Nivolumab: Largos supervivientes en 2ª línea de cáncer de pulmón no microcítico

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Definición de largo superviviente en cáncer de pulmón no microcítico avanzado

1. Supervivencia 1 año desde el diagnóstico
2. Supervivencia 2 años desde el diagnóstico
3. Supervivencia 3 años desde el diagnóstico
4. Supervivencia 5 años desde el diagnóstico

Long-Term Survivors

Literature series on long-term survivors with advanced NSCLC.

Study (year)	LTS	$N_{LTSpatients}$	Stage	Predictive factors	Remarks
Okamoto et al. [3]	>2 years	17 of 222	IV	PS, adenocarcinoma, surgery, lower *N*-stage	19 patients surgery
Satoh et al. [4]	>2 years	14 of 109	Advanced	PS, EGFR-TKI	
Kaira et al. [5]	>5 year	10 of 124	Advanced	PS, adenocarcinoma, EGFR-TKI	2 resections of solitary brain mets
Dujon et al. [6]	>2 years	23 of 169	Advanced	PS, comorbidity, response, EGFR-TKI	
Giroux Leprieur et al. [7]	>2 years	39 of 245	Advanced	PS, response, surgery, *N* of lines, treatment-free interval	Resectable patients
This series	>2 years	31 vs. 34	Advanced	(PS), (gender), response, *N* of lines, treatment-free interval	

LTS: definition of long-term survival; $N_{LTS\ patients}$: number of long-term survivors; *N*-stage: lymph node stage; PS: performance status; EGFR-TKI: epidermal growth factor tyrosine kinase inhibitor; mets: metastases; *N* of lines: number of metastatic treatment lines.

Van Damme V, *Lung Cancer* 2013

Treatment factors predictive of Long-term survival

Treatment factors.

	Short survivors	Long survivors	P
Total	34	31	
Number of systemic lines			
Mean	2.1	3.2	**0.0023**
Use of palliative radiotherapy			0.2378
No	17 (50%)	11 (35%)	
Yes	17 (50%)	20 (65%)	
Use of EGFR TKI			0.3878
No	15 (44%)	17 (55%)	
Yes	19 (56%)	14 (45%)	
Response to 1st line chemotherapy			**0.0001**
PR	9 (26%)	21 (68%)	
SD	9 (26%)	9 (29%)	
PD	16 (47%)	1 (3%)	
Treatment-free interval			
Mean (months)	2.8	23.4	**0.0009**

EGFR-TKI: epidermal growth factor receptor tyrosine kinase inhibitor.

Van Damme V, *Lung Cancer* 2013

Factors associated with long-term survival

Multivariate analysis (Cox model) of factors associated with survival of patients with NSCLC

Variable	Hazard ratio	95% CI	*P* value
Number of treatment lines[†]	0.69	0.57–0.84	0.0002
PS of 0–1 at first progression of tumour	0.14	0.03–0.76	0.02
LDH <500 IU/L	0.50	0.34–0.74	0.0005
No surgery	4.40	1.63–11.88	0.003
No maintenance therapy	4.42	2.03–9.64	0.0002
Time to first progression of tumour >3 months	0.25	0.14–0.45	<0.0001

[†] Continuous variable.

Giroux E, et al. *Respirology* 2012

Five-year follow-up from the CA209-003: *Phase 1 Study of Nivolumab in Advanced Solid Tumors (NSCLC Cohorts):* **Long-term survivors**

Key eligibility criteria

- Advanced NSCLC
- ECOG PS 0 or 1[a]
- 1–5 lines of prior systemic therapy

(N = 129)

Randomize 1:1:1[b]

- **Nivolumab 1 mg/kg IV Q2W** (n = 33)
- **Nivolumab 3 mg/kg IV Q2W** (n = 37)
- **Nivolumab 10 mg/kg IV Q2W** (n = 59)

- **Maximum of 96 weeks of treatment**
- **Response per RECIST 1.0**
- **Post-treatment survival assessed every ~3 months**
- **Tissue collection for exploratory PD-L1 expression in a limited number of available samples (per protocol amendment)**

Primary objective: Safety and tolerability

Secondary objective: Antitumor activity (ORR)

Exploratory objectives: OS and exploratory PD-L1 analysis

- Primary safety/efficacy and 3-year follow-up data have been published previously[1,2]
- **Minimum follow-up** for the present analysis was **58.25 months** (15-Nov-2016 database lock)

[a]Prior to the implementation of protocol amendment 4 in October 2010, eligibility included ECOG PS of 0–2

[b]Randomization did not include the first 19 patients (most of whom were treated at 10 mg/kg) enrolled in the initial part of the study

