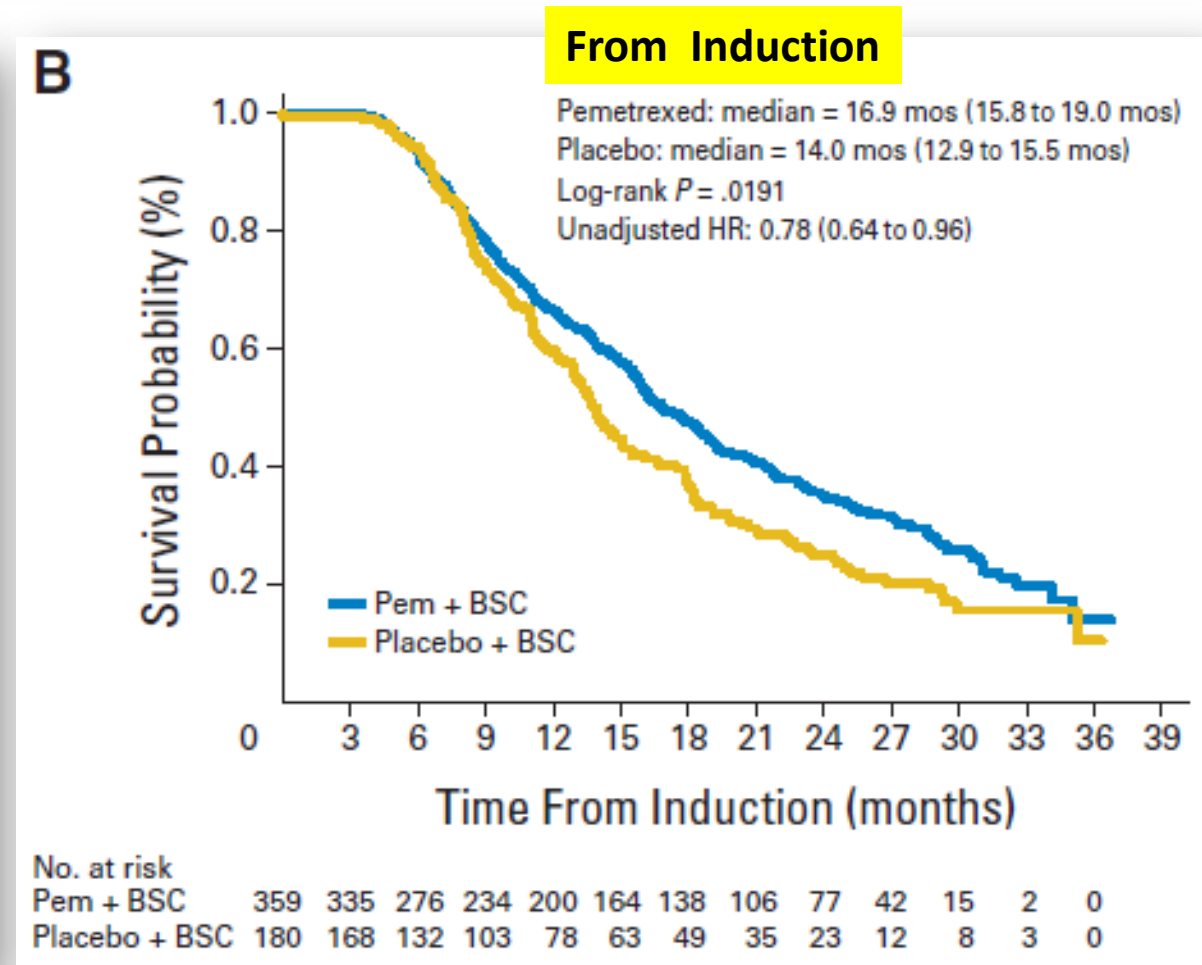
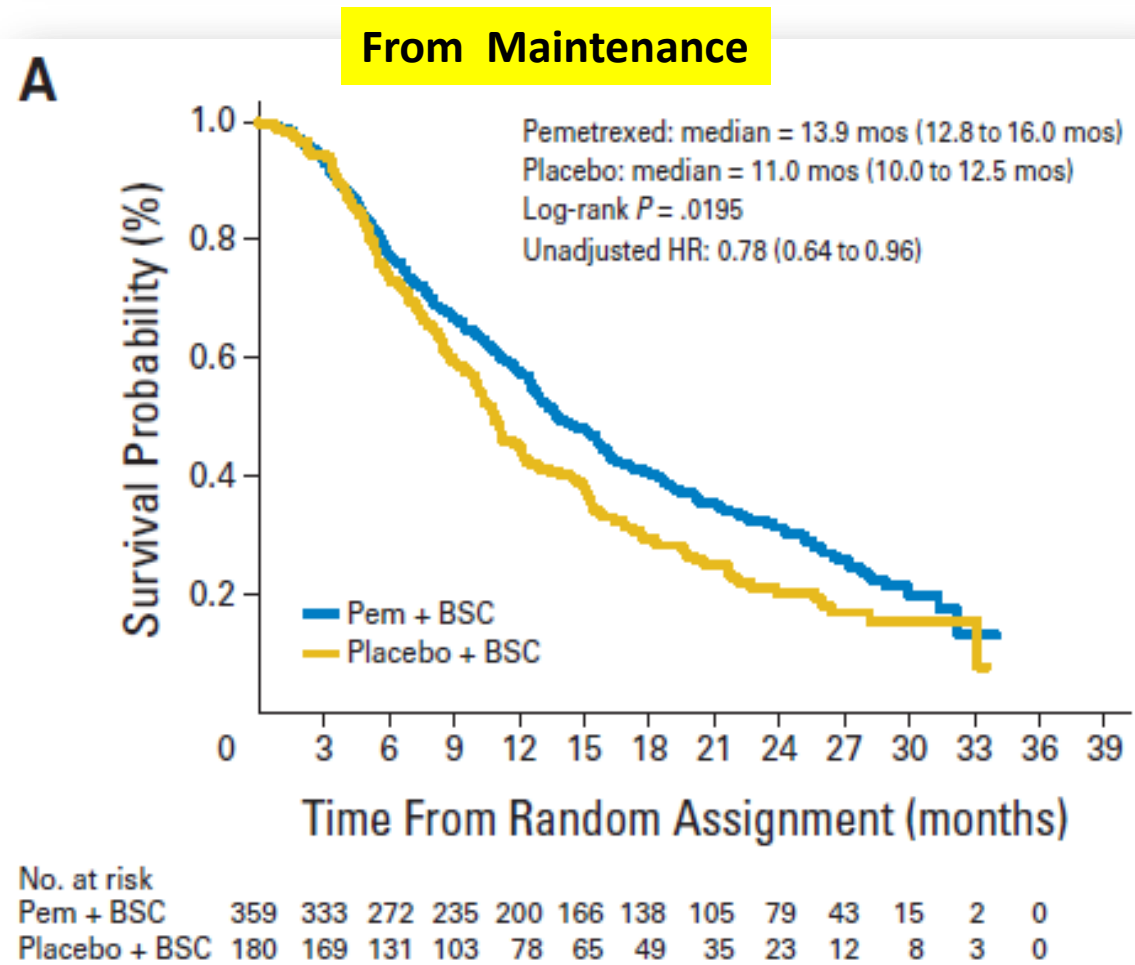
maintenance treatment

