June 3-7, 2016

McCormick Place | Chicago, Illinois

#ASCO16

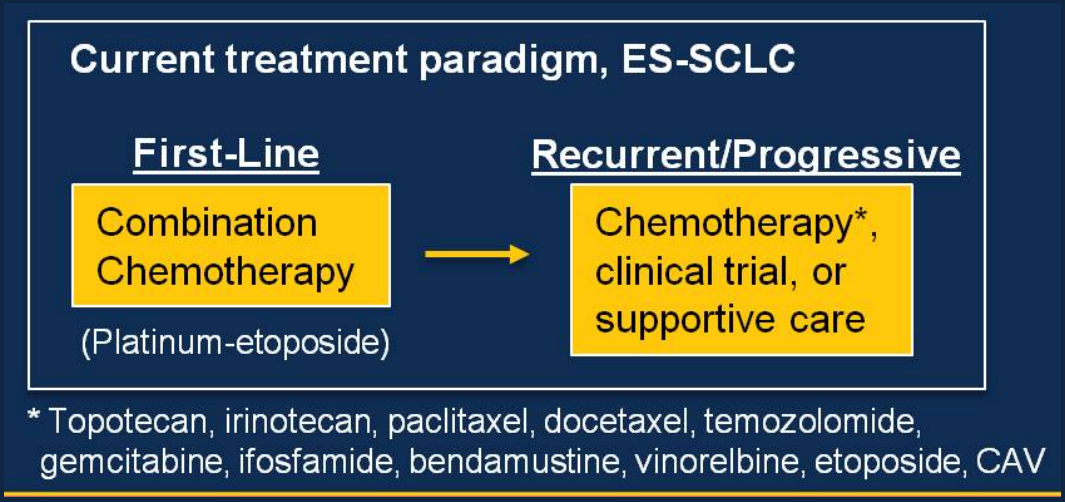
ASCO®

- **Ca. Células pequeñas**
- **Mesotelioma**
- **Ca. Timico**

Dr. Miguel Angel Muñoz
Instituto Valenciano de Oncología

Carcinoma de células pequeñas

- 200.00 nuevos casos/año (15% Ca. Pulmón)
- Alto porcentajes de respuestas en 1ª línea, recaídas frecuentes
- Supervivencia 5ª <15%
- Tasa de respuestas, SLP, SG no han cambiado significativamente en las ultimas 3 décadas
- Topotecan único fármaco aprobado(1996) por FDA para recaída Amrubicina 2002/Japon
- NCCN y ESMO recomiendan considerar ensayos clínicos o tratamiento paliativo
- No biomarcadores conductores

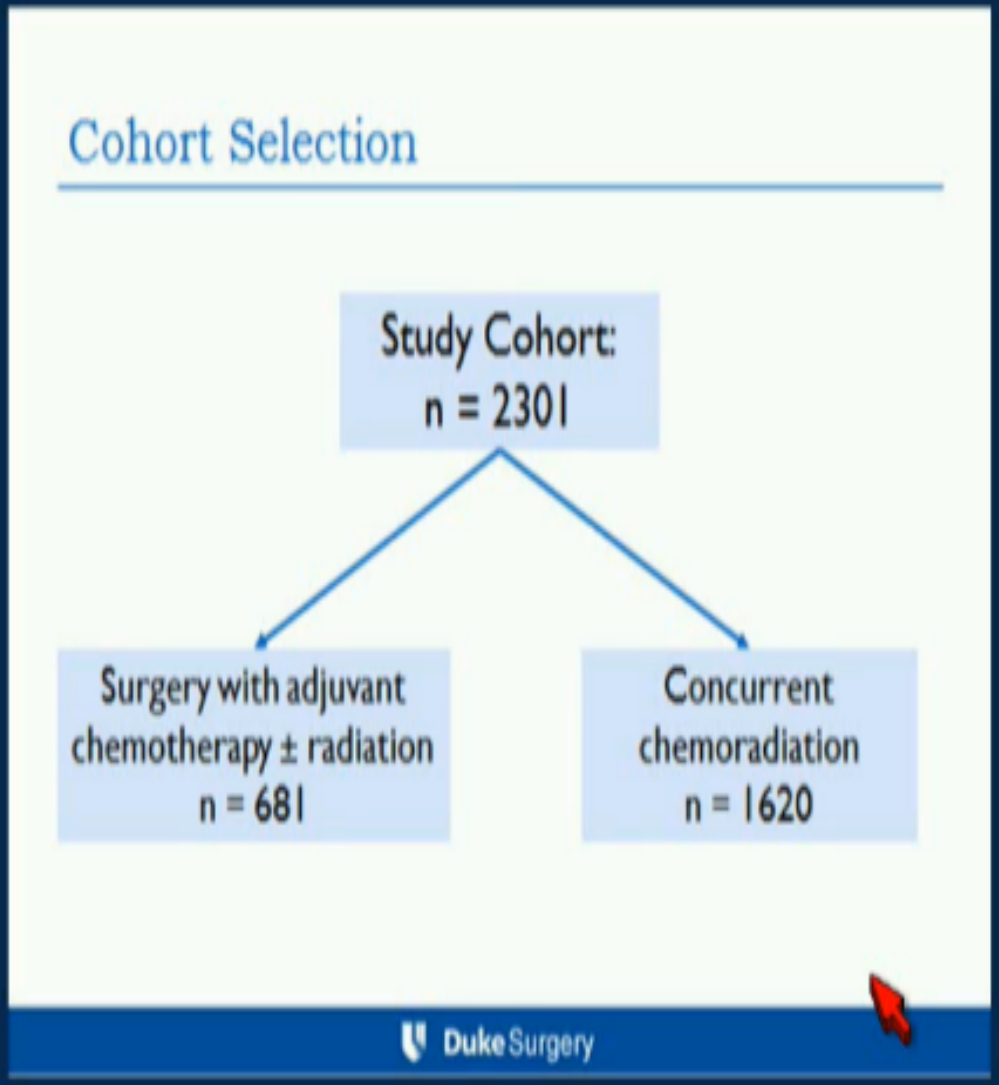


Carcinoma de células pequeñas

- Cirugía/QT/RT versus QT/RT
- Antiangiogénicos en Enf. Extendida
- Radioterapia
- Nuevas dianas

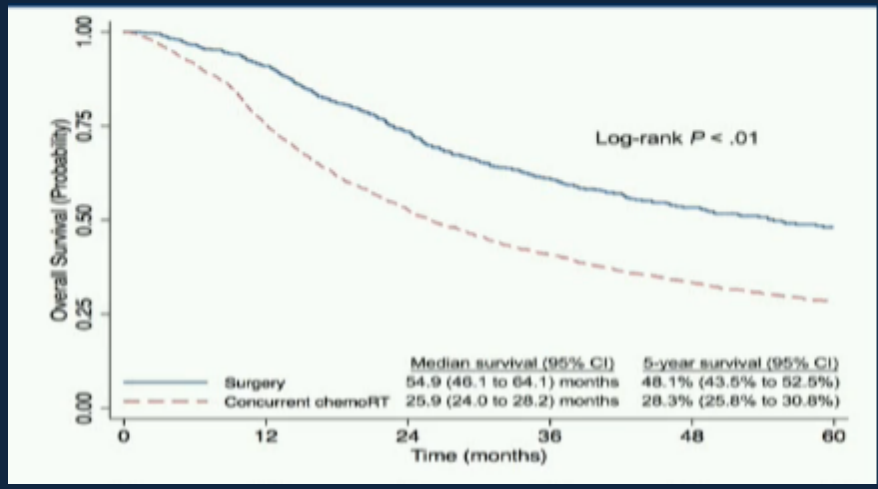
Overall Survival of cT1-2N0M0 SCLC Patients, stratified by Surgery vs. Concurrent Chemoradiation # 8511 Yang et al.

- Retrospective population based study of National Cancer Data Base 2003 -2011
- Identified 4729 cT1-2N0M0 patients
- 2301 eligible



Overall Survival of cT1-2N0M0 SCLC Patients, stratified by Surgery vs. Concurrent Chemoradiation # 8511 Yang et al.

Sup. 5ª :48,1% Cirugía
28,3% QT +RT **P=0,01**



Estudio retrospectivo no randomizado

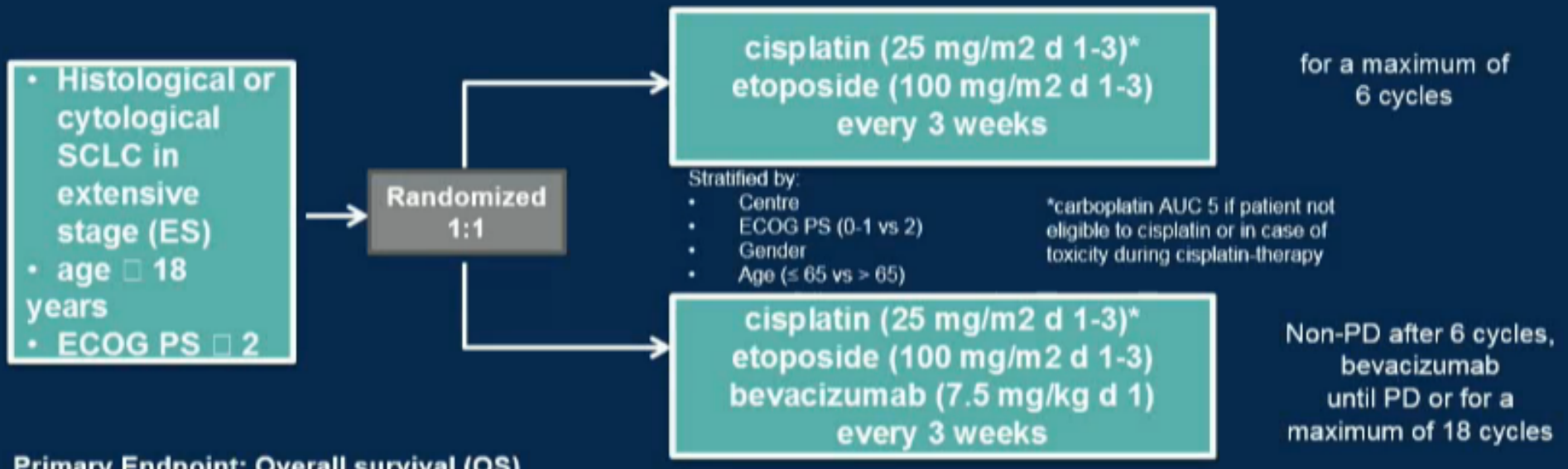
Sin datos :

- Dosis de QT o RT
- Supervivencia cáncer especifica, Sup. libre de recaída, localización de recaída y tratamientos ulteriores
- T1-T2; 4729 n QT+RT secuencial: 2428 (51%)
  Solo QT: 661 20%
  Cirugía; 391 8.2%
  RT 240 5%
- Gran selección de pacientes

Italian multicenter phase III randomized study of cisplatin-etoposide with or without bevacizumab as first-line treatment in extensive stage small cell lung cancer (SCLC): GOIRC-AIFA FARM6PMFJM trial.