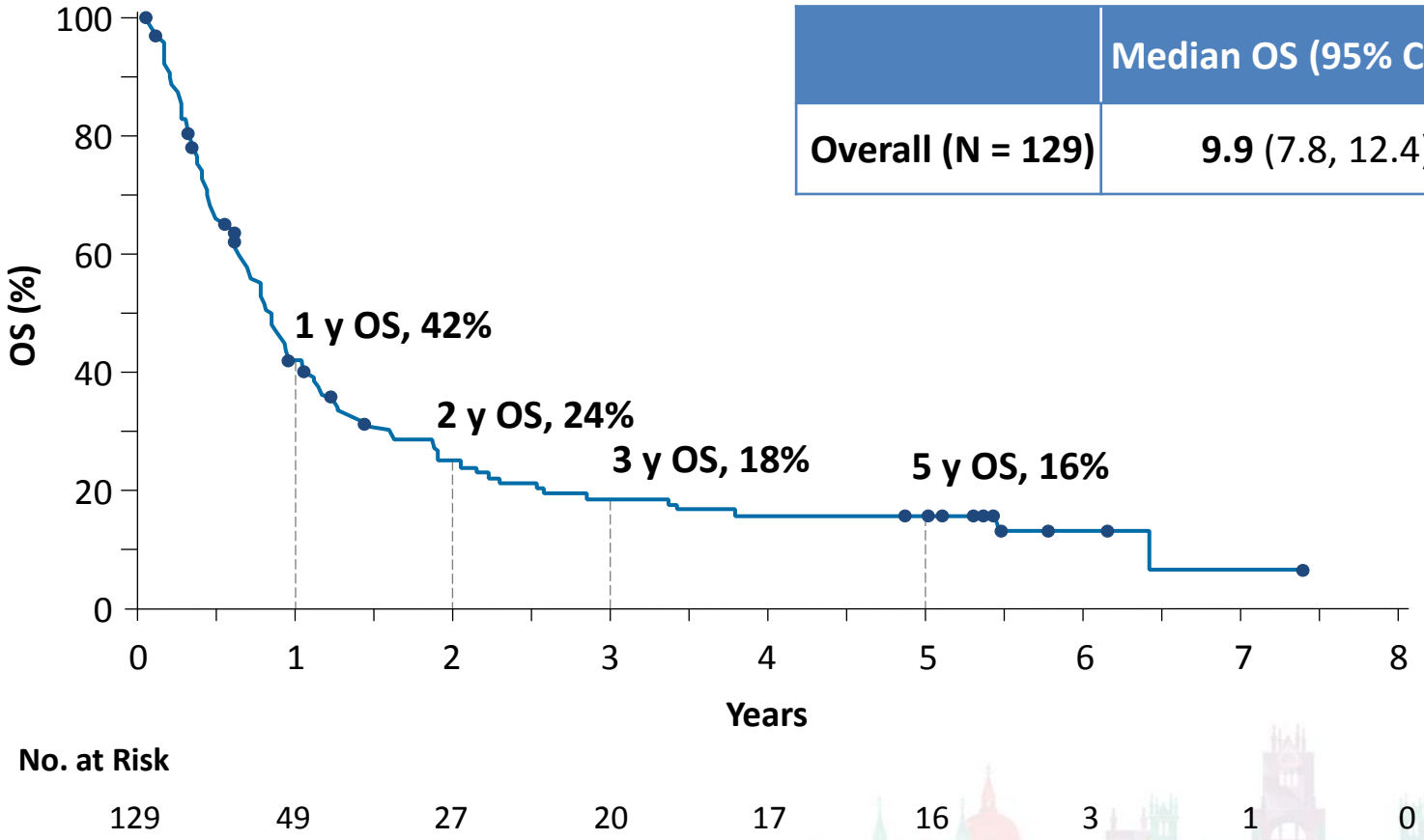
1. Topalian S, et al. *N Engl J Med* 2012;366:2443–2454; 2. Gettinger S, et al. *J Clin Oncol* 2015;33:2004–2012.

Brahmer J, et al. AACR 2017. Oral CT077

5-Year Estimates of OS[a]

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

	Median OS (95% CI), mo
Overall (N = 129)	**9.9** (7.8, 12.4)

