Treating second-line and beyond in non-mutated, non-squamous NSCLC: now and tomorrow

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Disclosures

- **Personal financial interests:**
  - Honoraria: BMS, Roche, Takeda, AstraZeneca, Chugai, Novartis, Pfizer, MSD, EMD Serono, Guardant Health, AbbVie, Boehringer Ingelheim, Medscape, Tesaro, OncLive
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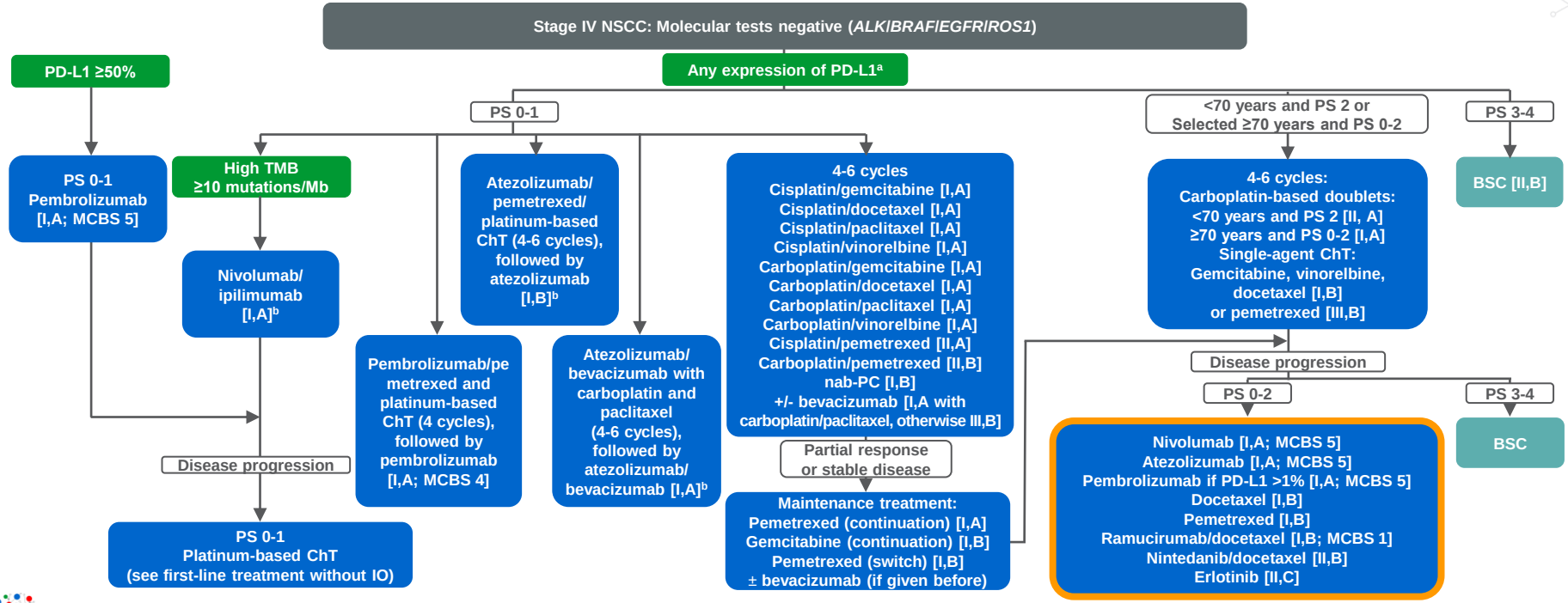
Nonsquamous NSCLC

- NSCLC accounts for 85%-90% of lung cancers[1]
  - ADC accounts for 40% of all lung cancers, and is the most common NSCLC subtype
- Driver mutations have been identified in NSCLC and are used to guide therapy[2]
  - *EGFR* mutations: 10%-12% of whites[1]
  - ALK rearrangement: 5% of patients[1]
- First-line immunotherapy trial outcomes have led to a rapid shift in treatment paradigms for patients with NSCLC with no *EGFR* or *ALK* mutations[3–5]
  - In the EU, pembrolizumab is approved as a first-line monotherapy for patients with metastatic NSCLC and PD-L1 ≥50% and in combination with chemotherapy for patients with metastatic nonsquamous NSCLC regardless of PD-L1 tumour expression status[4,5]
- Despite recent advancements, treatment of refractory or progressive disease after first-line chemotherapy remains a challenge[6]