Thiseo
Abstract: 8513

Phase 3 multicenter Italian study supported by Agenzia Italiana del Farmaco (AIFA) (EudraCT 2007-007949-13)



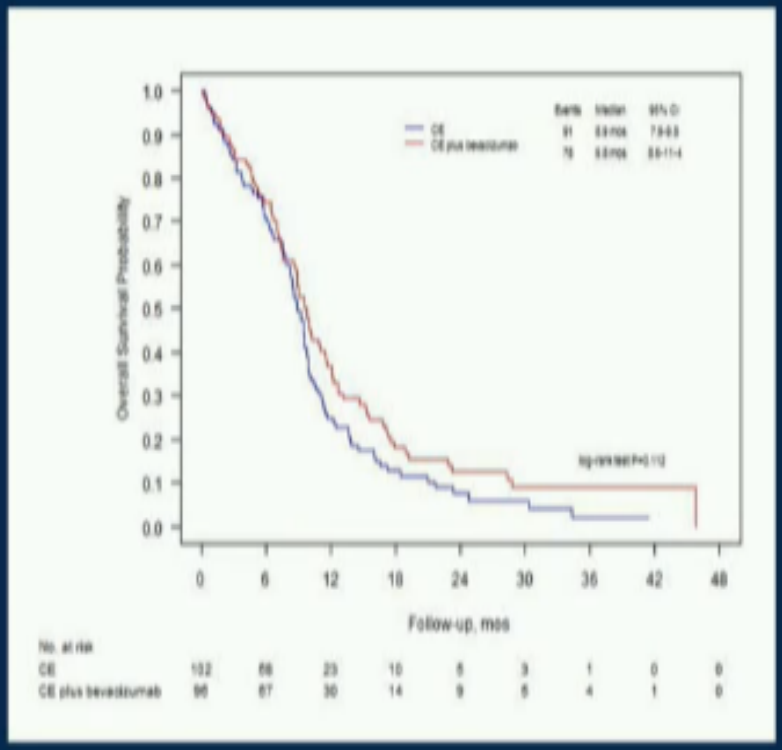
Primary Endpoint: Overall survival (OS)

Secondary Endpoints: Response rate (RR), Progression-Free Survival (PFS), Toxicity

Statistical Considerations: assuming that the cumulative probability of survival at 1-year in the control arm is equal to 40% (median survival 9 months), the experimental treatment will be considered more effective if associated to a relative reduction of the risk of death than at least 40% respect to the control arm. This correspond to a cumulative probability of survival at 1-year in the bevacizumab arm equal or superior to 58%.

Italian multicenter phase III randomized study of cisplatin-etoposide with or without bevacizumab as first-line treatment in extensive stage small cell lung cancer (SCLC): GOIRC-AIFA FARM6PMFJM trial.

- Numeric non-significant improvement with bevacizumab sufficient to warrant further investigation ?
- No significant imbalances in demographics or treatment delivery
- ≥ 90% pts received cisplatin
- Subgroup analysis in SALUTE suggested PFS benefit with carboplatin
- Lack of biomarkers for pt selection limits potential for succesful development of bevacizumab



HR: 0.78 [95%CI 0.58-1.06]
1YS : 24.9% for CE vs. 36.7% CE + Bevacizumab, p =0.112

CONVERT trial

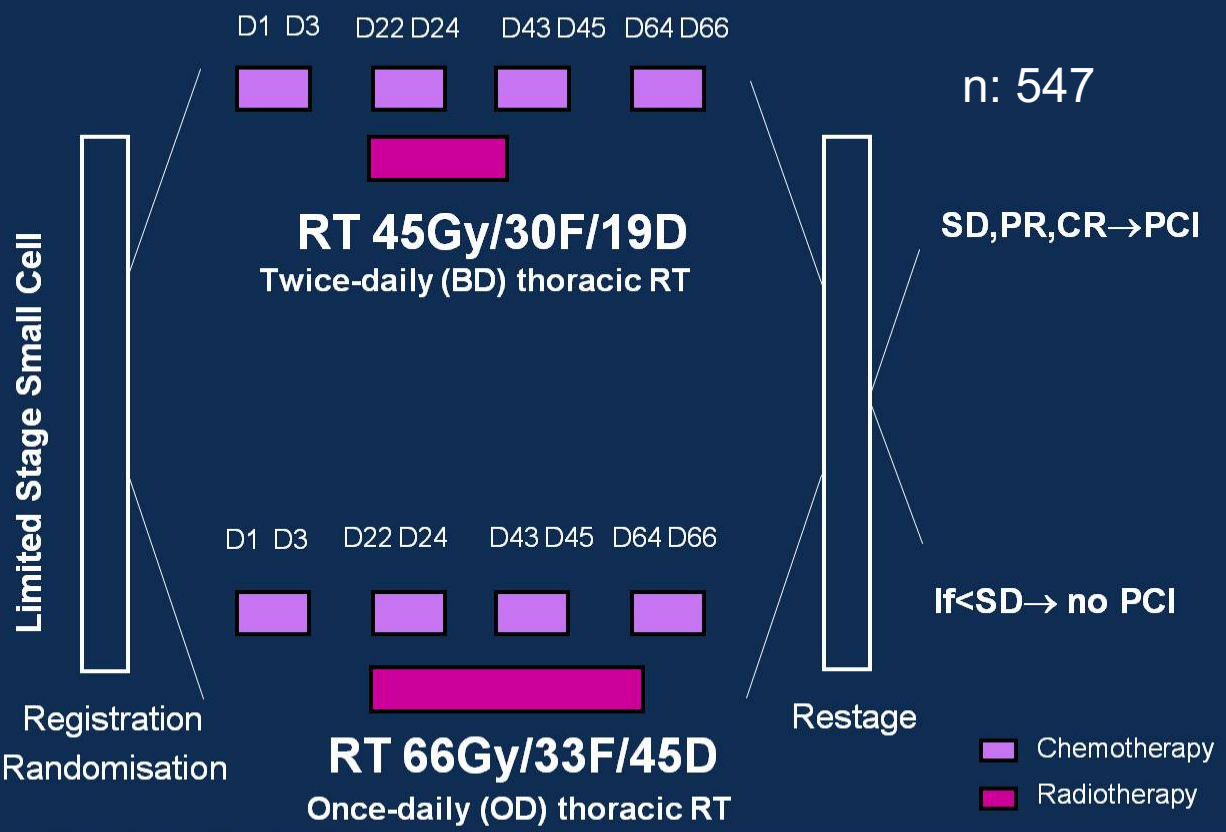
Concurrent ONce-daily VErsus twice-daily RadioTherapy: A 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited-stage small cell lung cancer and good performance status

Corinne Faivre-Finn[1], Michael Snee[2], Linda Ashcroft[3], Wiebke Appel[4], Fabrice Barlesi[5], Adi Bhatnagar[6], Andrea Bezjak[7], Felipe Cardenal[8], Pierre Fournel[9], Susan Harden[10], Cecile Le Pechoux[11], Rhona McMenemin[12], Nazia Mohammed[13], Mary O'Brien[14], Jason Pantarotto[15], Veerle Surmont[16], Jan Van Meerbeeck[16], Penella Woll[17], Paul Lorigan[1], Fiona Blackhall[1]

*1. The University of Manchester, Institute of Cancer Sciences, Manchester, UK; 2. St James Hospital, Leeds, UK; 3. MAHSC-CTU, The Christie NHS Foundation Trust, UK; 4. Royal Preston Hospital, UK; 5. CHU de Marseille, France; 6.Southampton General Hospital, UK; 7.*Canadian Cancer Trials Group, Princess Margaret Cancer Center, Toronto, Canada*; 8. GECP , Institut Català d'Oncologia, Barcelona, Spain; 9. GFPC, Institut de Cancérologie de la Loire, France; 10. Addenbrookes Hospital, Cambridge, UK; 11. Institut Gustave Roussy, Villejuif, France; 12. Freeman Hospital, Newcastle-upon-Tyne, UK; 13. Beatson Cancer Centre, Glasgow, UK; 14. Royal Marsden Hospital, Surrey, UK; 15. Ottawa Health Research Institute, Canada; 16. Universiteit Gent, Belgium; 17. Weston Park Hospital, Sheffield, UK*

Study design

multinational, phase III randomised study



RTP after randomisation
RT started on D22 cycle 1
- **3DCRT or IMRT**
- **No ENI**

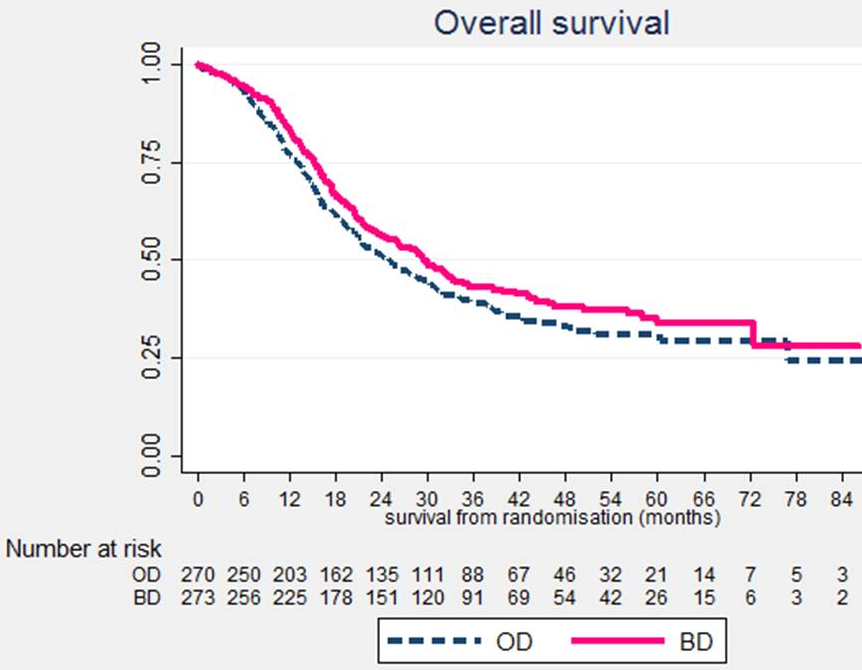
QA programme

Chemotherapy
4 to 6 cycles
- **Cisplatin 25mg/m2 D1-3 or 75mg/m2 D1**
- **Etoposide 100mg/m2 D1-3**

