Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Chemotherapeutic and Immunotherapeutic Approaches to Wild-Type NSCLC — Corey J Langer, MD

Select Publications

Borghaei H et al. **Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer.** *N Engl J Med* 2015;373(17):1627-39.

Brahmer J et al. **Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer.** *N Engl J Med* 2015;373(2):123-35.

Garon EB et al. **Pembrolizumab for the treatment of non-small-cell lung cancer.** *N Engl J Med* 2015;372(21):2018-28.

Langer CJ et al. **Weekly *nab*-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Analysis of safety and efficacy in patients with renal impairment.** *Clin Lung Cancer* 2015;16(2):112-20.

Paz-Ares L et al. **Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC).** *Proc ASCO* 2015;**Abstract LBA109**.

Rizvi NA et al. **Safety and efficacy of first-line nivolumab (NIVO; anti-programmed death-1 [PD-1]) and ipilimumab in non-small cell lung cancer (NSCLC).** *Proc IASLC* 2015;**Abstract ORAL02.05**.

Senan S et al. **Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC).** *Proc ASCO* 2015;**Abstract 7506**.

Spigel D et al. **A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC).** *Proc ASCO* 2015;**Abstract 8009**.

Thatcher N et al. **Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): An open-label, randomised, controlled phase 3 trial.** *Lancet Oncol* 2015;16(7):763-74.

Chemotherapeutic and Immunotherapeutic Approaches to Wild-Type NSCLC

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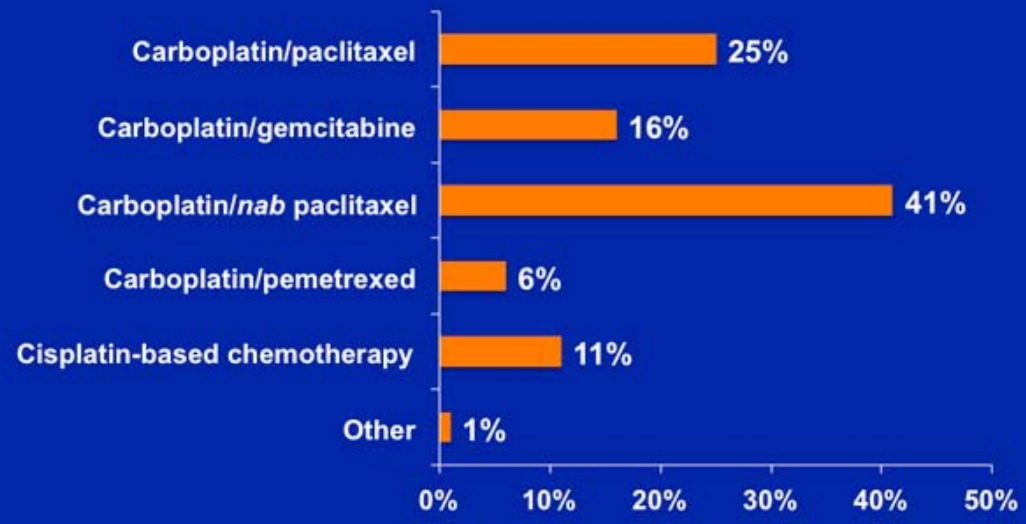
Disclosures

Advisory Committee	Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Lilly, Merck, Novartis Pharmaceuticals Corporation, Pfizer Inc
Consulting Agreements	Abbott Laboratories, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Lilly, Merck, Pfizer Inc
Contracted Research	Astellas Scientific and Medical Affairs Inc, Celgene Corporation, Genentech BioOncology, GlaxoSmithKline, Merck
Data and Safety Monitoring Board	AbbVie Inc, Amgen Inc, Lilly, Peregrine Pharmaceuticals Inc, Synta Pharmaceuticals Corp

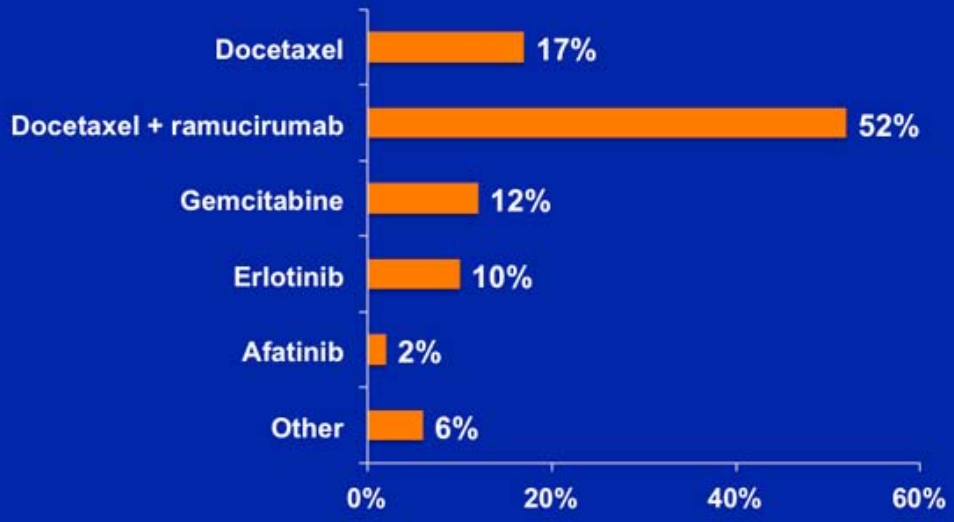
AUDIENCE POLL

In general, what first-line chemotherapy regimen would you most likely recommend for an otherwise healthy 65-year-old patient (PS = 0) with metastatic squamous cell cancer (mSCC) of the lung?



