Non-Mutated, Non-Squamous NSCLC (adenocarcinoma): Failing First-Line Immunotherapy + Chemotherapy, What Now?

Treatment Options and the Role of the Angio-Immunogenic Switch

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- Honoraria: AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squib, Pfizer, Lilly, MSD, Roche, Takeda

Changing Treatment Landscape for Non-SQ NSCLC

- For decades, 1L SOC for most patients with advanced/metastatic NSCLC without an actionable oncogenic driver has been platinum-doublet chemotherapy[1-3]
- 1L I-O trial outcomes have led to a rapid shift in treatment paradigms for patients with NSCLC without treatable EGFR, ALK, ROS1, or BRAF alterations[2-5]

1L I-O approvals in the EU

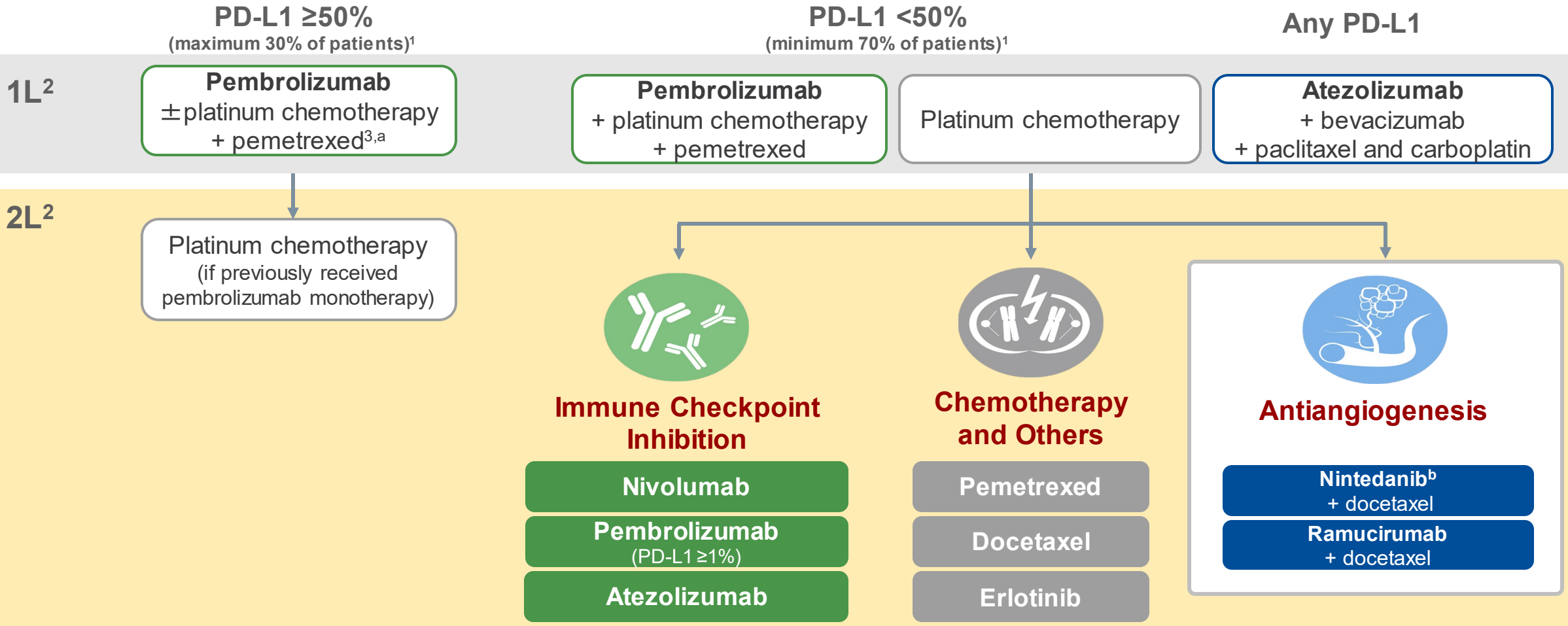
Monotherapy	Combination Therapy
Pembrolizumab for the 1L treatment of metastatic NSCLC in adults whose tumours express PD-L1 ≥50%[a,4]	Pembrolizumab plus pemetrexed and platinum chemotherapy for the 1L treatment of metastatic non-SQ NSCLC in adults[a,4]
	Atezolizumab plus bevacizumab, paclitaxel, and carboplatin, for the 1L treatment of adults with metastatic NSCLC[b,5]