Stratification factors
- **Centre**
- **No. of cycles chemo: 4 vs.6**
- **PS: 0,1 vs. 2**

- International, randomized phase III study.
- Same XRT, chemotherapy as CALGB/INT trial
- XRT commences in cycle 2
- Hypothesis:
  - Daily XRT will be ***superior***
  - A survival benefit of 12% at 2 years (from 44% with the BD arm to 56% in the OD arm) was considered to be clinically significant

Overall survival

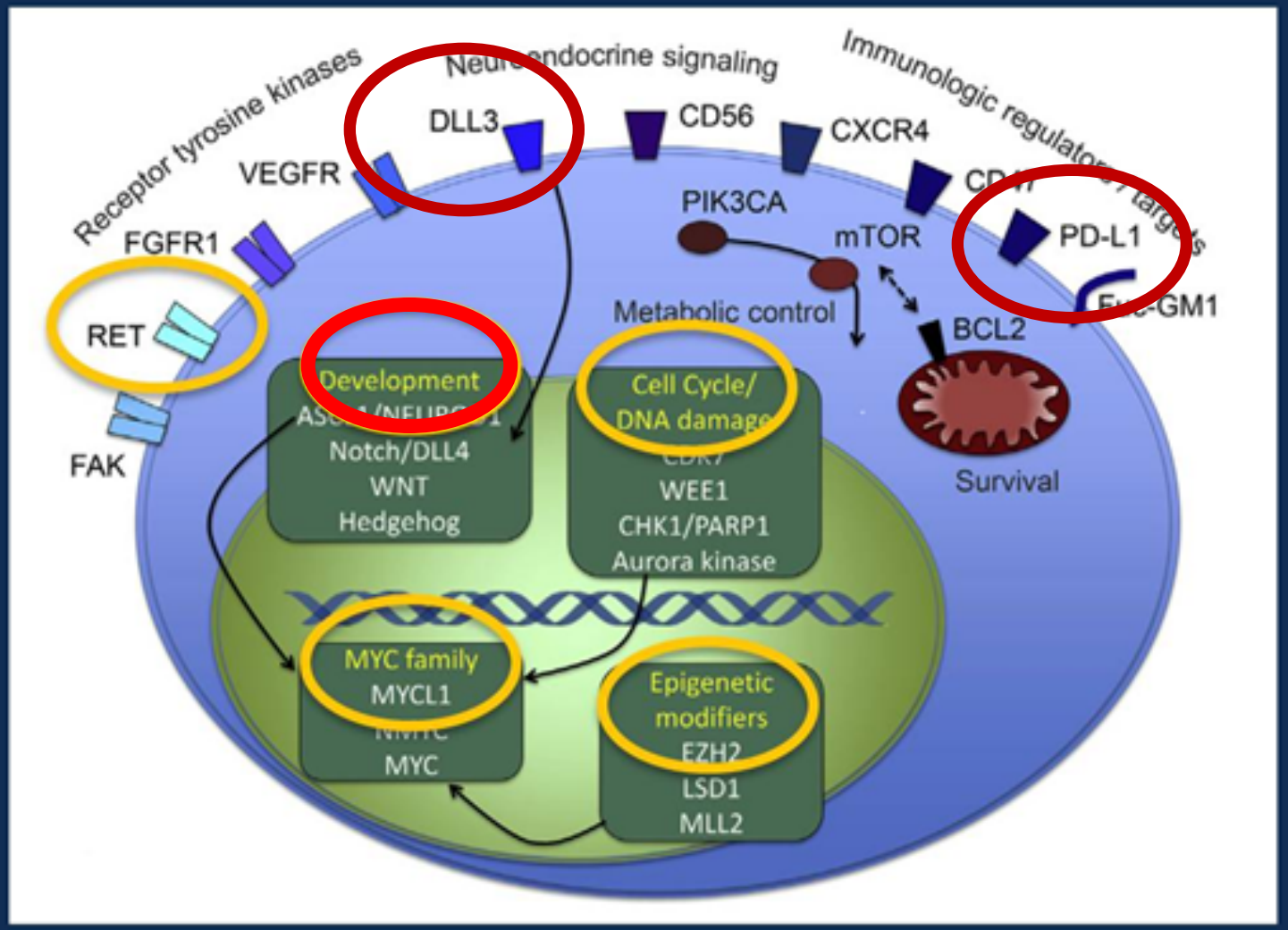


Primary objective-survival at 2-years
Expected survival BD arm 44%
Projected survival OD arm 56%

Median follow-up: 45 months

Overall survival (n=543)	BD	OD	Log-rank
Median (months)	30 (24-34)	25 (21-31)	p=0.15
1-year	83% (78-87)	76% (71-81)	
2-year	56% (50-61)	51% (45-57)	
3-year	43% (37-49)	39% (33-45)	

Nuevas dianas



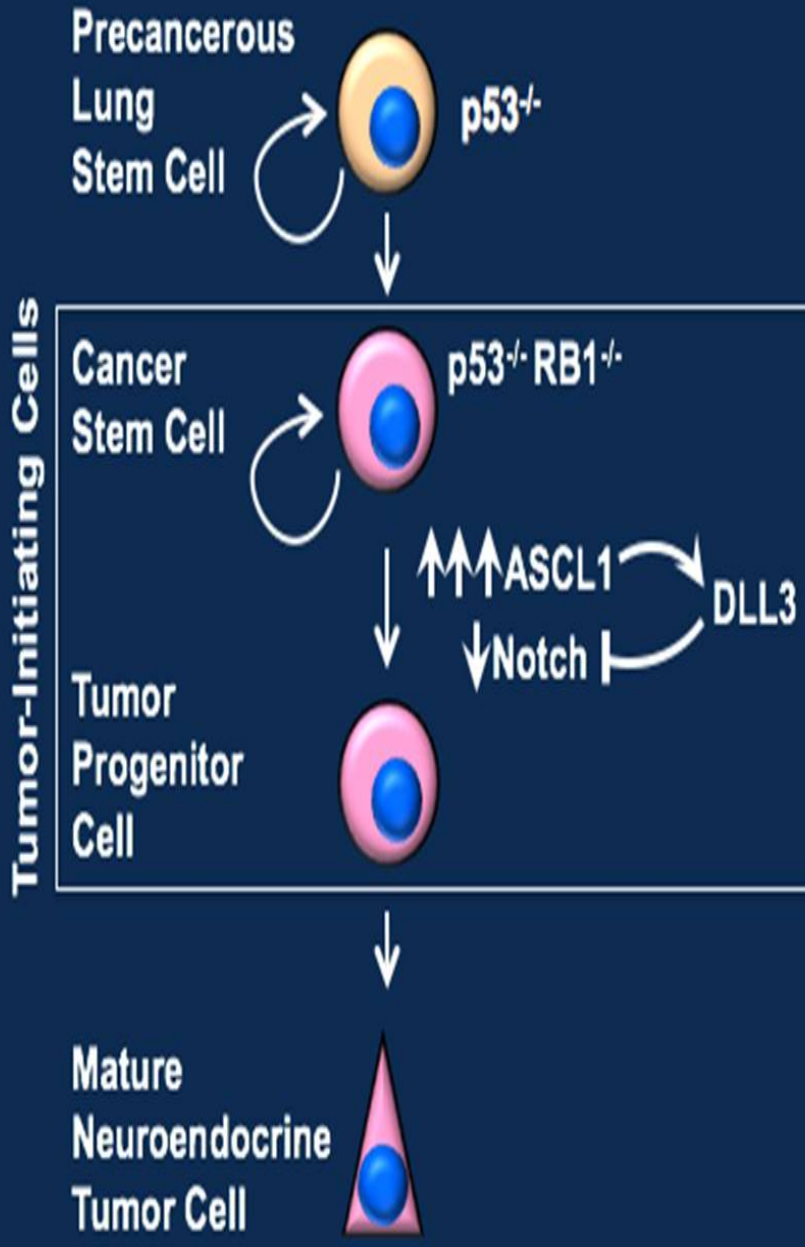
Safety and efficacy of single agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC)

Rudin CM[1], Pietanza MC[1], Bauer TM[2,3], Spigel DR[2,3], Ready N[4], Morgensztern D[5], Glisson BS[6], Byers LA[6], Johnson ML[2,3], Burris HA III[2,3], Robert F[7], Strickland DK[3], Zayed H[8], Govindan R[5], Dylla SJ[8], Peng SL[8]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Tennessee Oncology, PLLC., Nashville, TN; [3]Medical Oncology, Sarah Cannon Research Institute, Nashville, TN; [4]Duke University Medical Center, Durham, NC; [5]Washington University School of Medicine in St. Louis, St. Louis, MO; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; [8]AbbVie Stemcentrx LLC, South San Francisco, CA

Delta- like Protein 3 (DLL3)

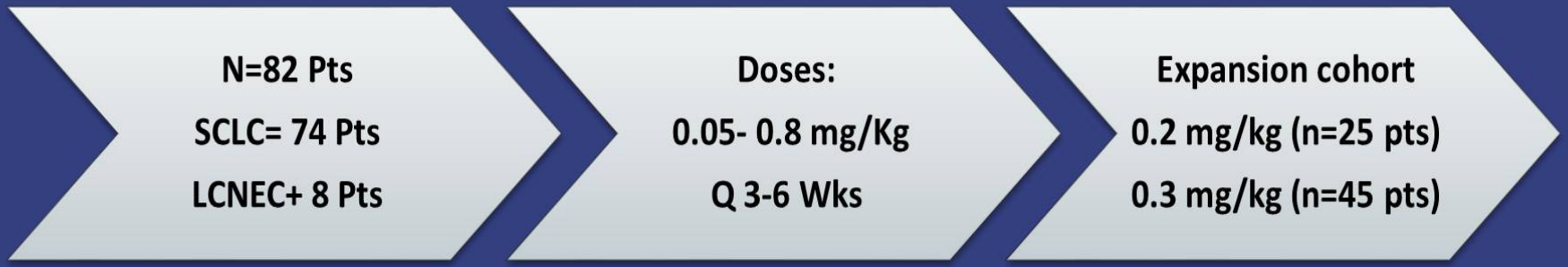
- An atypical inhibitory Notch ligand
- Induced by the key neuroendocrine transcription factor, ASCL1
- Aberrant cell surface expression in >80% of small cell lung and large cell neuroendocrine cancers
  - On both cancer stem and tumor cells but not normal adult tissues
- Not prognostic, and does not predict response to chemotherapy



Saunders et al, Sci Transl Med, 2015

Rovalpituzumab Tesirine (Rova-T™, SC16LD6.5)

