Module 4.4: Sequencing of systemic therapies and clinical trial options for patients with metastatic non-squamous cell lung cancer

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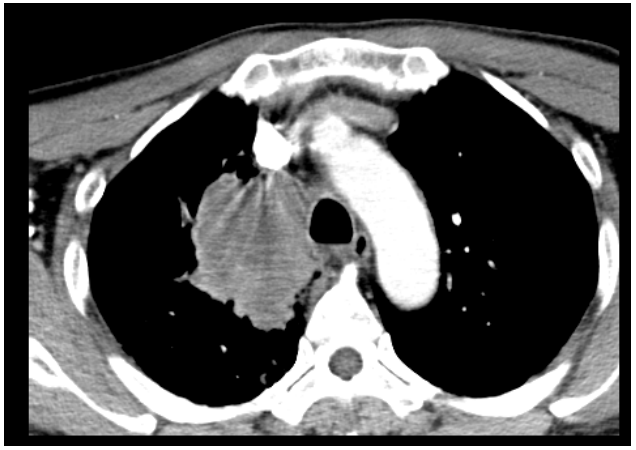
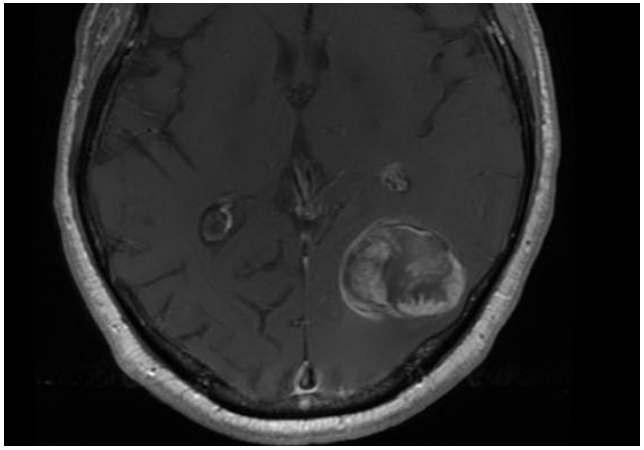
Case presentation

- 68M with 20 pack-year smoking history presents with right lung mass on CXR after motor vehicle accident
- Biopsy and staging demonstrate stage IIIA NSCLC adenocarcinoma (T3N1)
- Right upper lobectomy and adjuvant cisplatin/vinorelbine x 3 cycles
- Disease recurrence after 6 months: symptomatic 4 cm brain mass (resected) plus mediastinal, supraclavicular, and porta hepatis nodes



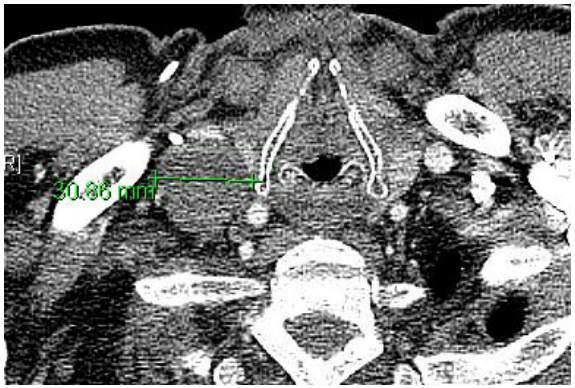


Case presentation

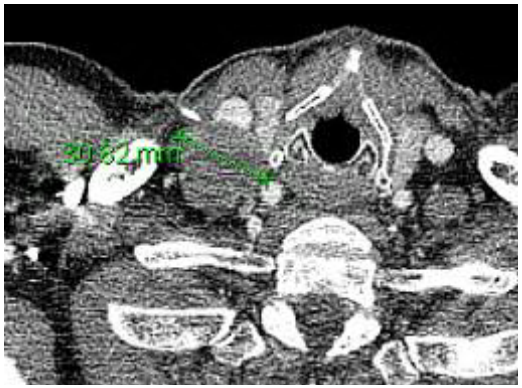
- Molecular testing of the tumor is negative for EGFR, ALK, ROS1, KRAS, BRAF, HER2, RET
- Chemotherapy is initiated with carboplatin and pemetrexed followed by maintenance pemetrexed
- He has a good response to therapy, but after 8 months develops a new 1 cm brain metastasis and growth of the lymph nodes
- He receives stereotactic brain radiation
- He is started on cabozantinib monotherapy, 60 mg daily

