GASCO Best of ASCO® Lung Cancer Abstracts

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Non Small Cell Lung Cancer – Abstracts: 8500, LBA9008, LBA9007,
Small Cell Lung Cancer – Abstracts: 8503, 8505
Mesothelioma – Abstract # LBA8507

Disclosures

- Consultant/Advisory Board
  - AbbVie
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  - EMD Serono/Merck

- Research Funding
  - AbbVie
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  - AstraZeneca
  - Pfizer

Presented by:

Gefitinib (G) versus vinorelbine / cisplatin (VP) as adjuvant treatment in stage II-IIIA (N1-N2) non-small-cell lung cancer (NSCLC) with *EGFR* activating mutation (ADJUVANT): A randomized, Phase III trial (CTONG 1104)

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Abstract 8500 presented by Y-L Wu
Guangdong Lung Cancer Institute, Guangdong General Hospital, China
June 5,2017

Background

- Approximately 20–25% of patients diagnosed with NSCLC are suitable for surgical resection with curative intent[1]
- Median DFS and 3-year DFS for patients with N2 stage disease are 12.2 months and 23%, respectively[2]
- Adjuvant cisplatin-based chemotherapy is standard of care for patients with stage II-IIIA completely resected NSCLC[3]

1. Arriagada R et al. *Lancet* 2010;375:1267-1277
2. Andre F et al. *J Clin Oncol* 2000;18:2981-2989
3. Burdett S et al. *Cochrane Database Syst Rev* 2015;CD011430

DFS, disease free survival; N, lymph node;
NSCLC, non-small-cell lung cancer; OS, overall survival

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Background

- Based on data from nine RCT trials, EGFR TKIs are standard first-line therapy for *EGFR* mutation-positive advanced NSCLC [1]
- EGFR TKIs had limited benefit in the adjuvant setting for patients with resected NSCLC in the BR19 and RADIANT trials[2,3]
- ADJUVANT (NCT01405079) is the first prospective randomized trial comparing gefitinib with vinorelbine plus cisplatin in completely resected pathological stage II-IIIA (N1-N2) *EGFR* mutation-positive NSCLC

EGFR, epidermal growth factor receptor; RCT, randomized control trial; TKI, tyrosine kinase inhibitor

1. Ke EE, Wu YL. *Trend Pharm Sci* 2016; 11:887-903
2. Goss GD et al. *J Clin Oncol* 2013; 31: 3320-3326
3. Kelly K et al. *J Clin Oncol* 2015; 33: 4007-4014

Statistical considerations

Improvement in DFS was determined as follows:

- To detect a 40% (HR=0.6) or more improvement in DFS
- 80% power and 0.05 significance level using 2-sided
- Approximately 220 randomized patients (≥122 events observed) would be required by log rank test

CI, confidence interval; HR, hazard ratio

1. Rusch VW et al. *J Thorac Oncol* 2007;2:603-612
2. Janjigian YY et al. *J Clin Oncol* 2009; 27 (15 suppl): abstr 7523
3. Winton T et al. *N Engl J Med* 2005; 352: 2589-2597

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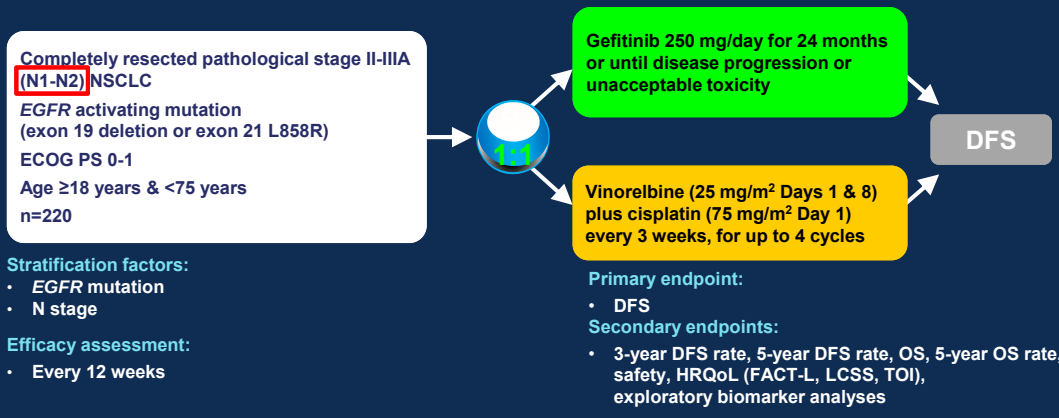
ADJUVANT study design (NCT01405079)



Stratification factors:
- *EGFR* mutation
- N stage

Efficacy assessment:
- Every 12 weeks

Primary endpoint:
- DFS

Secondary endpoints:
- 3-year DFS rate, 5-year DFS rate, OS, 5-year OS rate, safety, HRQoL (FACT-L, LCSS, TOI), exploratory biomarker analyses

ECOG PS, Eastern Cooperative Oncology Group Performance Status; DFS, disease-free survival; FACT-L, Functional Assessment of Cancer Therapy – Lung; HRQoL, health-related quality of life; LCSS, Lung Cancer Symptom Scale; OS, overall survival; R, randomization; TOI, Trial Outcome Index

Baseline demographics (ITT population)

	Vinorelbine plus cisplatin (n=111)	Gefitinib (n=111)
Age, years, median (range)	60 (26–76)	58 (32–74)
Female, n (%)†	65 (58.6)	65 (58.6)
Never smoker, n (%)	85 (76.6)	82 (73.9)
Baseline ECOG PS, n (%)		
1	85 (76.6)	72 (64.9)
Pathology stage, n (%)		
IIA	33 (29.7)	33 (29.7)
IIB	4 (3.6)	4 (3.6)
IIIA	71 (64.0)	72 (64.9)
Not available	3 (2.7)	2 (1.8)
Pathology, n (%)		
Adenocarcinoma	105 (94.6)	102 (91.9)
Squamous carcinoma	1 (0.9)	5 (4.5)
Adenosquamous carcinoma	3 (2.7)	2 (1.8)
Not available	2 (1.8)	2 (1.8)

†Sex was not available for two patients in the gefitinib arm and one patient in the vinorelbine plus cisplatin arm

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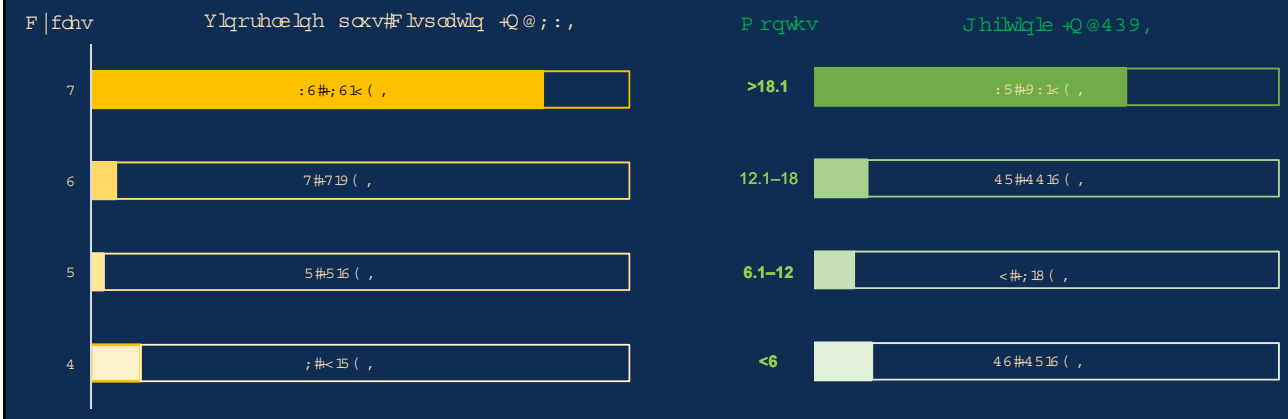
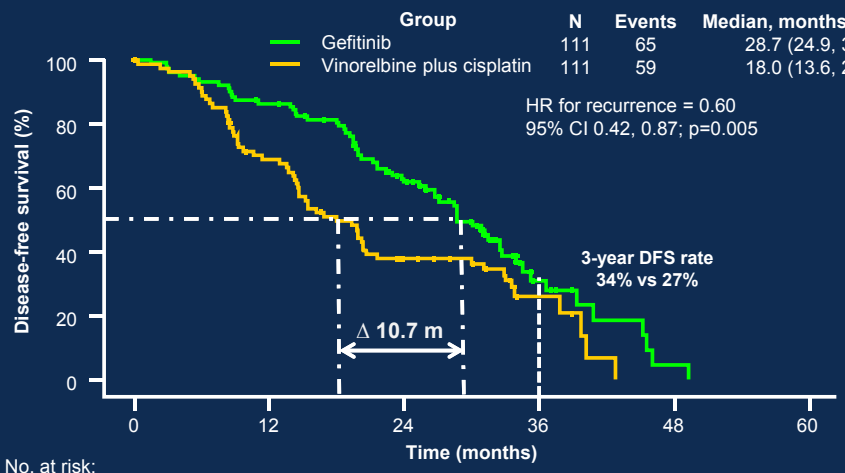
Baseline demographics (ITT population)

	Vinorelbine plus cisplatin (n=111)	Gefitinib (n=111)
***EGFR* mutation status, n (%)**		
Exon 19 deletion	57 (51.4)	58 (52.3)
Exon 21 L858R	53 (47.7)	53 (47.7)
EGFR false positive	1 (0.9)	0 (0)
Lymph node status, n (%)		
N1	37 (33.3)	40 (36.0)
N2	72 (64.9)	71 (64.0)
Not available	2 (1.8)	0 (0)
Type of resection, n (%)		
Lobectomy	91 (82.0)	93 (83.8)
Bilobectomy	14 (12.6)	13 (11.7)
Pneumonectomy	3 (2.7)	3 (2.7)
Wedge	2 (1.8)	0 (0)
Not available	1 (0.9)	2 (1.8)

Drug exposure



Primary endpoint: DFS (ITT population)



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AEs in ≥10% of patients (safety population)

AE, n (%)	Gefitinib (n=106)		Vinorelbine plus cisplatin (n=87)	
	All grades	Grade ≥3	All grades	Grade ≥3
Total AEs	**61 (57.5)**	**13 (12.3)**	**70 (80.5)**	**42 (48.3)**
Neutropenia	3 (2.8)	0 (0.0)	46 (52.9)	30 (34.5)
Anemia	2 (1.9)	1 (0.9)	44 (50.6)	5 (5.7)
Leukopenia	4 (3.8)	0 (0.0)	41 (47.1)	14 (16.1)
Myelosuppression	0 (0.0)	0 (0.0)	12 (13.8)	3 (3.4)
Nausea	3 (2.8)	0 (0.0)	38 (43.7)	6 (6.9)
Vomiting	5 (4.7)	0 (0.0)	36 (41.4)	8 (9.2)
Anorexia	2 (1.9)	0 (0.0)	20 (23.0)	0 (0.0)
Rash	43 (40.6)	1 (0.9)	0 (0.0)	0 (0.0)
Elevated ALT	29 (27.4)	2 (1.9)	3 (3.4)	0 (0.0)
Elevated AST	12 (11.3)	2 (1.9)	1 (1.1)	0 (0.0)
Diarrhea	28 (26.4)	1 (0.9)	4 (4.6)	0 (0.0)
Cough	11 (10.4)	0 (0.0)	15 (17.2)	0 (0.0)
Fatigue	4 (3.8)	0 (0.0)	10 (11.5)	0 (0.0)
Fever	1 (0.9)	0 (0.0)	9 (10.3)	1 (1.1)

AE, adverse evevnt; ALT, alanine aminotransferase; AST, aspartate transaminase

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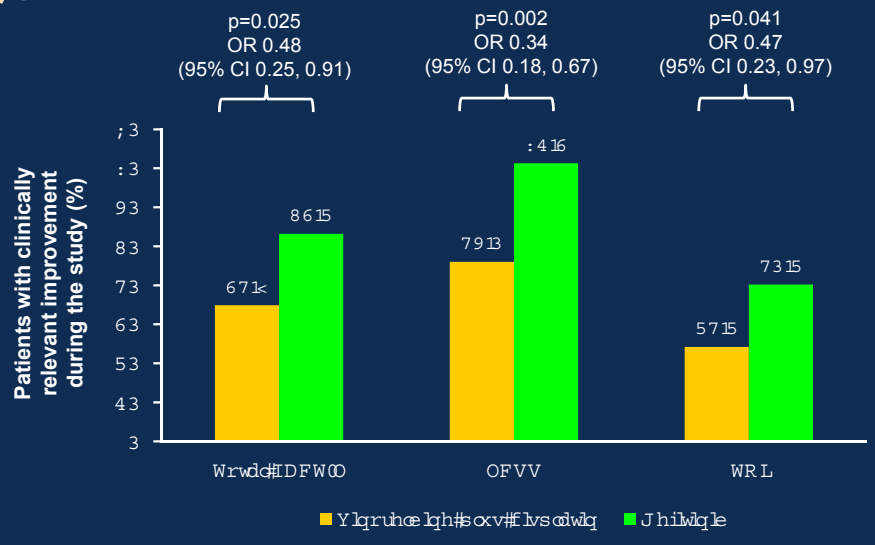
HRQoL