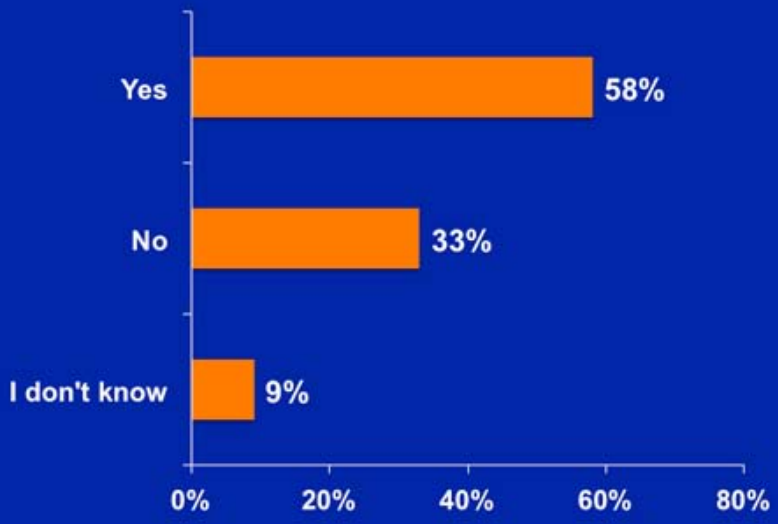
AUDIENCE POLL

A 65-year-old patient with mSCC of the lung receives first-line therapy with carboplatin/*nab* paclitaxel and responds to 4 cycles of treatment but then experiences disease progression 3 months later. The patient is started on an anti-PD-1 antibody but experiences disease progression. What would be your most likely treatment recommendation?



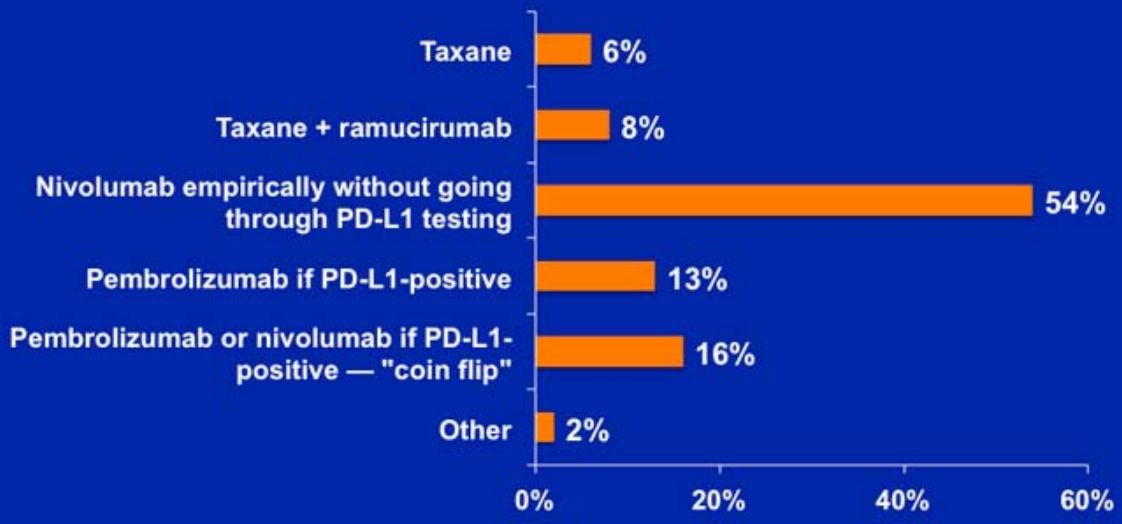
AUDIENCE POLL

A patient with metastatic adenocarcinoma of the lung experiences disease progression after first-line chemotherapy followed by maintenance. Would you order an anti-PD-L1 assay on the tumor?



AUDIENCE POLL

A 65-year-old patient with metastatic adenocarcinoma of the lung with no targetable mutations receives carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance during which disease progression occurs. What would be your most likely treatment recommendation?



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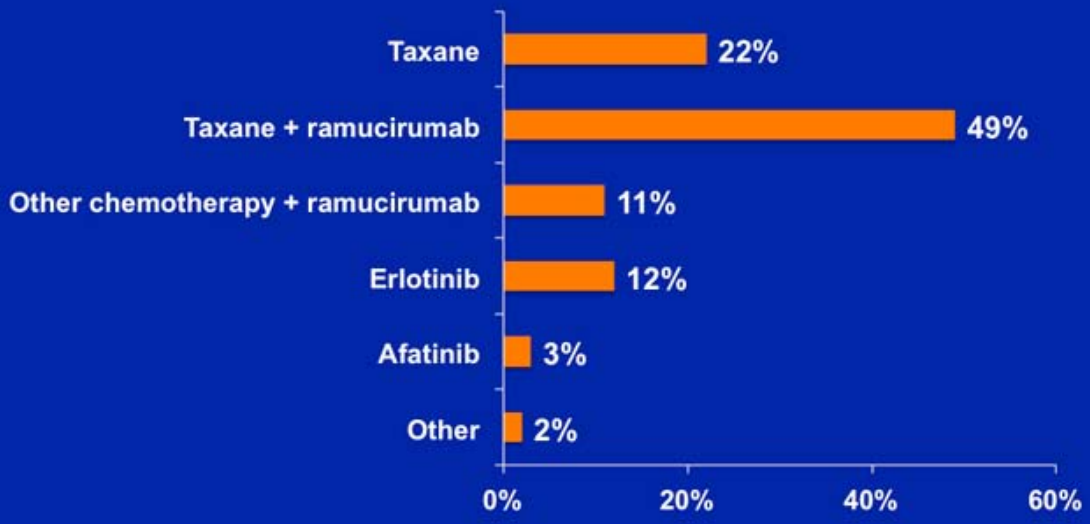
A 65-year-old patient with metastatic adenocarcinoma of the lung with no targetable mutations receives carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance during which disease progression occurs. The patient is started on an anti-PD-1 antibody but experiences disease progression. What would be your most likely treatment recommendation?