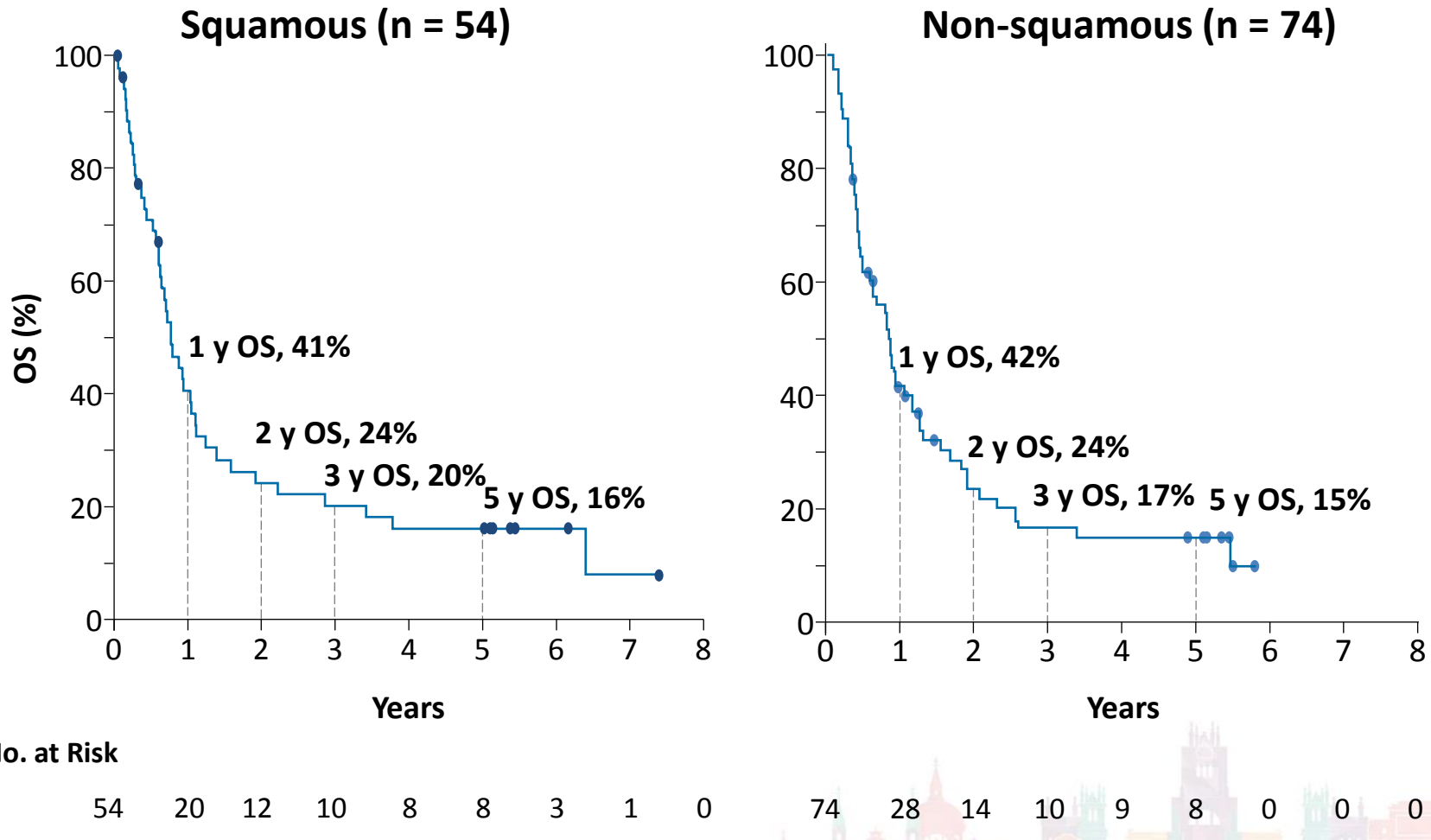


[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

Brahmer J, et al. AACR 2017. Oral CT077

5-Year Estimates of OS by Histology

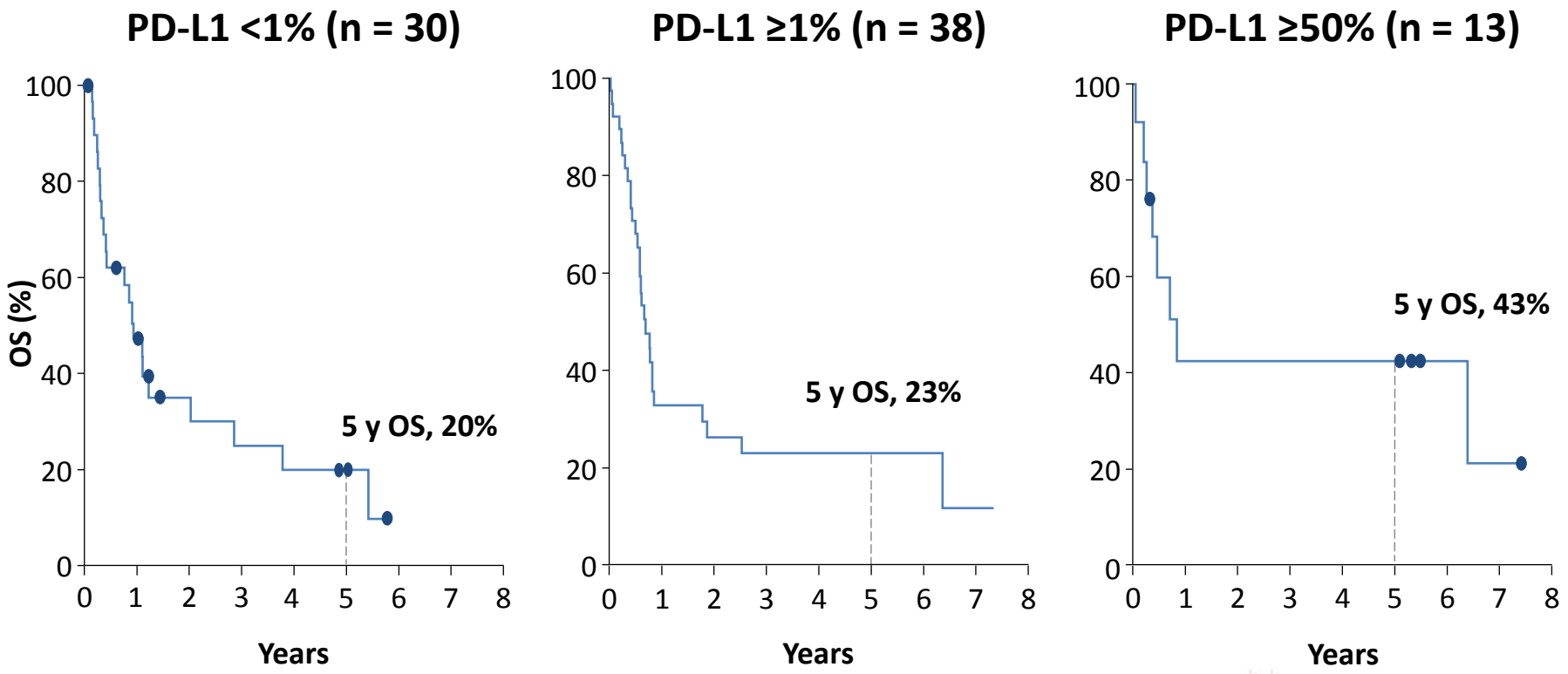
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