OR, odds ratio

Conclusions

- ADJUVANT met its primary endpoint:
  - Gefitinib demonstrated statistically meaningful efficacy over VP, median DFS: 28.7 vs 18.0 months (HR 0.60, *P*=0.005)
  - 3-year DFS: 34% vs 27%
- AE profile of gefitinib was in line with that reported previously; there were no cases of interstitial lung disease
- 2-year treatment duration for gefitinib is rational and safe in the adjuvant setting
- OS data is immature.
- Adjuvant gefitinib could be the preferred approach in patients with resected N1/N2 *EGFR*-mutant NSCLC

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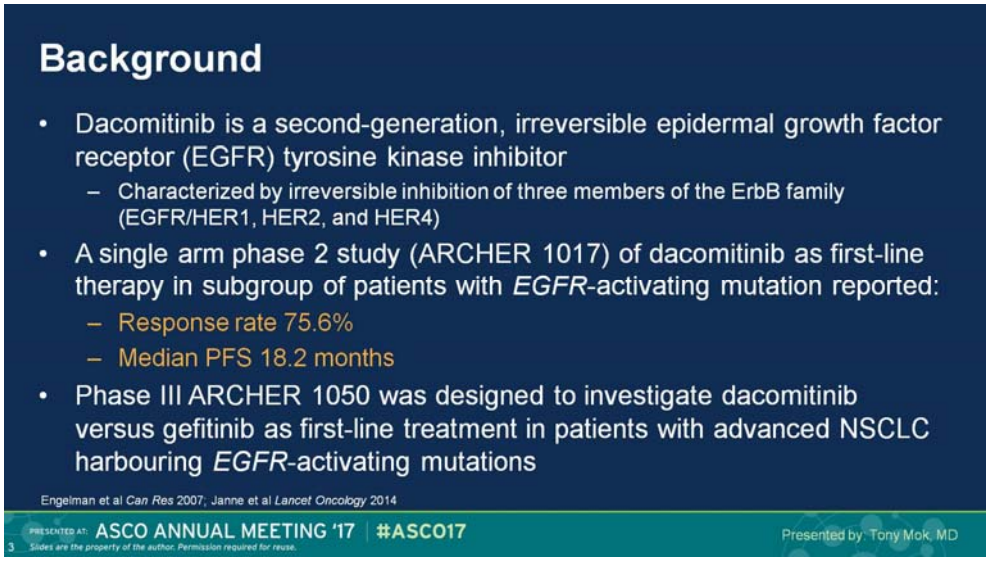

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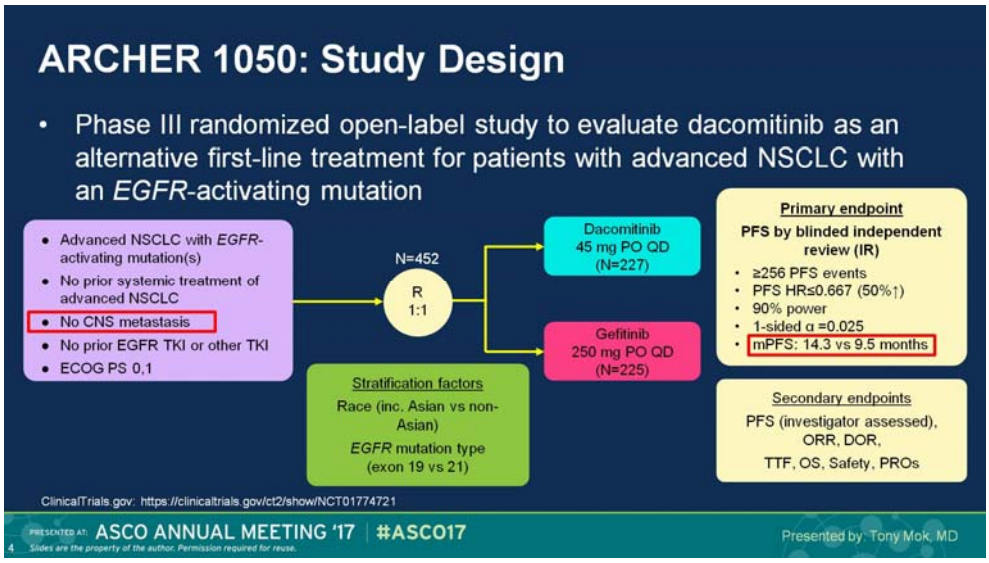

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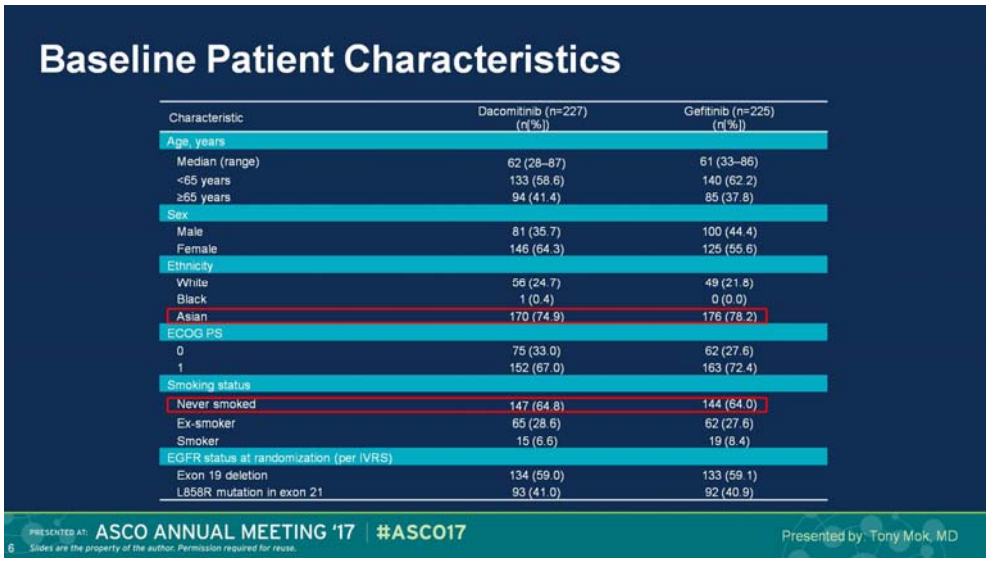

Characteristic	Dacomitinib (n=227) (n[%])	Gefitinib (n=225) (n[%])
Age, years		
Median (range)	62 (28–87)	61 (33–86)
<65 years	133 (58.6)	140 (62.2)
≥65 years	94 (41.4)	85 (37.8)
Sex		
Male	81 (35.7)	100 (44.4)
Female	146 (64.3)	125 (55.6)
Ethnicity		
White	56 (24.7)	49 (21.8)
Black	1 (0.4)	0 (0.0)
Asian	170 (74.9)	176 (78.2)
ECOG PS		
0	75 (33.0)	62 (27.6)
1	152 (67.0)	163 (72.4)
Smoking status		
Never smoked	147 (64.8)	144 (64.0)
Ex-smoker	65 (28.6)	62 (27.6)
Smoker	15 (6.6)	19 (8.4)
EGFR status at randomization (per IVRS)		
Exon 19 deletion	134 (59.0)	133 (59.1)
L858R mutation in exon 21	93 (41.0)	92 (40.9)

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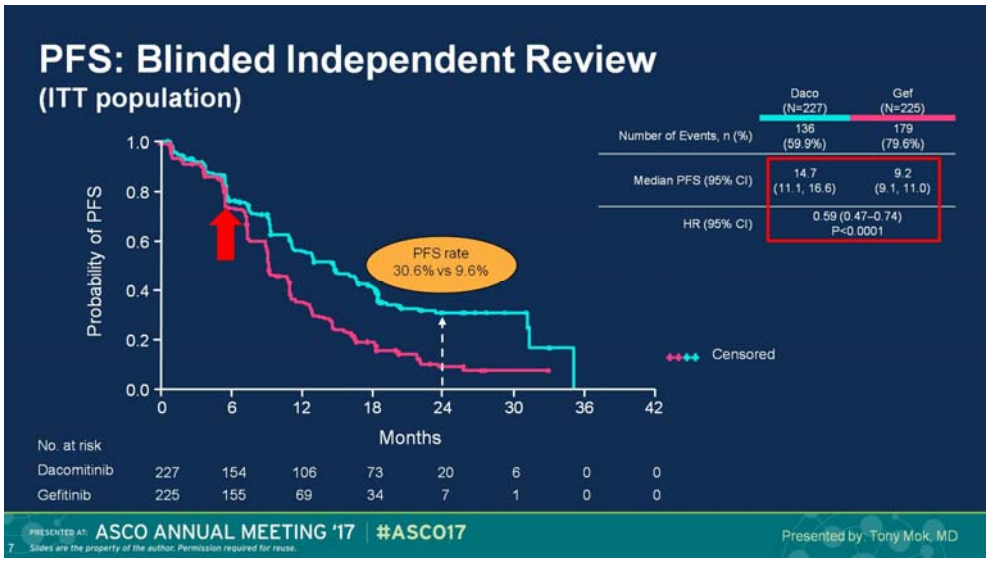

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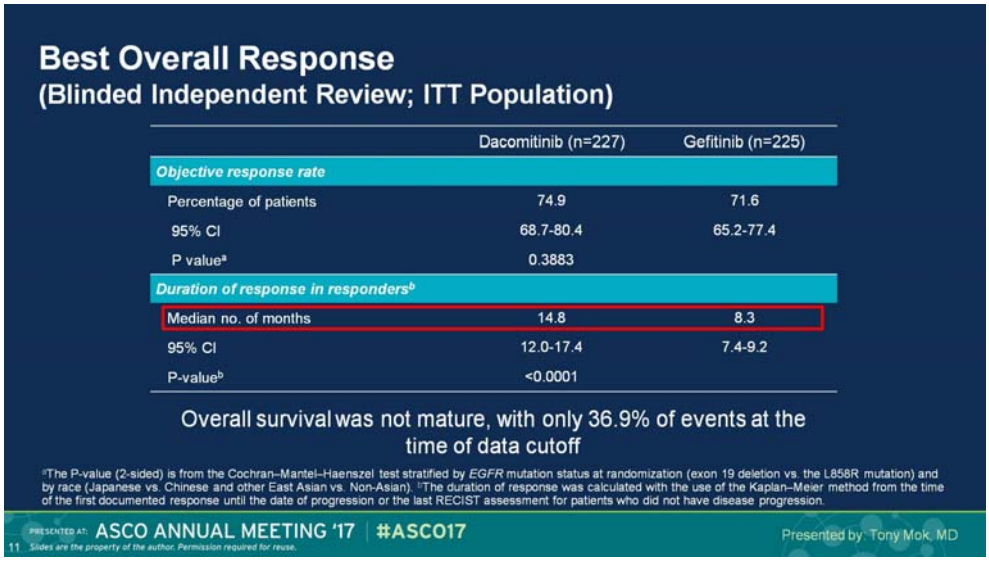

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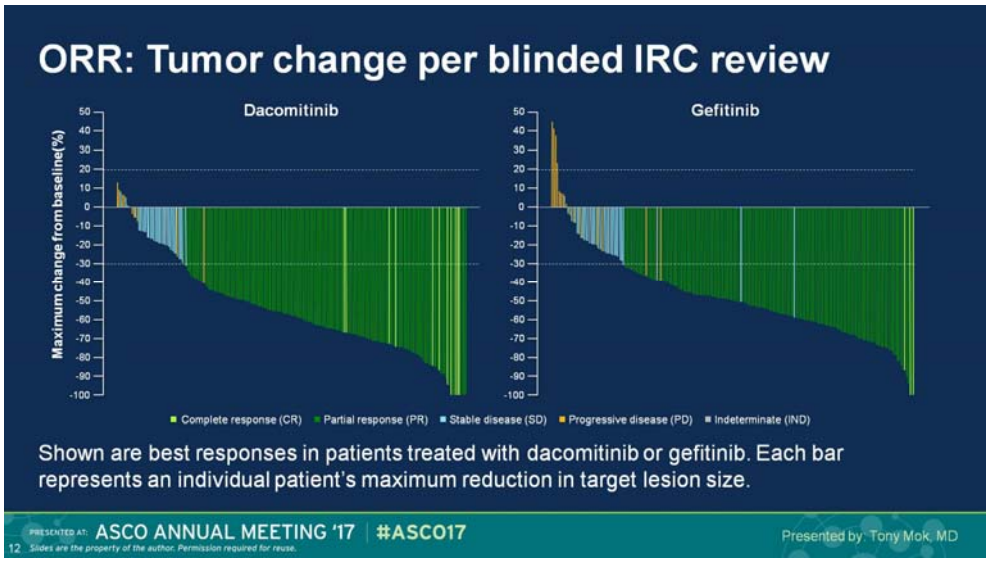

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Adverse Events from Any Cause