The NEW ENGLAND JOURNAL of MEDICINE

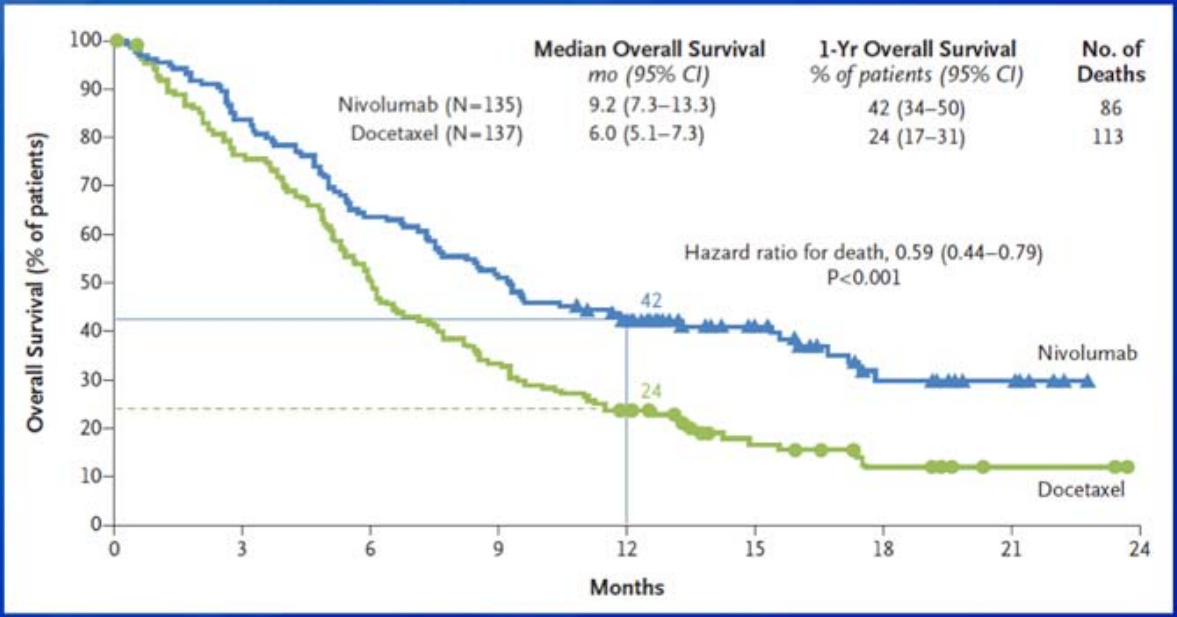
ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

Brahmer J et al. *N Engl J Med* 2015;373(2):123-35.

Overall Survival



Brahmer J et al. *N Engl J Med* 2015;373(2):123-35.

Treatment and Safety Summary

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

- Median number of doses was 8 (range, 1–48) for nivolumab and 3 (range, 1–29) for docetaxel

[a] No grade 5 events were reported with nivolumab. [b] 1% pts had increased ALT/AST, increased lipase, myasthenic syndrome, or rash, and 2% pts had pneumonitis. [c] Peripheral neuropathy (3%) and fatigue (2%). [d] Interstitial lung disease, pulmonary hemorrhage, and sepsis (1 pt each).

Brahmer J et al. *N Engl J Med* 2015;373(2):123-35; Spigel D et al. *Proc ASCO* 2015; Abstract 8009.

Conclusions

Critical finding(s):

- Statistically significant and clinically meaningful improvement in response rate, PFS and OS for nivolumab, independent of PD-L1 status, versus SOC docetaxel in 2L squamous NSCLC
- Substantially less toxicity compared to docetaxel

Clinical implication(s):

- Nivolumab is the new SOC in the second-line management of advanced squamous NSCLC
- Docetaxel relegated to third line (or clinical irrelevance)