Continuing pemetrexed following completion of first-line cisplatin plus pemetrexed chemotherapy is therefore recommended in patients with non-squamous histology, tumour stabilisation, or response after first-line chemotherapy and recovery from toxicity of the previous treatment [I, B].

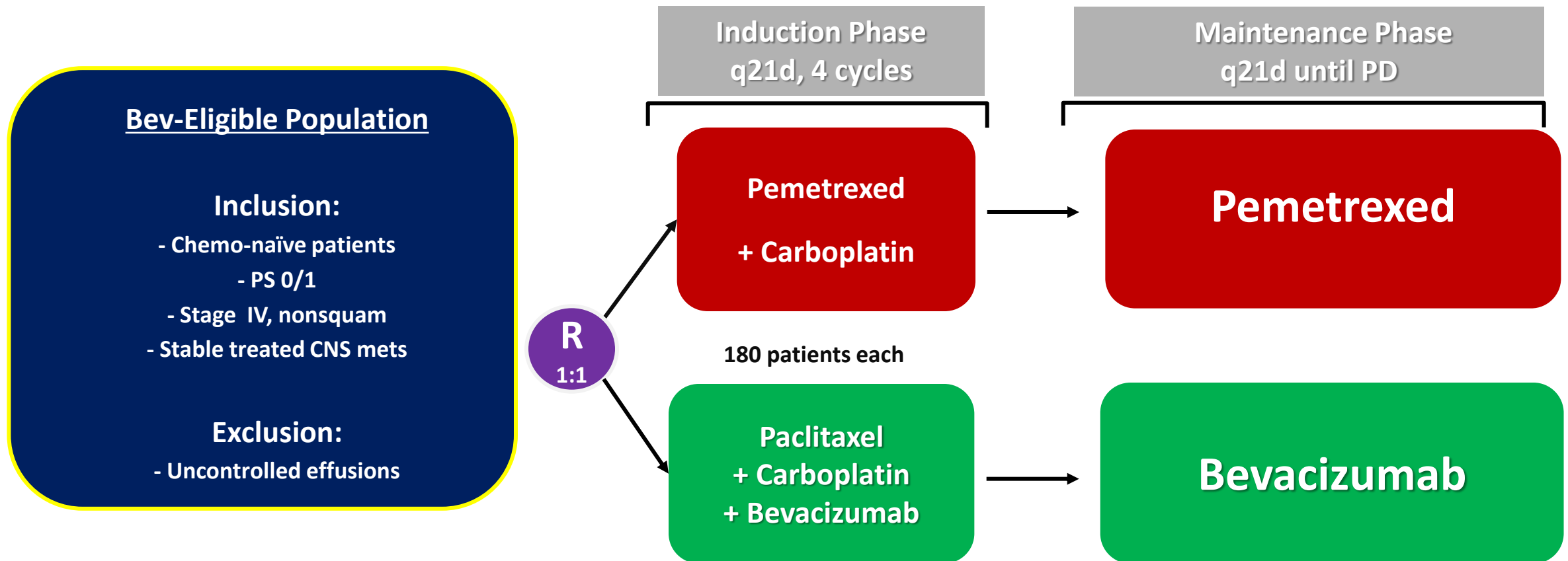
- ♦ Randomized, placebo-controlled, double-blind phase III study
- ♦ Pemetrexed 500 mg/m²; Cisplatin 75 mg/m²
- ♦ Folic acid and vitamin B₁₂ administered to both arms



PARAMOUNT: Final Overall Survival Results of the Phase III Study of Maintenance Pemetrexed Versus Placebo Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non-Small-Cell Lung Cancer