Adverse event	Dacomitinib (N = 227)						Gefitinib (N = 224)					
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Number of patients (percent)											
Diarrhea	198 (87.2)	113(49.8)	65 (28.6)	19 (8.4)	0	1 (0.4)	125 (55.8)	103 (46.0)	20 (8.9)	2 (0.9)	0	0
Paronychia	140 (61.7)	46 (20.3)	77 (33.9)	17 (7.5)	0	0	45 (20.1)	30 (13.4)	12 (5.4)	3 (1.3)	0	0
Dermatitis acneiform	111 (48.9)	37 (16.3)	43 (18.9)	31 (13.7)	0	0	64 (28.6)	43 (19.2)	21 (9.4)	0	0	0
Stomatitis	99 (43.6)	51 (22.5)	40 (17.6)	8 (3.5)	0	0	40 (17.9)	33 (14.7)	6 (2.7)	1 (0.4)	0	0
Decreased appetite	70 (30.8)	40 (17.6)	23 (10.1)	7 (3.1)	0	0	55 (24.6)	48 (21.4)	6 (2.7)	1 (0.4)	0	0
Dry skin	63 (27.8)	42 (18.5)	18 (7.9)	3 (1.3)	0	0	38 (17.0)	35 (15.6)	3 (1.3)	0	0	0
Weight decreased	58 (25.6)	31 (13.7)	22 (9.7)	5 (2.2)	0	0	37 (16.5)	22 (9.8)	14 (6.3)	1 (0.4)	0	0
Alopecia	53 (23.3)	41 (18.1)	11 (4.8)	1 (0.4)	0	0	28 (12.5)	26 (11.6)	2 (0.9)	0	0	0
Cough	48 (21.1)	39 (17.2)	9 (4.0)	0	0	0	42 (18.8)	36 (16.1)	5 (2.2)	1 (0.4)	0	0
Pruritus	45 (19.8)	27 (11.9)	17 (7.5)	1 (0.4)	0	0	31 (13.8)	24 (10.7)	4 (1.8)	3 (1.3)	0	0
ALT increased	44 (19.4)	37 (16.3)	5 (2.2)	2 (0.9)	0	0	88 (39.3)	45 (20.1)	24 (10.7)	19 (8.5)	0	0

Adverse events occurring in at least 15% of the patients in either study group in the safety population.
Events are listed in descending order of frequency in the dacomitinib group.

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Dose Modification

Dacomitinib

- First dose reduction: 30 mg/day
- Second reduction: 15 mg/day

Gefitinib

- 250 mg every two days

	Median time to dose reduction	Median duration of dose reduction	Reduction to 30 mg daily	Reduction to 15 mg daily	Total number of patients with dose modification
Dacomitinib (n=227)	2.8 months (range, 0.3 to 20.3)	11.3 months (range, 0.1 to 33.6)	87 (38.3%)	63 (27.8%)	150 (66.1%)
Gefitinib (n=224)	3.3 months (1.2 to 25.7)	5.2 months (0.3 to 17.8)	NA	NA	18 (8.0%)

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Conclusions

- ARCHER 1050 is the first randomized Phase 3 study to compare a second-generation EGFR TKI with a standard first-generation EGFR TKI for first-line treatment of patients with advanced *EGFR*-mutated NSCLC
- Dacomitinib was superior to gefitinib with respect to PFS and DOR
  - Median PFS at 14.7 months is among the highest
- Incidence of diarrhea, skin rash and mucositis is higher with dacomitinib while incidence of hepatic toxicity is higher with gefitinib
- Incidence of AEs reported for dacomitinib was comparable to that reported for other dacomitinib studies; no new safety signals were identified
- Dose modification is more frequent with dacomitinib
- Patients treated with dacomitinib shared similar improvements in patient-reported measures of key disease-associated symptoms as the gefitinib group
- **Dacomitinib should be considered as a new treatment option for first-line management of patients with advanced *EGFR*-mutated NSCLC**

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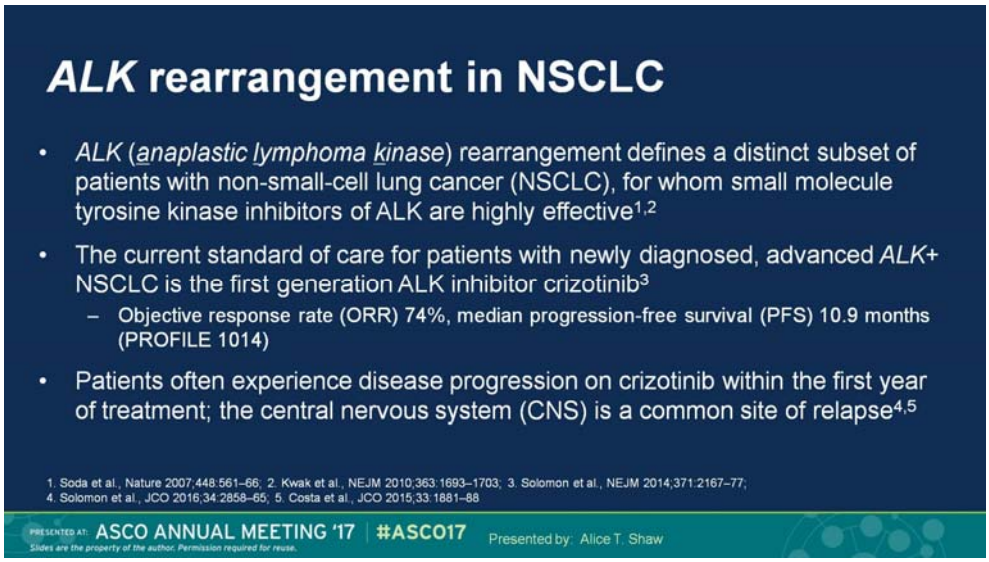

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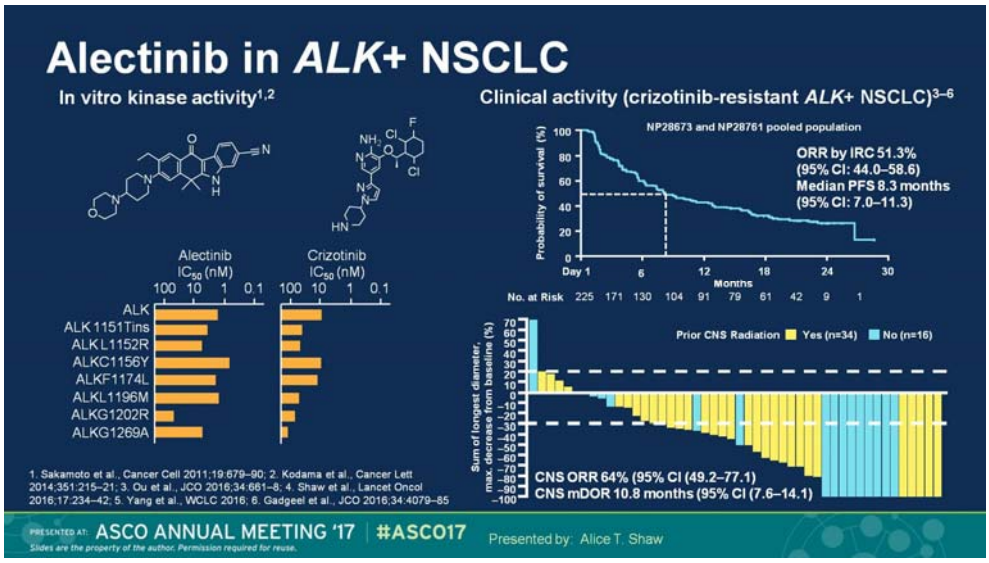

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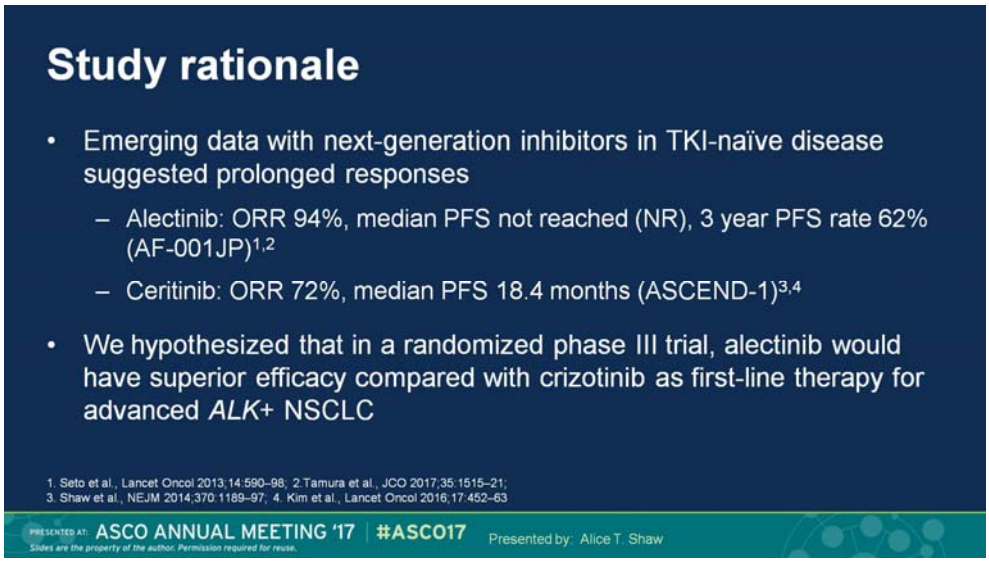

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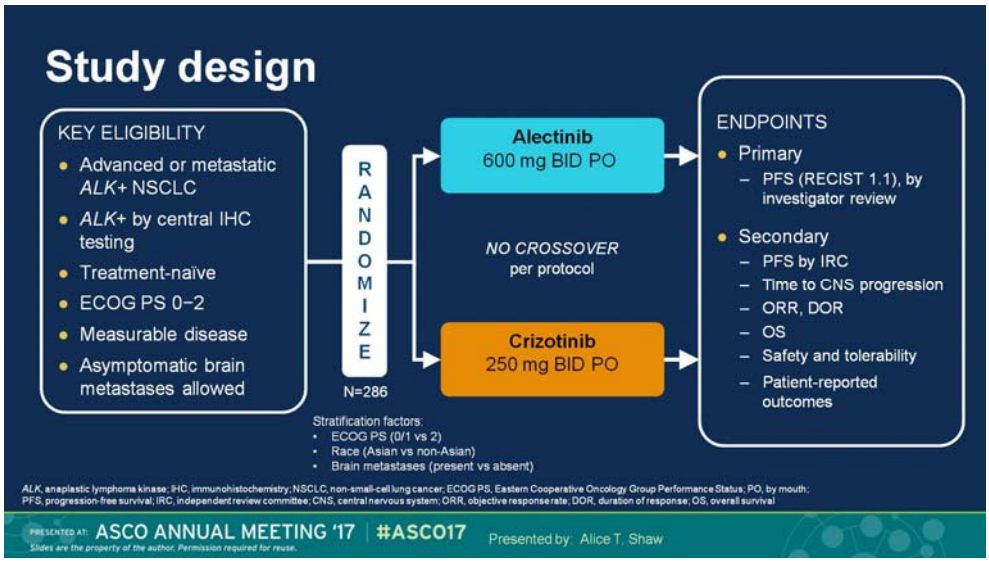

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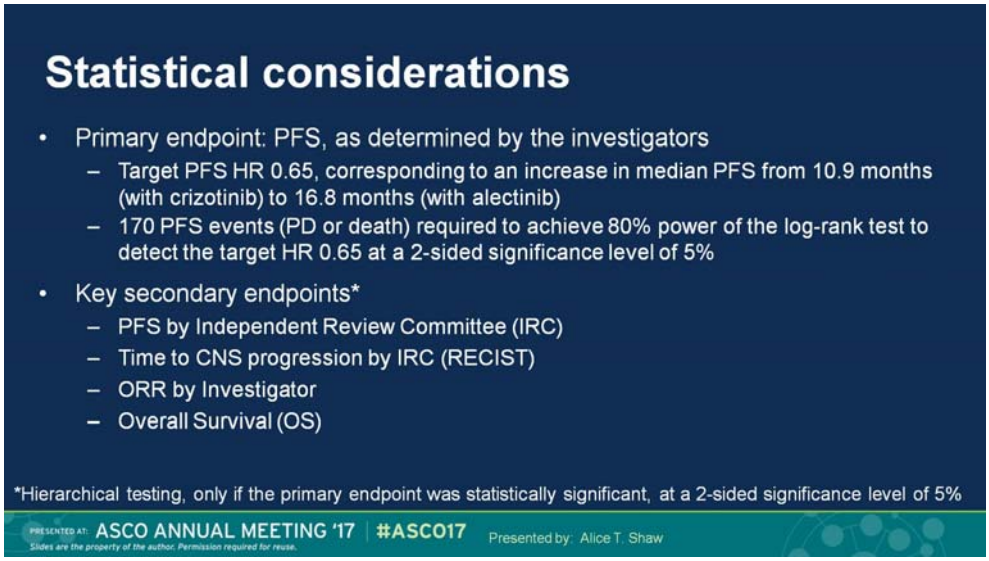