Case presentation

- Tumor stabilizes on cabozantinib monotherapy for 9 months

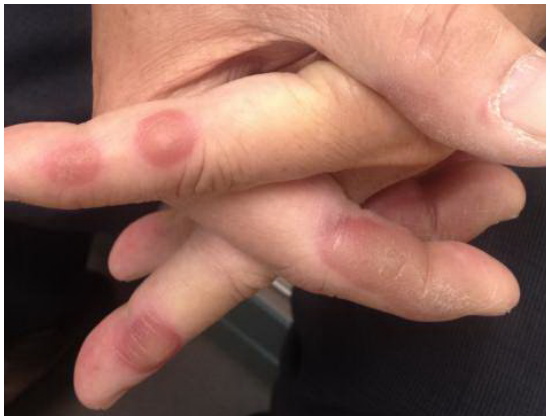


4/2014



1/2015

- Side effects of diarrhea managed with loperamide, and hand-foot managed with urea and steroids
- Eventually non-target node progressed and therapy was changed to docetaxel



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“Targeting” wild type non-squamous NSCLC

- EGFR inhibitors: historical evidence for erlotinib in the second line and maintenance setting

- VEGF inhibitors appear modestly active but have no predictive marker of response

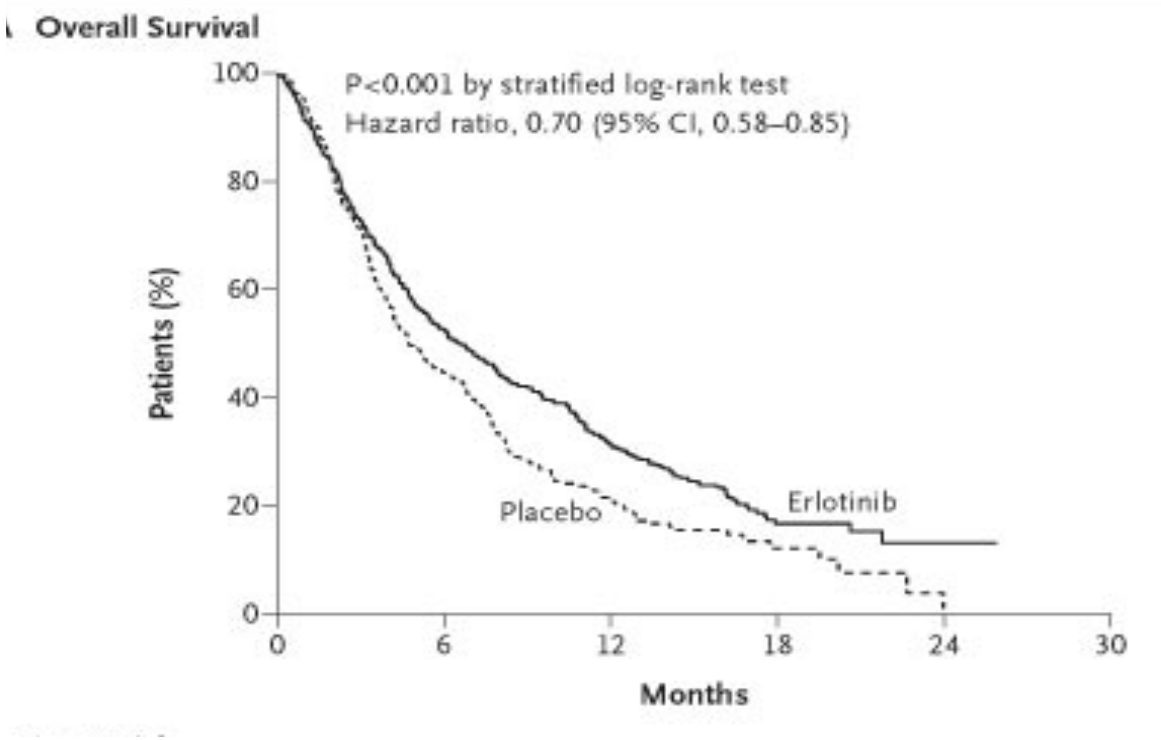
BR.21

- Erlotinib has modest single agent activity in 2nd and 3rd line treatment of EGFR wild type patients with NSCLC