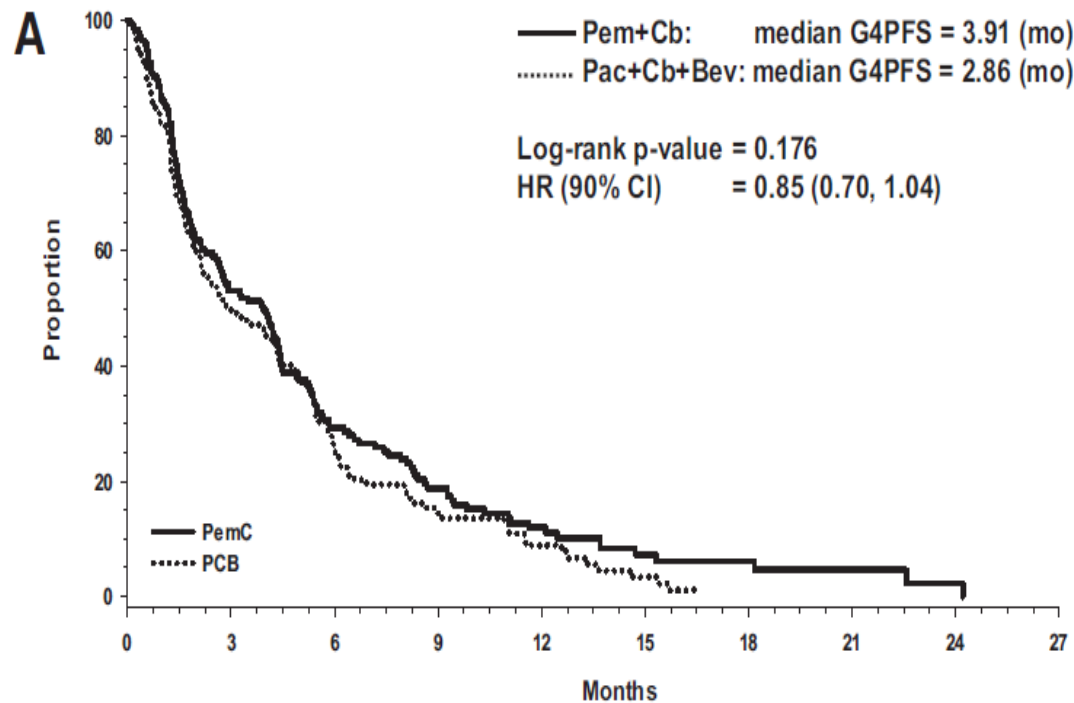


PRONOUNCE: Randomized, Open-Label, Phase III Study of First-Line Pemetrexed + Carboplatin Followed by Maintenance Pemetrexed versus Paclitaxel + Carboplatin + Bevacizumab Followed by Maintenance Bevacizumab in Patients with Advanced Nonsquamous Non-Small-Cell Lung Cancer



PRONOUNCE: Randomized, Open-Label, Phase III Study of First-Line Pemetrexed + Carboplatin Followed by Maintenance Pemetrexed versus Paclitaxel + Carboplatin + Bevacizumab Followed by Maintenance Bevacizumab in Patients with Advanced Nonsquamous Non-Small-Cell Lung Cancer