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Baseline characteristics

		Crizotinib (N=151)	Alectinib (N=152)
Age, years	Median (range)	54 (18–91)	58 (25–88)
Gender, n (%)	Female	87 (58)	84 (55)
	Male	64 (42)	68 (45)
Race, n (%)	Non-Asian	82 (54)	83 (55)
	Asian	69 (46)	69 (45)
ECOG PS, n (%)	0–1	141 (93)	142 (93)
	2	10 (7)	10 (7)
Smoking status, n (%)	Non-smoker	98 (65)	92 (61)
	Past smoker	48 (32)	48 (32)
	Active smoker	5 (3)	12 (8)
Histology, n (%)	Adenocarcinoma	142 (94)	137 (90)
	Other*	9 (6)	15 (10)

*Other histology included: large cell carcinoma, mixed with predominantly adenocarcinoma component, squamous cell carcinoma, undifferentiated

ECOG PS, Eastern Cooperative Oncology Group Performance status

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Baseline CNS disease

		Crizotinib (N=151)	Alectinib (N=152)
CNS metastases by IRC (%)	Present	58 (38)	64 (42)
	Absent	93 (62)	88 (58)
CNS metastases treatment (%)	n	58	64
	None	36 (62)	37 (58)
	Whole brain RT	16 (28)	17 (27)
	Radiosurgery	4 (7)	5 (8)
	Other*	1 (2)	4 (6)
	Brain surgery	1 (2)	1 (2)

*1 patient in the alectinib arm received both radiosurgery and whole brain radiotherapy; 1 patient in the crizotinib arm and 3 patients in the alectinib arm had brain surgery combined with radiotherapy

CNS, central nervous system; IRC, Independent Review Committee, RT, radiotherapy

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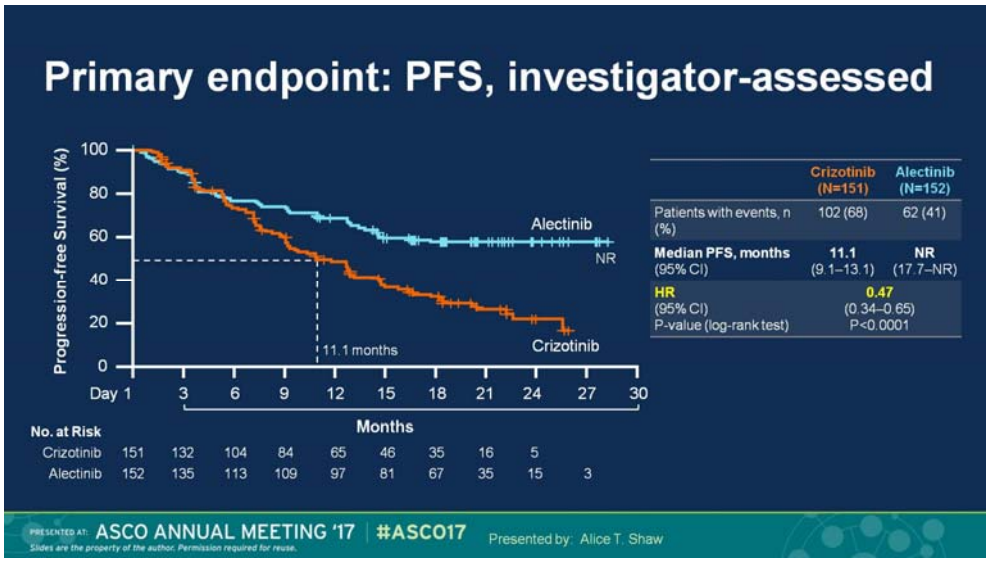

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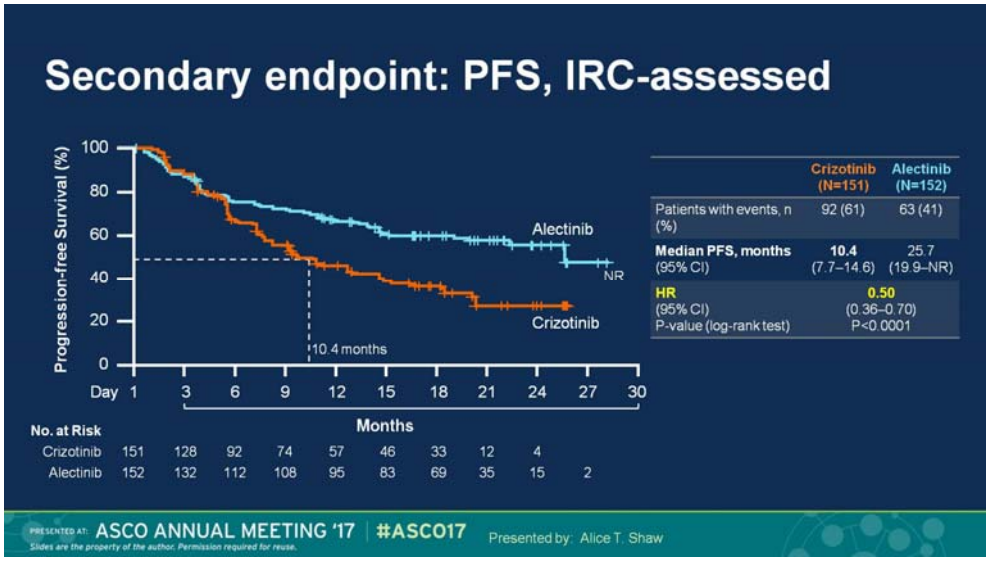

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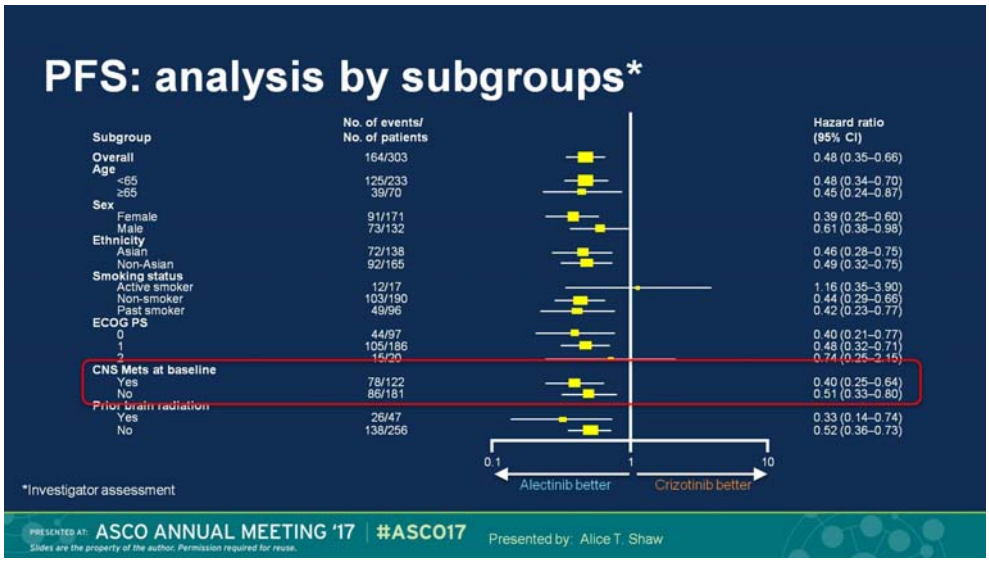

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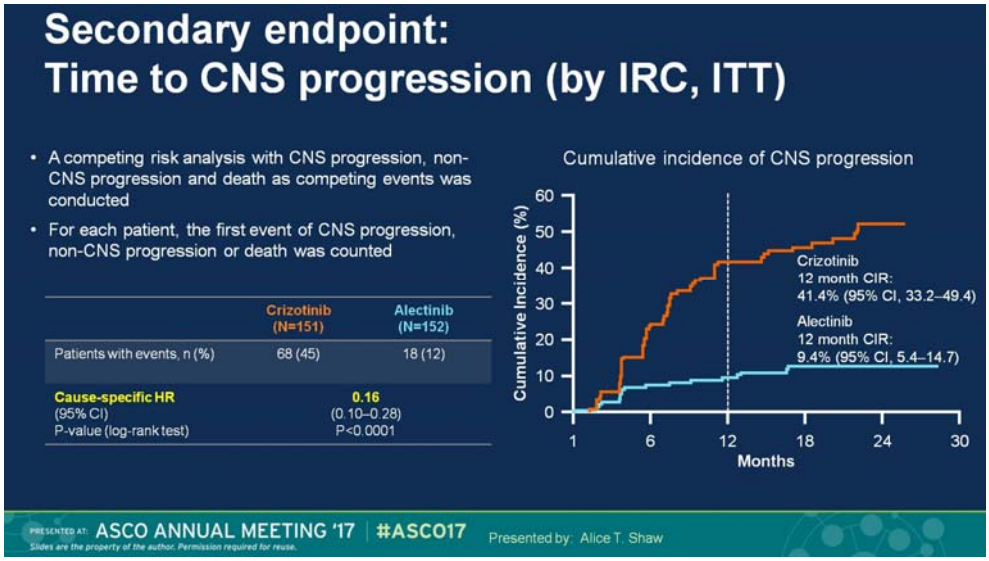

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Objective response rate*

	Crizotinib (N=151)		Alectinib (N=152)
Responders, n (%)	114 (76)		126 (83)
(95% CI)	(68–82)	P=0.09	(76–89)
Complete response, n (%)	2 (1)		6 (4)
Partial response, n (%)	112 (74)		120 (79)
Stable disease, n (%)	24 (16)		9 (6)
Median DOR (months)	11.1		NR
(95% CI)	(7.9–13.0)	HR=0.36	(NR)

*Investigator assessment

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CNS objective response rate*

Measurable CNS lesions at baseline

	Crizotinib (N=22)	Alectinib (N=21)
CNS responders, n (%)	11 (50)	17 (81)
(95% CI)	(28–72)	(58–95)
CNS complete response, n (%)	1 (5)	8 (38)
Median DOR in the CNS, months	5.5	17.3
(95% CI)	(2.1–17.3)	(14.8–NR)

Measurable and non-measurable CNS lesions at baseline

	Crizotinib (N=58)	Alectinib (N=64)
CNS responders, n (%)	15 (26)	38 (59)
(95% CI)	(15–39)	(46–72)
CNS complete response, n (%)	5 (9)	29 (45)
Median DOR in the CNS, months	3.7	NR
(95% CI)	(3.2–6.8)	(17.3–NR)

*IRC assessment

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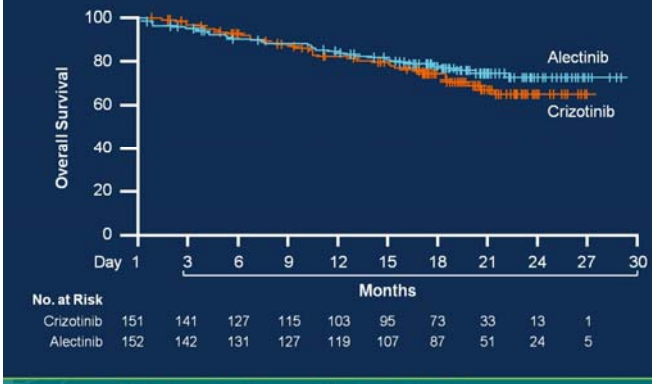
Secondary endpoint: OS



	Crizotinib (N=151)	Alectinib (N=152)
Patients with events, n (%)	40 (27)	35 (23)
Median OS, months (95% CI)	NR (NR)	NR (NR)
HR (95% CI) P-value (log-rank test)	0.76 (0.48–1.20) P=0.24	

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Safety summary and exposure

	Crizotinib (N=151)	Alectinib (N=152)
Median treatment duration, months (range)	10.7 (0–27)	17.9 (0–29)
Total number of patients with any AEs, n (%)	146 (97)	147 (97)
Serious AEs, n (%)	44 (29)	43 (28)
Grade 3–5 AEs, n (%)	76 (50)	63 (41)
Fatal AEs, n (%)*	7 (5)	5 (3)
AEs leading to treatment discontinuation, n (%)	19 (13)	17 (11)
AEs leading to dose reduction, n (%)	31 (21)	24 (16)
AEs leading to dose interruption, n (%)	38 (25)	29 (19)
Mean dose intensity, % (SD)	92.4 (14.1)	95.6 (10.3)

AE, adverse event. *Two events in crizotinib arm and none in alectinib arm were reported as related to study treatment

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Adverse events, ≥10% between treatment arms

	Crizotinib (N=151)		Alectinib (N=152)	
N (%)	Any grade	Grade 3–5	Any grade	Grade 3–5
Nausea	72 (48)	5 (3)	21 (14)	1 (1)
Diarrhea	68 (45)	3 (2)	18 (12)	0
Vomiting	58 (38)	5 (3)	11 (7)	0
Peripheral edema	42 (28)	1 (1)	26 (17)	0
Dysgeusia	29 (19)	0	4 (3)	0
ALT increased	45 (30)	22 (15)	23 (15)	7 (5)
AST increased	37 (25)	16 (11)	21 (14)	8 (5)
Visual impairment	18 (12)	0	2 (1)	0
Blood bilirubin increased	2 (1)	0	23 (15)	3 (2)
Myalgia	3 (2)	0	24 (16)	0
Anemia	7 (5)	1 (1)	30 (20)	7 (5)
Weight increased	0	0	15 (10)	1 (1)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase

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Summary

- This is the first global randomized phase III study to compare next- versus first-generation ALK inhibitors in previously untreated, advanced *ALK*+ NSCLC
- Compared to crizotinib, alectinib:
  - significantly prolonged PFS
    - HR 0.47, 95% CI 0.34-0.65; p<0.0001
  - significantly delayed time to CNS progression
  - significantly improved intracranial ORR and DOR
  - had a more favorable AE profile

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SMALL CELL LUNG CANCER

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Nivolumab ± Ipilimumab in Advanced Small Cell Lung Cancer: First Report of a Randomized Cohort From CheckMate 032

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CheckMate 032: Nivolumab ± Ipilimumab in Advanced Small Cell Lung Cancer (SCLC): Background

- Patients with recurrent SCLC have limited treatment options and poor survival[1–6]
- CheckMate 032, a phase I/II trial, is evaluating nivolumab ± ipilimumab in recurrent SCLC and other tumor types[7]
- Initial results showed durable responses and encouraging survival[7,8]
  - Data supported the inclusion of nivolumab ± ipilimumab in NCCN Guidelines[9]
- A randomized cohort was added to further evaluate nivolumab ± ipilimumab in patients with SCLC whose disease progressed after platinum-based therapy

NCCN = National Comprehensive Cancer Network

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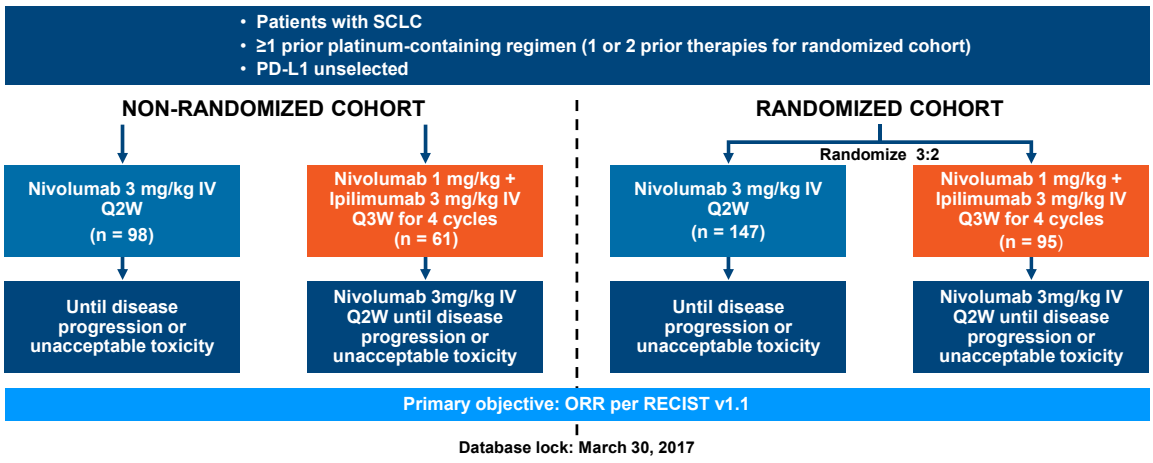
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC Phase I/II CheckMate 032 Study Design



ORR = objective response rate; PD-L1 = programmed death ligand 1

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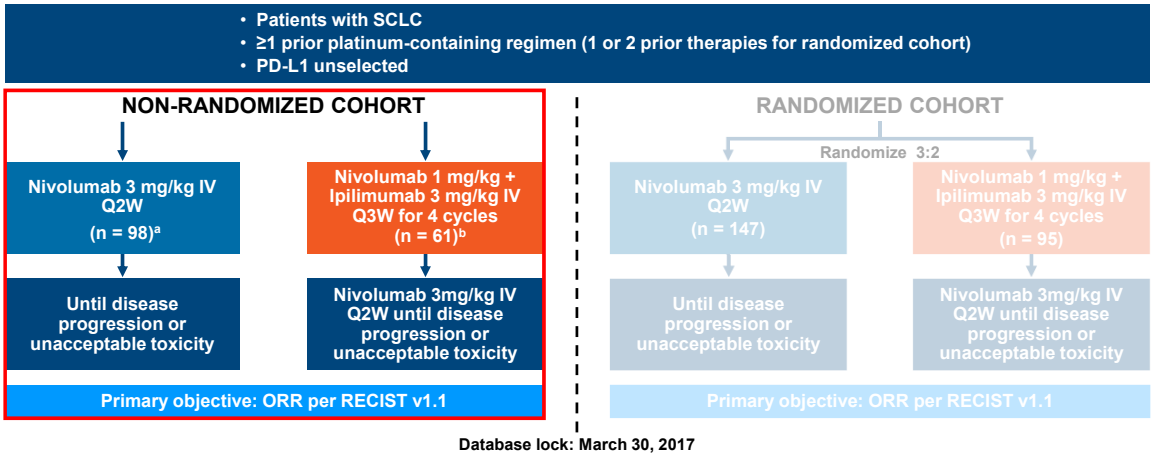
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
Phase I/II CheckMate 032 Study Design – Non-Randomized Cohort



- Update includes response per blinded independent central review (BICR)
  - Additional follow-up of ~6 months from prior disclosure[8]

[a]Median follow-up 23.3 mo; [b]Median follow-up 28.6 mo
Follow-up was calculated as time from first dose to database lock

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CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
Summary of Response per BICR – Non-Randomized Cohort

Summary of response

	Nivolumab (n = 98)	Nivolumab + Ipilimumab (n = 61)
ORR, % (95% CI)	**11** (6, 19)	**23** (13, 36)
Median time to response, mo (range)	1.4 (1.1–4.1)	2.0 (1.0–4.1)
Median DOR, mo (range)	17.9 (2.8–34.6+)	14.2 (1.5–26.5+)
Patients with ongoing responses at 2 yr,[a] %	45	36

DOR = duration of response; ipi = ipilimumab; nivo = nivolumab; [a]Percentage of responders (nivo, n = 11; nivo + ipi, n = 14)

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CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
Summary of Response per BICR – Non-Randomized Cohort

Summary of response

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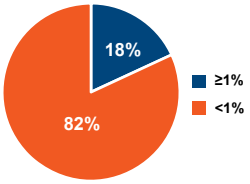
Patients with ongoing responses at 2 yr,[a] %	45	36

Tumor PD-L1 expression in non-randomized cohort (n = 159)[b]



ORR by tumor PD-L1 expression

PD-L1 expression	ORR, % (n/N)	
	Nivolumab (n = 98)	Nivolumab + Ipilimumab (n = 61)
Less than 1%	14 (9/64)	32 (10/31)
1% or more	9 (1/11)	10 (1/10)

DOR = duration of response; ipi = ipilimumab; nivo = nivolumab; [a]Percentage of responders (nivo, n = 11; nivo + ipi, n = 14)
[b]Percentage of patients with quantifiable PD-L1 expression; PD-L1 expression was not evaluable/missing in 43 patients (27%)

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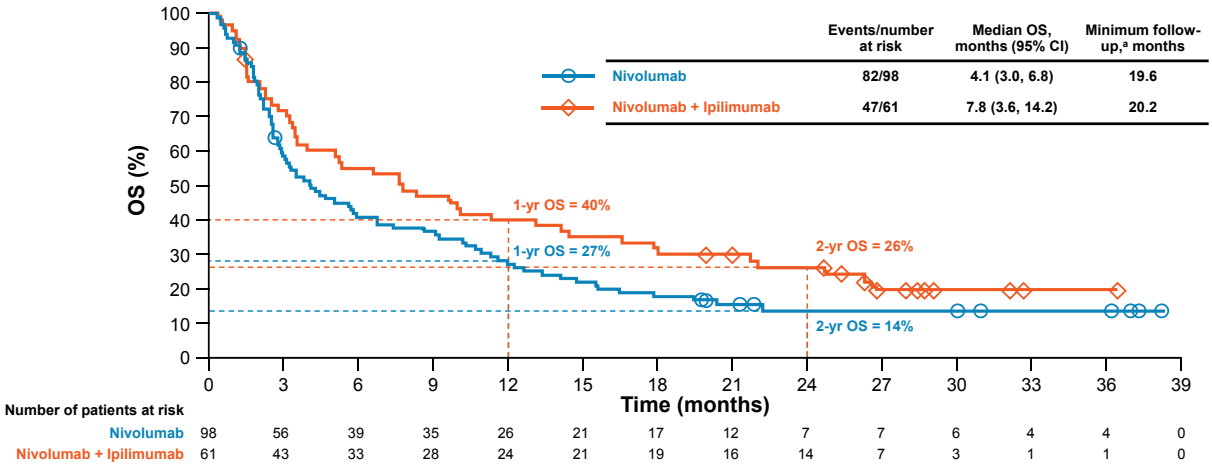
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
OS – Non-Randomized Cohort



OS = overall survival; [a]Between first dose and database lock; follow-up shorter for patients who died prior to database lock

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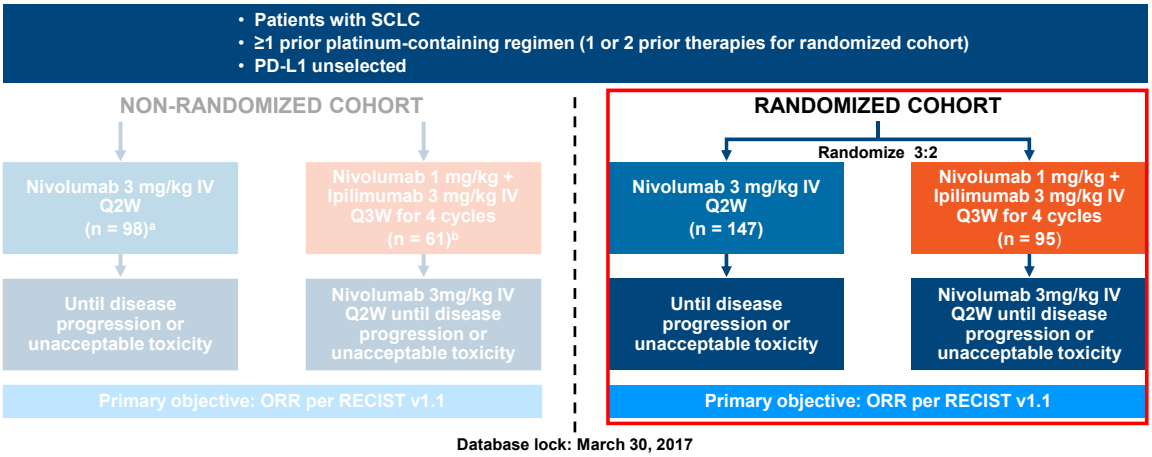
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
Phase I/II CheckMate 032 Study Design – Randomized Cohort



Database lock: March 30, 2017

- Interim descriptive analysis of the randomized cohort
  - Median follow-up: nivo, 10.8 mo; nivo + ipi, 11.2 mo

[a]Median follow-up 23.3 mo; [b]Median follow-up 28.6 mo
Follow-up was calculated as time from first dose to database lock

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CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
Baseline Patient Characteristics – Randomized Cohort

	Nivolumab (n = 147)	Nivolumab + Ipilimumab (n = 95)
Median age, yr (range)	63.0 (29–83)	65.0 (41–91)
≥65 yr, %	44	51
Male, %	59	63
Prior treatment regimens, %		
1	67	67
2–3	33	33
Platinum sensitivity, %		
Sensitive	50	42
Resistant	49	57
Unknown/not reported	1	1
Smoking status, %		
Current/former smoker	92	95
Never-smoker	7	4
Unknown	1	1
ECOG PS, %		
0	33	28
1	67	71
Not reported	0	1

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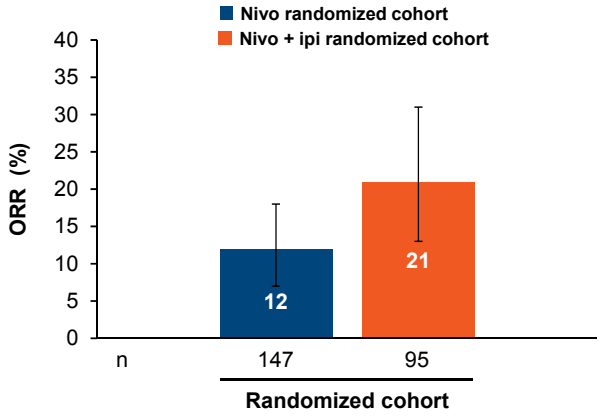
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC Summary of Response per BICR



- Complete responses were achieved in 2 patients in the randomized cohort (nivolumab, n = 1; nivolumab + ipilimumab, n = 1)
- Median time to response in the randomized cohort was comparable to that in the non-randomized cohort
  - Nivolumab, 1.5 mo; nivolumab + ipilimumab, 1.4 mo