BR.21 study,

<u>Erlotinib vs BSC</u>

- RR: 9% vs <1%
- PFS: 2.2 vs 1.8 mo
- OS: 6.7 vs 4.7 mo



Shepherd et al. *NEJM* 2005

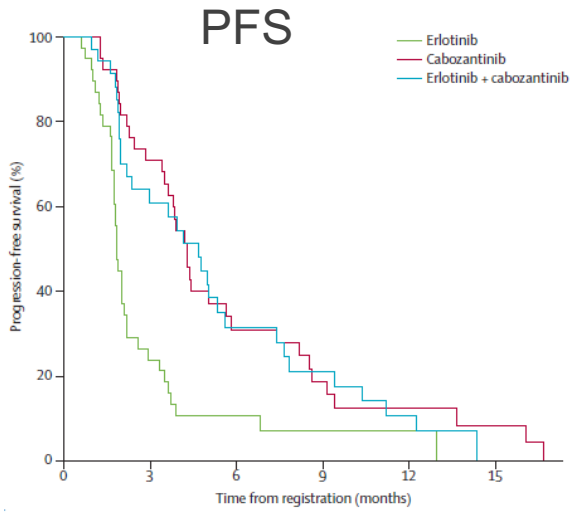
Erlotinib in EGFR wild-type NSCLC

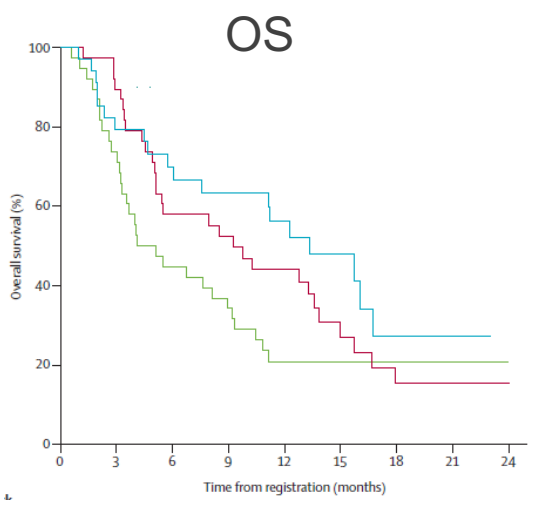
	N	mPFS (HR)	mOS (HR)
E1512			
Erlotinib	39	1.8	5.1
Cabozantinib	39	4.3 (0.39*)	9.2 (0.68*)
Erlot+Cabo	37	4.7 (0.37*)	13.3 (0.51*)
TITAN			
Erlotinib	203	1.4	5.3
Doc or Pem	221	2.0 (0.89)	5.5 (0.96)
TAILOR			
Erlotinib	110	2.4	5.4
Docetaxel	112	2.9 (0.71*)	8.2 (0.73*)
DELTA (wt pts)			
Erlotinib	109	1.3	9.0
Docetaxel	90	2.9 (1.45)	10.1 (0.98)

* = statistically significant difference

Neal Lancet Oncol 2016
Ciuleanu Lancet Oncol 2012
Grassino Lancet Oncol 2014
Kawaguchi J Clin Oncol 2014