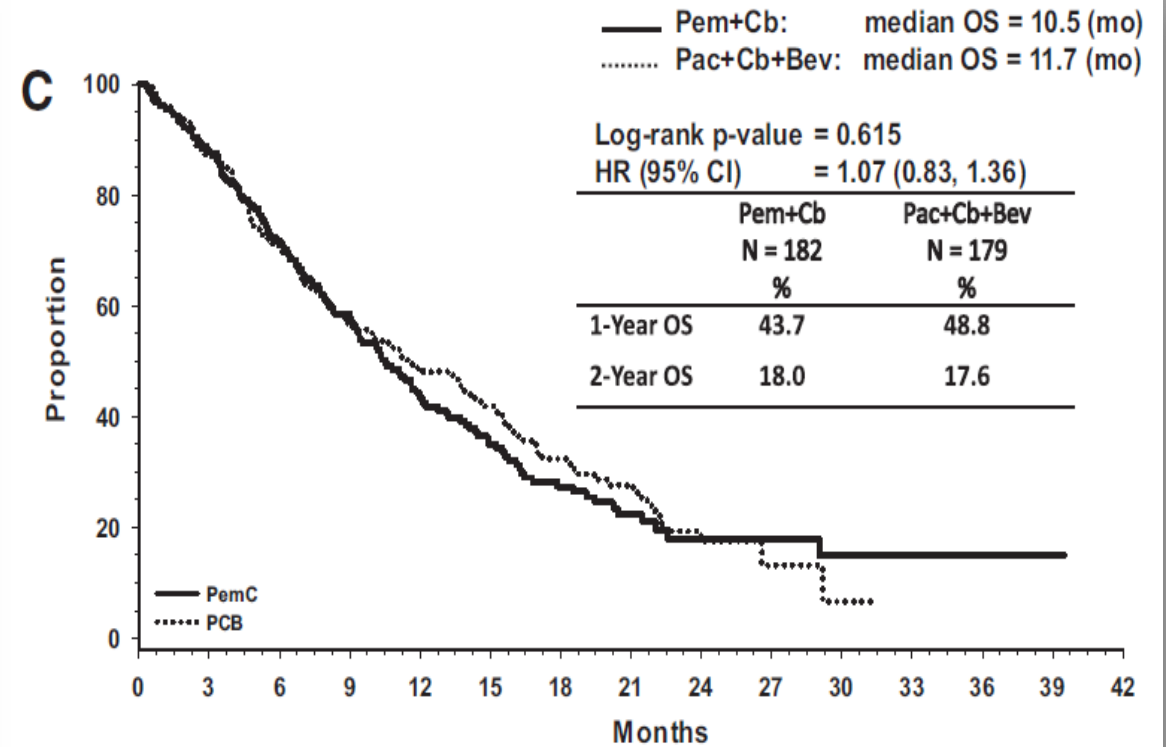
PRONOUNCE PRIMARY ENDPOINT: G4 PFS



Patients at Risk

Pem+Cb	182	87	44	26	14	7	5	3	1	0
Pac+Cb+Bev	179	75	33	17	9	3	0	0	0	0

PRONOUNCE SECONDARY ENDPOINT: OS

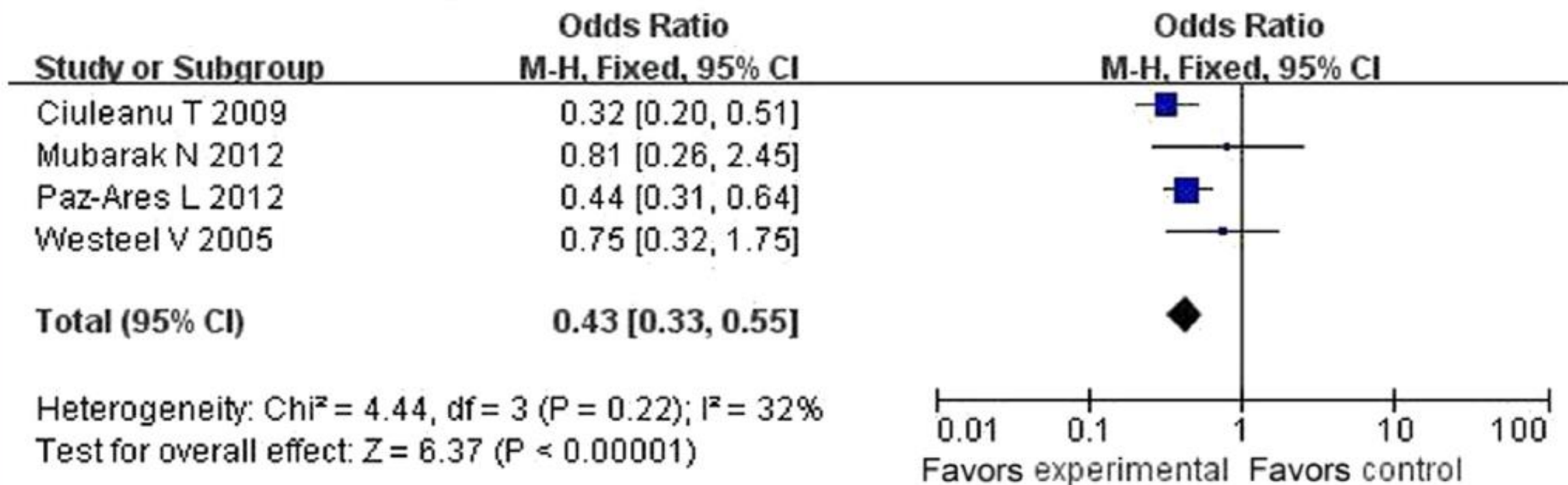


Patients at Risk

Pem+Cb	182	156	125	102	72	48	33	20	11	11	5	5	5	5	5
Pac+Cb+Bev	179	151	121	96	73	59	38	28	10	3	1	1	0	0	0

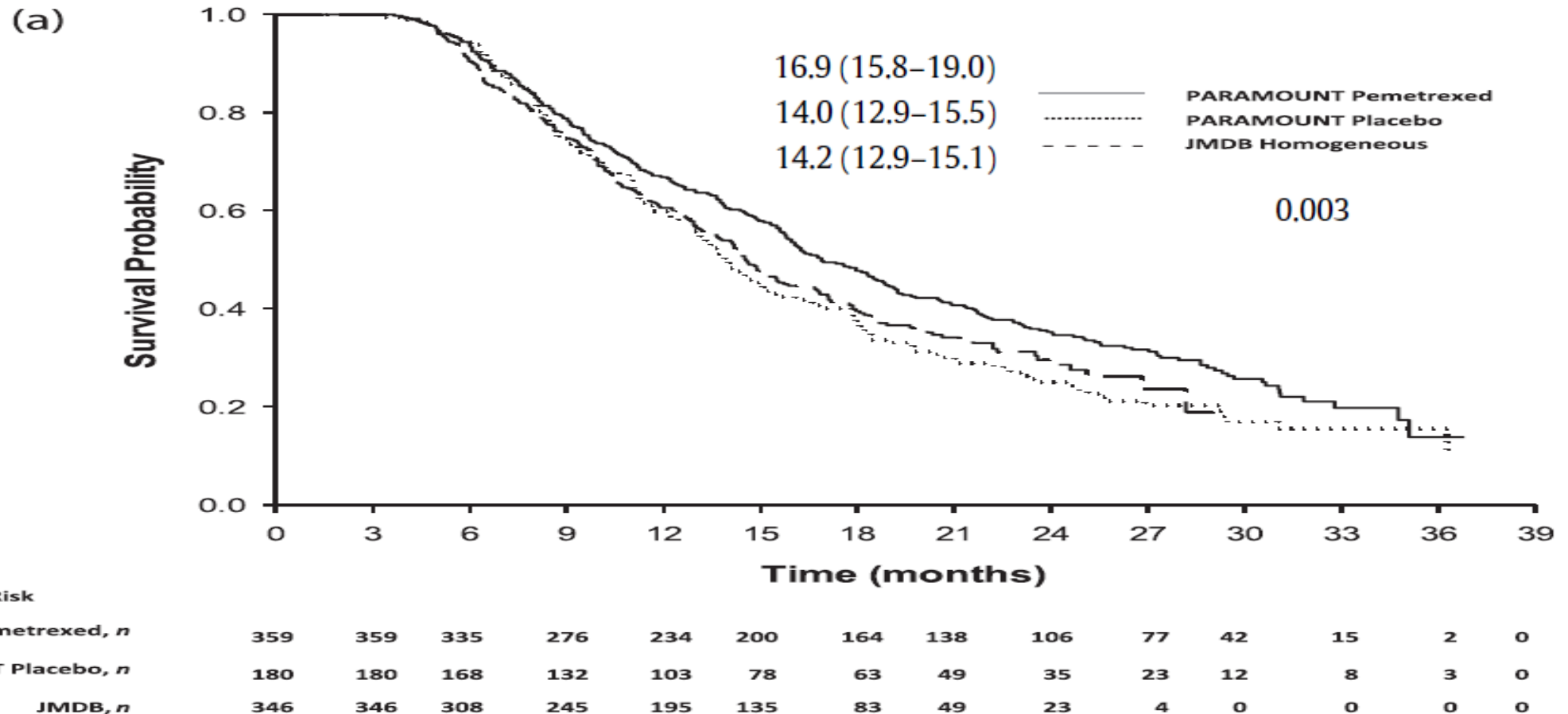
Maintenance or Consolidation Therapy for Non—Small-Cell Lung Cancer: A Meta-Analysis Involving 5841 Subjects

Chemotherapy



Annotated Forest Plot For Meta-Analysis of Progression-Free Survival of Patients Who Underwent Maintenance Therapy

Efficacy and safety of maintenance pemetrexed in patients with advanced nonsquamous non-small cell lung cancer following pemetrexed plus cisplatin induction treatment: A cross-trial comparison of two phase III trials☆



2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease



should we offer 'continuation' maintenance
treatment and, if yes, to which patients?

Recommendation 10: continuation maintenance treatment with pemetrexed may be offered to patients with advanced non-squamous NSCLC not progressing after first-line pemetrexed-cisplatin therapy.