Error bars indicate 95% CIs; 95% CIs are as follows – nivo (randomized): 7, 18; nivo + ipi (randomized): 13, 31

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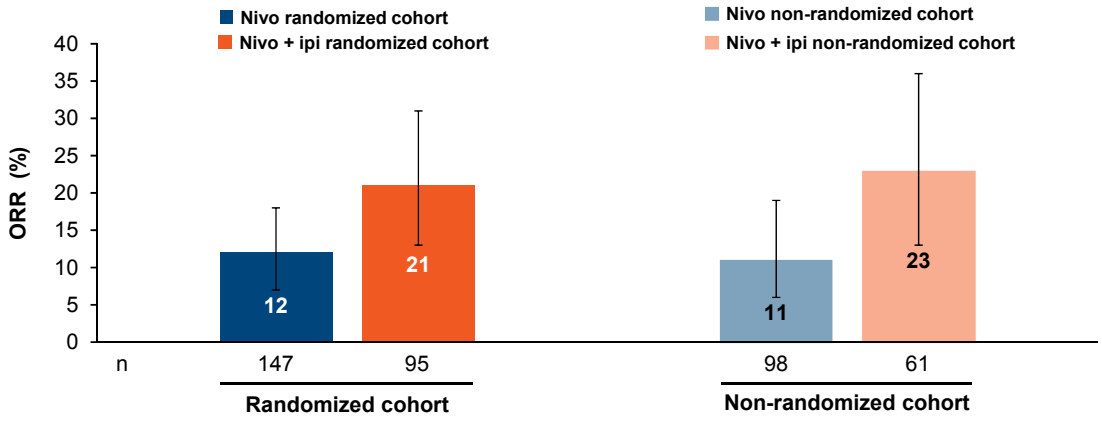
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC Summary of Response per BICR



- Complete responses were achieved in 2 patients in the randomized cohort (nivolumab, n = 1; nivolumab + ipilimumab, n = 1)
- Median time to response in the randomized cohort was comparable to that in the non-randomized cohort
  - Nivolumab, 1.5 mo; nivolumab + ipilimumab, 1.4 mo

Error bars indicate 95% CIs; 95% CIs are as follows – nivo (randomized): 7, 18; nivo + ipi (randomized): 13, 31; nivo (non-randomized): 6, 19; nivo + ipi (non-randomized): 13, 36

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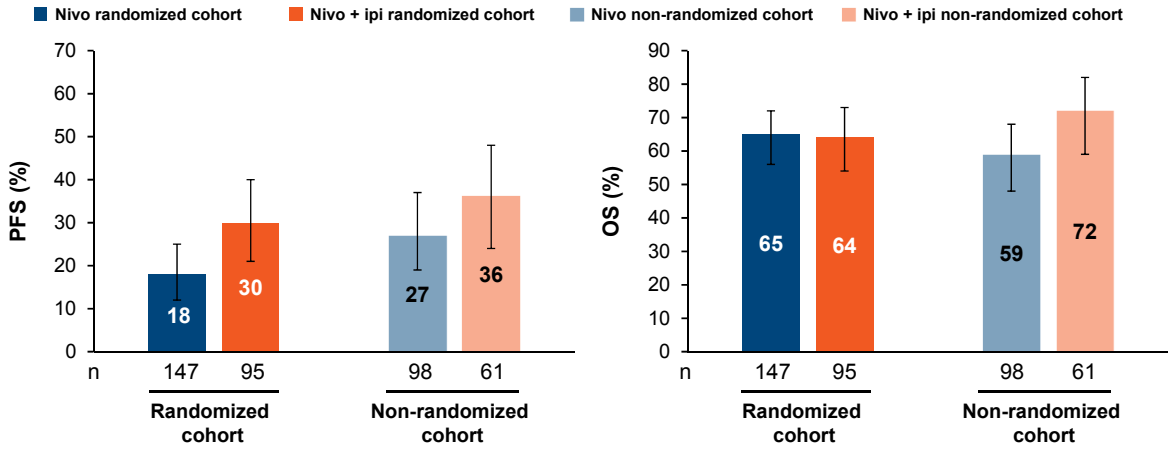
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC 3-month PFS[a] and OS Rates



- Minimum follow-up time was 12 weeks at the time of database lock

PFS = progression-free survival; Error bars indicate 95% CIs; [a]Per BICR

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CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC ORR by Subgroups – Pooled Cohorts

	Nivolumab			Nivolumab + Ipilimumab		
	n	ORR, %	95% CI	n	ORR, %	95% CI
Overall population	245	**11**	8, 16	156	**22**	16, 29
Line of therapy						
Second-line	137	**12**	7, 18	98	**19**	12, 29
Third-line and beyond	108	**11**	6, 19	58	**26**	15, 39
Platinum sensitivity (all treated patients)[a]						
Platinum-sensitive	133	**13**	8, 20	85	**26**	17, 36
Platinum-resistant	110	**10**	5, 17	65	**15**	8, 26

[a]Platinum sensitivity was unknown for 2 patients in the nivo arm and 6 patients in the nivo + ipi arm

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CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC Summary of Safety – Pooled Cohorts

	Nivolumab (n = 245)		Nivolumab + Ipilimumab (n = 156)	
	Any grade, %	Grade 3–4, %	Any grade, %	Grade 3–4, %
Any TRAEs	**55**	**12**	**73**	**37**
TRAEs leading to discontinuation	**3**	**2**	**13**	**10**
Select TRAEs by category				
Skin	16	<1	36	6
Endocrine	8	0	21	3
Hepatic	6	2	12	6
Gastrointestinal	5	0	24	8
Hypersensitivity/infusion reaction	5	0	1	0
Pulmonary	3	2	4	3
Renal	1	<1	1	0
Grade 3–4 select TRAEs that resolved, %[a]	45		78	

- Median time to resolution of grade 3–4 select TRAEs ranged from 1.8 wk (gastrointestinal events) to 16.3 wk (hepatic events) in the nivolumab + ipilimumab arm and from 3.4 wk (pulmonary events) to not reached (renal and hepatic events) in the nivolumab arm
- There were a total of 5 treatment-related deaths[b]
  - 4 with nivolumab + ipilimumab (due to myasthenia gravis, pneumonitis, seizures/encephalitis, and autoimmune hepatitis)[c]
  - 1 with nivolumab (due to pneumonitis)

TRAE = treatment-related adverse event; [a]Percentage of total number of grade 3-4 select TRAEs across categories (nivo + ipi, n = 40; nivo, n = 11); [b]In addition, there was one death in the nivo + ipi arm for which both disease progression and colitis were felt to be contributing factors; [c]A previously reported death due to renal failure was subsequently determined to not be related to treatment

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CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC Summary

- With BICR and longer follow-up in the non-randomized cohort, responses remained durable and survival promising
  - 2-yr OS: nivolumab + ipilimumab, 26%; nivolumab, 14%
- In a randomized, phase 2 cohort of 242 patients, initial efficacy was consistent with that in the non-randomized cohort
  - ORR: nivolumab + ipilimumab, 21%; nivolumab, 12%
- Responses observed regardless of platinum sensitivity, line of therapy or PD-L1 status
- Grade 3/4 TRAEs and deaths were more common with nivolumab + ipilimumab than with nivolumab
- Additional exploratory analyses are ongoing (QoL, biomarkers) towards improving predictors of response to immunotherapy in SCLC and optimizing management

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Ongoing Phase 3 Studies With Nivolumab ± Ipilimumab in SCLC

CheckMate 451: study design[10]

- *Currently enrolling patients*

Key eligibility criteria
- ED-SCLC
- Ongoing SD/PR/CR after 4 cycles of 1L PLT-CT
- No symptomatic CNS metastases
- Toxicities from prior therapy resolved to grade ≤1
- ECOG PS ≤1

N = 810

Randomize 1:1:1

- Nivolumab
- Nivolumab + Ipilimumab
- Placebo

- **Primary outcome measures:**
  - OS, PFS
- **Secondary outcome measures:**
  - OS and PFS descriptive analyses: nivolumab vs nivolumab + ipilimumab

CheckMate 331: study design[11]

Key eligibility criteria
- SCLC
- Recurrence/PD after 1L PLT-CT or CRT (≥4 cycles)
- ECOG PS ≤1
- No symptomatic CNS metastases
- No prior therapy with anti–CTLA-4, anti–CD137, anti–PD-1/PD-L1/PD-L2

N = 480

Randomize 1:1

- Nivolumab
- Topotecan or Amrubicin[a]

- **Primary outcome measures:**
  - OS
- **Secondary outcome measures:**
  - PFS, ORR

1L = first-line; CT = chemotherapy; CRT = chemoradiation therapy; CTLA-4 = cytotoxic T lymphocyte antigen-4; PD-1 = programmed-death 1; PD-L2 = PD ligand 2
PLT = platinum-based; [a]Where locally approved

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Background

- Poly (ADP) ribose polymerase (PARP) family of enzymes is involved in DNA damage repair, through its central role in base excision repair (BER) and other repair pathways including HRR and NHEJ[1,2]
- Higher expression of PARP in SCLC may be associated with drug resistance and the ability of tumor cells to withstand genotoxic stress[3]
- Genetic ablation and pharmacological inhibition of PARP enzyme activity enhance cytotoxicity of DNA damaging chemotherapeutic agents and ionizing radiation[2-4]

1. Konstantinopoulos et al. Cancer Discov 2015;5:1137-1154
2. Farmer H et al. Nature. 2005 Apr 14;434(7035):917-21.
3. Byers L A et al. Cancer Discovery 2012;2:798-811
4. Owonikoko et al. Cancer Med. 2014 Dec;3(6):1579-94

Background

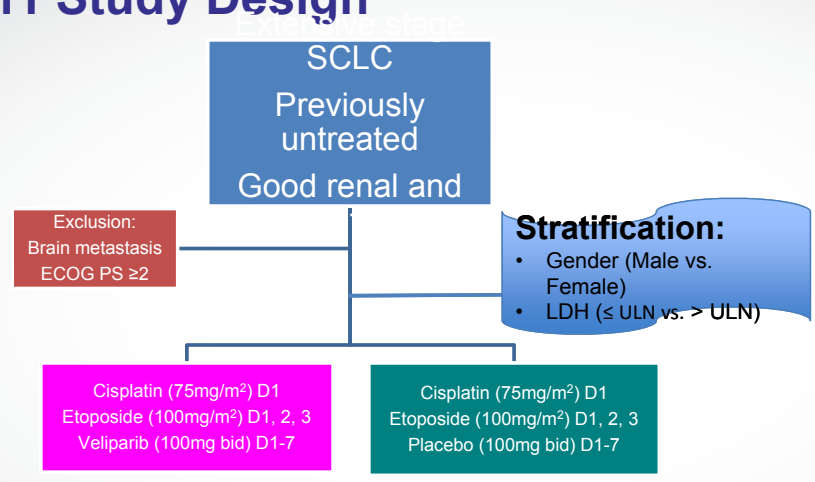
- Outcome for patients with extensive stage small cell lung cancer (ES-SCLC) remains very poor due to limited therapeutic options for this disease[1,2]
- Veliparib, an orally available pharmacological inhibitor of PARP enzyme, potentiates standard platinum doublet chemotherapy in preclinical models of SCLC (cell lines and xenografts)[1,3]
- E2511 study was designed to evaluate the combination of veliparib (V) with cisplatin/etoposide (CE) doublet as first-line therapy of extensive stage SCLC (ES-SCLC)

1. Sabari et al. Nat Rev Clin Oncol. 2017 May 23.
2. Johnson D, et al. J Clin Oncol; 20:4665-4672 2002
3. Owonikoko et al. Cancer Med. 2014 Dec;3(6):1579-94

Objectives

- Primary Objective:
  - To determine whether the addition of veliparib to cisplatin etoposide (CE) resulted in improved progression free survival (PFS) over CE with placebo in the frontline therapy of newly diagnosed extensive stage small-cell lung cancer.
- Secondary Objectives
  - Overall survival (OS)
  - Overall response rate (ORR)
  - Safety and toxicity profile

E2511 Study Design



- Patients received a maximum of 4 cycles of therapy
- Restaging scan obtained every 2 cycles and Q 3 months from end of treatment
- PCI at the discretion of the treating physician
- Consolidation TRT was not allowed