ECOG E1512: Cabozantinib, erlotinib, or the combination in EGFR wild-type NSCLC





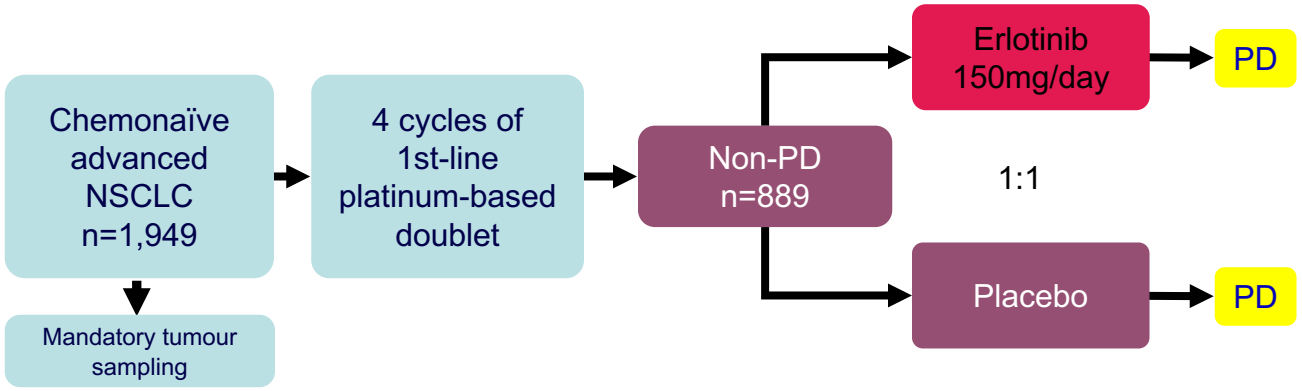
	Erlotinib (n=38)	Cabozantinib (n=38)	Erlotinib plus Cabozantinib (n=35)
Progression-free survival			
Deaths or disease progression	36 (95%)	34 (89%)	30 (86%)
Progression-free survival (months)	1·8 (1·7–2·2)	4·3 (3·6–7·4)	4·7 (2·4–7·4)
Overall survival			
Deaths	30 (79%)	29 (76%)	19 (54%)
Overall survival (months)	5·1 (3·3–9·3)	9·2 (5·1–15·0)	13·3 (7·6–NR)

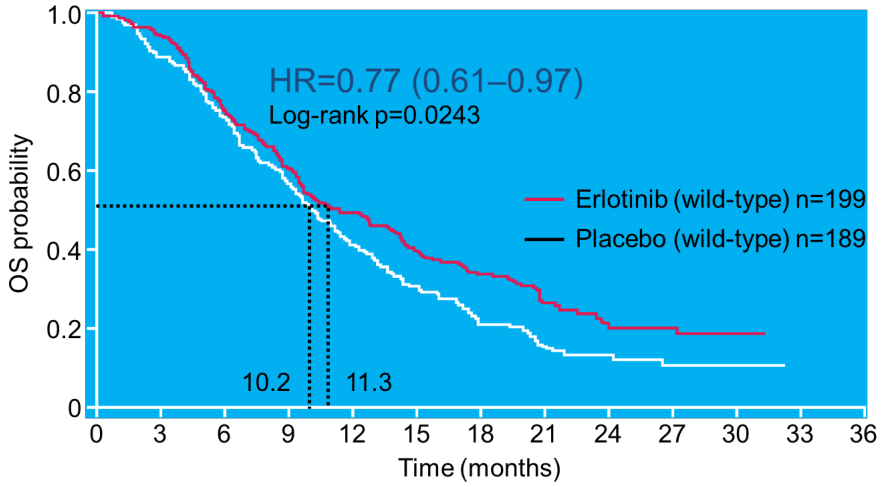
Adverse events across arms:

Diarrhea, acneiform rash, fatigue, anorexia, mucositis, hypertension, hand-foot syndrome