1. ESMO Web site. www.esmo.org/content/download/7252/143219/file/EN-Non-Small-Cell-Lung-Cancer-Guide-for-Patients.pdf. Accessed 2 October 2018; 2. Planchard et al. *Ann Oncol*. 2018; 29 (suppl 4): iv192–iv237.; 3. Pabani and Butts. *Curr Oncol*. 2018;25:S944: 4. Keytruda SmPC. Merck Sharp & Dohme B.V. 2018; 5. Merck press release. https://investors.merck.com/news/press-release-details/2018/European-Commission-Approves-Mercks-KEYTRUDA-pembrolizumab-in-Combination-with-Pemetrexed-and-Platinum-Chemotherapy-for-the-First-Line-Treatment-of-Patients-with-Metastatic-Nonsquamous-NSCLC-with-No-EGFR-or-ALK-Genomic-Tumor-Aberrations/default.aspx. Accessed 2 October 2018; 6. Corrales et al. *Front Med* (Lausanne). 2017;4:13. doi: 10.3389/fmed.2017.00013.

Current Treatment Landscape for Stage IV Nonsquamous NSCLC: ESMO Guidelines



[a] In the absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy will be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 < 50%. Alternatively, if TMB can accurately be evaluated, and conditioned by the registration and accessibility, nivolumab plus ipilimumab should be preferred to platinum-based standard ChT in patients with NSCLC with a high TMB. [b]Not EMA-approved. ESMO = European Society for Medical Oncology; PD-L1 = programmed death-ligand 1; PS = performance status; Mb = megabases; MCBS = Magnitude of Clinical Benefit Scale; ChT = chemotherapy; nab-PC, albumin-bound paclitaxel and carboplatin; BSC = best supportive care; IO = immuno-oncology; EMA = European Medicines Agency. Planchard et al. Ann Oncol. 2018; 29 (suppl 4): iv192–iv237.

First-Line Immunotherapy for Patients With NSCLC[a]

Trial	Treatment		Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)
KEYNOTE-024[1,2,e]	≥50% PD-L1: Pembrolizumab (n=154) vs chemo (n=151) *Mixed: nonsquamous (pembrolizumab, n=125; chemo, n=124)*		10.3 vs 6.0 –	0.50[b] 0.55	30.0 vs 14.2 –	0.63[c] –	45.5 vs 29.8 –
KEYNOTE-042[3]	≥1% PD-L1: Pembrolizumab (n=637) vs chemo (n=637) *Mixed: nonsquamous (pembrolizumab, n=394; chemo, n=388)*		TPS ≥50%: 7.1 vs 6.4 TPS ≥20%: 6.2 vs 6.6 TPS ≥1%: 5.4 vs 6.5 –	0.81[d] 0.94 1.07 –	20.0 vs 12.2 17.7 vs 13.0 16.7 vs 12.1 –	0.69[b] 0.77[c] 0.81[c] 0.86	39.5 vs 32.0 33.4 vs 28.9 27.3 vs 26.5 –
KEYNOTE-189[4,e]	Pembrolizumab + chemo (n=410) vs placebo + chemo (n=206) *All nonsquamous*		8.8 vs 4.9	0.52[b]	NR vs 11.3	0.49[b]	47.6 vs 18.9
IMpower150[5,6]	Arm A: atezolizumab + chemo (n=402) Arm B: atezolizumab + bevacizumab + chemo (n=400) Arm C: bevacizumab + chemo (n=400) *All nonsquamous*	B vs C A vs C	8.3 vs 6.8 –	0.59[b] –	19.2 vs 14.7 19.4 vs 14.7	0.78[d] 0.88	56 vs 41 40 vs 41
IMpower132[7]	Atezolizumab + chemo (n=292) vs chemo (n=286) *All nonsquamous*		7.6 vs 5.2	0.60[b]	18.1 vs 13.6	0.81	47 vs 32
Checkmate 227 Part I[8,9]	≥1% PD-L1: nivo + ipi (n=396); chemo (n=397); or nivo (n=396) <1% PD-L1: nivo + ipi (n=187); chemo (n=186); or nivo + chemo (n=177) *Mixed: nonsquamous (n=1252)*	Nivo + ipi vs chemo TMB ≥10 mut/Mb):	7.2 vs 5.5 9.5 vs 5.6	0.58[b] 0.55	23.0 vs 16.4 –	0.79 –	45.3 vs 26.9 –

IMpower130 (N=724), an ongoing phase 3 clinical trial comparing atezolizumab + chemo with chemo alone, met its coprimary end points of OS and PFS[10,11]

[a] These are not head-to-head trials and study designs are different; direct cross-trial comparisons cannot be made; *P*<0.001; [c]*P*=0.002; [d]*P*<0.05; [e]Used as basis for regulatory approval in the United States and EU.
PFS = progression-free survival; HR = hazard ratio; OS = overall survival; ORR = objective response rate; chemo = chemotherapy; nivo = nivolumab; ipi = ipilimumab.