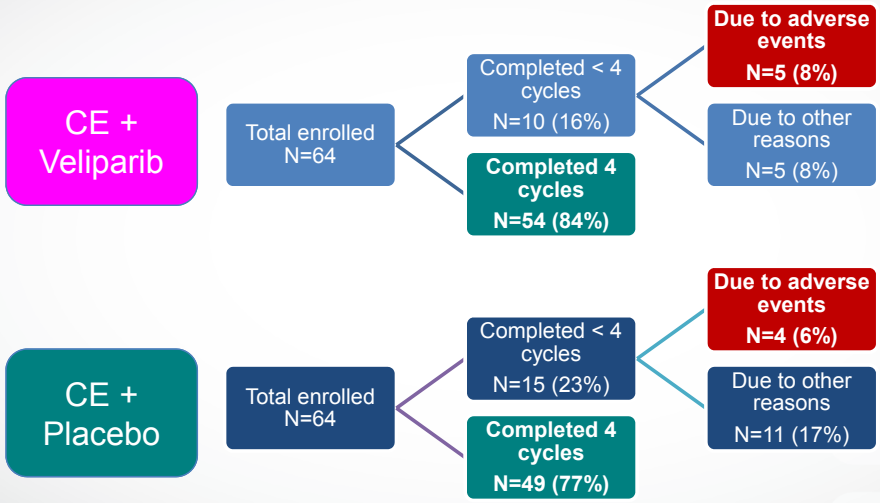
Statistics

- Primary endpoint:
  - Progression-free survival (PFS)
- Population:
  - All eligible patients who started assigned therapy
  - Accrual goal of 135 patients with planned accrual of 150 patients in anticipation of a 10% ineligibility rate
  - Stratification by gender and LDH
  - Randomized 1:1 (67 patients per arm)
- Power of 88% with a one-sided alpha of 0.10
  - To detect a 37.5% reduction in the PFS hazard rate based on a total of 113 PFS events
  - Corresponds to improved median PFS from 5 months on CE plus placebo to 8 months on CE plus veliparib
- Data cut as of December 8, 2016
  - Median follow-up of 18.5 months (18.1 vs. 21.5 for Veliparib and Placebo arms)

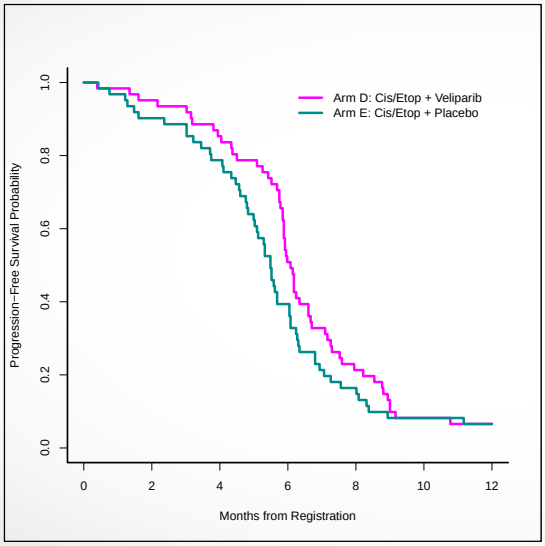
Study population characteristics

Variable	Category	CE + Veliparib	CE + Placebo	Total
Gender	Female	30(47)	32(50)	62(48)
	Male	34(53)	32(50)	66(52)
Age	Median (Q1,Q3)	66 (59,72)	66 (59,70)	64 (59,71)
Race	Asian	1(2)	2(3)	3(2)
	Black/African American	2(3)	2(3)	4(3)
	Not Reported Or Unknown	0(0)	3(5)	3(3)
	White)	61(95)	57(89	118(92)
ECOG PS	0	15(23)	22(34)	37(29)
	1	49(77)	42(66)	91(71)
LDH >ULN	No	20(31)	21(33)	41(32)
	Yes	44(69)	43(67)	87(68)

Patient disposition on study



Progression free survival (PFS)

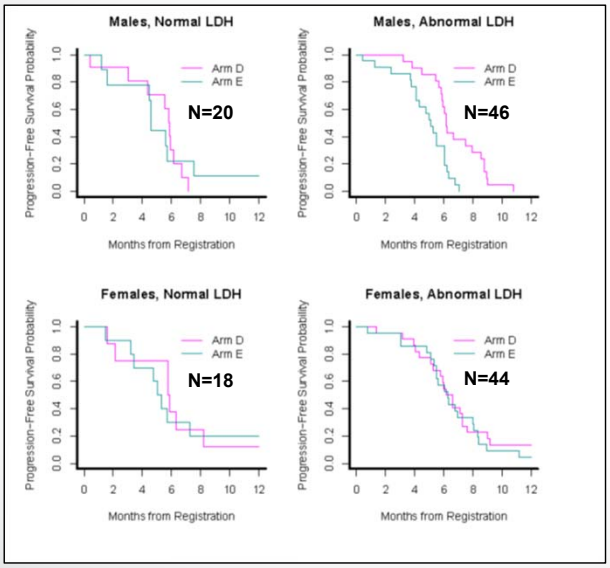


Unadjusted PFS HR: 0.75
1-sided p=0.06

Adjusted PFS HR: 0.63
1-sided p=0.01

Median PFS: 6.1 vs. 5.5 months for CE+V and CE+P respectively

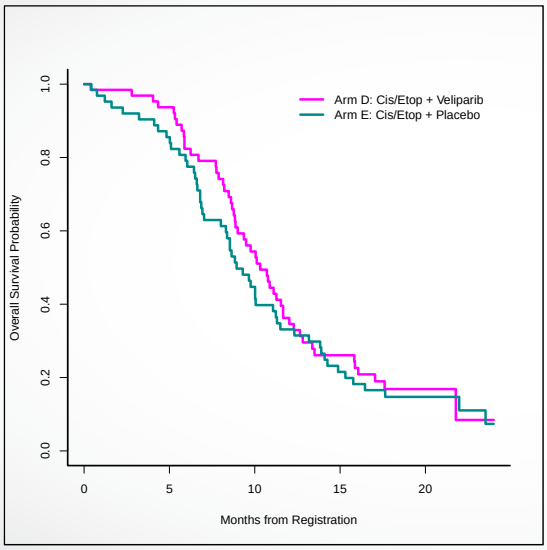
PFS analysis by strata



Male/abnormal LDH stratum
Adjusted PFS HR: 0.34 80% CI: 0.22 - 0.51
1-sided p<0.001

Other Strata:
Adjusted PFS HR: 0.81 80% CI: 0.60 - 1.09
1-sided p=0.18

Overall survival (OS)

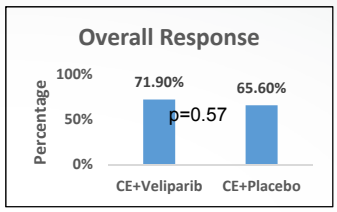


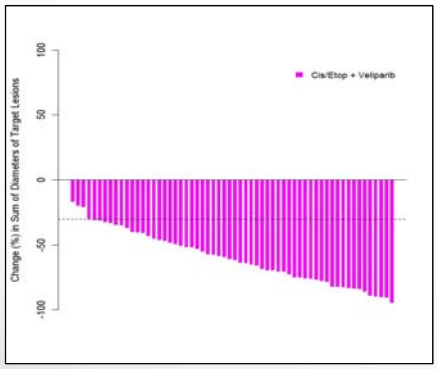
OS HR: 0.83 (80% CI 0.64-1.07); 1-sided p=0.17.

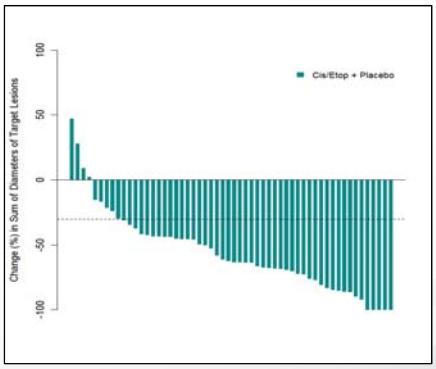
Median OS: 10.3 vs. 8.9 months for CE+V and CE+P respectively

Overall response by RECIST

	CE+V	CE+P	Overall
CR	0 (0)	1 (1.6)	1 (<1)
PR	46 (72)	41 (64)	87 (68)
SD	8 (13)	8 (13)	16 (13)
PD	6 (9)	6 (9)	12 (9)
NE	4 (6)	8 (13)	12 (9)







Most Frequent (≥5%) Treatment Emergent Grade ≥ 3 Adverse Events

Toxicity Type	CE + Veliparib			CE + Placebo		
	Grade (%)			Grade (%)		
	3	4	5	3	4	5
Hematologic						
Neutropenia	**20**	**29**	**-**	**14**	**18**	**-**
Leukopenia	**8**	**11**	**-**	**12**	**2**	**-**
Anemia	**17**	**2**	**-**	**12**	**-**	**-**
Thrombocytopenia	8	2	-	2	3	-
Lymphopenia	10	-	-	5	-	-
Febrile Neutropenia	5	-	-	3	-	2
Non Hematologic						
Hyponatremia	12	-	-	2	5	
Dehydration	5	2	-	3	-	-
Acute kidney injury	5			2	2	
Hyperglycemia	5	-	-	-	-	-
Fatigue	3	-	-	5	-	-

Conclusions

1. E2511 signals potential benefit of PARP inhibitor, veliparib, when added to platinum doublet chemotherapy in patients with extensive stage SCLC
2. Addition of veliparib increased hematologic toxicity but did not compromise chemotherapy delivery
3. Biomarker enrichment strategy will be needed in order to optimize the benefit of PARP inhibition as a therapeutic strategy in this patient population
4. A randomized phase II study of carboplatin/etoposide with or without veliparib (NCT02289690) is currently accruing

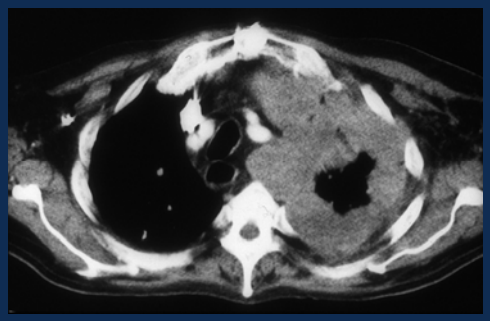
MESOTHELIOMA

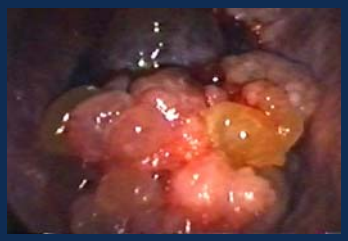
Second or 3rd line Nivolumab (Nivo) versus Nivo plus Ipilimumab (Ipi) in Malignant Pleural Mesothelioma (MPM) patients: results of the IFCT-1501 MAPS-2 randomized phase 2 trial.

EUDRACT N° 2015-004475-75 - ClinicalTrials.gov : NCT 02716272

Arnaud SCHERPEREEL, Julien MAZIERES, Laurent GREILLER, Radj GERVAIS, Olivier BYLICKI, Isabelle MONNET, Romain CORRE, Denis MORO-SIBILOT, Clarisse AUDIGIER-VALETTE, Myriam LOCATELLI, Olivier MOLINIER, Luc THIBERVILLE, Thierry URBAN, Catherine LIGEZA-POISSON, David PLANCHARD, Elodie AMOUR, Franck MORIN and Gérard ZALCMAN, on behalf of the French Cooperative Thoracic Intergroup (IFCT)

MPM: an aggressive and quite rare cancer….





…without any validated curative treatment

First-line treatment (Pemetrexed−Cisplatin): mOS of 13-15 months[1], recently improved by bevacizumab addition (18.8 months) in the phase III MAPS trial[2]
... But NO validated treatment beyond Pem-based chemotherapy failure

[1]Vogelzang NJ et al. *J Clin Oncol.* 2003; [2]Zalcman G et al, *Lancet* 2016

MPM treatment in patients beyond 1rst line chemotherapy

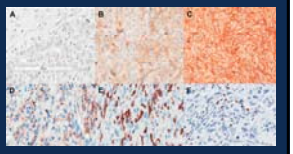
TREATMENT	N pts	%ORR	mOS (months)
Doxorubicin	11	9%	4.5
ZD0473	43	0	6.7
Oxaliplatin/Raltitrexed	14	0	3.2
Doxo vs Cyclophosphamide	11	0	-
Pemetrexed	28	**21**	9.8
Pemetrexed/Carboplatin	11	**18**	8.6
Gemcitabine*	15	2	4.9
Vinorelbine*	33	0	5.4
Erlotinib/Bevacizumab	24	0	5.8

→**Except selected patients with long-lasting response to 1st line Pem-based chemo, DCR usually < 30% and mOS < 6-9 months**

Scherpereel and al, *Eur Respir J* 2010, updated with Zauderer and al, *Lung Cancer* 2014, and Buikhuisen and al, *Lung Cancer* 2015

Rationale to target CTLA-4 and/or PD-L1 in MPM

- Inflammatory phenotype (T cells) and **tumor expression of PD-L1 by MPM cells** (and stroma): at least 20-40% of cases (Sarcomatoïd>Biphasic>Epithelioïd)[1]
- **PD-L1 expression associated with bad prognosis in MPM**[2] :
  - mOS: 5.0 months if PD-L1+ tumor vs 14.5 months if PD-L1 negative
  - PD-L1+ expression is an independent risk factor for OS: RR = 1.71



Thapa, *JTO* 2017 12, 850-9

- Conversely, patients with **highest level of intra-tumor cytotoxic CD8+ T cells in resected MPM had a better prognosis**[3]
- **First results of trials assessing anti-PD-1 or anti-PD-L1 (± anti-CTLA-4) Ab in MPM were encouraging**[4], opposed to anti-CTLA-4 alone[5]…