- Optimal treatment sequence after progression on chemotherapy or an I-O ± chemotherapy remains to be established[6,7]

[a]No EGFR- or ALK-positive tumour mutations. [b]In those with EGFR mutant or ALK-positive NSCLC, this combination is indicated only after the failure of appropriate targeted therapies.
ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; I-O = immuno-oncology; PD-L1 = programmed death-ligand 1; ROS = reactive oxygen species; SOC = standard of care; 1L = first-line.
1. Novello S et al. *Ann Oncol*. 2016;27(suppl 5):v1; 2. Planchard D et al. *Ann Oncol*. (2018) 29 (suppl 4): iv192–iv237 (Updated 18 September 2019 by the ESMO Guidelines Committee); 3. Peters S et al. *Ann Oncol*. 2019;30:884; 4. Keytruda SmPC 2019; 5. Roche Press Release 8 March 2019. Accessed 13 March 2019; 6. Corrales L et al. *Front Med (Lausanne)*. 2017;4:13; 7. Grohé C et al. Presented at ESMO 2019. Abstract 1505P.

I-O + Chemotherapy 1L: What treatment options remain for 2L Non-SQ NSCLC without an actionable oncogenic driver?

Overview: Treatment Landscape for Stage IV Non-SQ NSCLC



[a]In the EU, pembrolizumab is approved as a 1L monotherapy for patients with metastatic NSCLC and PD-L1 ≥50% and in combination with chemotherapy for patients with metastatic non-SQ NSCLC regardless of PD-L1 tumour expression status; [b]NSCLC of adenocarcinoma histology.

1. Reck M et al. *N Engl J Med.* 2016;375:1823; 2. Planchard D et al. *Ann Oncol.* (2018) 29 (suppl 4): iv192–iv237 (Updated 18 September 2019 by the ESMO Guidelines Committee); 3. Keytruda SmPC 2019.

2L Trials in Patients With NSCLC

All approved therapies in the 2L setting demonstrated improved OS in comparison with docetaxel; therefore, docetaxel monotherapy is no longer the SOC

- **CheckMate 057:** a phase III study evaluating nivolumab vs docetaxel in non-SQ NSCLC[1]
  - mOS (ITT): 12.2 vs 9.4 mo (HR, 0.73; *P*<0.01)
- **KEYNOTE-010:** a phase II/III study evaluating pembrolizumab vs docetaxel in NSCLC (PD-L1 ≥1%)[2,3]
  - mOS (ITT): 2 mg/kg; 10.5 vs 8.6 mo (HR, 0.73; *P*<0.001)
    10 mg/kg; 13.4 vs 8.6 mo (HR, 0.59; *P*<0.001)
  - mOS (non-SQ): pooled pembrolizumab doses (HR, 0.63)
- **OAK:** a phase III study evaluating atezolizumab vs docetaxel in NSCLC[4,5]
  - mOS (ITT): 13.8 vs 9.6 mo (HR, 0.75; *P*<0.001)
  - mOS (non-SQ): 15.6 vs 11.2 mo (HR, 0.75; *P*<0.01)
- **REVEL:** a phase III study evaluating ramucirumab plus docetaxel vs docetaxel in NSCLC[6]
  - mOS (ITT): 10.5 vs 9.1 mo (HR, 0.86; *P*<0.05)
  - mOS (non-SQ): 11.1 vs 9.7 mo (HR, 0.83; *P*<0.05)
- **LUME-Lung 1:** a phase III study evaluating nintedanib plus docetaxel vs docetaxel in NSCLC[7-10]
  - mOS (ITT): 10.1 vs 9.1 mo (HR, 0.94)
  - mOS (ADC): 12.6 vs 10.3 mo (HR, 0.83; *P*<0.05)
  - mOS (European ADC): 13.4 vs 8.7 mo (HR, 0.79; *P*=0.0254)
  - mOS (ADC with TSFLT <9 month): 10.9 vs. 7.9 mo; (HR, 0.75; *P*=0.0073)
  - mOS (ADC with PD as BR to 1L therapy): 9.8 vs. 6.3 mo; (HR, 0.62; *P*=0.0246)

HR = hazard ratio; ITT = intention to treat; mOS = median overall survival; OS = overall survival; PFS = progression-free survival; TSFLT = time from start of first-line chemotherapy.