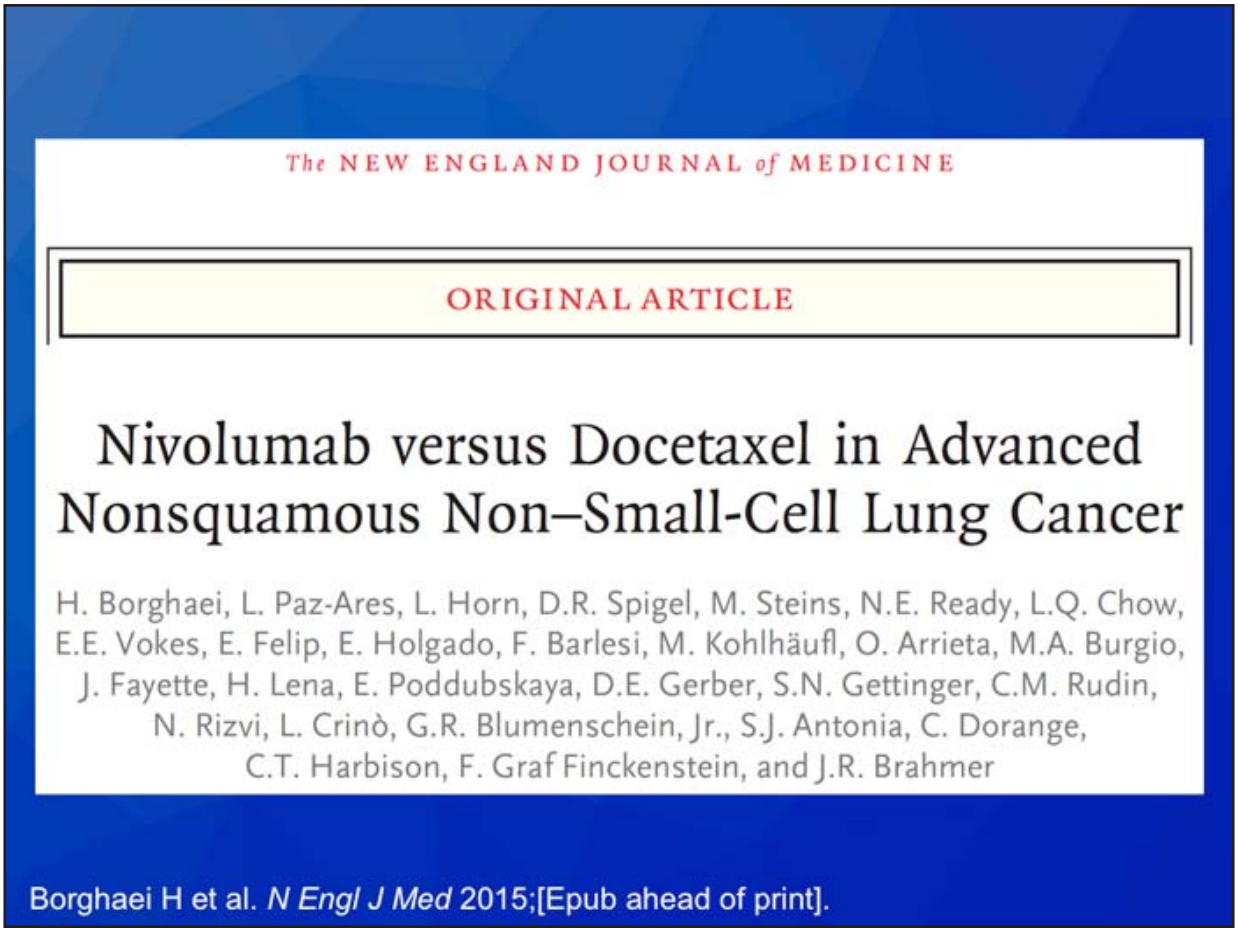
Conclusions

Research relevance:

- Combination regimens with nivolumab and other I/Os in this venue
- Studies to identify *a priori* those patients unlikely to benefit from nivolumab

Phase III, Randomized Trial (CheckMate 057) of Nivolumab (NIVO) versus Docetaxel (DOC) in Advanced Non-Squamous Cell (Non-SQ) Non-Small Cell Lung Cancer (NSCLC)

Paz-Ares L et al.
Proc ASCO 2015;Abstract LBA109.

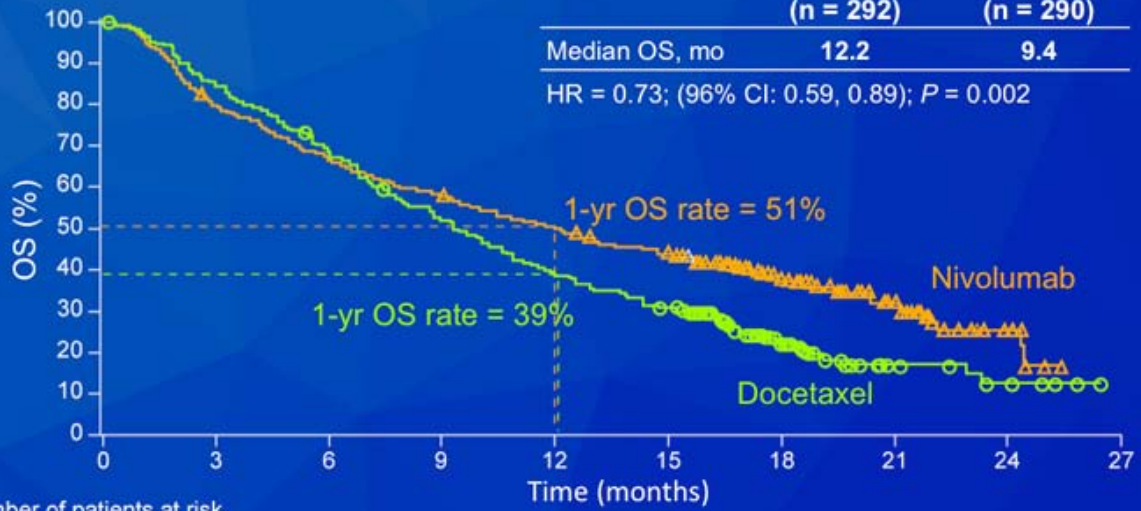


Borghaei H et al. *N Engl J Med* 2015;[Epub ahead of print].

Nivolumab vs Docetaxel in Advanced Nonsquamous NSCLC (CheckMate 057): Overall Survival

	Nivolumab (n = 292)	Docetaxel (n = 290)
Median OS, mo	12.2	9.4

HR = 0.73; (96% CI: 0.59, 0.89); *P* = 0.002



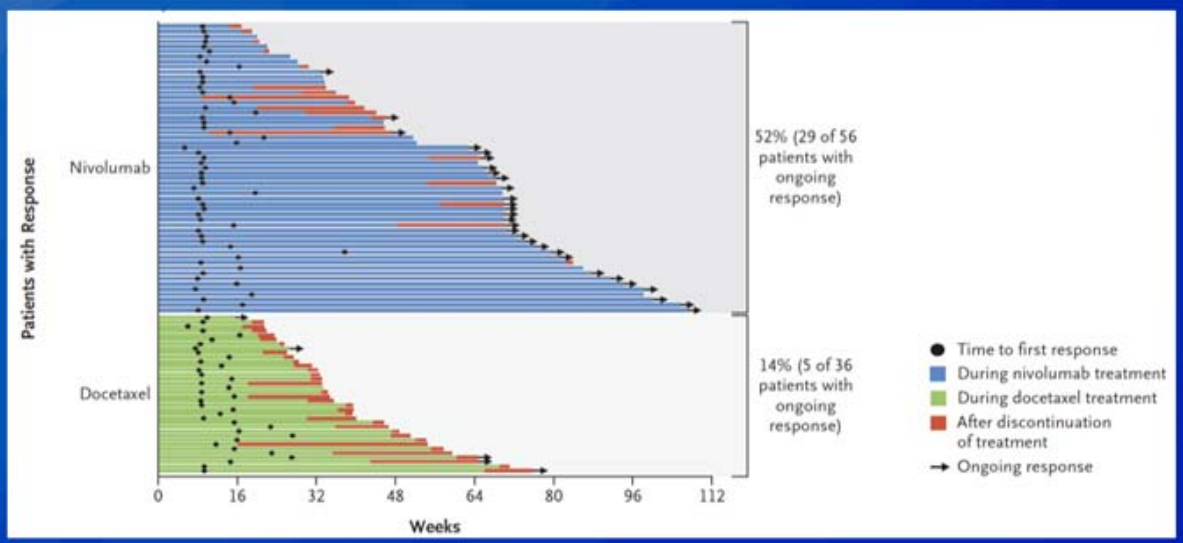
Number of patients at risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