1. Reck et al. *N Engl J Med*. 2016;375:1823; 2. Brahmer et al. WCLC 2017. Abstract OA 17.06. 3. Lopes et al. ASCO 2018. Abstract LBA4; 4. Gandhi et al. *N Engl J Med*. 2018;378:2078;
5. Socinski et al. *N Engl J Med*. 2018;378:2288; 6. Socinski et al. ASCO 2018. Abstract 9002; 7. Papadimitrakopoulou et al. WCLC 2018. Abstract OA05.07. 8. Hellmann et al. *N Engl J Med*. 2018;378:2093; 9. Hellmann et al. AACR 2018. Abstract CT077; 10. Roche. Media release. May 2018. www.roche.com/media/releases/med-cor-2018-05-29.htm. Accessed 2 October 2018; 11. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02367781. Accessed 3 August 2018.

Second-Line Trials in Patients With NSCLC[a]

Use of first-line immunotherapy will affect which treatments, including immunotherapy, will be available for use in second-line therapy and beyond

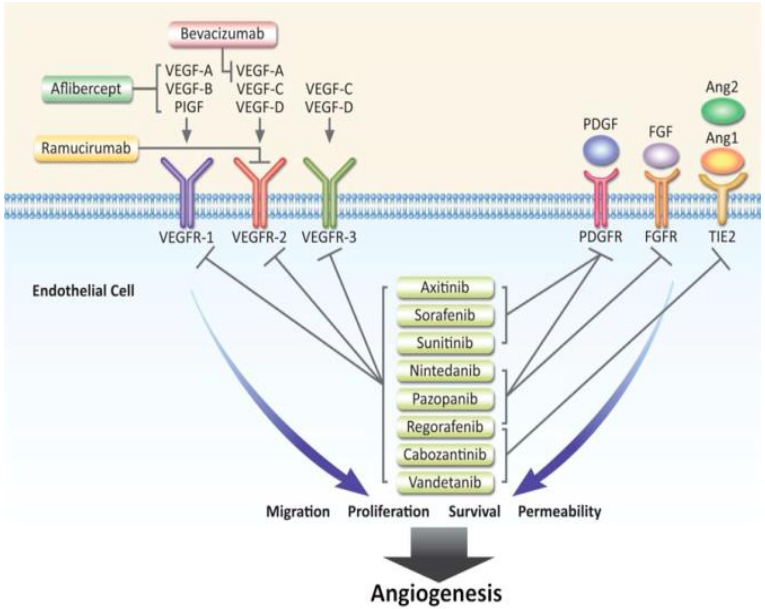
Trial	Treatment	Median PFS (mo)	HR for PFS	Median OS (mo)	HR for OS	ORR (%)
Checkmate 057[1f]	Nivolumab (n=292) vs docetaxel (n=290) *All nonsquamous*	2.3 vs 4.2	0.92	12.2 vs 9.4	0.73[b]	19 vs 12[c]
KEYNOTE-010[2,3,f]	≥1% PD-L1: Pembrolizumab (2 mg/kg n=344; 10 mg/kg, n=346) vs docetaxel (n=343) *Mixed: nonsquamous (pembrolizumab 2 mg/kg, n=240; 10 mg/kg, n=244; docetaxel, n=240)*	2 mg: 3.9 vs 4.0 10 mg: 4.0 vs 4.0 –	2 mg: 0.88 10 mg: 0.79[b] 0.86[e]	10.5 vs 8.6 13.4 vs 8.6 –	0.73[d] 0.59[d] 0.63[e]	18.0 vs 9.0[d] 18.0 vs 9.0[d] –
OAK[4,5,f]	Atezolizumab (n=425) vs docetaxel (n=425) *Mixed: nonsquamous (atezolizumab, n=313; docetaxel, n=315)*	2.8 vs 4.0 –	0.93 –	13.8 vs 9.6 15.6 vs 11.2	0.75[d] 0.74[b]	14.6 vs 13.4 –
REVEL[6,f]	Ramucirumab + docetaxel (n=628) vs placebo + docetaxel (n=625) *Mixed: nonsquamous (ramucirumab + docetaxel, n=465; docetaxel, n=447)*	4.5 vs 3 4.6 vs 3.7	0.76[d] 0.77[d]	10.5 vs 9.1 11.1 vs 9.7	0.86[c] 0.83[c]	22.9 vs 13.6[d] 21.9 vs 14.5[b]
LUME-Lung 1[7,8,f]	Nintedanib + docetaxel (n=655) vs placebo + docetaxel (n=659) *Mixed:nonsquamous ADC (nintedanib + docetaxel, n=322 vs placebo + docetaxel, n=336)*	3.4 vs 2.7 4.0 vs 2.8	0.79[b] 0.77[c]	10.1 vs 9.1 12.6 vs 10.3	0.94 0.83[c]	4.4 vs 3.3[g] 4.7 vs 3.6[g]