Neal Lancet Oncol 2016

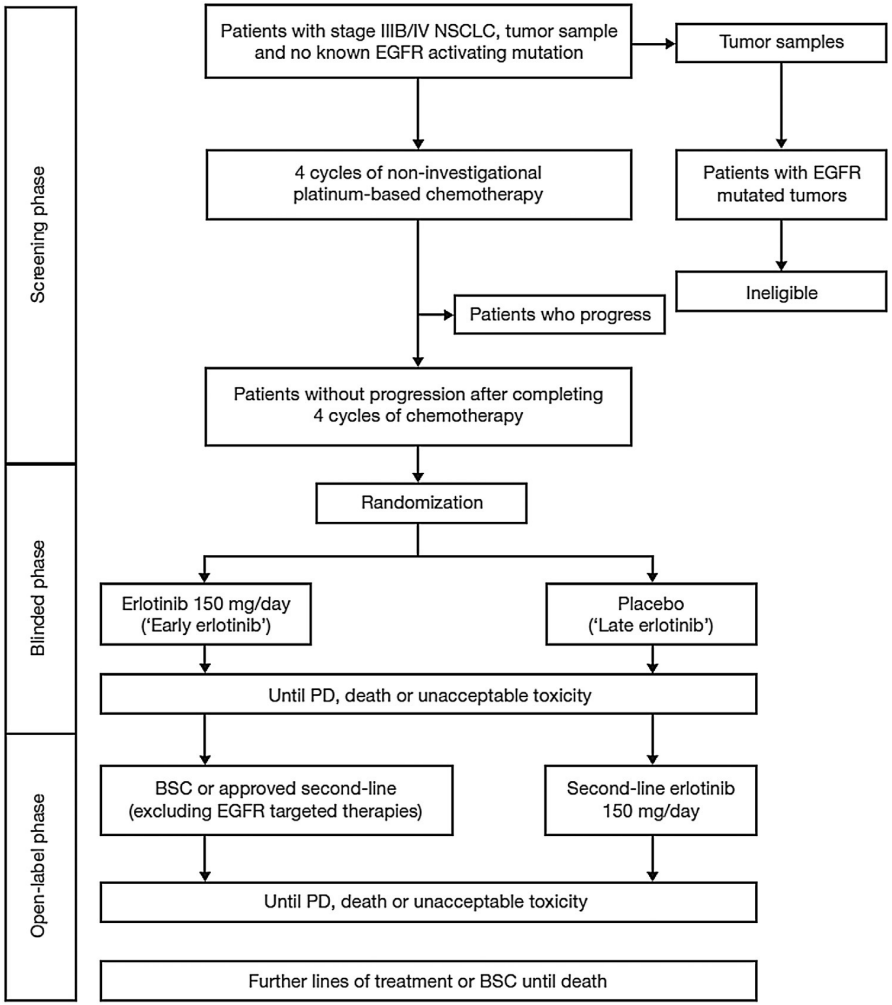
SATURN: Switch maintenance erlotinib

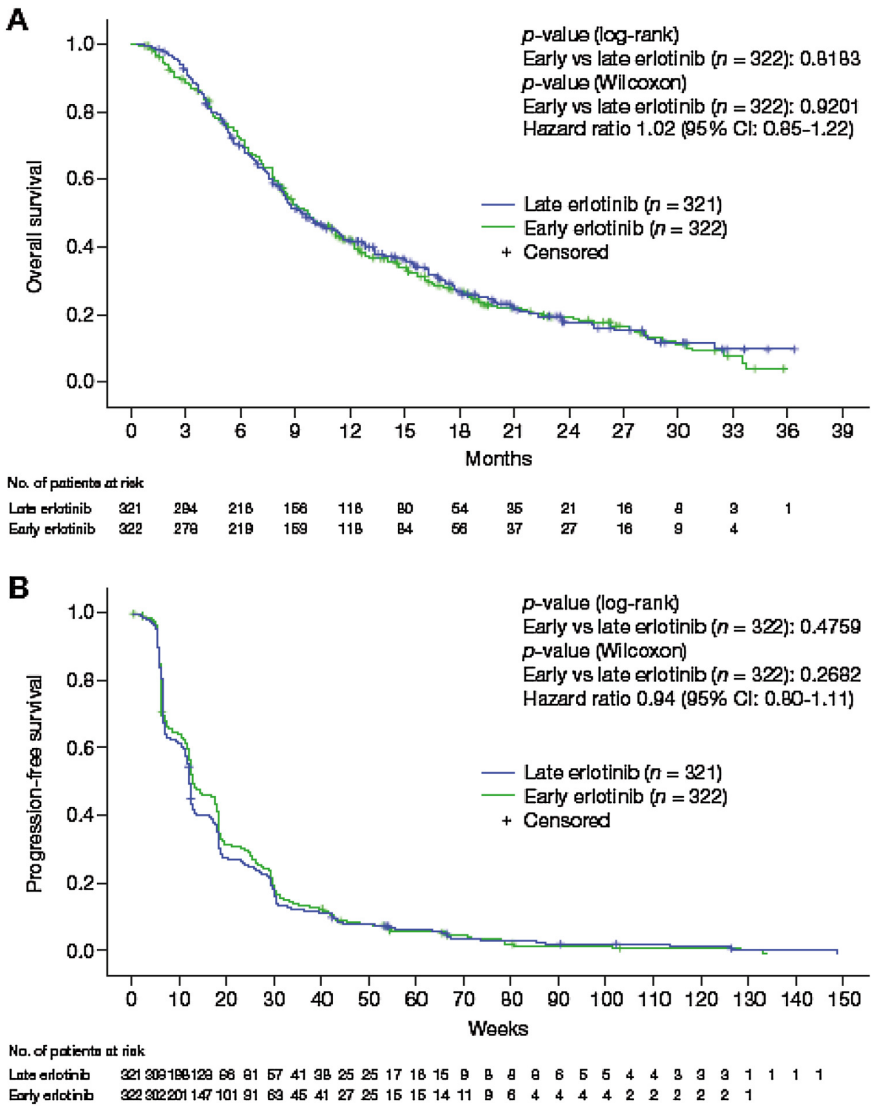