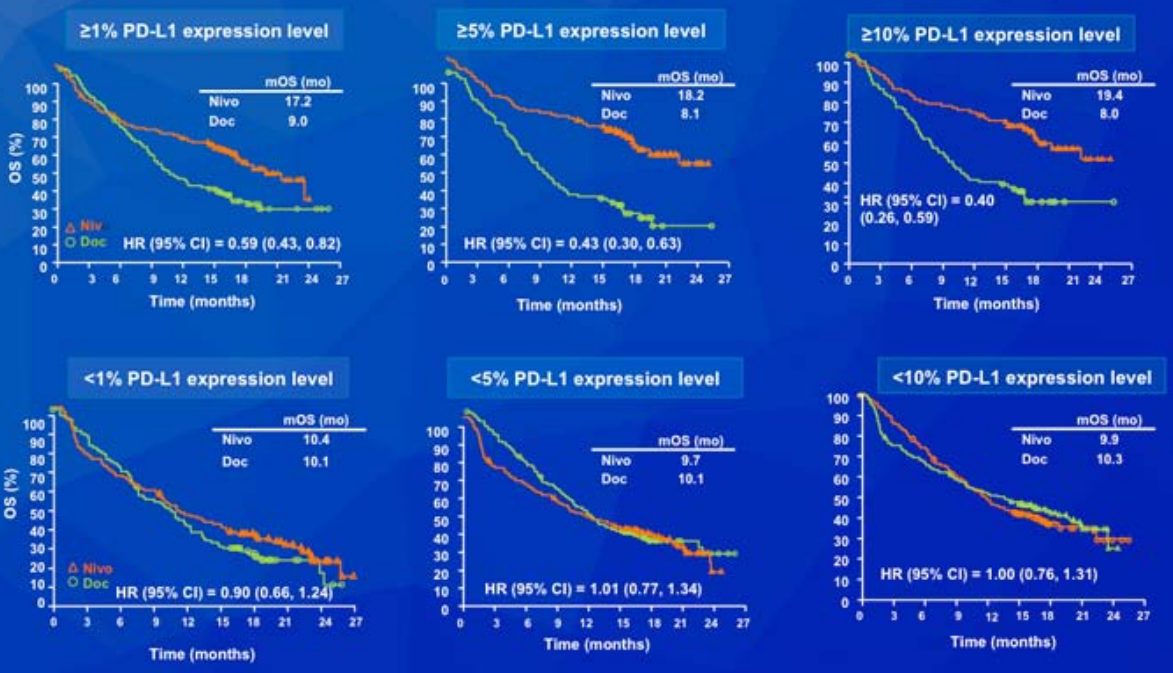
Borghaei H et al. *N Engl J Med* 2015;[Epub ahead of print].

Duration of Response



Borghaei H et al. *N Engl J Med* 2015;[Epub ahead of print].

CheckMate 057: OS by PD-L1 Expression



Paz-Ares L et al. *Proc ASCO* 2015;Abstract LBA109.

Conclusions

Critical finding(s):

- Significant improvement in ORR and OS for nivolumab compared to docetaxel in the second-line setting in advanced nonsquamous NSCLC
- No significant improvement in PFS overall, and in subanalysis, no overt survival advantage for never smokers or patients with EGFR mutations
- Statistically significant improvement (~10 to 12 months) in OS and PFS for PD-L1 (+) patients, which is not seen in PD-L1 (-) subjects
- Major advantage with respect to toxicity for nivolumab over docetaxel

Conclusions

Clinical implication(s):

- Nivolumab is the new SOC (for most patients) in the second-line management of advanced nonsquamous NSCLC after PD on prior platinum-based combinations, with recent FDA approval (independent of PD-L1 status) in 10/15
- PFS curves suggest two distinct patient populations with an early advantage for docetaxel that disappears beyond the median

Conclusions

Research relevance:

- Combination regimens with nivolumab and other I/Os as well as other "gentler" cytotoxics in this venue
- Critical work needs to be done to identify patients unlikely to benefit, focusing on PD-L1 status, immunophenotyping, mutation burden and smoking status