[a] These are not head-to-head trials and study designs are different; direct cross-trial comparisons cannot be made;
[b] $P<0.01$; [c] $P<0.05$; [d] $P<0.001$; [e] Pooled pembrolizumab doses; [f] Used as basis for regulatory approval; [g] By independent central review.

1. Borghaei et al. *N Engl J Med*. 2015;373:1627; 2. Herbst et al. *Lancet*. 2016;387:1540; 3. Herbst et al. ASCO 2017. Abstract 9090; 4. Rittmeyer et al. *Lancet*. 2017;389:255;
5. Fehrenbacher et al. *J Thorac Oncol*. 2018;13:1156; 6. Garon et al. *Lancet*. 2014;384:665; 7. Reck et al. *Lancet Oncol*. 2014;15:143; 8. Nintedanib SmPC 2018.

Multiple Targets of Angiogenesis Inhibitors

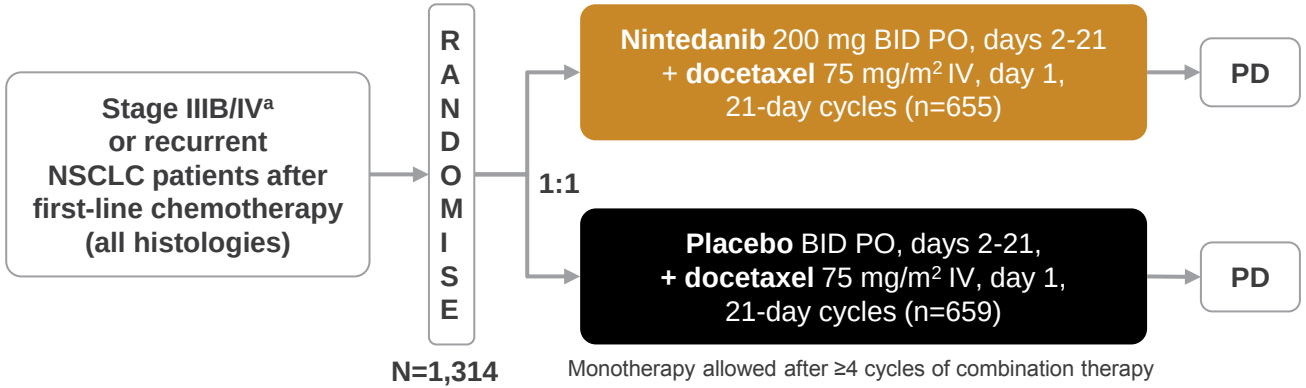
- Currently available antiangiogenic therapies target different signalling pathways
- Many patients are intrinsically refractory or develop resistance to existing antiangiogenic agents that principally target VEGF-A or -B and VEGFR-2
- A multitargeted approach to treatment may limit the development of resistance and maximise antitumour efficacy
- Nintedanib is an oral triple angiokinase inhibitor targeting VEGFR 1-3, FGFR 1-3, PDGFR α/β



VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; FGFR = fibroblast growth factor receptor; PDGFR = platelet-derived growth factor receptor; FLT-3 = fms-like tyrosine kinase 3.

Zhao and Adjei. *Oncologist*. 2015;20:660.