Brahmer J, et al. AACR 2017. Oral CT077

5-Year Estimates of OS by PD-L1 Status[a]

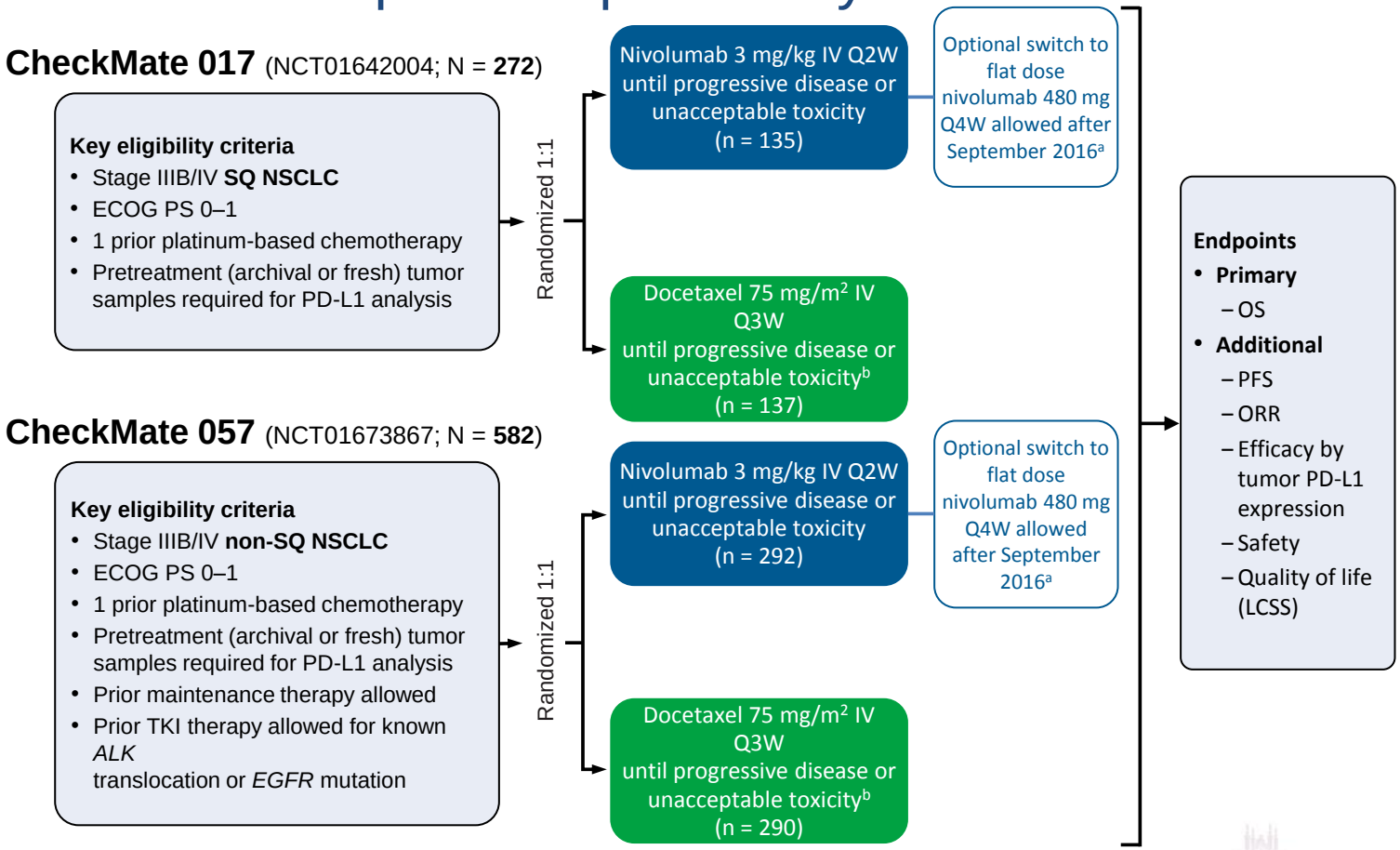
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



[a]PD-L1 status was not evaluable in 61 (47%) of 129 patients; the estimated 5-y OS rate in patients with unknown PD-L1 status was 10%

Brahmer J, et al. AACR 2017. Oral CT077

Three-year follow-up from CheckMate 017 and 057: Nivolumab vs Docetaxel in patients previously treated advanced NSCLC



Minimum follow-up for survival was 40.3 months in both studies (June 2017, database locks)