Strength of recommendation: A

Level of evidence: I

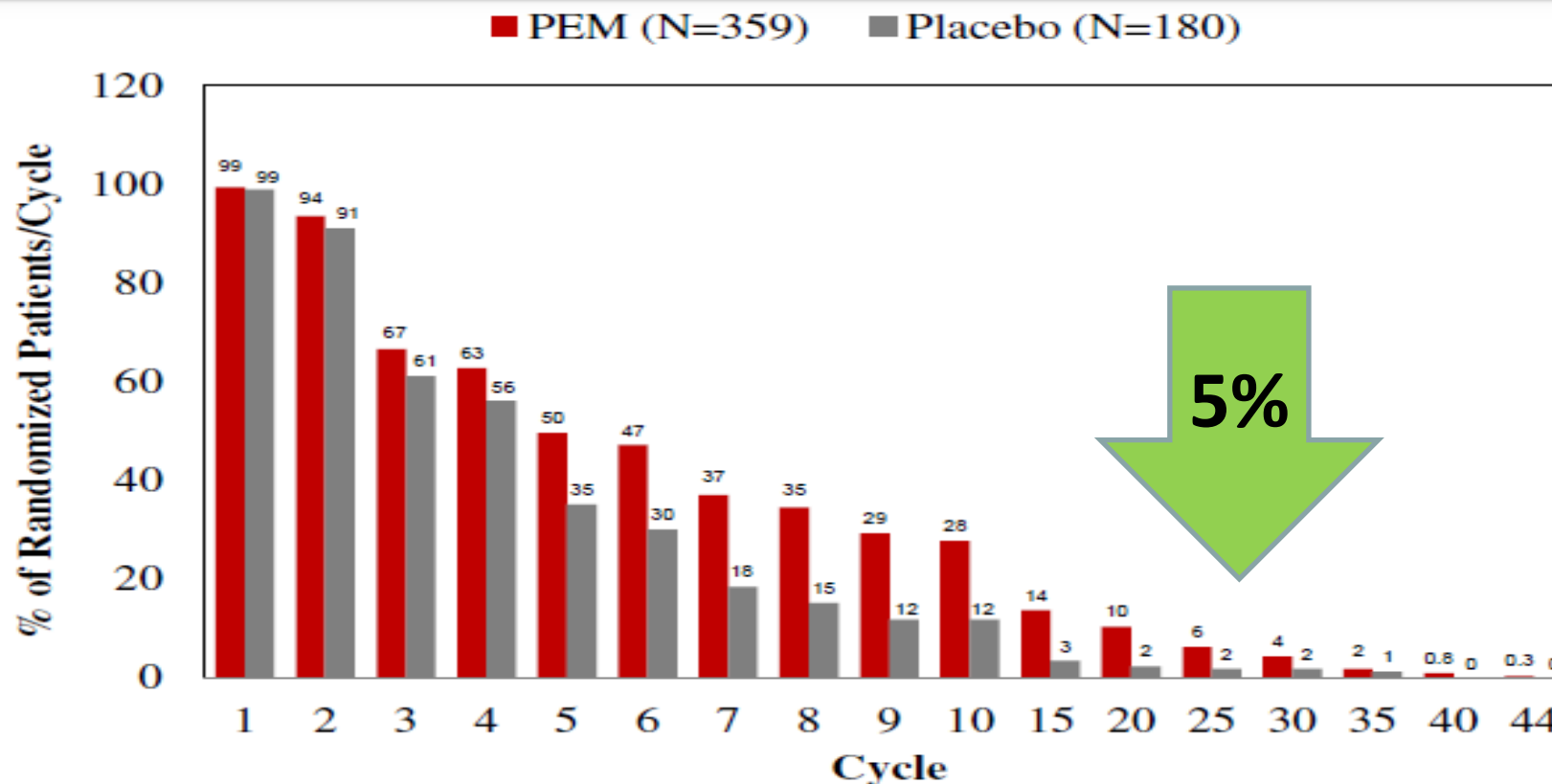
THREE «*CASES*» IN ONE !



**ADRENAL GLAND MET
TREATMENT**

**MAINTENANCE
CHEMOTHERAPY**

Long-Term and Low-Grade Safety Results of a Phase III Study (PARAMOUNT): Maintenance Pemetrexed Plus Best Supportive Care Versus Placebo Plus Best Supportive Care Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non—Small-Cell Lung Cancer☆



Summary of Maintenance Cycles Administered. The Percentage of Randomized Patients Per Maintenance Cycle (Cycles 1-44) in the Pemetrexed and Placebo Groups. Percentages (> 1%) Were Rounded to the Nearest Whole Number

JL Pujol...F de Marinis et al, Clin Lung Cancer 2014

AFTER LOCAL-REGIONAL TREATMENT: HOW DO WE PROCEED?