Cappuzzo Lancet Oncol 2010

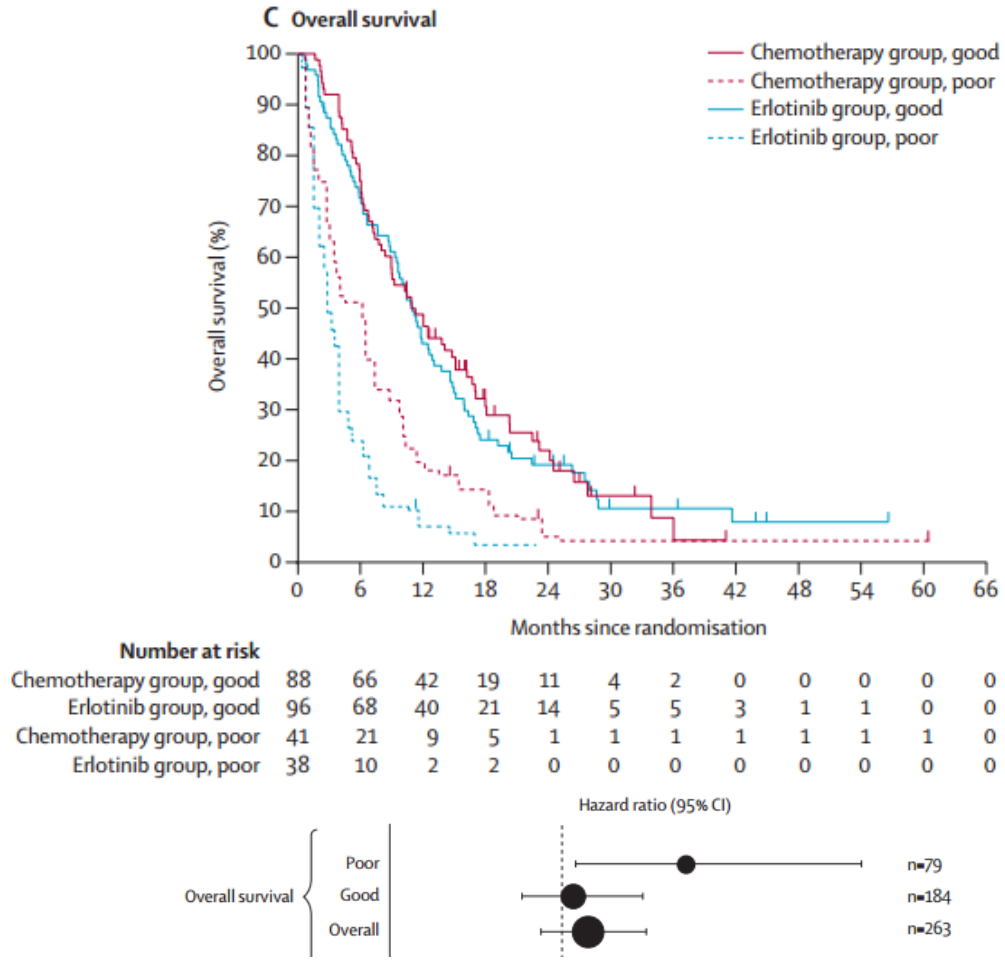
IUNO: Maintenance erlotinib in *EGFR* wild-type