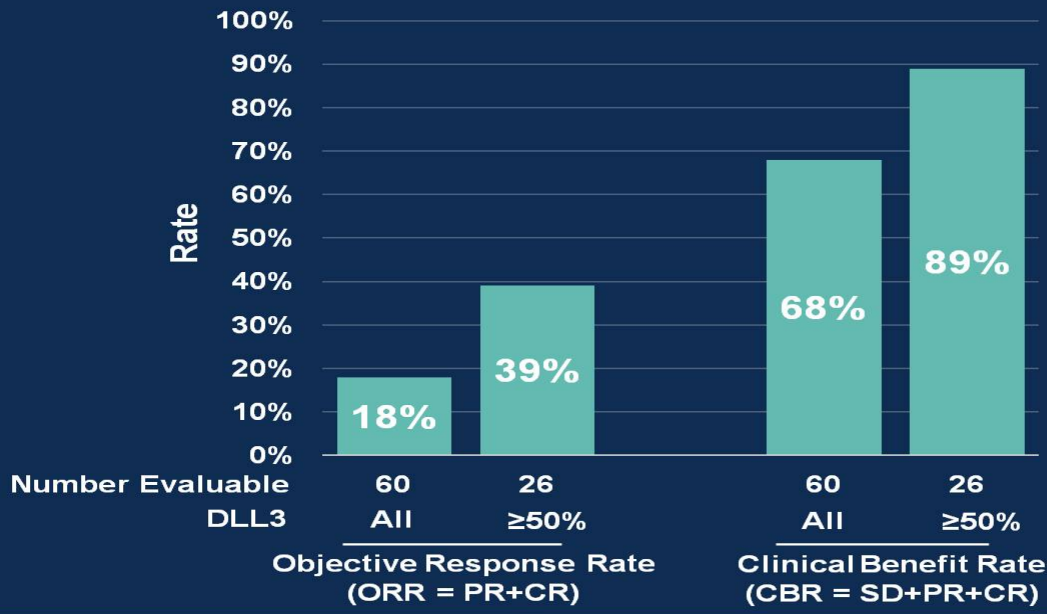
A delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC)



Phase 2 Dose: 0.3 mg/kg, Q 6 weeks

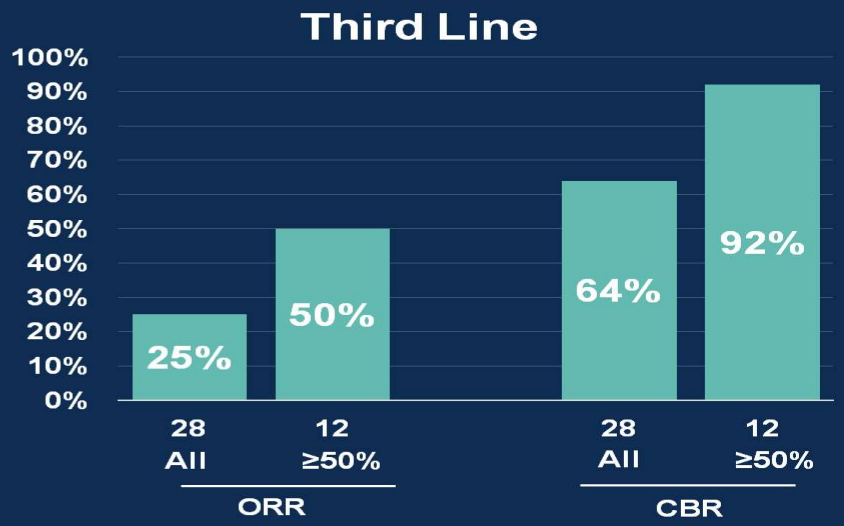
DLT: thrombocytopenia, elevation of liver enzymes, serosal effusions.

RECIST Confirmed Responses per Investigator

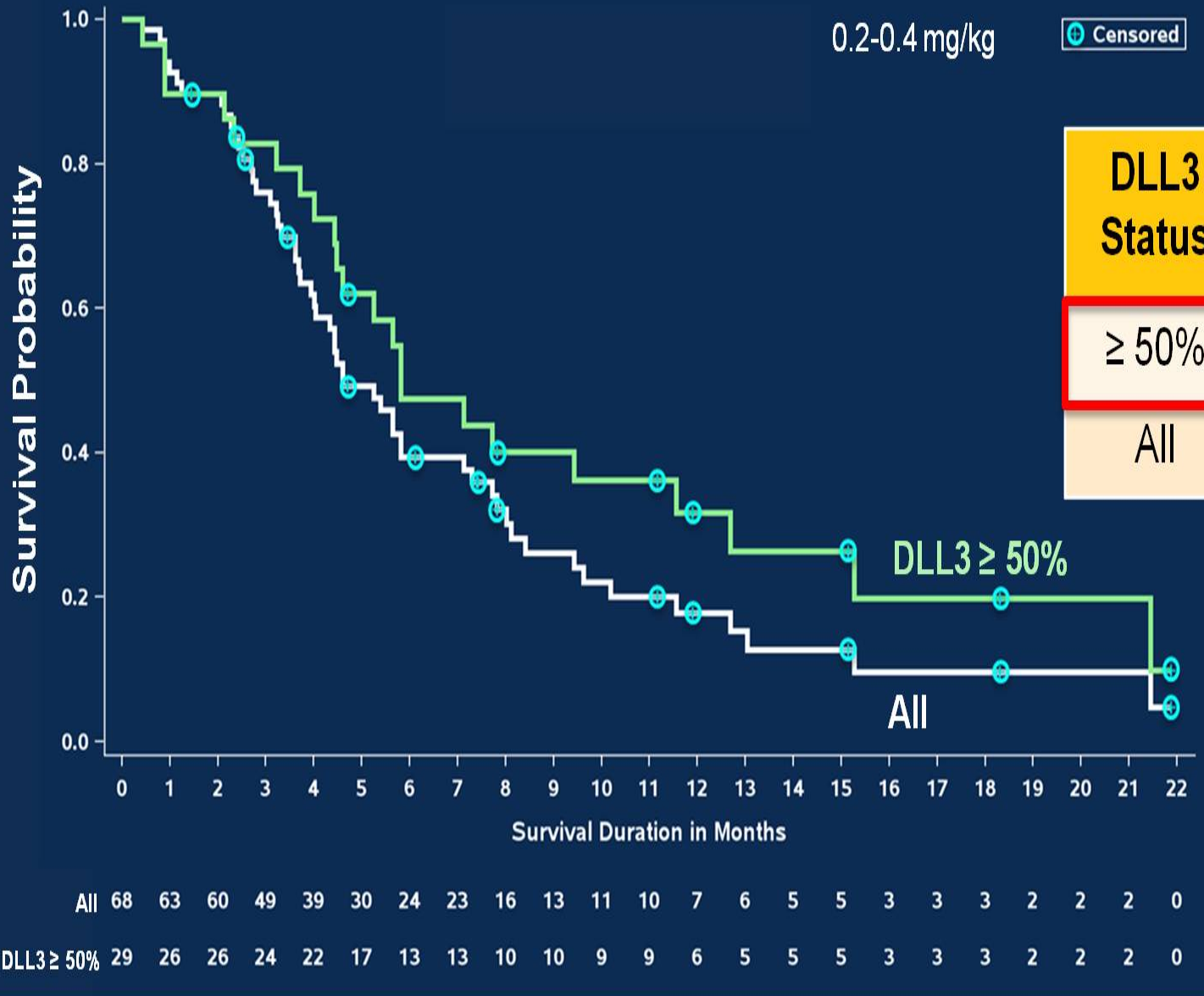


Response-Evaluable Subjects
Active Doses (0.2-0.4 mg/kg)

Confirmed Responses Comparable in 2nd & 3rd Line



SCLC Kaplan-Meier Overall Survival



DLL3 Status	Overall Survival	
	Median	1-Year
≥ 50%	5.8 mo	32%
All	4.6 mo	18%

Adverse Event Profile in SCLC Subjects (n=74)

Highest Related TEAE Terms ≥ 15%

Adverse Event PT	Grade 3+	All Grades
All	28 (38%)	65 (88%)
Fatigue	3 (4%)	26 (35%)
Pleural effusion	6 (8%)	23 (31%)
Oedema peripheral	2 (3%)	20 (27%)
Nausea	0 (0%)	14 (19%)
Hypoalbuminemia	0 (0%)	13 (18%)
Thrombocytopenia	8 (11%)	12 (16%)
Rash Maculo-Papular	2 (3%)	12 (16%)
Decreased Appetite	0 (0%)	12 (16%)

Highest Related TEAE Groups Grade 3+

Adverse Event Group	Grade 3+	All Grades
Thrombocytopenia[1]	9 (12%)	15 (20%)
Serosal Effusions[2]	8 (11%)	26 (35%)
Skin Reaction[3]	6 (8%)	36 (49%)

[1] Thrombocytopenia or platelet count decreased

[2] Pleural or pericardial effusion, ascites, or "Capillary Leak Syndrome" (serosal effusions, peripheral edema, and/or hypoalbuminemia; recoding performed after cases were not adjudicated as CLS by a Data Monitoring Committee of CLS experts)

[3] Blister, Dermatitis Acneiform, Dry Skin, Erythema, Erythema Multiforme, Palmar-Plantar Erythrodysaesthesia Syndrome, Photosensitivity Reaction, Pruritus, Pruritus Generalised, Rash, Rash Erythematous, Rash Maculo-Papular, Skin Exfoliation, Skin Irritation