Continue PEMETREXED maintenance

STOP PEMETREXED maintenance

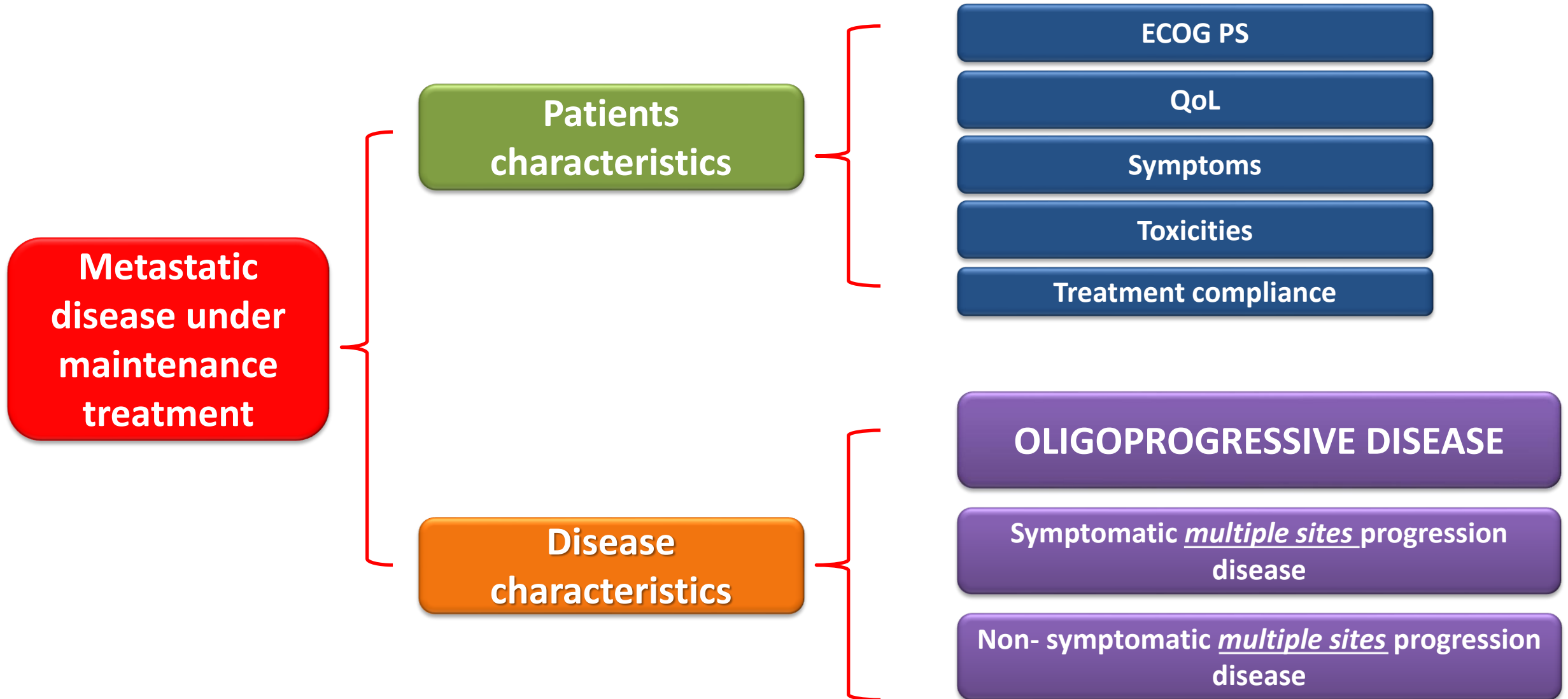
FOLLOW-UP

STOP PEMETREXED maintenance



Start SECOND LINE-THERAPY

DATA TO BE EVALUATED TO KEEP ONGOING PEMETREXED MAINTENANCE BEYOND PROGRESSION.....IN WT PTS



Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial

PRONOUNCE: Randomized, Open-Label, Phase III Study of First-Line Pemetrexed + Carboplatin Followed by Maintenance Pemetrexed versus Paclitaxel + Carboplatin + Bevacizumab Followed by Maintenance Bevacizumab in Patients with Advanced Nonsquamous Non-Small-Cell Lung Cancer

	Pemetrexed (N=359)	Placebo (N=180)
Sex		
Male	201 (56%)	112 (62%)
Female	158 (44%)	68 (38%)
Age at randomisation (years)		
Median (range)	61 (32–79)	62 (35–83)
Age group		
<65 years	238 (66%)	112 (62%)
≥65 years	121 (34%)	68 (38%)
Ethnic origin		
Asian	16 (4%)	8 (4%)
African	4 (1%)	1 (<1%)
White	339 (94%)	171 (95%)
Smoking status		
Ever smoker	275 (77%)	144 (80%)
Never smoker	82 (23%)	34 (19%)
Unknown	2 (<1%)	2 (1%)
ECOG PS at randomisation		
0	115 (32%)	55 (31%)
1	243 (68%)	123 (68%)
2–3*	1 (<1%)	2 (1%)
Disease stage before maintenance therapy†		
Stage IIIB	31 (9%)	19 (11%)
Stage IV	328 (91%)	161 (89%)
Best tumour response to induction therapy		
Complete or partial response	166 (46%)	76 (42%)

TABLE 1. Patient Baseline Demographic and Disease Characteristics of Intent-to-Treat Population

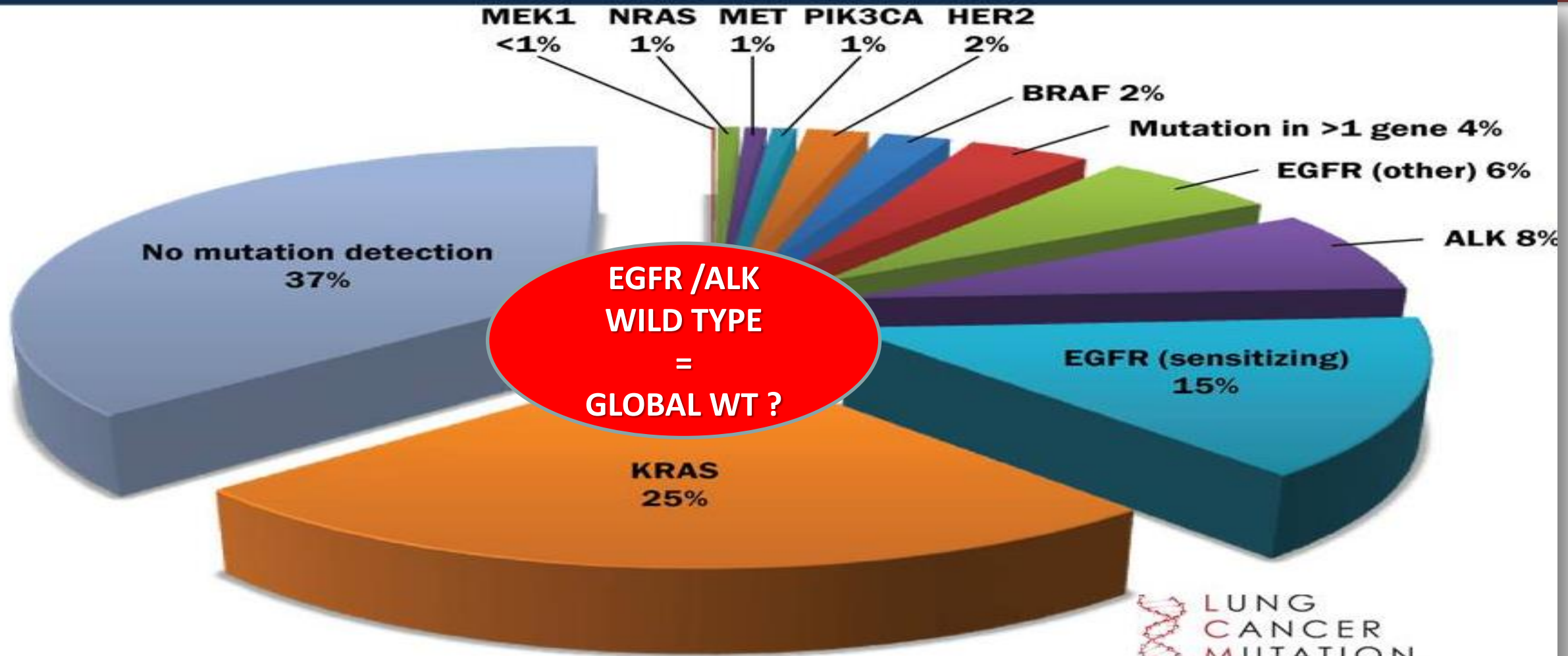
Characteristic	Pem+Cb N = 182 n (%)	Pac+Cb+Bev N = 179 n (%)
Age, years, median (range)	65.8 (38.4–84.1)	65.4 (41.2–86.2)
>70 years	59 (32.4)	51 (28.5)
Gender		
Female	77 (42.3)	75 (41.9)
Race/ethnicity		
White ^a	165 (90.7)	157 (87.7)
African American	11 (6.0)	20 (11.2)
Asian	4 (2.2)	0 (0.0)
American Indian	0 (0.0)	2 (1.1)
Multiple	2 (1.1)	0 (0.0)
ECOG PS		
0	85 (46.7)	84 (46.9)
1	96 (52.7)	95 (53.1)
Disease stage IV	181 (99.5)	179 (100.0)
M1a	52 (28.6)	53 (29.6)