Cicenas Lung Cancer 2017

PROSE: 2nd line erlotinib vs doc/pemetrexed by serum proteomic signature



Median OS
10.9 months
6.4 months
11.0 months
3.0 months

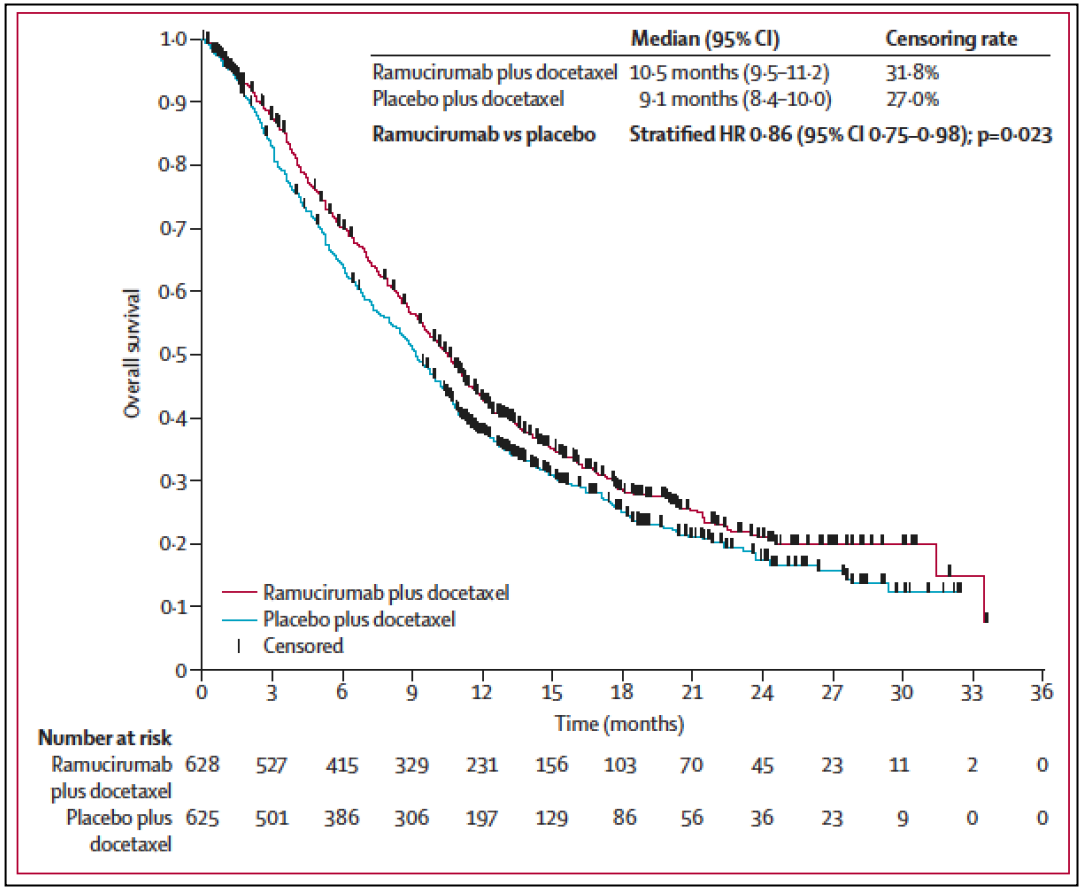
Gregorc Lancet Oncol 2014

Bevacizumab in non-squamous NSCLC

- Phase III ECOG 4599
  - 878 patients : Carboplatin/Paclitaxel +/- Bevacizumab
  - PFS 6.2 vs 4.5 mo, response 35% vs 15%
  - MST 12.3 mo (10.3 mo control)
- Phase III AVAiL
  - 1043 patients: Cisplatin/Gemcitabine +/- Bevacizumab
  - PFS HR 0.75, p.003 at 7.5 mg/kg 0.85, p.046 at 15 mg/kg
  - RR 32% vs 20%
  - MST 13.6m (7.5); 13.4m (15); 13.1m (plac), NS