1. Borghaei H et al. *N Engl J Med*. 2015;373:1627; 2. Herbst RS et al. *Lancet*. 2016;387:1540; 3. Herbst RS et al. *J Clin Oncol*. 2017;35(suppl 15):9090 (poster presentation); 4. Rittmeyer A et al. *Lancet*. 2017;389:255; 5. Fehrenbacher L et al. *J Thorac Oncol*. 2018;13:1156; 6. Garon EB et al. *Lancet*. 2014;384:665; 7. Reck M et al. *Lancet Oncol*. 2014;15:143; 8. Vargatef SmPC 2018; 9. Gottfried M et al. *Target Oncol*. 2017;12:475; 10. Heigener D et al. *Ann Oncol*. 2016;27(suppl 6):1276P.

SENECA: Efficacy and Safety of 2L Nintedanib/Docetaxel With Either Weekly or Q3W Docetaxel Schedule

SENECA: a phase IIb, Italian multicentre study to investigate the real-life efficacy and safety of nintedanib plus docetaxel in patients with NSCLC progressing after 1L chemotherapy

- **Treatment groups (investigator's choice)**
  - T1 - Nintedanib + docetaxel; 33 mg/mq on days 1 and 8 in a 21-day cycle
  - T2 - Nintedanib + docetaxel; 75 mg/mq q3w, over ≤6 chemotherapy cycles
- **Stratification:** Patients were stratified by relapse-timing from the end of 1L chemotherapy
  - C1 - ≤3 months
  - C2 - >3 months
- **Primary endpoint:** PFS by investigator's assessment
- **Secondary endpoints:** OS, disease response rate (RECIST 1.1), and safety
- **Median follow-up:** 35.5 months
- **Results:**
  - No significant change in PFS or OS were seen regardless of docetaxel schedule
  - A trend of higher toxicities for the docetaxel q3w schedule (T2) was observed, especially for AEs related to chemotherapy (**afebrile neutropenia**, fatigue, and oral mucositis of any grade, and grade ≥3 diarrhoea)

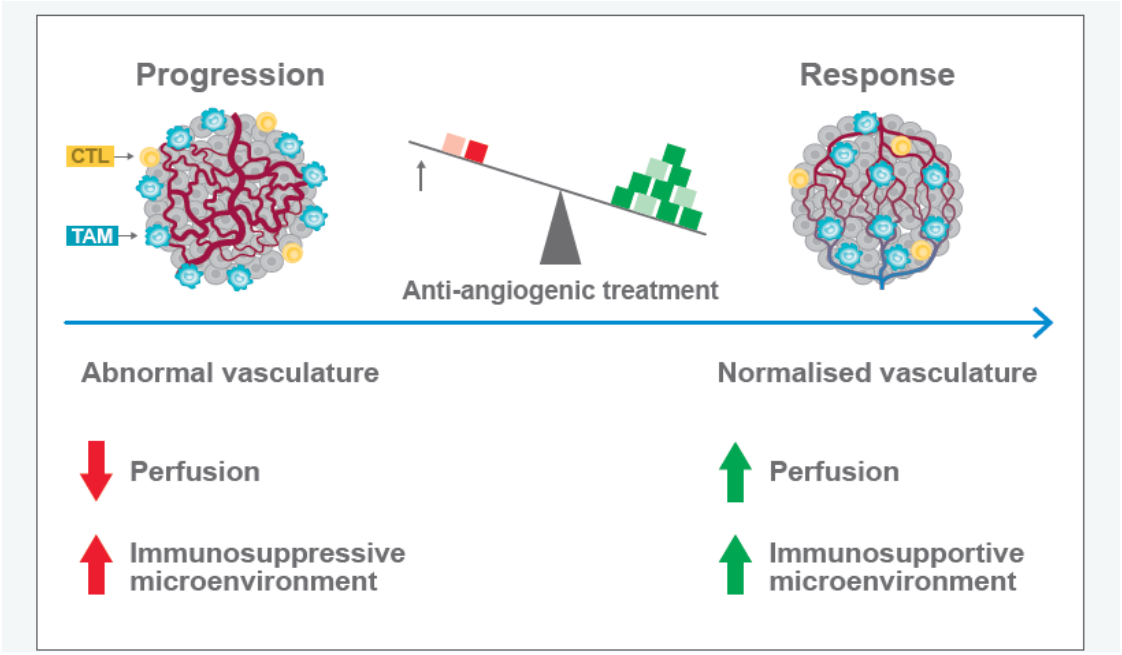
Data cutoff: 25 December 2018.

Capelletto et al. *Lung Cancer*. 2019;134:210.

What is known about the efficacy of antiangiogenesis after progression on I-O?

Tipping the Balance Towards an Immunosupportive TME via the Angio-Immunogenic Switch?