ALL “UNSELECTED” PATIENTS!!

Adenocarcinoma	304 (85%)	158 (88%)
Large-cell carcinoma	24 (7%)	12 (7%)
Other or indeterminate†	25 (7%)	8 (4%)

Ever	164 (90.1)	172 (96.1)
No previously treated brain metastasis	159 (87.4)	147 (82.1)

INCIDENCE OF SINGLE DRIVER MUTATIONS

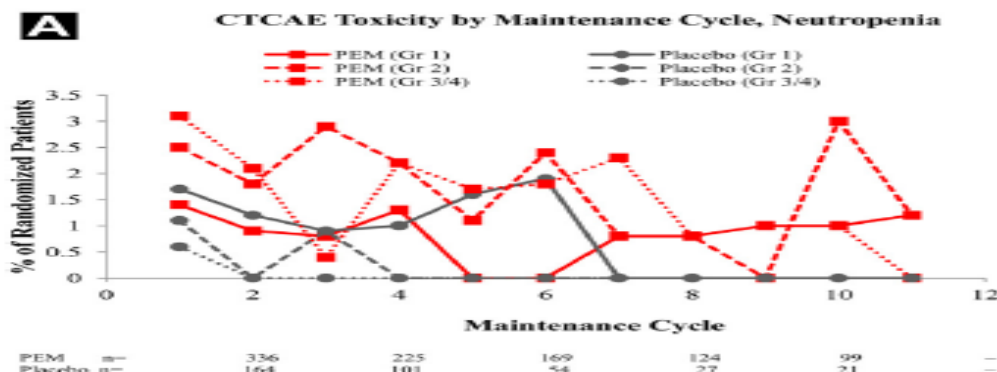


PARAMOUNT: Descriptive Subgroup Analyses of Final Overall Survival for the Phase III Study of Maintenance Pemetrexed versus Placebo Following Induction Treatment with Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non–Small-Cell Lung Cancer

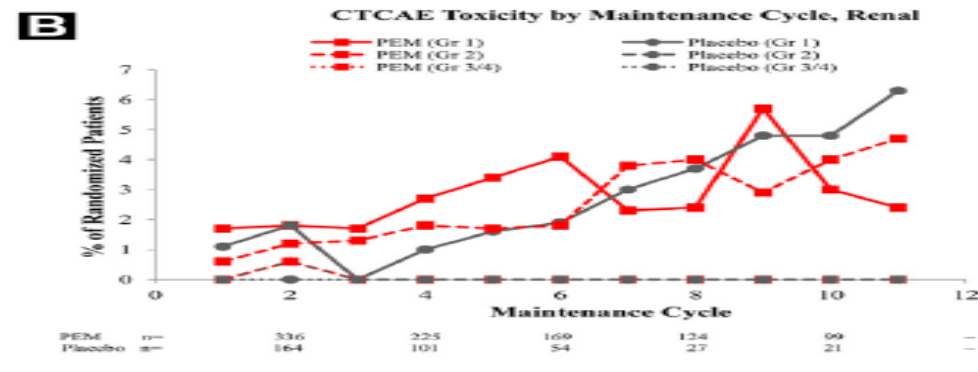
TABLE 2. Select AEs as Indicators of Length of Overall Survival among Patients Receiving Pemetrexed Continuation Maintenance Therapy^a

Grade 3/4 AE Types	Pemetrexed (<i>n</i> = 359) <i>n</i> (%)	Patients with Specific AEs during Induction in Subgroups Defined by Survival Intervals					
		0–3 Mo, <i>n</i> (%) ^{<i>b</i>}	>3–6 Mo, <i>n</i> (%)	>6–12 Mo, <i>n</i> (%)	>12–18 Mo, <i>n</i> (%)	>18–24 Mo, <i>n</i> (%)	>24 Mo, <i>n</i> (%)
Hematologic toxicities							
Any hematologic toxicity	52 (14.5)	7 (1.9)	7 (1.9)	11 (3.1)	11 (3.1)	4 (1.1)	12 (3.3)
Anemia	13 (3.6)	4 (1.1)	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	4 (1.1)
Neutropenia	35 (9.7)	3 (0.8)	6 (1.7)	9 (2.5)	8 (2.2)	2 (0.6)	7 (1.9)
Leukopenia	4 (1.1)	0	1 (0.3)	0	1 (0.3)	0	2 (0.6)
Thrombocytopenia	2 (0.6)	0	0	0	0	1 (0.3)	1 (0.3)
Febrile neutropenia	5 (1.4)	0	0	1 (0.3)	3 (0.8)	0	1 (0.3)
Nonhematologic toxicities							
Nausea	13 (3.6)	1 (0.3)	1 (0.3)	1 (0.3)	4 (1.1)	3 (0.8)	3 (0.8)
Fatigue	6 (1.7)	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Vomiting	16 (4.5)	3 (0.9)	2 (0.6)	1 (0.3)	2 (0.6)	6 (1.7)	2 (0.6)
Mucositis–stomatitis	1 (0.3)	0	0	0	1 (0.3)	0	0
Renal failure	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0	0