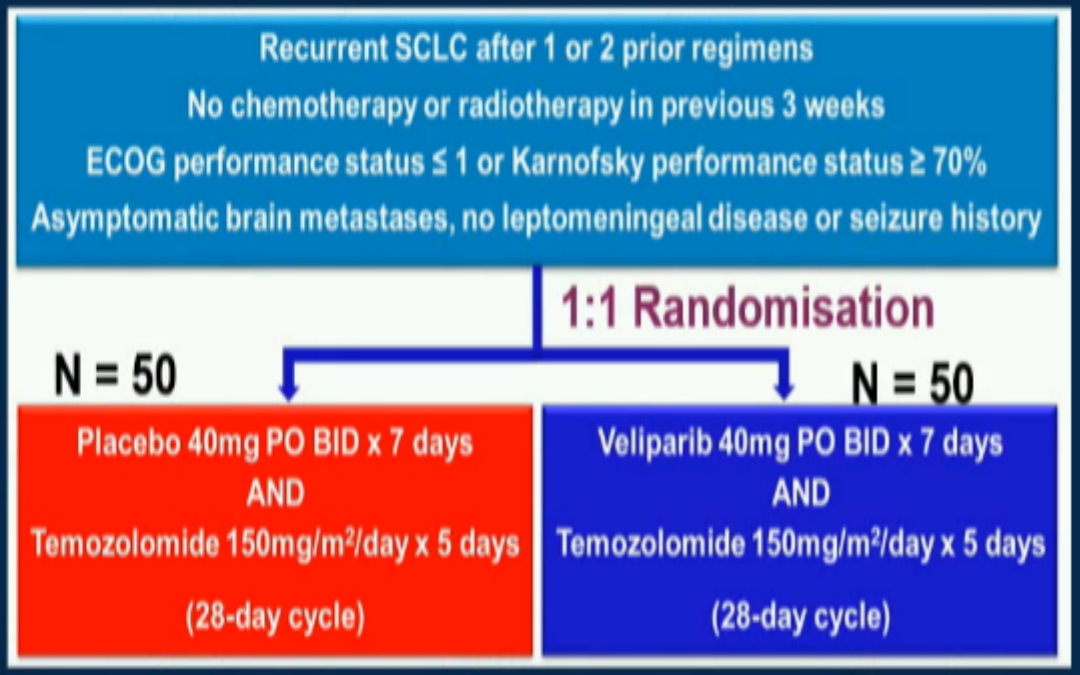
Rovalpituzumab Tesirine (Rova-T™, SC16LD6.5)

A delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC)

- Eficacia prometedora en 2ª y 3ª línea
- Mayores respuestas y supervivencia vs Tto. aprobados
- Fuerte eficacia en DLL3>50%
- La alta tasa de respuestas en expresión DLL3 > 50% requiere un validación prospectiva
- A pesar de las repuestas modesta SLP y SG
- Perfil de seguridad aceptable
- **Primer biomarcador para terapias dirigidas**
- Estudios en marcha: Trinity (NCT 02674568)
  Frontline study (NCT 02709889)

A multi-center, randomized, double-blind phase II study comparing temozolomide (TMZ) plus either veliparib (ABT-888), a PARP inhibitor, or placebo as 2nd or 3rd-line therapy for patients (Pts) with relapsed small cell lung cancers (SCLCs).

Maria Catherine Pietanza MD

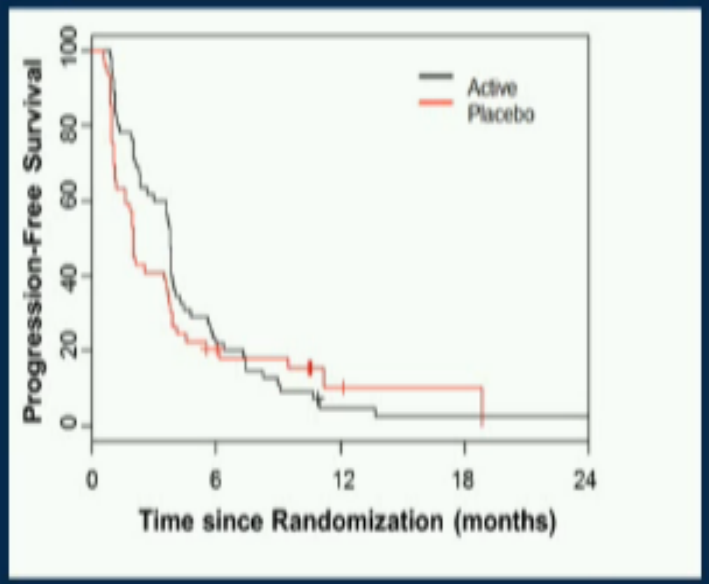


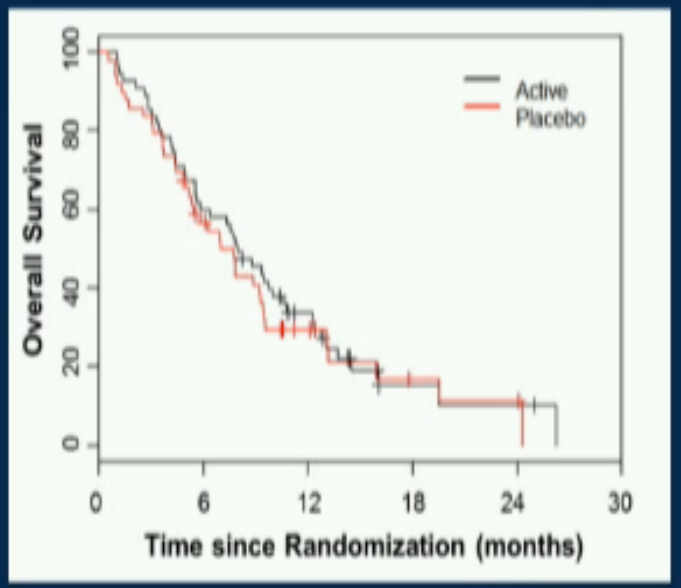
Objectives : 4 mth PFS, , ORR, OS, **Translational** : Tumor expression of DNA repair proteins including PARP-1, MGMT; CTC # at baseline + week 4

Temozolamide + Veliparib or Placebo in 2nd or 3rd line SCLC Pietanza et al # 8512

	Median PFS (months)	95% CI	p
Veliparib	3.8	3.0 – 4.1	0.39
Placebo	2.0	1.6 – 3.7	

	Median OS (months)	95% CI	p
Veliparib	8.2	6.4 – 12.2	0.5
Placebo	7.0	5.3 – 9.5	



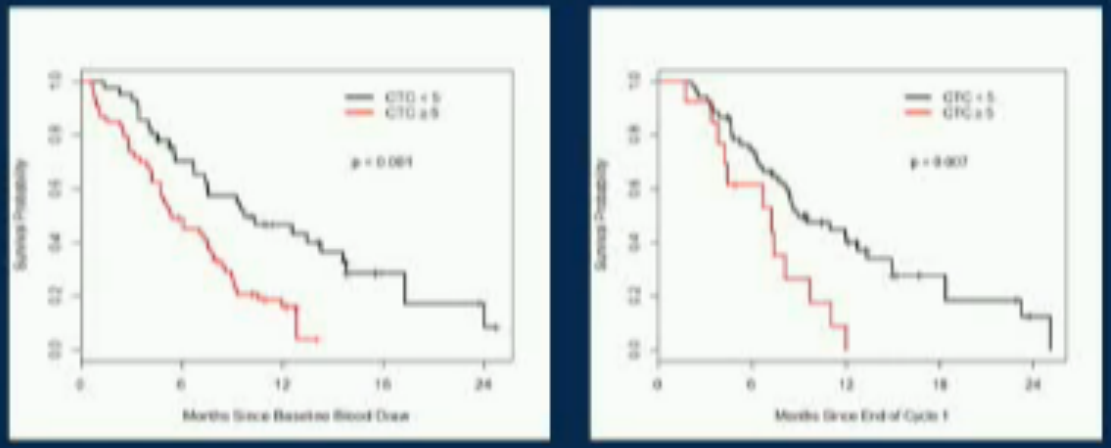


Objetivo primario no alcanzado a 4 meses

Temozolamide + Veliparib or Placebo in 2nd or 3rd line

SCLC : Translational analysis Pietanza et al # 8512

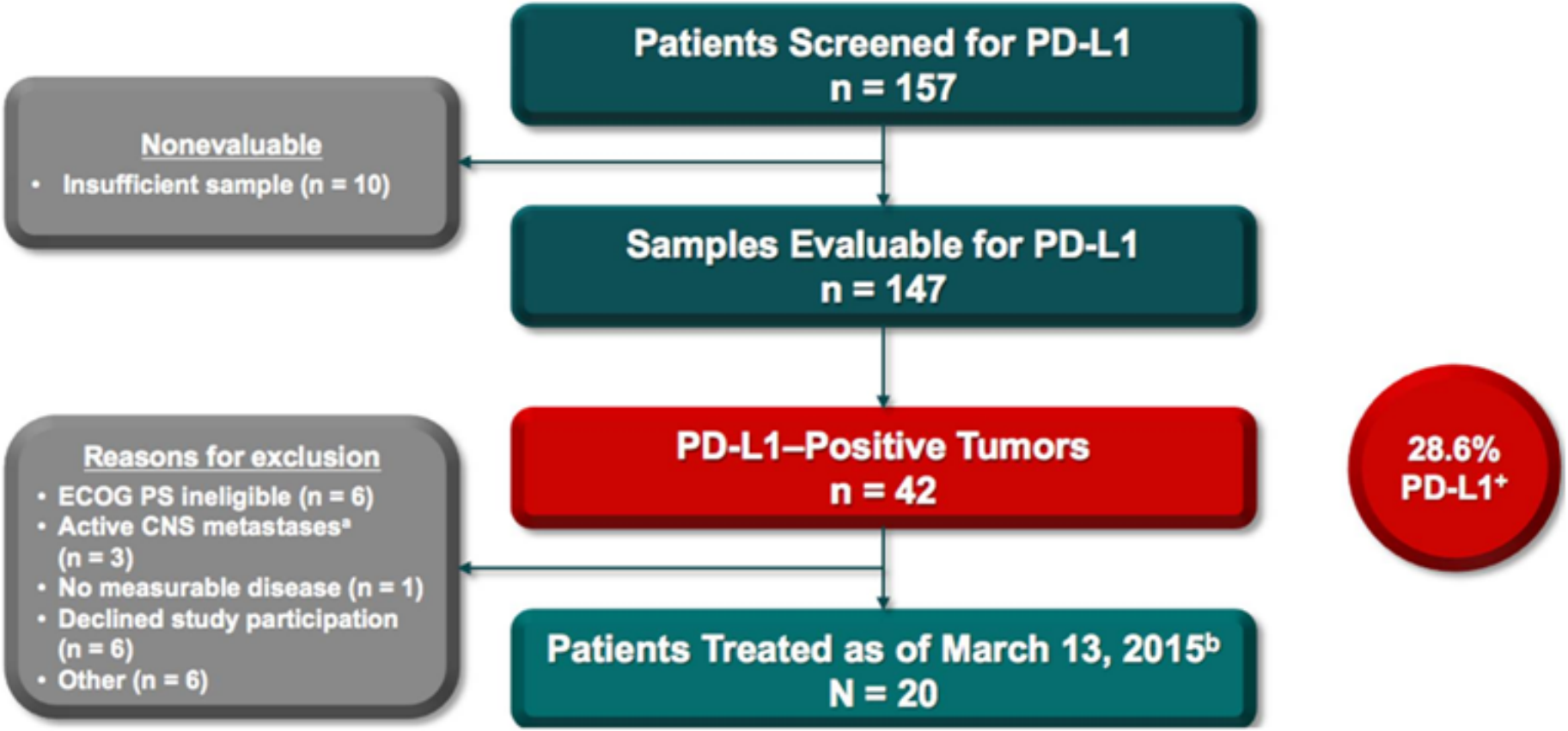
Circulating tumor cell number (CTC#) by CellSearch in 64 patients