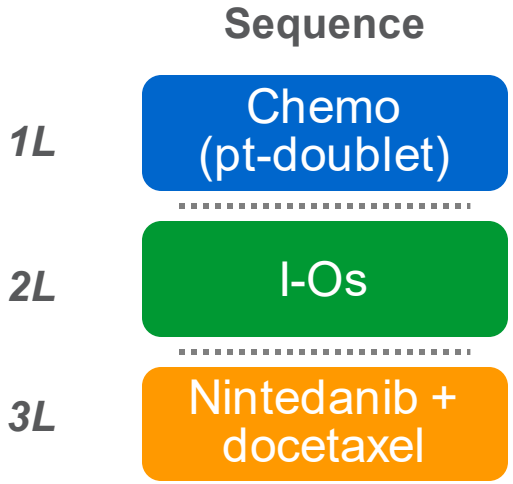
- VEGF creates an immunosuppressive (protumour) microenvironment[1,2]
  - Upregulation of immunosuppressive cells
    - Regulatory T cells (Tregs)
    - MDSCs
  - Impaired antigen presentation
    - Suppression of DC maturation, macrophages (TAMs)
    - Impaired T-cell function (CTLs)
- Hypoxia-induced VEGF secretion leads to an immune tolerant TME[3]



1. Fukumura D et al. *Nat Rev Clin Oncol*. 2018;15:325; 2. Khan KA and Kerbel RS. *Nat Rev Clin Oncol*. 2018;15:310;
3. Chouaib S et al. *Front Immunol*. 2012;3:21; 4. Grohé C et al. *J Clin Oncol*. 2019;37(suppl):abstract 9074.

Nintedanib + Docetaxel After I-O: Clinical Data

Spanish Nintedanib Named Patient Use (NPU) Programme



Response	2L I-O n (%) (N=11)	3L Nintedanib + Docetaxel n (%) (N=11)
ORR	18.2%	36.5%
CR	0	0
PR	2 (18.2)	4 (36.5)
SD	3 (27.3)	5 (45.5)
PD	6 (54.5)	2 (18.2)
DCR	45.5%	81.8%

Encouraging ORR and DCR with nintedanib + docetaxel after prior I-O and chemotherapy

CR = complete response; DCR = disease control rate.
Corral J et al. *Clin Transl Oncol*. 2019;21:1270.

Nintedanib + Docetaxel After I-O: Clinical Data

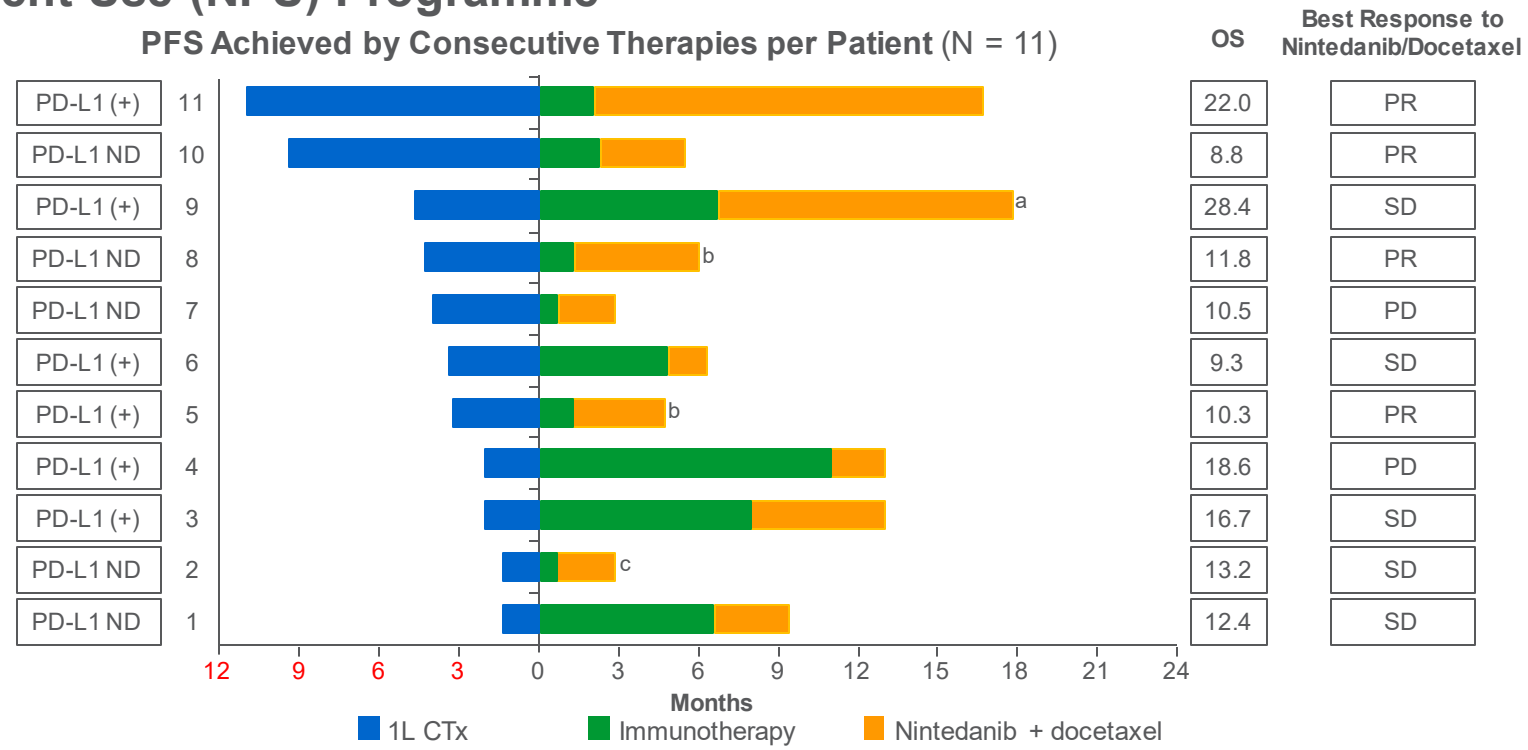
Spanish Nintedanib Named Patient Use (NPU) Programme