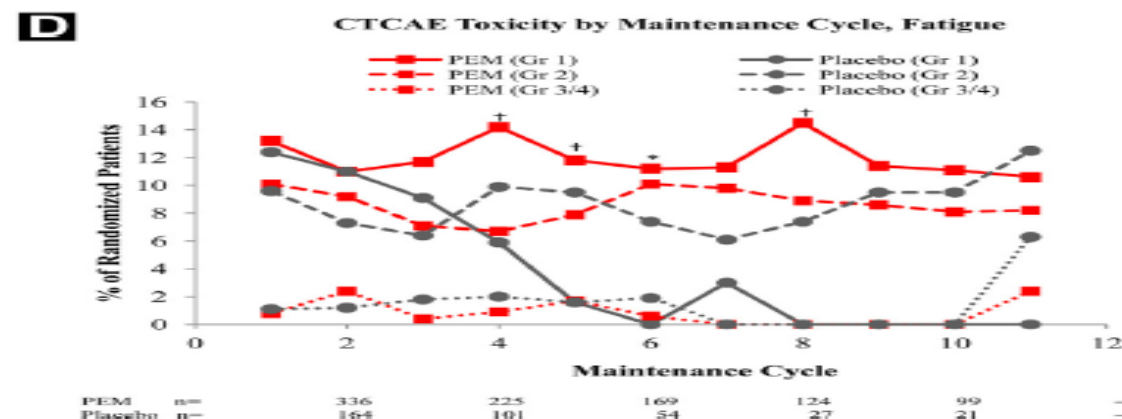
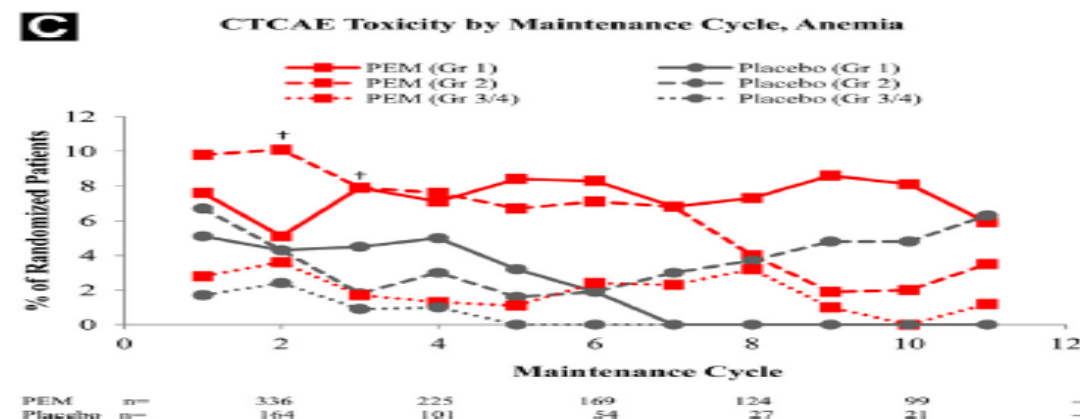
Long-Term and Low-Grade Safety Results of a Phase III Study (PARAMOUNT): Maintenance Pemetrexed Plus Best Supportive Care Versus Placebo Plus Best Supportive Care Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non-Small-Cell Lung Cancer[☆]



Note: PEM (grade 1) and PEM (grade 2) graphs overlap between cycles 7–8 and PEM (grade 1) and PEM (grade 3/4) graphs overlap between cycles 8–10.



Note: No grade 3/4 events were reported in the placebo group. Grade 3/4 events were reported in the PEM group at cycle 2 (incidence <1%). Similarly, grade 2 events were reported in the placebo group at cycle 2, with a low incidence (<1%). These 3 lines overlap and appear as a single line from cycles 3–11.



Safety, Resource Use, and Quality of Life in PARAMOUNT

A Phase III Study of Maintenance Pemetrexed Versus Placebo after Induction Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non–Small-Cell Lung Cancer

TABLE 4. Summary of All Hospitalizations Because of AEs in PARAMOUNT

	Induction	Maintenance		<i>p</i> ^a
	Pemetrexed + Cisplatin (N = 939)	Pemetrexed (N = 359)	Placebo (N = 180)	
Patients with at least 1 hospitalization, <i>n</i> (%)	229 (24.4)	69 (19.2)	32 (17.8)	0.727
All hospitalizations	295	91	37	
Mean (SD) length of stay, nights	7.87 (7.18)	8.57 (7.01)	8.95 (9.66)	0.807
Median (range) length of stay, nights	5.00 (0.00, 45.00)	6.00 (1.00, 34.00)	6.00 (1.00, 53.00)	
Patients hospitalized because of drug-related AEs, <i>n</i> (%)	126 (13.4)	30 (8.4)	6 (3.3)	0.028
Hospitalizations involving drug-related AEs	148	35	7	
Mean (SD) length of stay, nights	8.08 (7.06)	8.14 (7.00)	10.57 (8.26)	0.421
Median (range) length of stay, nights	6.00 (0.00, 45.00)	6.00 (1.00, 31.00)	9.00 (2.00, 27.00)	

Final Efficacy and Safety Results of Pemetrexed Continuation Maintenance Therapy in the Elderly from the PARAMOUNT Phase III Study

TABLE 2. Cycles of Maintenance Therapy Administered and Dose Intensity

	Elderly (≥70 Yrs) Subgroup		Non-Elderly (<70 Yrs) Subgroup	
	Pem (N = 52)	Plc (N = 40)	Pem (N = 307)	Plc (N = 140)
Patients treated, <i>n</i>	51	40	306	138
Number of cycles/patient, median (range)	4.0 (1–36)	4.0 (1–15)	4.5 (1–44)	4.0 (1–38)
Number of cycles, mean (SD)	7.4 (7.3)	4.5 (2.8)	8.0 (8.4)	5.1 (5.7)
Patients completing ≥6 cycles (%)	46	35	47	29
Patients completing ≥10 cycles (%)	31	5	27	14
Dose intensity ^a (%)	91	NA	94	NA

HOW DO WE PROCEED AFTER 28Q PEMETREXED AND LOCALLY TREATED OLIGOPROGRESSION?