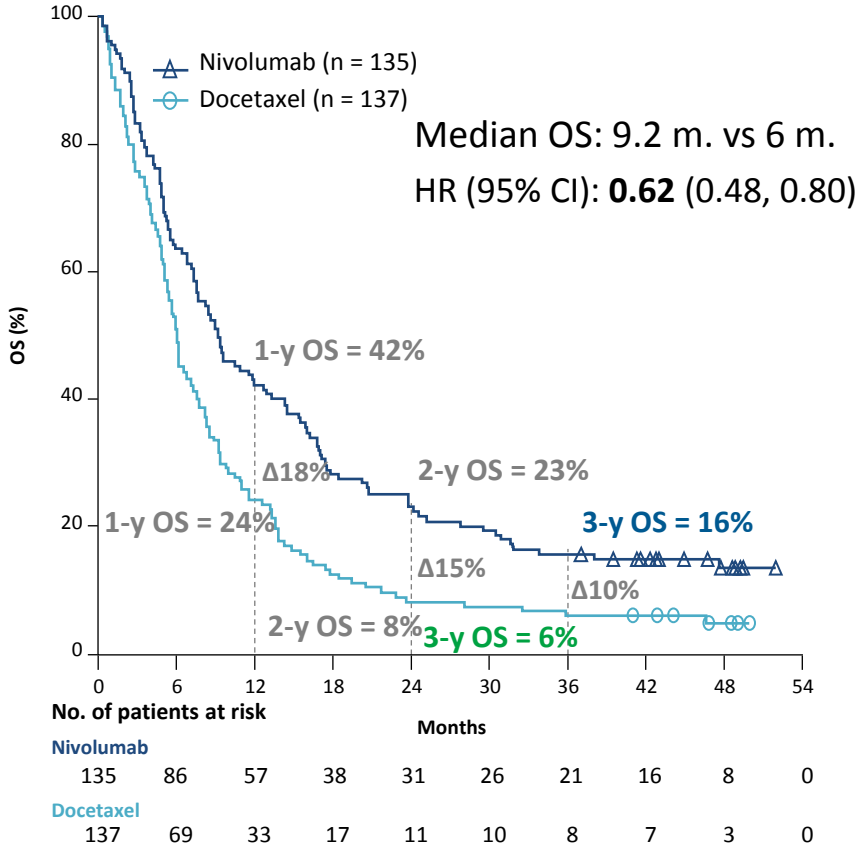
[a]The protocols of both studies were amended in September 2016, when minimum follow-up was approximately 2.5 years, allowing patients to switch to nivolumab 480 mg Q4W starting 2 weeks after their last 3-mg/kg Q2W dose;

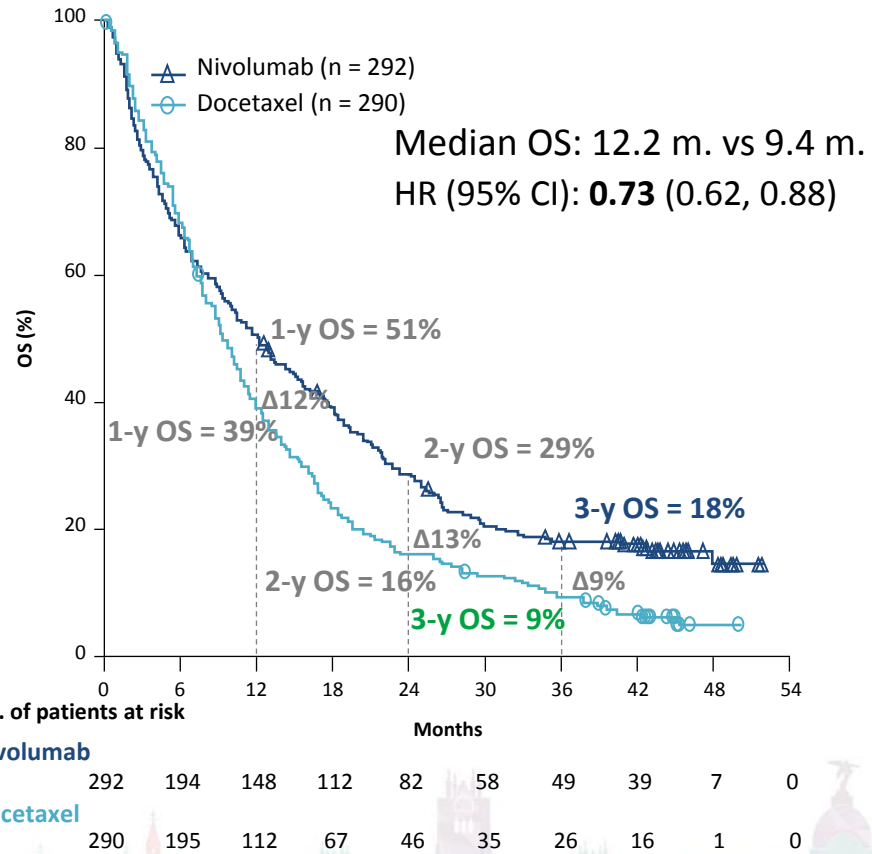
[b]After completion of the primary analyses,[3,4] patients in the docetaxel arms who ended treatment at any time during the studies were **allowed to cross over** to nivolumab

Felip E, et al. ESMO 2017

CheckMate 017 & 057: OS (3 years' minimum follow-up)

- After >3 years' minimum follow-up in CheckMate 017 and 057, **5%** and **7%** of nivolumab-treated patients remained **on study treatment**, respectively; no docetaxel-treated patients remained on study treatment