Nintedanib for NSCLC: Phase 3 LUME-Lung 1 Study



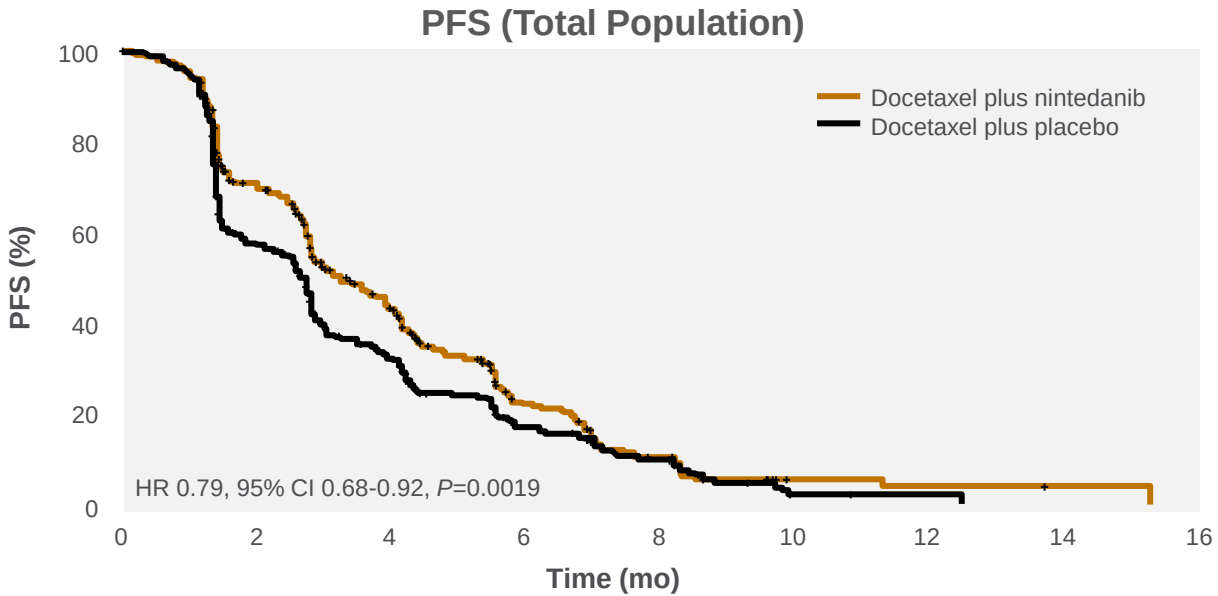
Primary Endpoint:	PFS by independent central review
Key Secondary Endpoint:	OS, prespecified hierarchical analyses of patients with ADC who progressed in <9 months after start of first-line therapy, all patients with ADC, and ITT population

Stratification:
ECOG PS (0 vs. 1)
Prior bevacizumab (yes vs no)
Histology (squamous vs nonsquamous)
Brain metastases (yes vs no)

Regions: Europe/Asia/South Africa
Accrual: 23 Dec 2008 to 09 Feb 2011

PO = orally; IV = intravenously; PD = disease progression; ITT = intent-to-treat.
Reck et al. *Lancet Oncol*. 2014;15:143.

LUME-Lung 1:
Consistent PFS Benefit Regardless of Histology



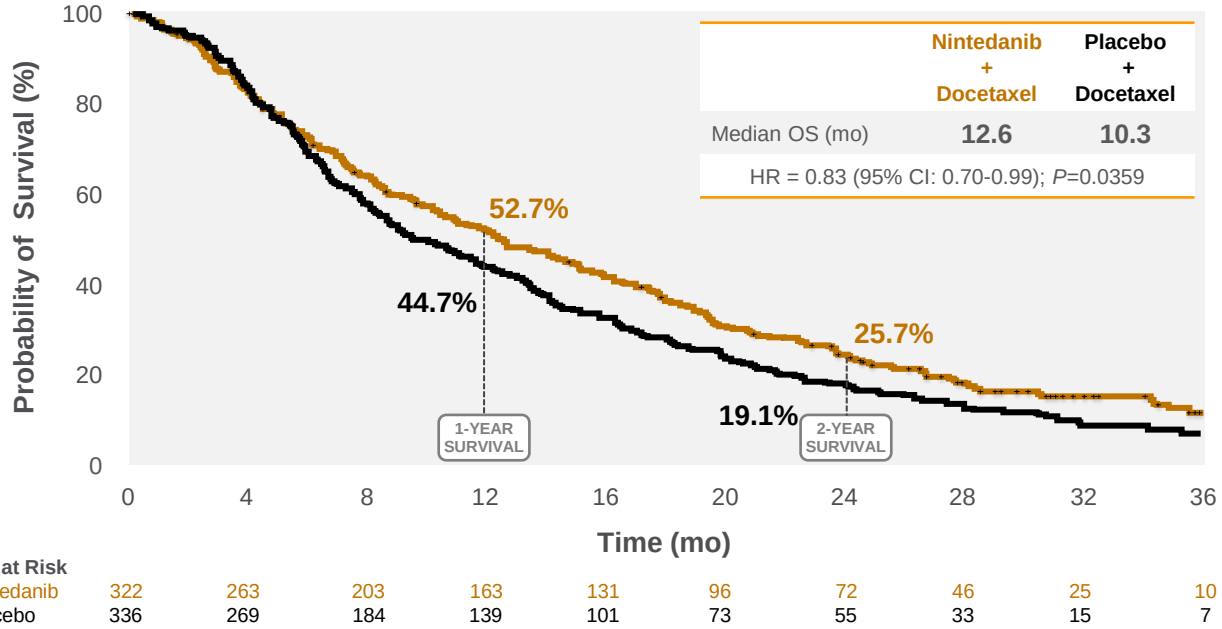
- For patients with **adenocarcinoma histology, median PFS was 4 vs 2.8 months** (HR [95% CI], 0.77 [0.62-0.96]; *P*=0.0193) for nintedanib + docetaxel vs placebo + docetaxel
- For patients with **SqCC histology, median PFS was 2.9 vs 2.6 months** (HR [95% CI], 0.77 [0.62-0.96]; *P*=0.02) for nintedanib + docetaxel vs placebo + docetaxel