Sequence

1L Chemo (pt-doublet)

2L I-Os

3L Nintedanib + docetaxel



- mPFS for nintedanib + docetaxel was 3.2 months (range, 1.4-14.6)
- mPFS for immunotherapy was 2.3 months (range, 0.7-11)

Safety:

- No relevant or unexpected toxicities were reported
- Reported drug-related grade ≥3 AEs were neutropaenia (n=3, 27.3%) and asthenia (n=1)

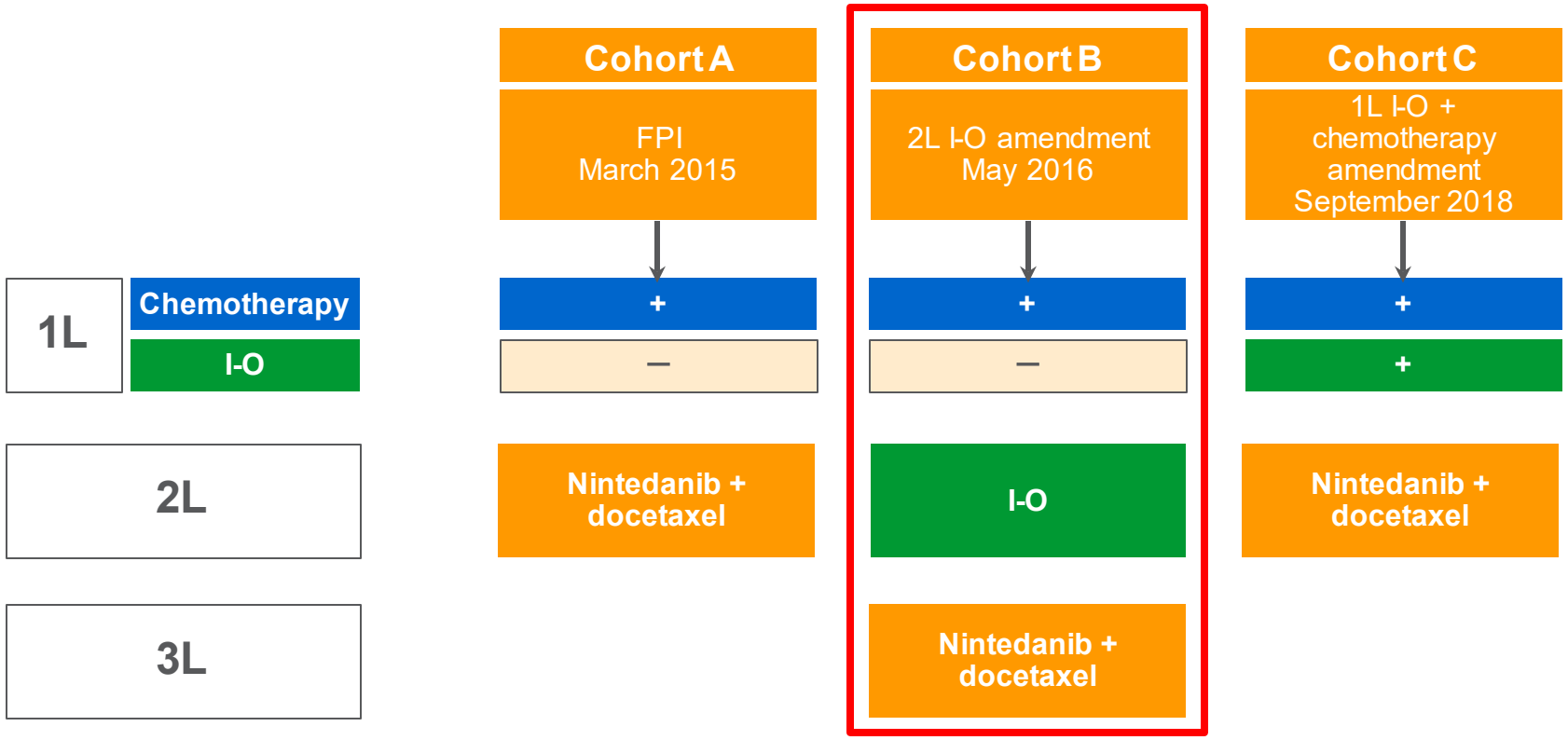
AE = adverse event; CTx = chemotherapy; ND = not determined.