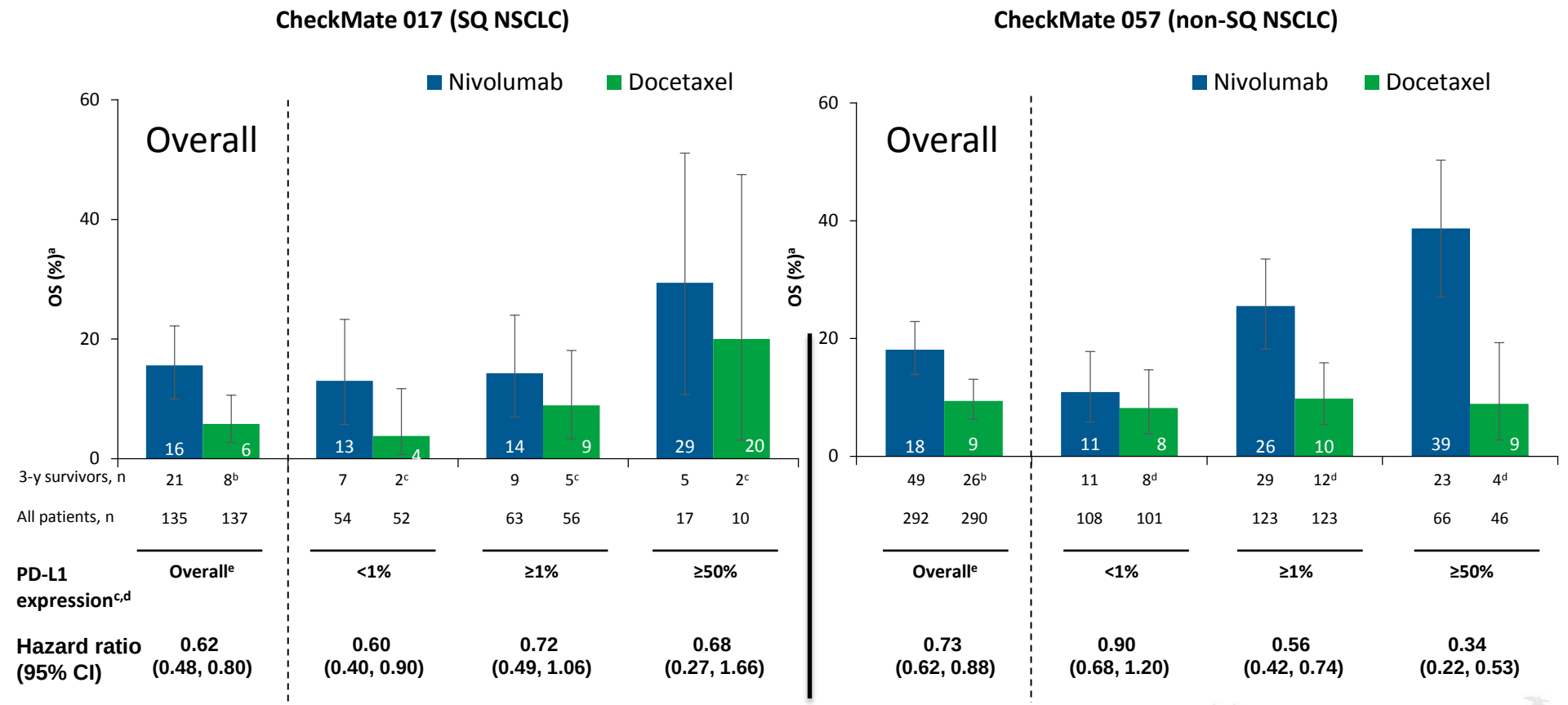




Of the 3-year survivors treated with docetaxel, the majority received subsequent immunotherapy, either during crossover to nivolumab or as post-study treatment (CheckMate 017: **75%** [6/8 patients]; CheckMate 057: **73%** [19/26 patients])

Felip E, et al. ESMO 2017

CheckMate 017 & 057: 3-year estimated OS rates, overall and by PD-L1 expression level



[a]Kaplan-Meier estimates, with error bars indicating 95% CIs; [b]Of the 3-year survivors treated with docetaxel (n = 34) in CheckMate 017 and CheckMate 057, 25 (74%) received subsequent immunotherapy, either during crossover to nivolumab or as post-study treatment; [c]Of the 3-year survivors treated with docetaxel in CheckMate 017 who had <1%, ≥1%, or ≥50% PD-L1 expression levels, 2, 4, and 2 patients, respectively, received subsequent immunotherapy; [d]Of the 3-year survivors treated with docetaxel in CheckMate 057 who had <1%, ≥1%, or ≥50% PD-L1 expression levels, 5, 8, and 4 patients, respectively, received subsequent immunotherapy; [e]Overall population includes those with no quantifiable PD-L1 expression (CheckMate 017: nivolumab, n = 18 [3-y OS, 28%] and docetaxel, n = 29 [3-y OS, 3%]; CheckMate 057: nivolumab, n = 61 [3-y OS, 15%] and docetaxel, n = 66 [3-y OS, 10%])

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CheckMate 017 & 057: Tumor response (3 years' minimum follow-up)

	CheckMate 017 (SQ NSCLC)		CheckMate 057 (non-SQ NSCLC)	
	Nivolumab (n = 135)	Docetaxel (n = 137)	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR, % (95% CI)	20 (14, 28)	9 (5, 15)	19 (15, 24)	12 (9, 17)
Median DOR, months (95% CI)	**25.2** (9.8, NE)	8.4 (3.6, 14.0)	**18.3** (8.4, NE)	5.6 (4.4, 6.9)
Response ongoing, n/N (%)	7/27 (26)	0/12 (0)	13/56 (23)	0/36 (0)

DOR = duration of response; NE = not estimable

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Safety summary for nivolumab-treated patients in pooled CheckMate 017/057

	Pooled nivolumab (N = 418)	
	Any grade	Grade 3–4
TRAEs, %		
Any AE	67.7	10.5
AE leading to discontinuation	6.0	4.1
Most frequent TRAEs,[c] %		
Fatigue	17.0	1.0
Nausea	11.0	0.5
Decreased appetite	11.0	0.2
Asthenia	10.5	0.2
Diarrhea	8.9	1.0
Rash	8.1	0.5
Pruritus	6.9	0.2
Hypothyroidism	6.0	0
Arthralgia	5.7	0.2
Vomiting	5.0	0