CI = confidence interval; SqCC = squamous cell carcinoma.

1. Reck et al. *Lancet Oncol* 2014;15:143; Reck M et al. *J Clin Oncol* 2013;31(Suppl.):Abstract LBA8011.

LUME-Lung 1: Significant Improvement in Median OS in Patients With Adenocarcinoma

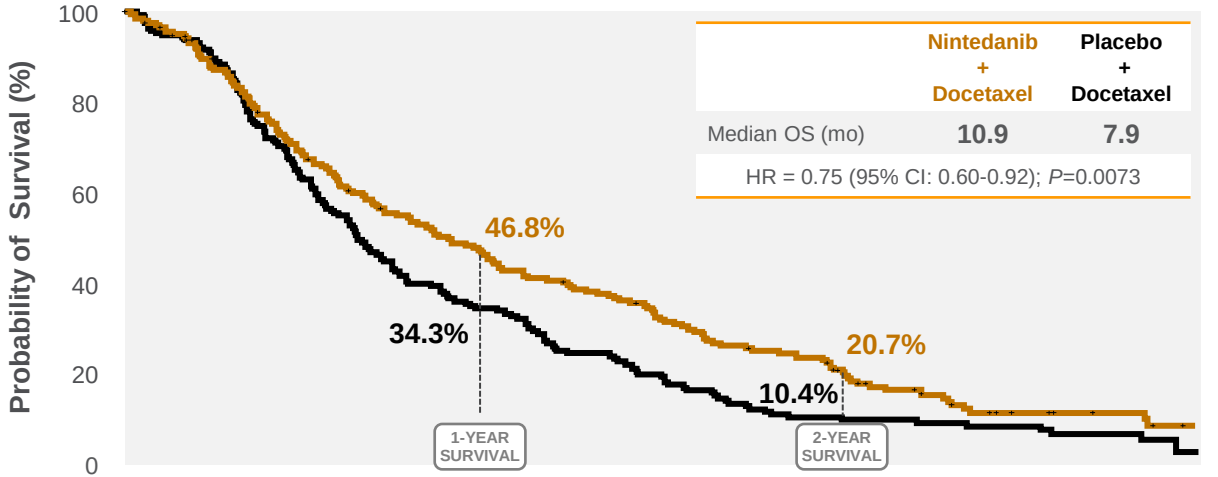
Key Secondary Endpoint, Prespecified Hierarchical Analysis



Reck et al. *Lancet Oncol*. 2014;15:143.

LUME-Lung 1: OS in Patients With ADC Who Progressed <9 Months After Start of First-Line Therapy