The NEW ENGLAND JOURNAL of MEDICINE

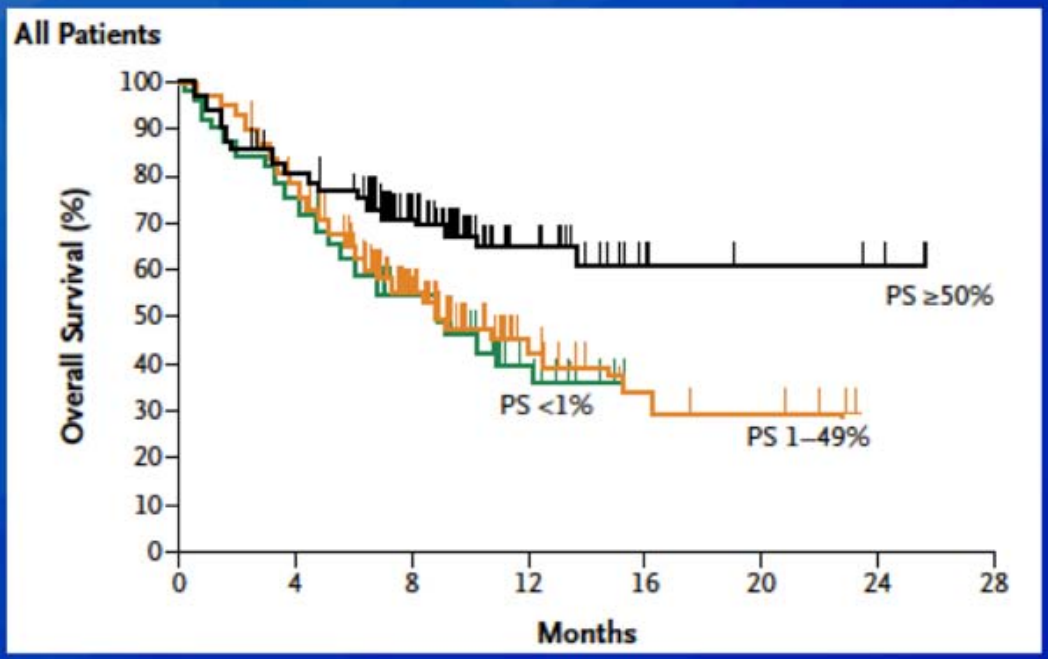
ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

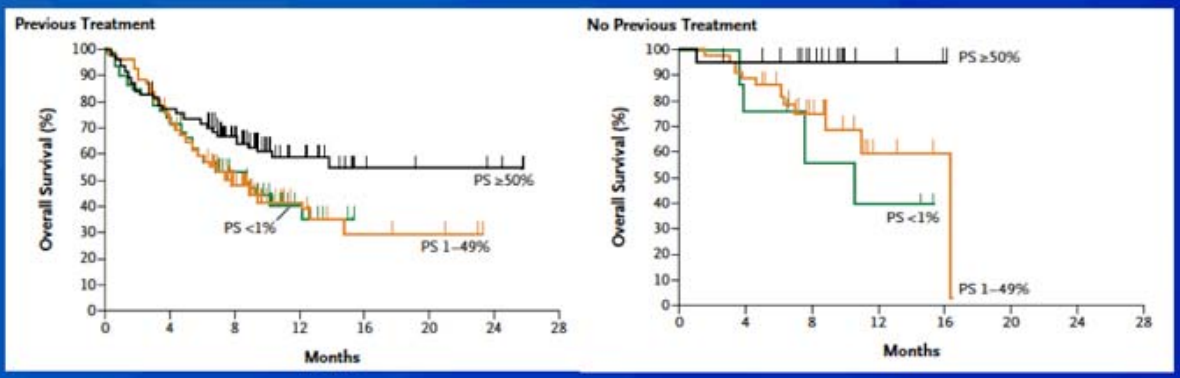
Garon EB et al. *N Engl J Med* 2015;372(21):2018-28.

KEYNOTE-001: OS by PD-L1 Proportion Score (PS)



Garon EB et al. *N Engl J Med* 2015;372(21):2018-28.

KEYNOTE-001: OS by PD-L1 PS and Previous Treatment or Not (Coprimary Endpoint)



Garon EB et al. *N Engl J Med* 2015;372(21):2018-28.

Conclusions

Critical finding(s):

- Pembrolizumab yields response rates exceeding 40% and PFS >6 months in second-line NSCLC patients with PD-L1 (+) tumors and IHC proportional scores >50% (~25% of all NSCLC patients)
- Toxicity is acceptable and mirrors nivolumab
- No data yet available on long-term survival

Clinical implication(s):

- Pembrolizumab now FDA approved in 2L advanced PD-L1 (+) NSCLC in patients with tumors harboring >50% staining intensity or "proportional score" on IHC

Conclusions

- Approval and use contingent on a companion diagnostic
- Not clear yet if pembrolizumab offers any advantage over nivolumab in this population

Research relevance:

- Await results of phase III trials comparing pembrolizumab to docetaxel in marker (+) NSCLC, second line
- Nuances of PD-L1 testing need further exploration

FDA Approves Pembrolizumab for Advanced NSCLC – October 2, 2015

First drug approved in lung cancer for patients whose tumors express PD-L1

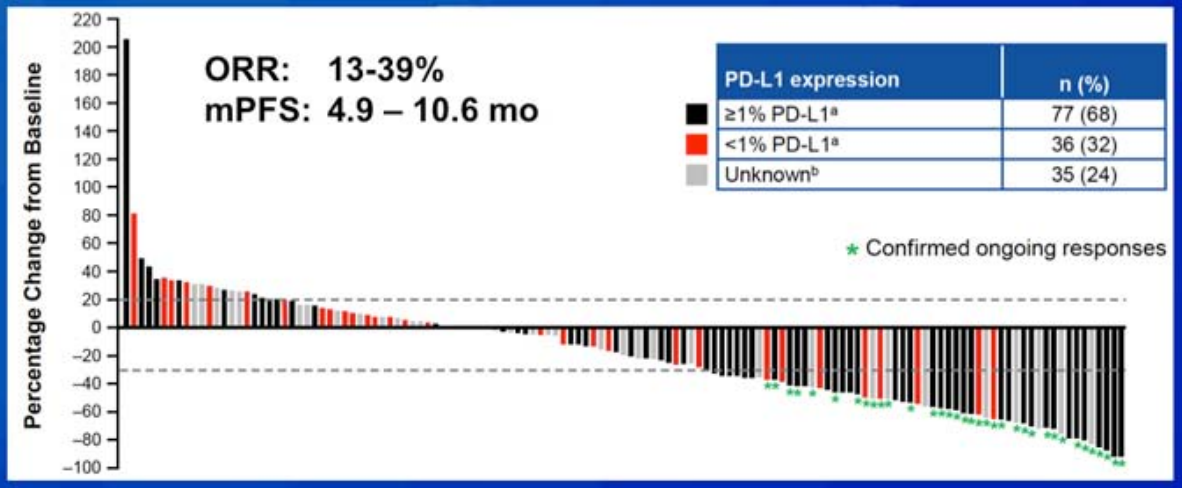
The U.S. Food and Drug Administration today granted accelerated approval for pembrolizumab to treat patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express a protein called PD-L1. Pembrolizumab is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in non-small cell lung tumors.