Sandler NEJM 2006
Reck J Clin Oncol 2009

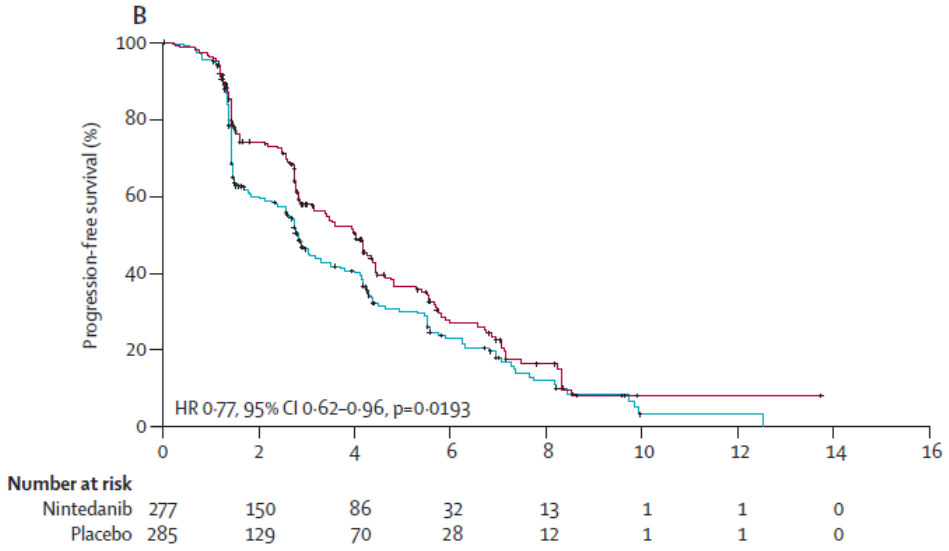
REVEL: Docetaxel + Ramucirumab

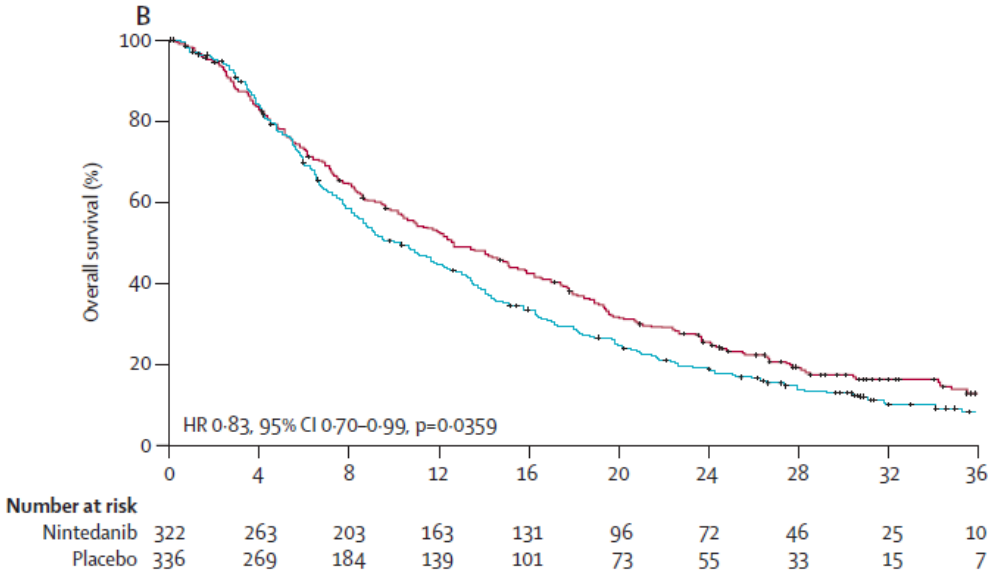


- Ramucirumab is anti-VEGFR2 antibody
- Improves overall survival as second-line treatment for patients with stage IV NSCLC
- Approved in 2014

Garon Lancet 2014

LUME-Lung 1: Docetaxel +/- Nintedanib (non-squamous subsets)





- Nintedanib is anti-VEGFR2 TKI
- Improves overall survival as second-line treatment in combination with docetaxel
- Approved in Europe

Reck Lancet Oncol 2014

“Targeting” wild type non-squamous NSCLC - Conclusions

- “Wild-type” is a moving bar – must rule out EGFR, ALK, ROS1, BRAF, HER2, RET, METe14/amp. KRAS counts as wild-type for now
- EGFR inhibitors have historically been indicated - but FDA withdrew the “wild type” second line indication on October 18, 2016
- VEGF inhibitors appear modestly active together with chemotherapy, but no predictive markers of response

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