[a]Patient who received erlotinib as 2L treatment prior to immunotherapy (PFS: 3 months). [b]Never smokers. [c]Patient with mutated EGFR who received gefitinib treatment followed by 1L platinum-based chemotherapy.

Corral J et al. *Clin Transl Oncol*. 2019;21:1270.

Patient Cohorts in VARGADO

VARGADO is an ongoing, prospective, noninterventional study of nintedanib plus docetaxel after 1L chemotherapy in the routine clinical treatment of patients with locally advanced, metastatic, or locally recurrent ADC NSCLC



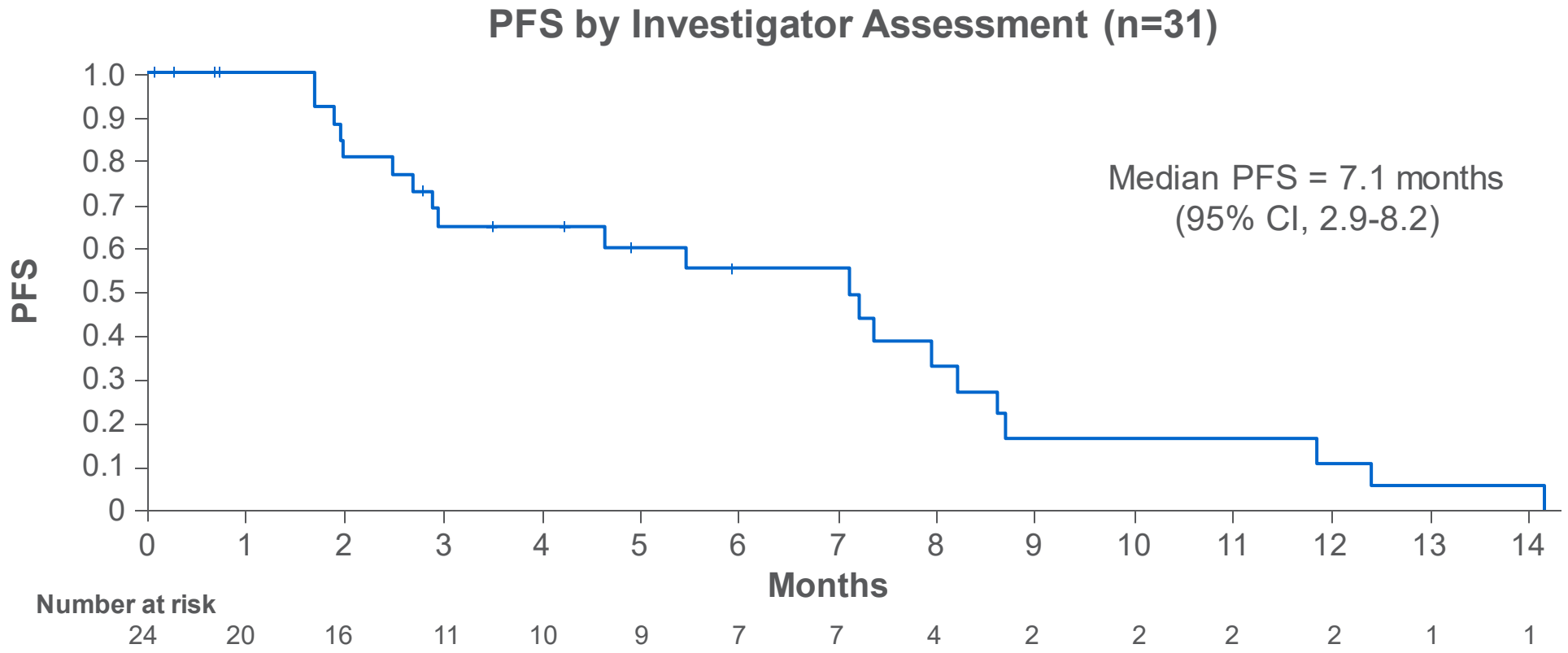
Following protocol amendments:

- Inclusion of patients who received previous 2L I-O therapy was allowed (May 2016)
- Inclusion of patients who received previous 1L therapy with an I-O plus chemotherapy was allowed (September 2018)

FPI = first patient in.

Grohé C et al. Presented at ESMO 2019. Abstract 1505P.

VARGADO Cohort B (Prior I-O): PFS by Investigator Assessment

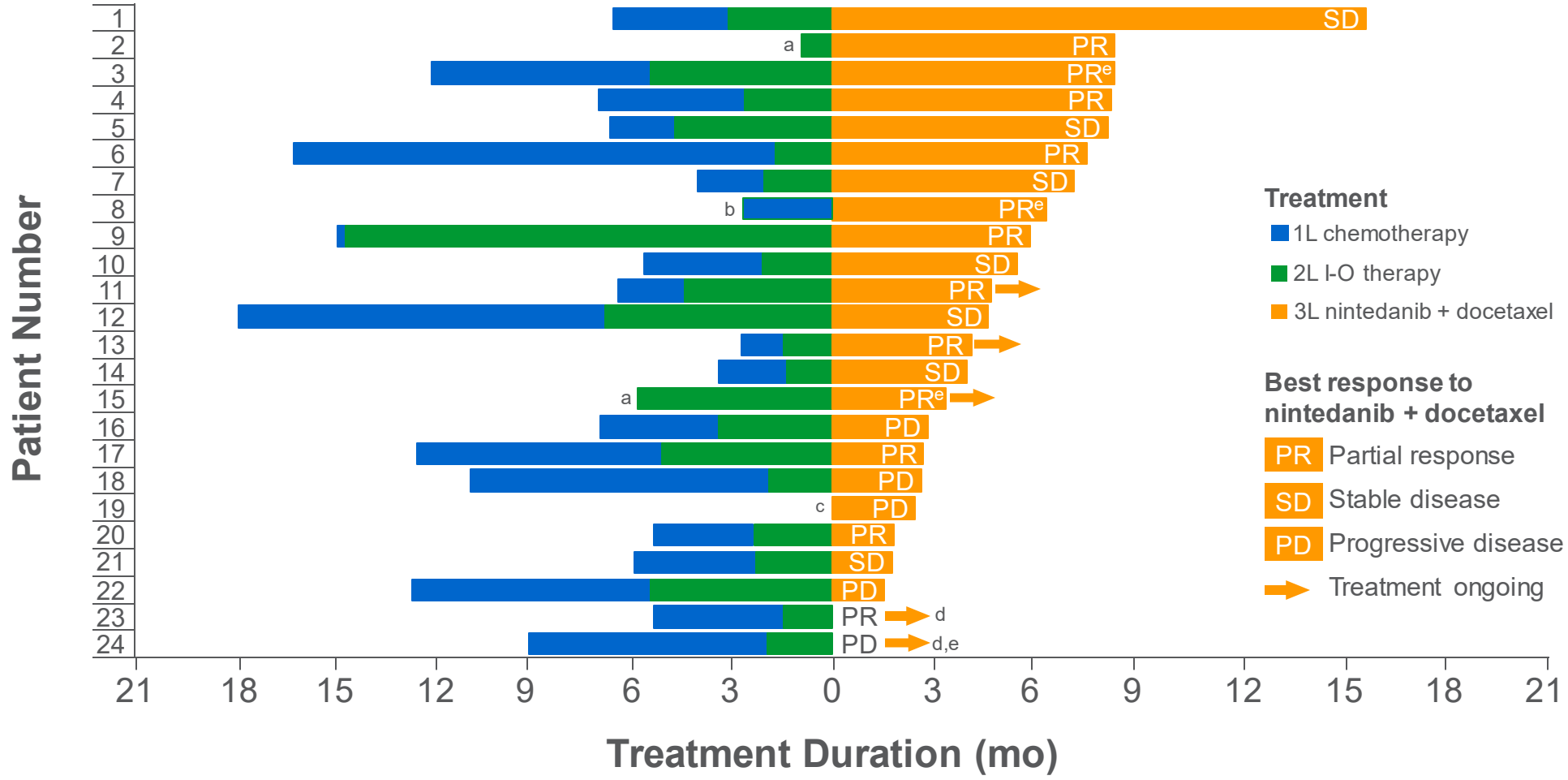


Safety

- Safety was evaluated in all 32 patients; 88% of patients had AEs, with 69% experiencing TRAEs
- Grade ≥3 TRAEs occurred in 56% of patients; serious TRAEs occurred in 50% of patients
  - Most common grade ≥3 nintedanib-related AEs were decreased WBC count (13%), stomatitis (9%), and nausea (3%)
  - Most common grade ≥3 docetaxel-related AEs were decreased WBC count (22%), stomatitis (9%), nausea (6%), and fatigue (3%)

Interim data cutoff: 1 April 2019.
TRAE = treatment-related adverse event; WBC = white blood cell.
Grohé C et al. Presented at ESMO 2019. Abstract 1505P.

VARGADO Cohort B (Prior I-O): Treatment Duration by Treatment (n=24)



Interim data cutoff: 1 April 2019.

[a]Time on chemotherapy not yet documented; 5 chemotherapy cycles documented; [b]Time on I-O therapy not yet documented; [c]Time on chemotherapy and I-O therapy not yet documented; 4 chemotherapy cycles documented; [d]Time on nintedanib plus docetaxel not yet documented; [e]Clinically documented response.

Grohé C et al. Presented at ESMO 2019. Abstract 1505P.

Efficacy Comparison of 3L Treatment With Nintedanib + Docetaxel in Patients With Prior I-O Treatment

PFS

	VARGADO (Cohort B)[1] Interim Analysis April 2019		Spanish NPU[2] Corral et al WCLC 2017	