Median OS 9.7mths for CTC<5 ; 5.4 mths CTC ≥ 5 at baseline

CTC # at baseline & after 1 cycle prognostic for survival ; no imbalance in CTC# per treatment arm

Pembrolizumab in SCLC: Screening for PDL-1 Expression



ORR:35%

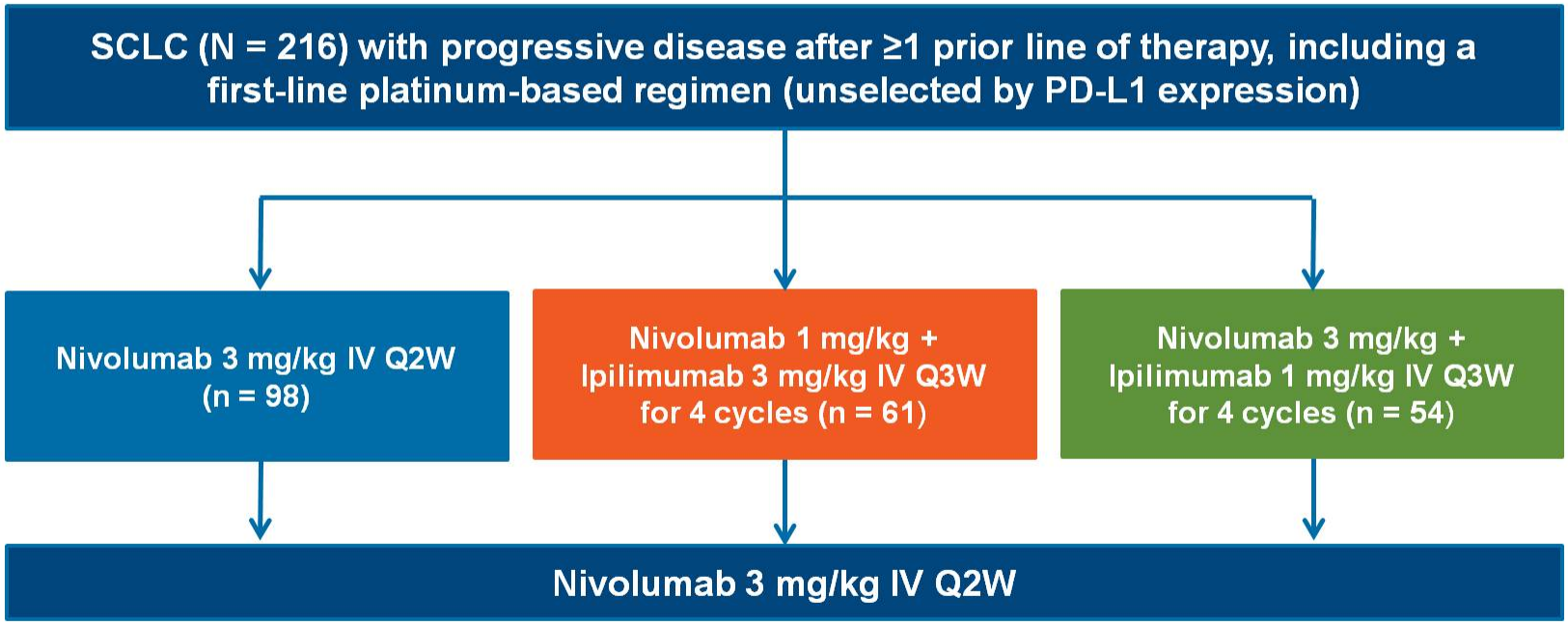
Ott et al, ASCO 2015

CheckMate 032: Nivolumab Alone or in Combination With Ipilimumab for the Treatment of Recurrent Small Cell Lung Cancer

Scott J. Antonia,[1] José A. López-Martin,[2] Johanna Bendell,[3] Patrick A. Ott,[4] Matthew Taylor,[5] Joseph Paul Eder,[6] Dirk Jäger,[7] Margaret K. Callahan,[8] Dung T. Le,[9] Filippo de Braud,[10] Michael A. Morse,[11] Paolo A. Ascierto,[12] Leora Horn,[13] Asim Amin,[14] Rathi N. Pillai,[15] Jeffry Evans,[16] Chris Harbison,[17] Chen-Sheng Lin,[17] Marina Tschaika,[17] Emiliano Calvo[18]

[1]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [2]Hospital Universitario 12 de Octubre, Madrid, Spain; [3]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Oregon Health & Science University, Portland, OR, USA; [6]Yale Comprehensive Cancer Center, New Haven, CT, USA; [7]Nationales Centrum für Tumorerkrankungen (NCT), University Medical Center, Heidelberg, Germany; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; [10]Fondazione IRCCS Instituto Nazionale dei Tumori Milano, Milan, Italy; [11]Duke University Medical Center, Durham, NC, USA; [12]Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; [13]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [14]Levine Cancer Institute, Carolinas Medical Center, Charlotte, NC, USA; [15]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [16]University of Glasgow, Glasgow, UK; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain

Nivolumab +/- Ipilimumab in Recurrent SCLC: CheckMate 032 Study Design

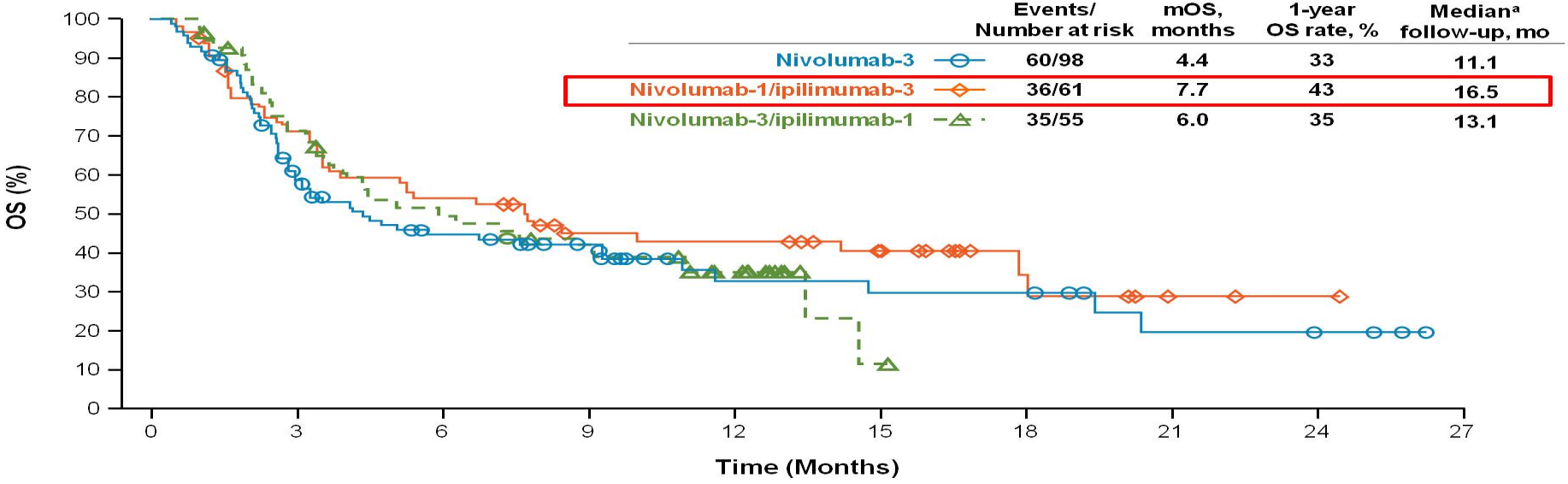


Summary of Response

	Nivolumab-3 (n = 98)	Nivolumab-1 + Ipilimumab-3 (n = 61)	Nivolumab-3 + Ipilimumab-1 (n = 54)
Objective response rate, % (n/N)			
Overall	**10 (10/98)**	**23 (14/61)**	**19 (10/54)**
Platinum-sensitive[a]	11 (6/55)	28 (7/25)	19 (4/21)
Platinum-resistant[a]	10 (3/30)	17 (4/23)	10 (2/21)
Best overall response, %			
Complete response	0	2	0
Partial response	10	21	19
Stable disease	22	21	17
Progressive disease	53	38	54
Unable to determine	12	13	11
Not evaluable (no tumor assessment follow-up)	2	5	0

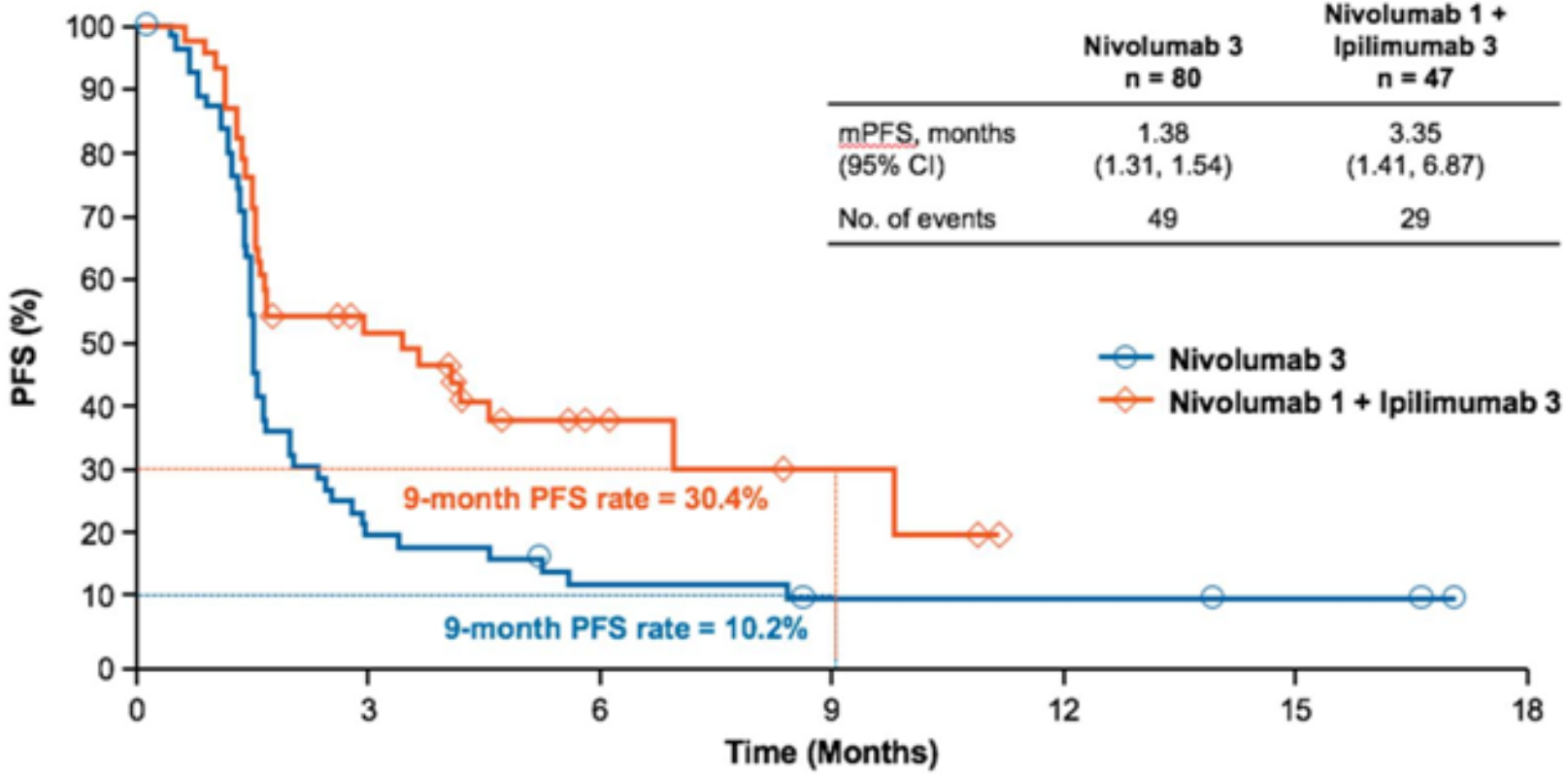
[a]Platinum sensitivity was unknown for 29 patients as follows: nivo-3, n = 10; nivo-1/ipi-3, n = 11; nivo-3/ipi-1, n = 8. 3 pts in the nivo-3 arm, 2 pts in the nivo-1/ipi-3 arm, and 4 pts in the nivo-3/ipi-1 arm did not receive first-line platinum therapy and did not meet eligibility criteria, although they were treated and included in the analysis