1. Thapa, *JTO* 2017; Lanteajoul, *JTO* 2017; Mansfield, *JTO* 2014; Khanna, *JTO* 2016; 2. Cedrés, *PLoS One* 2015; Combaz-Lair C, *Hum Pathol.* 2016; 3. Lievense, *AJRCCM*. 2017; 4. Alley, *Lancet Oncol.* 2017, Kindler H (*WCLC* 2016); Baas P (*WCLC* 2016); Quispel-Janssen (*iMig* 2016); Hassan R (*ESMO* 2015); Calabro (*iMig* 2014); 5. Kindler and al, *Lancet Oncol.* 2017

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Randomized, non-comparative phase 2 trial - One-step Fleming design (each arm independently)

- **Validated histological diagnosis of Malignant Pleural Mesothelioma**
- **Unresectable cancer with documented progression after maximum 1 or 2 previous lines of chemotherapy including a pemetrexed/platinum doublet**
- **Measurable disease**
- **ECOG PS 0-1**
- Weight loss <10%
- Age > 18 years (M or F)
- Available tumor tissue…

R 1:1

57 patients

Nivolumab
3 mg/kg IV / 2 weeks

until progression or unacceptable toxicity (or 2 years max)

CT-scan every 12 weeks

57 patients

Nivolumab
3 mg/kg IV / 2 weeks
+ Ipilimumab
1mg/kg IV / 6 weeks

until progression or unacceptable toxicity (or 2 years max)

Objectives

First endpoint:

- Disease control rate (DCR) at 12 weeks of treatment: *centrally evaluated by an independent and blinded expert panel of radiologists, according to modified RECIST-meso criteria**

Secondary goals:

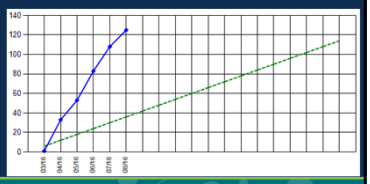
- Safety (CTCAE 4.0 criteria)
- Progression-free Survival (PFS)
- Overall Survival (OS)
- Quality of Life (LCSS-meso)
- Evaluation of predictive value of tumor PD-L1 score
- Evaluation of pronostic value of various biomarkers

Ongoing analysis; will not be shown during ASCO 2017 meeting

**Byrne M.J. & Nowak A. Ann. Oncol. 2004; 15: 257–260*

Statistical Plan

- Patients randomized according a minimisation plan with **stratification by**:
  - histologic subtype *(epithelioïd vs. sarcomatoïd+biphasic)*
  - line of treatment *(2nd vs 3rd line)*
  - chemosensitivity to Cisplatin/Pemetrexed *(progression ≥3 months vs <3 months)*
- To demonstrate a **disease control rate (DCR) after 12 weeks of 40%,** by a blinded independent central review
  - α-risk = 5% and power = 90%
  - **114 patients were to be randomized** *(assuming 5% of ineligibility)*, with one-step Fleming procedure *(H0 P≤20% vs H1 P≥40%)*
  - → **At least 16 failure-free patients** had to be observed at 12 weeks in either arm, **to conclude to the activity of the corresponding regimen**
- Planned patients follow-up was 2 years, and accrual duration was 18 months
  - **Accrual goal reached in less than 5 months !**



ASCO ANNUAL MEETING '17 | #ASCO17
Press briefing presentation

Presented by: Arnaud SCHERPEREEL, CHU Lille, France

Study Flowchart

Data cut-off: March 31th, 2017

Randomized ***n* = 125**

From March 2016 to August 2016

Allocated NIVOLUMAB ***n* = 63**

Allocated NIVOLUMAB + IPILIMUMAB ***n* = 62**

Ineligible (*n*=5)
- No progression to inclusion (n=1)
- Received 3 or more treatment lines before inclusion (n=3)
- No histological evidence (n=1)

Ineligible (*n*=2)
- No progression to inclusion (n=1)
- Received 3 or more treatment lines before inclusion (n=1)

Received treatment ***n* = 63**

Received treatment ***n* = 61**

Did not receive allocated treatment
- Death (n=1)

Study withdrawn (n=50)
- **Disease Progression (*n*=42, 84.0%)**
- Toxicity (n=3, 6.0%)
- Death (n=1, 2.0%)
- Second cancer (n=1, 2.0%)
- Intercurrent disease (n=1, 2.0%)
- Patient's choice (n=1, 2.0%)
- Other (n=1, 2.0%)

Ongoing *n* = 13

Ongoing *n* = 18

Study withdrawn (n=43)
- **Disease Progression (*n*=25, 58.1%)**
- **Toxicity (n=12, 27.9%)**
- Death (n=5, 11.6%)
- Other (n=1, 2.3%)

ASCO ANNUAL MEETING '17 | #ASCO17
Press briefing presentation

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Patients baseline characteristics (1)	Nivo Arm (n=63)	Nivo+Ipi Arm (n=62)
Gender N (%)		
Male	47 (75)	53 (85)
Female	16 (25)	9 (15)
Age (years)		
Mean +/- SD	71.2 ± 9.4	70.4 ± 9.0
Median [Range]	72.3 [32.5-87.2]	71.2 [48.1-88.1]
Histologic subtype N (%)		
Epithelioïd	51 (81)	53 (85)
Sarcomatoid or Mixed (biphasic)	12 (19)	9 (15)
Performance Status N (%)		
0	19 (31)	25 (40)
1	42 (69)	36 (58)
2	0	1 (2)
Smoking status N (%)		
Smoker / Never Smoker	33 (53) / 29 (47)	35 (56) / 27 (44)
Number of prior line(s) N (%)		
1	44 (70)	43 (69)
2	16 (25)	18 (29)
>2	3 (5)	1 (2)

Drug-related Adverse Events (AE)

→ *During the first 6 infusions of treatment*

AE	Nivo Arm (n=63)	Nivo+Ipi Arm (n=61)
All grade	49 (77.8%)	53 (86.9%)
Grade 3-4	6 (9.5%)	11 (18.0%)
Grade 5	0 (0%)	2 (3.3%)*

3 Treatment-related deaths in the combo arm as reported by local investigators:
*1 fulminant hepatitis, 1 encephalitis

Note: another one due to acute kidney failure occurred after 12 weeks

Main drug-related Non-Hematological AE during the first 6 infusions of treatment

AEs of any grade reported in >10% of patients are shown

AE	NIVO Arm (n=63)		NIVO+IPI Arm (n=61)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Asthenia/Fatigue	25 (39.7%)	0%	26 (42.6%)	2 (3.3%)
Diarrhea*	4 (6.3%)	0%	12 (19.7%)	0%
Decreased appetite	12 (19.0%)	0%	8 (13.1%)	0%
Nausea/Vomiting	8 (12.7%)	1 (1.6%)	8 (13.1%)	0%
Pruritus**	1 (1.6%)	0%	7 (11.5%)	0%

*p=0.035; **p=0.04

Tumor Response assessment after first 12 weeks

By a blinded, independent panel of Radiologists

in the **first 108 eligible patients**

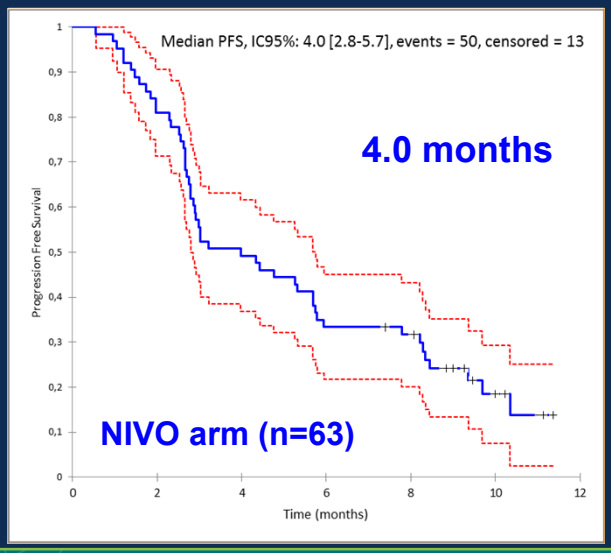
Wxp ru#dvvhvvp hqw# (#IF<8 ('+q#sw,	NIVO Arm (n=54)	NIVO+IPI Arm (n=54)
Remfwlyh#dhvsrqvh	18.5% [8.2-28.9%](10)	25.9% [14.2-37.6%](14)
Vwdedn#Glvhdvh	25.9% [14.2-37.6%](14)	24.1% [12.7-35.5%](13)
Glvhdvh frqwurc udwh	44.4% [31.2-57.7%](24)	50.0% [36.7-63.3%](27)
Glvhdvh Surjuhvvlrq#	51.9 [38.5-65.2%](28)	42.6% [29.4-55.8%](23)
Qrw#hydoxdedn2qrw# grqh 2p lvvlqj	3.7% [0.0-8.7%](2)	7.4% [0.4-14.4%](4)

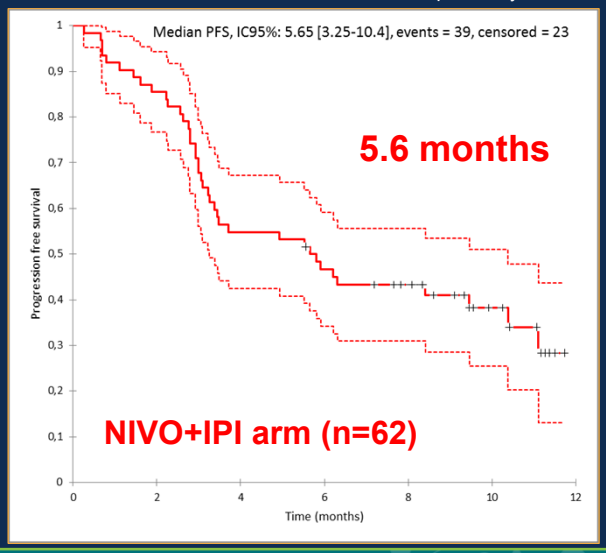
First endpoint based on the statistical plan

Efficacy: ITT median Progression-free Survival (PFS)

median follow-up= 10.4 mo [10.0-11.1]

Data cut-off: March 31th, 2017
Database export: May 2nd, 2017

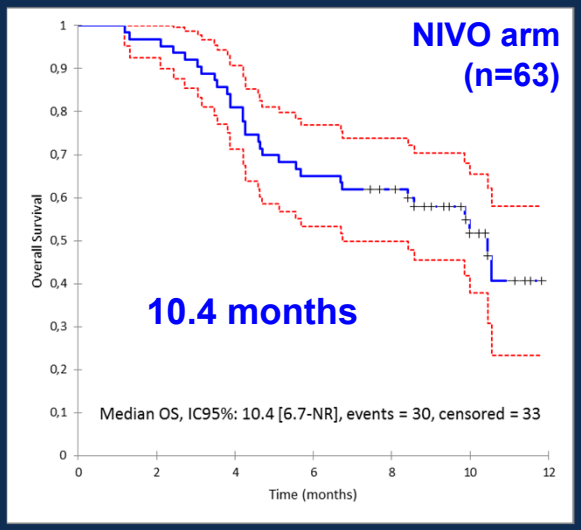


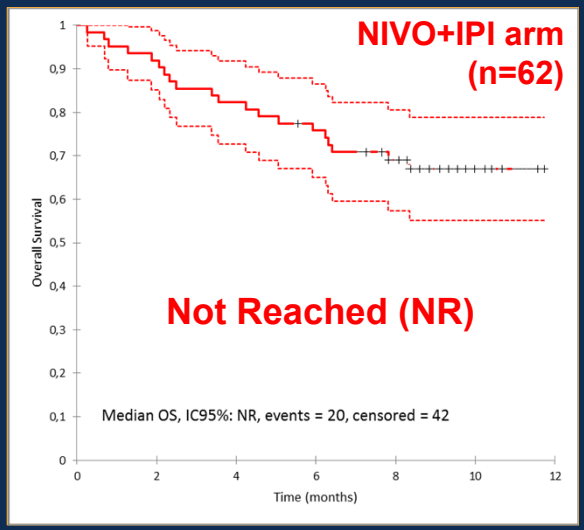


Efficacy: ITT preliminary Overall Survival (OS)

median follow-up= 10.4 mo [10.0-11.1]

Data cut-off: March 31th, 2017
Database export: May 2nd, 2017





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- Both Nivo alone Arm, and Nivo+Ipi Arm reached their 1rst endpoint in 2nd/3rd line MPM pts, increasing **meaningfully 12 weeks DCR**
- Moreover, patients from both arms of this study seem to have **prolonged median OS** than all previous reports in this setting
- Toxicity was **globally** manageable, **even if** 3 treatment-related deaths were reported in the combo arm
- Matured survival, QoL, biomarkers data, and subgroup analysis will be presented next Autumn, 1 year after accrual of the last patient

→ Immunotherapy (Nivo +/- Ipi) may provide new therapeutic options as 2nd/3rd line treatment for relapsing MPM patients