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465444.htm

Safety and Efficacy of First-Line Nivolumab (NIVO; Anti-Programmed Death-1 [PD-1]) and Ipilimumab in Non-Small Cell Lung Cancer (NSCLC)

Rizvi NA et al.
Proc IASLC 2015;Abstract ORAL02.05.

Best Percentage Change in Target Lesion Tumor Burden by Tumor PD-L1 Expression



[a] Based on patients with known PD-L1 expression; [b] Based on all treated patients

Rizvi NA et al. *Proc IASLC* 2015;Abstract ORAL02.05.

Conclusions

Critical finding(s):

- Combination can be delivered safely
- Response rates and PFS rival or exceed nivolumab alone, but Grade 3/4 toxicities are also higher

Clinical implication(s):

- None yet — not yet ready for prime time (despite approval of this combination in malignant melanoma)

Research relevance:

- In PD-L1 (-) first-line NSCLC, a recently initiated trial will compare two different doses of this combination to standard chemo

Conclusions

- In PD-L1 (+) first-line NSCLC, a similar trial will compare this combination as well as single-agent nivolumab to standard platinum-based chemo

Final Overall Survival (OS) Results of the Phase III PROCLAIM Trial: Pemetrexed (Pem), Cisplatin (Cis) or Etoposide (Eto), Cis plus Thoracic Radiation Therapy (TRT) Followed by Consolidation Cytotoxic Chemotherapy (CTX) in Locally Advanced Nonsquamous Non-Small Cell Lung Cancer (nsNSCLC)

Senan S et al.
Proc ASCO 2015;Abstract 7506.

PROCLAIM: Select Adverse Events During All Phases of Trial

Event	Pem/cis (n = 283)		Eto/cis (n = 272)	
	Any	Grade 3/4	Any	Grade 3/4
Esophagitis	48.1%	15.5%	50.7%	20.6%
Abnormal neutrophil/ granulocyte counts	42.8%	24.4%	54.8%	44.5%
Abnormal hemoglobin	40.3%	8.8%	45.6%	13.6%
Vomiting	38.9%	3.9%	33.1%	6.3%
Mucositis/stomatitis	21.9%	1.1%	14.7%	1.8%
Abnormal platelet count	19.4%	6.7%	31.3%	10.7%
Pneumonitis	17.0%	1.8%	10.7%	2.6%
Alopecia	8.1%	0%	36.0%	0.4%
Febrile neutropenia	5.7%	5.3%	10.3%	9.6%

Senan S et al. *Proc ASCO* 2015;Abstract 7506.

Conclusions

Critical finding(s):

- Despite a modest improvement in PFS, Pem/DDP failed to result in superior OS or ORR in locally advanced NSCLC versus standard Eto/DDP, in combination with XRT
- Pem/DDP resulted in more pneumonitis and stomatitis, while Eto/DDP caused numerically higher rates of anemia, thrombocytopenia, neutropenia, neutropenic fever, Grade 3/4 nausea/vomiting, Grade 3/4 esophagitis and alopecia

Conclusions

Clinical implication(s):

- Pem/DDP can be safely and effectively delivered in combination with standard radical thoracic XRT in nonsquamous locally advanced NSCLC, although it performs no better than standard EP/XRT, at substantially higher cost
- Heightened cost will likely limit uptake of this strategy

Research relevance:

- Pem/DDP/XRT: Reasonable platform regimen to test the addition of new agents, particularly in those more vulnerable to myelosuppression

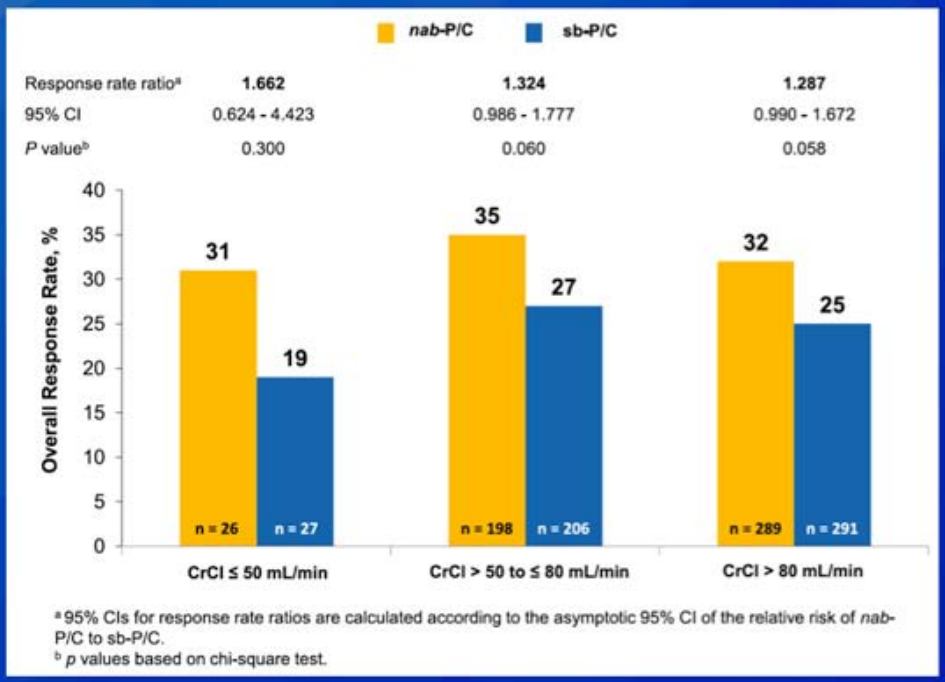
Original Study

Clinical Lung Cancer, Vol. 16, No. 2, 112-20

Weekly *nab*-Paclitaxel in Combination With Carboplatin as First-Line Therapy in Patients With Advanced Non–Small-Cell Lung Cancer: Analysis of Safety and Efficacy in Patients With Renal Impairment