Overall Survival



[a]Defined as time from first dose to date of DBL; follow-up was shorter for patients who died prior to DBL

PFS



	Nivolumab 3 n = 80	Nivolumab 1 + Ipilimumab 3 n = 47
mPFS, months (95% CI)	1.38 (1.31, 1.54)	3.35 (1.41, 6.87)
No. of events	49	29

Patients at risk							
Nivolumab 3 mg/kg	80	11	6	3	3	2	0
Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	47	21	6	3	0	0	0

Nivolumab +/- Ipilimumab in Recurrent SCLC: Treatment-Related AEs in ≥10% of Patients

	Nivolumab-3 (n = 98)		Nivolumab-1 + Ipilimumab-3 (n = 61)		Nivolumab-3 + Ipilimumab-1 (n = 54)	
	Any grade, %	Grade 3–4, %	Any grade, %	Grade 3–4, %	Any grade, %	Grade 3–4, %
Total treatment-related AEs	**53**	**13**	**79**	**30**	**74**	**19**
Fatigue	11	1	26	0	22	0
Pruritus	11	0	20	2	9	0
Diarrhea	7	0	21	5	17	2
Nausea	7	0	11	2	7	0
Decreased appetite	6	0	7	0	11	0
Hypothyroidism	3	0	16	2	7	0
Hyperthyroidism	2	0	11	0	6	0
Rash	2	0	20	3	7	0
Rash, maculopapular	1	0	13	3	4	0
Lipase increased	0	0	11	8	0	0
Treatment-related AEs leading to discontinuations	**6**		**11**		**7**	

- Two treatment-related deaths occurred in the nivolumab-1 + ipilimumab-3 arm: one due to myasthenia gravis and one due to worsening of renal failure. One treatment-related death due to pneumonitis occurred in the nivolumab-3 + ipilimumab-1 arm
- Treatment-related limbic encephalitis was reported in 2 (1%) patients; 1 case resolved, and outcome for 1 case was not reported
- Treatment-related pneumonitis occurred in 8 (4%) patients; 6 cases resolved, outcome for 1 case is unknown, and 1 case was fatal

Nivolumab +/- Ipilimumab in Recurrent SCLC: Conclusions

Nivolumab or Nivolumab plus Ipilimumab

- Safety profiles similar to that seen in other diseases
  - Higher rates of AEs occurred with combination therapy
    - 7%–11% of patients in the combination cohorts discontinued due to toxicity
  - Treatment-related limbic encephalitis occurred in 2 patients and resolved in 1 patient
  - Three treatment-related deaths (myasthenia gravis, worsening of renal failure, and pneumonitis)
  - Immune-related AEs were managed using established safety guidelines
- Durable objective responses in patients with relapsed SCLC
- Tumor responses occurred regardless of platinum sensitivity or tumor PD-L1 expression
- Survival results were encouraging
- Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W is the regimen selected for phase 3 study

Ongoing Studies With Nivolumab/Ipilimumab in SCLC

- **CheckMate 032:** nivolumab alone vs nivolumab-1 + ipilimumab-3 randomized expansion study (N = 250)

- **CheckMate 331:** nivolumab vs chemotherapy (topotecan or amrubicin) in patients with relapsed SCLC **(Poster TPS8578)**

- **CheckMate 451:** nivolumab alone vs nivolumab-1 + ipilimumab-3 vs placebo as consolidation/maintenance after platinum-based first-line therapy in patients with extensive-stage SCLC **(Poster TPS8579)**

THE LANCET Oncology

Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial

Authors

Scott J Antonia, José A López-Martin, Johanna Bendell, Patrick A Ott, Matthew Taylor, Joseph Paul Eder, Dirk Jäger, M Catherine Pietanza, Dung T Le, Filippo de Braud, Michael A Morse, Paolo A Ascierto, Leora Horn, Asim Amin, Rathi N Pillai, Jeffry Evans, Ian Chau, Petri Bono, Akin Atmaca, Padmanee Sharma, Christopher T Harbison, Chen-Sheng Lin, Olaf Christensen, Emiliano Calvo

Carcinoma de células pequeñas
Conclusiones

- Mínimos avances terapéuticos en las ultimas 2 décadas
- El mapa genómico revela pocas dianas terapéuticas
- Datos de Inmunoterapia son optimistas

Mesotelioma

- Se diagnostican 12.000 nuevos casos año
- Incidencia en aumento
- El pronostico global es pobre
- Mediana de supervivencia inferior a 12 meses
- Supervivencia a 5años inferior 5%
- Ocasionalmente resecable
- CDDP-Pem aprobado con un incremento de supervivencia de 2.8meses
- No tratamiento estándar de 2ª-3ª línea
- No tratamientos aprobados tras progresión a 1ª línea
- PD-L1 es expresado en 40-50% de Mesoteliomas
- Escasa respuesta a Inmunoterapia (Keynote -028, NivoMes)
- No predictores de respuesta

Tremelimumab as 2nd- or 3rd-line treatment of unresectable malignant mesothelioma: Results from the global, double-blind, placebo-controlled DETERMINE study

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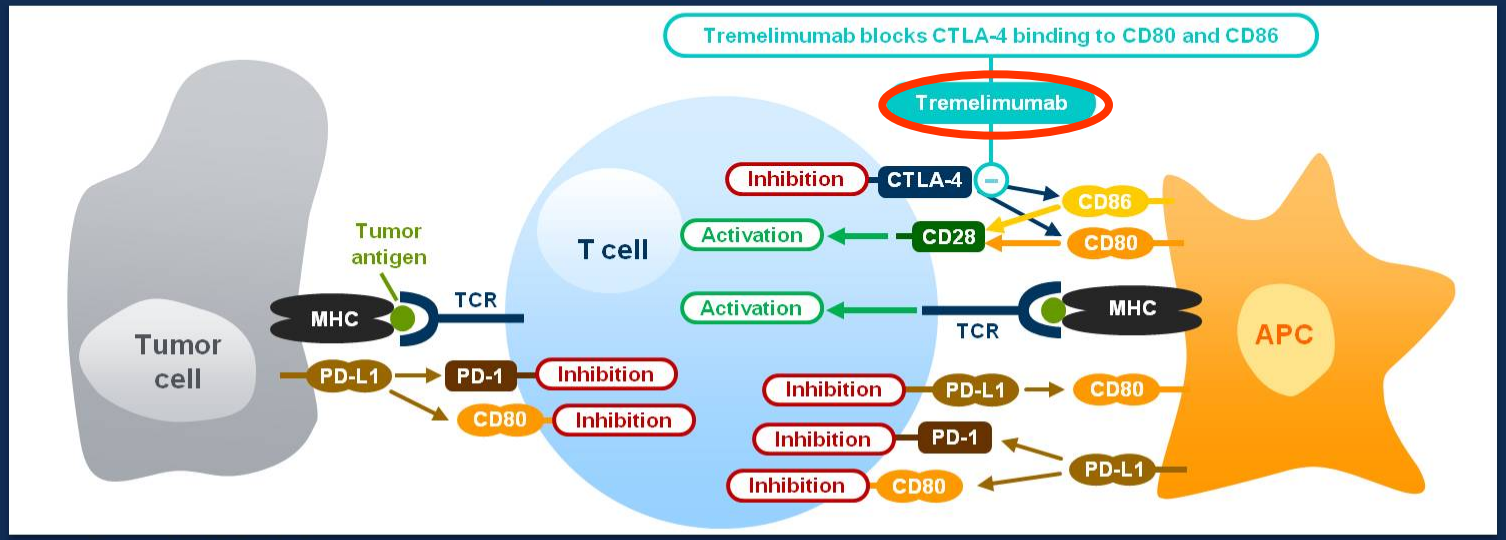
PRESENTED AT: ASCO ANNUAL MEETING '16

Tremelimumab: Mechanism of Action

- Tremelimumab blocks binding of CTLA-4 to CD80 and CD86, leading to:[1]
  - Enhanced T-cell activation
  - Enhanced antitumor immunity



1. Tarhini A.A. Immunotherapy 2013;5:215–29.

APC, antigen-presenting cell; MHC, major histocompatibility complex; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; TCR, T-cell receptor.