Median (range) duration of therapy for patients treated with nivolumab was 2.8 (0–51.8+) months

[a]Includes events reported between first nivolumab dose and 30 days after last nivolumab dose (3 mg/kg or 480 mg); [b]There were no grade 5 TRAEs; [c]Reported in ≥5% of patients

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Caso clínico

- Paciente de 54 años, fumadora de 20 c/d hasta el diagnóstico
- No antecedentes patológicos de interés
- Diagnosticada en marzo de 2014 de un carcinoma epidermoide de pulmón estadio IV:
  - Masa en hilio izquierdo con obstrucción completa del BPI, con atelectasia de pulmón izquierdo
  - No adenopatías
  - Dos lesiones metastásicas hepáticas en LHD, de 2.5 y 1.9 cm
- A.P. biopsia bronquial: Carcinoma epidermoide moderadamente diferenciado

Caso clínico: Tratamientos recibidos

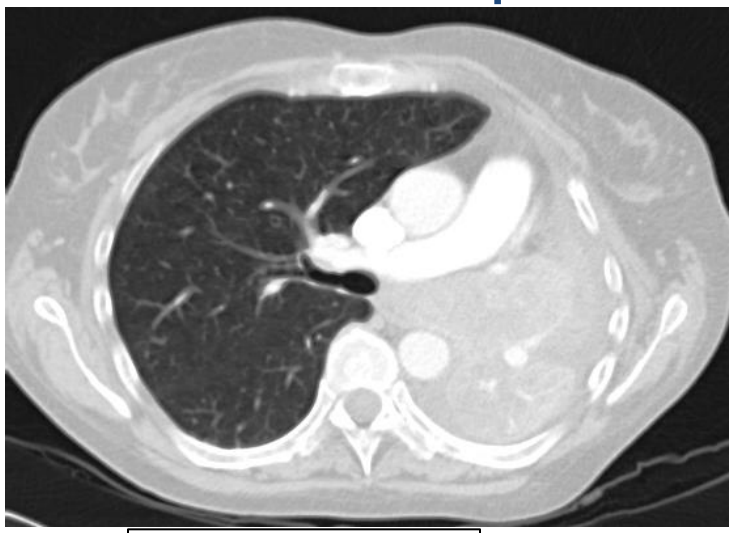
- Marzo 2014: Diagnóstico e inicio de tratamiento
  - Cisplatino-Paclitaxel x 6 ciclos (fin: julio 2014): RP pulmonar y hepática
- Noviembre 2014: Progresión pulmonar y ganglionar: SLP 9 meses
  - Tratamiento: Carboplatino-Gemcitabina quincenal: PE
- Enero 2015: Progresión pulmonar y ganglionar: SLP 2 meses
  - Tratamiento: Docetaxel x 7 c.: RP pulmonar y ganglionar
- Agosto 2015: Progresión pulmonar: SLP 6 meses
  - Tratamiento: Erlotinib: RP pulmonar
- Marzo 2016: Progresión pulmonar: SLP 6 meses

Caso clínico: Opciones terapéuticas

- Manejo de paciente con carcinoma epidermoide en progresión después de 4 líneas de tratamiento:

1. Tratamiento sintomático
2. Vinorelbina
3. Nivolumab
4. Nivolumab solo si PD-L1 +

Caso clínico: Nivolumab (inicio: mayo 2016): Respuesta pulmonar y hepática



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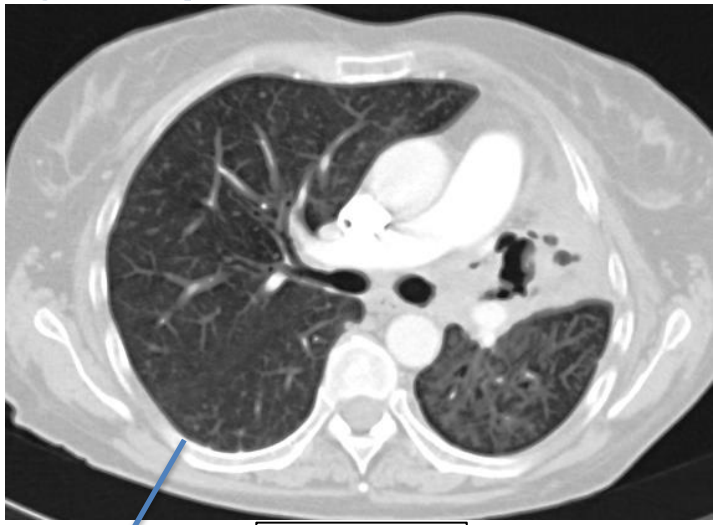

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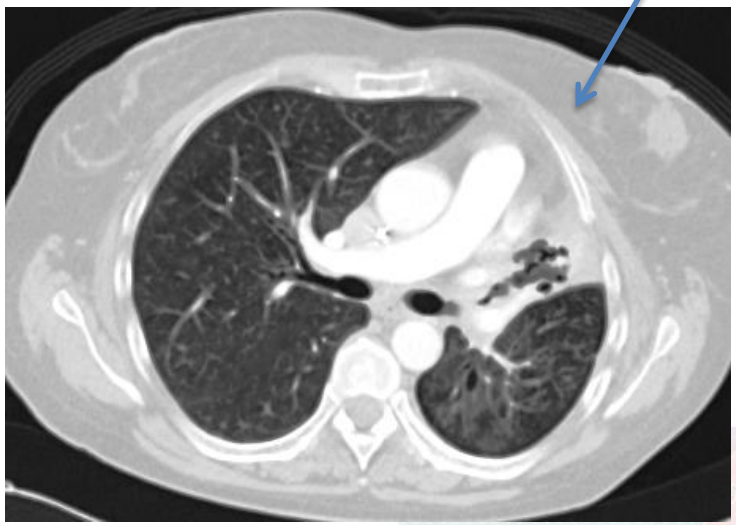