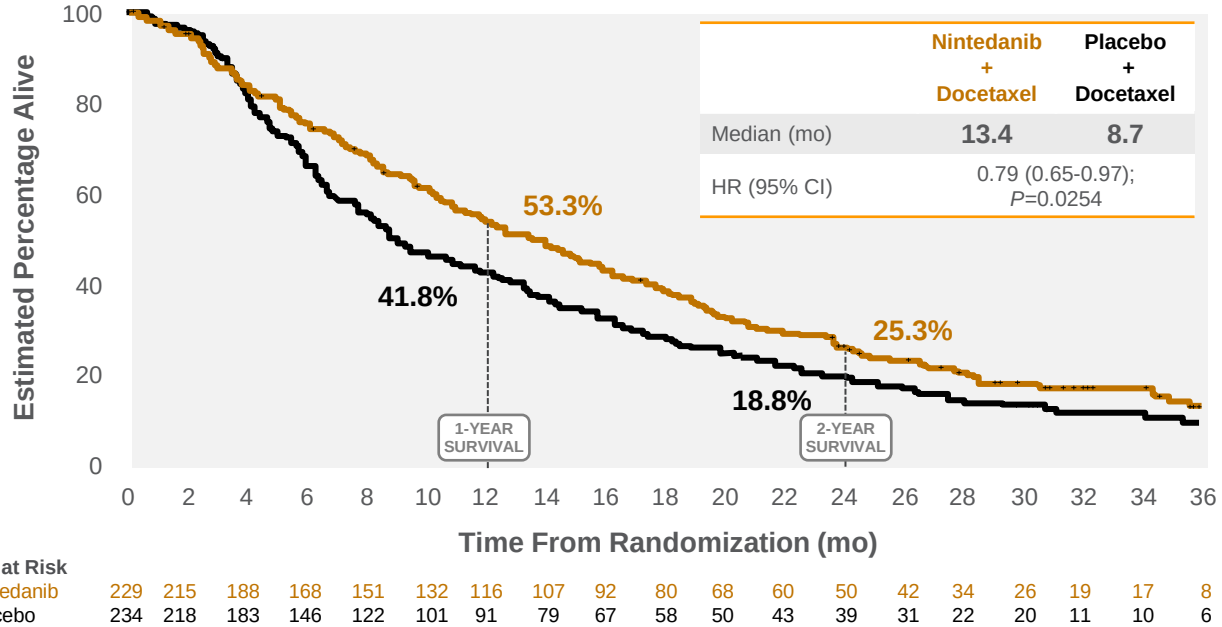
Key Secondary Endpoint, Prespecified Hierarchical Analysis



No. at Risk										
Nintedanib	206	167	119	92	73	51	35	16	9	3
Placebo	199	154	91	62	42	25	17	12	5	1

Reck et al. *Lancet Oncol*. 2014;15:143; Reck and Mellemgaard. *Biologics*. 2015;9:47.

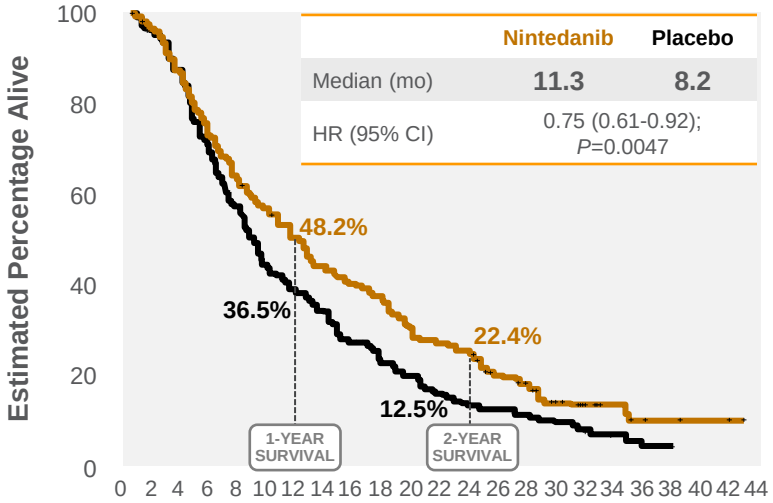
LUME-Lung 1:
OS in the European ADC Population[a,b]



[a] Exploratory analysis.
[b] Patients without documented death were censored at the date of last contact when the patient was known to be alive.
Gottfried et al. *Target Oncol*. 2017;12:475; Heigener et al. 1276P, ESMO 2016.

LUME-Lung 1:
OS in European Patients With Faster-Progressing ADC[a]

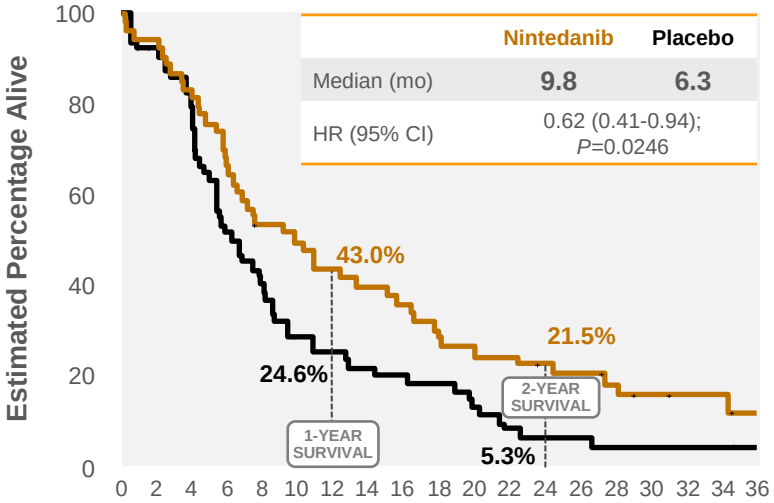
ADC and Time From End of First-Line Therapy ≤6 Months