Corey J. Langer,[1] Vera Hirsh,[2] Amy Ko,[3] Markus F. Renschler,[3] Mark A. Socinski[4]

Independent Radiologic Response Assessment by CrCl Level



[a] 95% CIs for response rate ratios are calculated according to the asymptotic 95% CI of the relative risk of *nab*-P/C to sb-P/C.
[b] *p* values based on chi-square test.

OS and PFS were nonsignificantly longer for *nab*-P/C versus sb-P/C in these subsets

Langer CJ et al. *Clin Lung Cancer* 2015;16(2):112-20.

Conclusions

Critical finding(s):

- Therapeutic benefits of *nab* paclitaxel are preserved in patients with mild to moderate renal impairment.
- Toxicity is manageable with no obvious exacerbations.

Clinical implication(s):

- *Nab* paclitaxel and carboplatin are safe in combination in patients with some degree of renal dysfunction, which makes this an attractive option in:
  - Those with some degree of baseline renal insufficiency
  - The elderly, who frequently have some degree of asymptomatic renal impairment, even with ostensibly normal creatinine

Conclusions

- This observation has not been documented with pemetrexed combinations.

Research relevance:

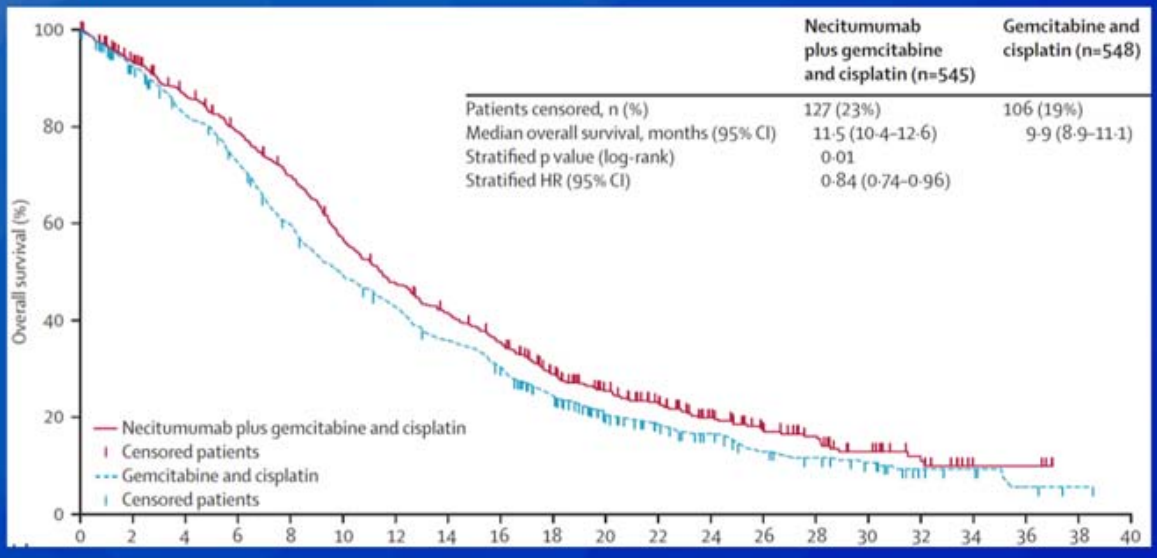
- These observations make *nab* paclitaxel/carboplatin an increasingly attractive option as a therapeutic platform for testing new agents, including immunotherapies.
- Formal studies of pemetrexed should be done in individuals with creatinine clearances between 30 and 45. To date, this has not occurred.

Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial

*Nick Thatcher, Fred R Hirsch, Alexander V Luft, Aleksandra Szczesna, Tudor E Ciuleanu, Mircea Dediu, Rodryg Ramlau, Rinat K Galiulin, Beatrix Bálint, György Losonczy, Andrzej Kazarnowicz, Keunchil Park, Christian Schumann, Martin Reck, Henrik Depenbrock, Shivani Nanda, Anamarija Kruljac-Letunic, Raffael Kurek, Luis Paz-Ares, Mark A Socinski, for the SQUIRE investigators**

Lancet Oncol 2015; 16: 763–74

SQUIRE: Overall Survival (ITT)



	Necitumumab plus gemcitabine and cisplatin (n=545)	Gemcitabine and cisplatin (n=548)
Patients censored, n (%)	127 (23%)	106 (19%)
Median overall survival, months (95% CI)	11·5 (10·4–12·6)	9·9 (8·9–11·1)
Stratified p value (log-rank)	0·01	
Stratified HR (95% CI)	0·84 (0·74–0·96)	

Thatcher N et al. *Lancet Oncol* 2015;16(7):763-74.

Conclusions

Critical finding(s):

- Necitumumab in combination with platinum and gemcitabine results in a statistically significant, albeit clinically modest, improvement in survival compared to chemotherapy alone.
- Toxicity, including rash, was manageable but persistent.

Clinical implication(s):

- Moot, unless the FDA approves this agent.
- Even if approved, it is unclear whether this agent will be adopted into the therapeutic lexicon of NSCLC.

Conclusions

Research relevance:

- Given the implications of S0819, we need to conduct a rigorous FISH analysis, if feasible, on patients enrolled on this study.
- If approved, we need to assess this agent in the setting of locally advanced NSCLC and in other venues; in addition, this agent is "ripe" for cost efficacy analyses.