Population	N	mPFS (mo) Invest[a]	N	mPFS (mo) Invest[a]
3L Nintedanib + docetaxel prior I-O	31	7.1	11	3.2

ORR and DCR

	VARGADO (Cohort B)[1] Interim Analysis April 2019			Spanish NPU[2] Corral et al WCLC 2017		
Population	N	ORR (%)	DCR (%)	N	ORR (%)	DCR (%)
3L Nintedanib + docetaxel prior I-O	24	50	79	11	36.5	81.8

[a]Invest. = investigator-assessed PFS.

1. Grohé C et al. Presented at ESMO 2019. *Abstract* 1505P; 2. Corral J et al. *Clin Transl Oncol*. 2019;21:1270.

Conclusions

- 1L use of I-Os is increasing, which affects treatment options for 2L use[1,2]
- An immunosuppressive TME is closely linked with hypoxia-induced, VEGF-promoted angiogenesis and upregulation of immunosuppressive cells[3-5]
- An antiangiogenic treatment strategy involving inhibition of VEGF tips the balance towards an immunosupportive TME: an 'angio-immunogenic switch'[6]
- Nintedanib + docetaxel demonstrated a nearly 5-month median OS (4.7 months) improvement for European population subgroup vs placebo + docetaxel[7]
- Initial data with nintedanib + docetaxel in patients with advanced lung ADC following treatment with chemotherapy and I-Os, showed clinically relevant efficacy and an adequate safety profile[6]

1. Peters et al. *Ann Oncol*. 2019. [Epub ahead of print]; 2. Planchard D et al. *Ann Oncol*. (2018) 29 (suppl 4): iv192–iv237 (Updated 18 September 2019 by the ESMO Guidelines Committee).; 3. Fukumura et al. *Nat Rev Clin Oncol*. 2018;15:325; 4. Khan and Kerbel. *Nat Rev Clin Oncol*. 2018;15:310; 5. Chouaib et al. *Front Immunol*. 2012;3:21; 6. Grohé C et al. Presented at ESMO 2019. *A*bstract 1505P; 7. Gottfried et al. *Target Oncol*. 2017;12:475.