No. at Risk

Nintedanib	237	225	193	162	141	123	109	96	86	72	60	55	44	34	24	17	11	8	3	2	2	1	0
Placebo	230	210	178	138	111	89	77	64	53	44	34	28	24	21	15	13	5	2	0				

ADC and Progressive Disease as Best Response to First-Line Therapy



No. at Risk

Nintedanib	53	50	44	35	27	25	22	20	18	14	13	12	10	9	7	5	4	4	2
Placebo	64	57	51	31	24	16	14	12	11	10	7	4	3	3	2	2	2	2	1

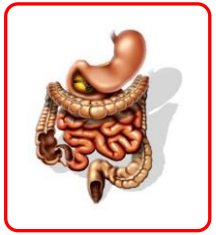
[a] Exploratory analysis.
Gottfried et al. *Target Oncol*. 2017;12:475; Heigener et al. 1276P, ESMO 2016.

Summary of AEs in Patients With ADC

AEs in Patients With ADC[1,2,a]

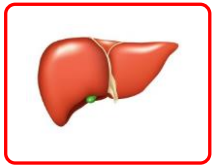
Patients With AEs, n (%)	Nintedanib + Docetaxel (n=320)	Placebo + Docetaxel (n=333)
Any AE, all grades	**308 (96.3)**	**314 (94.3)**
Drug-related AEs, all grades	260 (81.3)	241 (72.4)
Any AE, grades ≥3	**243 (75.9)**	**228 (68.5)**
Drug-related AEs, grades ≥3	176 (55.0)	152 (45.6)
Any AE leading to discontinuation	**67 (20.9)**	**59 (17.7)**
Any serious AE	**111 (34.7)**	**107 (32.1)**

Main AEs (Any Grade) That Were More Common With Nintedanib[1]



Gastrointestinal events

- Diarrhea, nausea, and vomiting
- Manageable with supportive treatment and dose modification



Liver enzyme elevations (ALT/AST)

- Reversible upon dose modification in the majority of patients

Median duration of treatment in ADC population:

- Overall treatment: nintedanib (4.3 mo) vs placebo (3.0 mo)
- Nintedanib/placebo treatment: nintedanib (4.2 mo) vs placebo (3.0 mo)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events ([a]version 3.0 was used)

1. Reck et al. *Lancet Oncol*. 2014;15(suppl):143; 2. Boehringer Ingelheim. Data on file.

Conclusions

- Pembrolizumab, as a monotherapy or in combination with chemotherapy, has become the first-line standard of care in patients with NSCLC without driver mutations[1–3]
- First-line use of immunotherapies is increasing, which will affect treatment options for second-line use[2–3]
- LUME-Lung 1 trial of nintedanib + docetaxel in advanced NSCLC demonstrated[4]
  - Significant prolongation of PFS regardless of histology
  - Significant improvement in OS in patients with adenocarcinoma histology
  - Manageable safety profile
- An exploratory analysis demonstrated a nearly 5-month median OS improvement for European patients treated with nintedanib + docetaxel vs placebo + docetaxel[5]
- Nintedanib in combination with docetaxel is a viable second-line option for the treatment of refractory or progressive adenocarcinoma NSCLC[4,5]

1. Pabani and Butts. *Curr Oncol*. 2018;25:S944: 2. Keytruda SmPC. Merck Sharp & Dohme B.V. 2018; *3.* Merck press release. https://investors.merck.com/news/press-release-details/2018/European-Commission-Approves-Mercks-KEYTRUDA-pembrolizumab-in-Combination-with-Pemetrexed-and-Platinum-Chemotherapy-for-the-First-Line-Treatment-of-Patients-with-Metastatic-Nonsquamous-NSCLC-with-No-EGFR-or-ALK-Genomic-Tumor-Aberrations/default.aspx. Accessed 2 October 2018; 4. Reck et al. *Lancet Oncol*. 2014;15:143; 5. Gottfried et al. *Target Oncol*. 2017;12:475.