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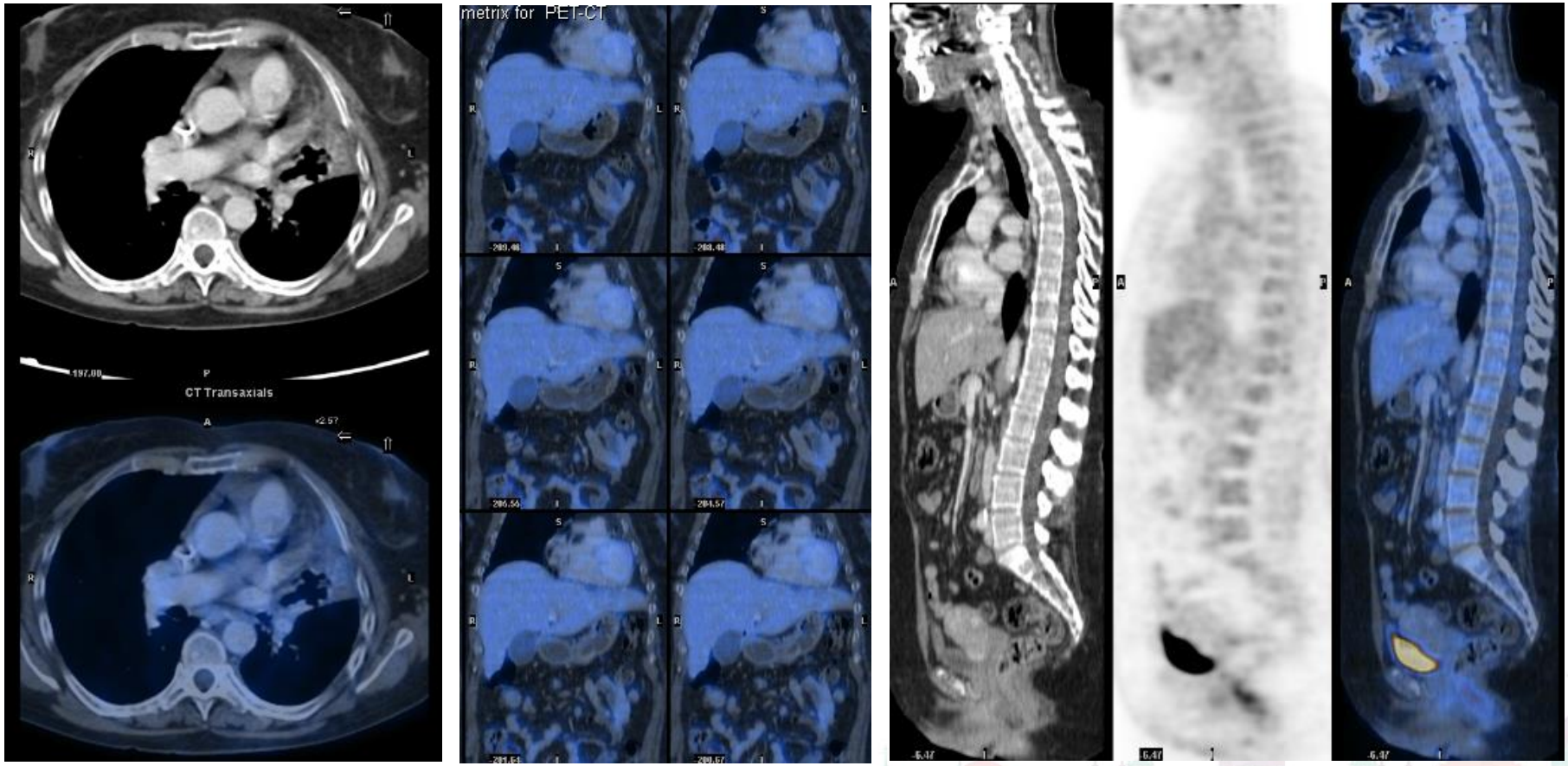
PD-L1+ 70%

Caso clínico: RC en PET-TAC (06.03.17)



La paciente continúa tratamiento activo con Nivolumab

Nivolumab: Largos supervivientes en 2ª línea de cáncer de pulmón no microcítico - Conclusiones

- Long-term survivors in advanced NSCLC: Survival ≥ 2 years
- After 3-years' minimum follow-up, Nivolumab continues to demonstrate long-term efficacy in prev. treated Sq and non-Sq NSCLC:
  - 2-year OS: 23-29%
  - 3-year OS: 16-18%
  - DoR: 25 months (017), 18.3 months (057)
- Good tolerability and QoL
- Benefit observed in patients with <1% and ≥1% PD-L1 expression
- Higher levels of PD-L1 associated with a greater benefit in non-Sq NSCLC
- PD-L1 expression and TMB level: useful tools to select the best candidates to LTS with Nivolumab as ≥ 2nd-line therapy