Tremelimumab in Mesothelioma

- In two investigator-sponsored phase 2 trials in mesothelioma patients, treatment with tremelimumab achieved durable tumor regression and disease stabilization[1,2]

	Tremelimumab 15mg/kg i.v. every 3 months[1]	Tremelimumab i.v. 10 mg/kg q4w for 6 doses, then q12w[2]
Median OS, months (95% CI)	10.7 (0–21.9)	11.3 (3.4–19.2)
1-year survival rate, % (95% CI)	48.3 (30.1–66.5)	48.3 (30.1–66.5)
Median PFS, months (95% CI)	6.2 (1.3–11.1)	6.2 (5.7–6.7)
Disease control rate, % (n/N)	31.0 (9/29)	51.7 (15/29)

- These early promising data led to the DETERMINE study, investigating tremelimumab in a randomized setting in MM

1. Calabrò L.A, et al. Lancet Oncol 2013;14:1104–11; 2. Calabrò L.A, et al. Lancet Respir Med 2015;3:301–9.

CI, confidence interval; MM, malignant mesothelioma; OS overall survival; PFS, progression-free survival; q#w, every # weeks.

DETERMINE Study Design

Global, Randomized, Double-Blind, Placebo-Controlled, Phase 2b Trial

N=571
- Pleural/peritoneal MM
- ECOG PS 0–1
- 1–2 prior regimens (including a platinum)
- Measurable disease

2:1 randomization

Stratification:
- Pleural vs. peritoneal
- 2nd vs. 3rd line
- EORTC low vs. high risk

Tremelimumab i.v.
10 mg/kg q4w x 7 doses, then q12w
n=382

Placebo i.v.
n=189

Primary endpoint: Overall survival (OS)

Key secondary endpoints: 18-month OS, PFS, overall response rate and duration, disease control rate (DCR), durable DCR, safety

Statistics: 90% power to detect an overall HR of 0.71 (increase in median OS from 7 to 9.3 mo) using a 2-sided 0.05 level test

ECOG PS, Eastern cooperative oncolo

DETERMINE Analysis Sets

658 patients enrolled

19 meses

ITT Analysis Set
571 patients randomized
(382 tremelimumab : 189 placebo)

Safety Set
569 patients received study treatment
(380 tremelimumab : 189 placebo)

- Patients randomized between May 22, 2013 and December 15, 2014
- Final analysis data cut-off: January 24, 2016

ITT, intention-to-treat; all patients randomized to study treatment. Safety set; all patient who received study treatment.

Baseline Characteristics (ITT Population)

Characteristics		Tremelimumab (n=382)	Placebo (n=189)
Median age, years (range)		66 (28–87)	67 (38–83)
Gender, n (%)	Male	283 (74)	151 (80)
ECOG PS, n (%)	PS 1	273 (72)	132 (70)
Site, n (%)	Pleural Peritoneal	364 (95) 18 (5)	181 (96) 8 (4)
Histology, n (%)	Epithelioid Sarcomatoid Biphasic	318 (83) 22 (6) 40 (11)	157 (83) 16 (9) 16 (9)
Stage, n (%)	III IV	95 (25) 263 (69)	39 (21) 133 (70)
Line of therapy, n (%)	2nd 3rd	240 (63) 142 (37)	119 (63) 70 (37)
Prior pemetrexed, n (%)	Yes	377 (99)	187 (99)
EORTC, n (%)	High risk	162 (42)	79 (42)

Antitumor Activity (ITT Population)

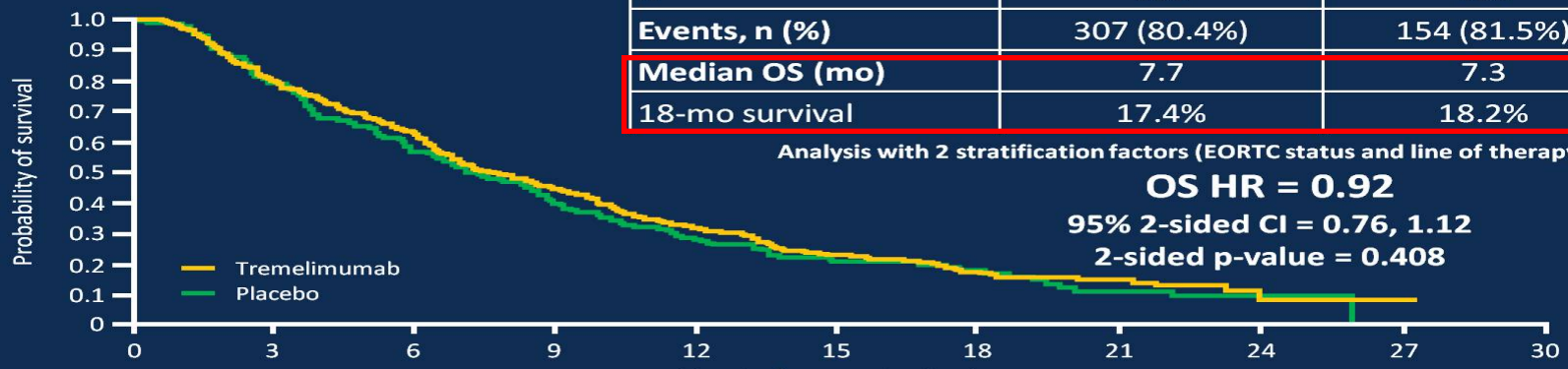
Endpoint	Tremelimumab (n=382)	Placebo (n=189)
Best response:		
Complete response	0	0
Partial response	4.5%	1.1%
Stable disease[a]	27.2%	21.7%
Progressive disease	45.8%	58.7%
Not evaluable	22.5%	18.5%
Objective response rate	4.5% (95% CI: 2.6, 7.0)	1.1% (95% CI: 0.1, 3.8)
Median duration of response, mo (range)	4.8 (0.0–13.4)	5.6 (2.8–8.3)
Disease control rate	31.7%	22.8%
Durable disease control rate (DCR ≥6 mo)	16.8% (95% CI: 13.1, 20.9)	11.6% (95% CI: 7.4, 17.1)

DETERMINE: Overall Survival (ITT Population)

	Tremelimumab	Placebo
n	382	189
Events, n (%)	307 (80.4%)	154 (81.5%)
Median OS (mo)	7.7	7.3
18-mo survival	17.4%	18.2%

Analysis with 2 stratification factors (EORTC status and line of therapy)[a]

OS HR = 0.92
95% 2-sided CI = 0.76, 1.12
2-sided p-value = 0.408



Number of patients at risk:

Tremelimumab	382	300	232	163	116	69	36	16	3	1	0
Placebo	189	147	103	70	48	32	17	8	2	0	0

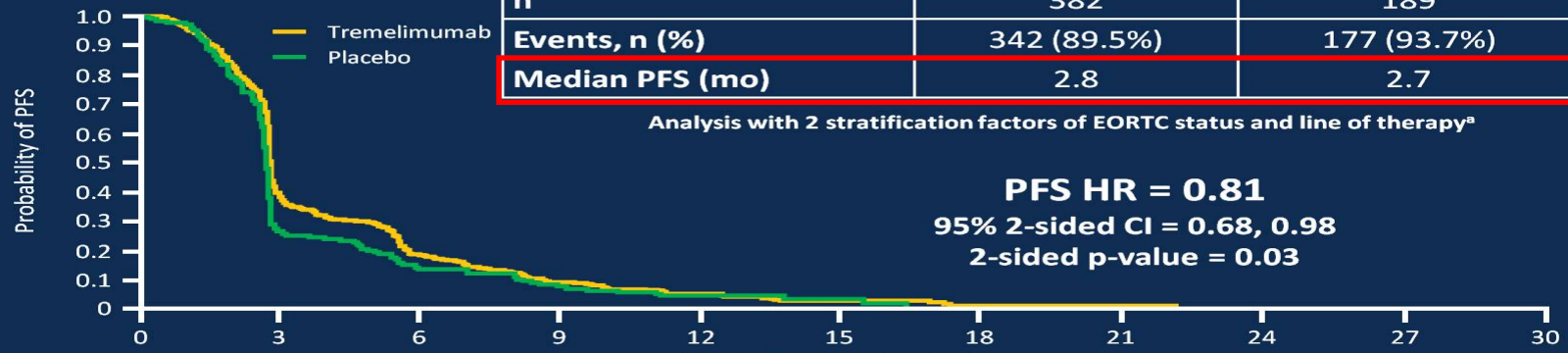
[a]p-value for OS derived from stratified Log-rank test; HR and its CI derived from stratified Cox regression. HR<1 implies a lower risk of death with tremelimumab.

Investigator-assessed PFS (ITT Population)

	Tremelimumab	Placebo
n	382	189
Events, n (%)	342 (89.5%)	177 (93.7%)
Median PFS (mo)	2.8	2.7

Analysis with 2 stratification factors of EORTC status and line of therapy[a]

PFS HR = 0.81
95% 2-sided CI = 0.68, 0.98
2-sided p-value = 0.03



Number of patients at risk:

Tremelimumab	382	130	59	26	14	5	1	1	0	0	0
Placebo	189	48	21	11	6	3	0	0	0	0	0

[a]Event not counted if it occurs immediately after ≥2 consecutively missed disease assessments – PFS is instead censored at last assessment date prior to missed assessment; p-value derived from stratified Log-rank test; HR and its CI derived from stratified Cox regression; HR<1 implies a lower risk of progression with tremelimumab.

Category of AE, n (%)	Tremelimumab (n=380)	Placebo (n=189)
Any AE	364 (96)	179 (95)
Any Grade ≥3 AE	246 (65)	91 (48)
Any SAE	218 (57)	85 (45)
Any AE leading to discontinuation of study treatment	104 (27)	10 (5)
Any AE leading to death	36 (10)	12 (6)

Common all-grade AEs (≥15% overall incidence), n (%)	Tremelimumab (n=380)	Placebo (n=189)
Diarrhea	179 (47)	36 (19)
Dyspnea	121 (32)	69 (37)
Decreased appetite	110 (29)	46 (24)
Fatigue	92 (24)	60 (32)
Nausea	107 (28)	38 (20)
Constipation	66 (17)	53 (28)
Pruritus	103 (27)	15 (8)
Vomiting	77 (20)	22 (12)
Cough	67 (18)	31 (16)
Rash	79 (21)	13 (7)
Musculoskeletal chest pain	51 (13)	34 (18)

DETERMINE: Conclusions (1)

- In 2nd/3rd-line MM, treatment with tremelimumab did not achieve a statistically significant improvement in OS compared with placebo
- Safety data are consistent with the known toxicity profile of tremelimumab and other anti-CTLA-4 agents
- The rapid accrual to this trial underscores the unmet need for new treatment options for MM patients
- Since CTLA-4 inhibitors can induce PD-L1 expression[1], combining anti-CTLA-4 with anti-PD-L1 agents may be an effective therapeutic strategy
  - An ongoing Phase 2 study (NIBIT-MESO-1; NCT02588131) evaluates tremelimumab in combination with the PD-L1 inhibitor durvalumab (MEDI4736) in MM patients

Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced unresectable mesothelioma from the JAVELIN Solid Tumor phase 1b trial: safety, clinical activity, and PD-L1 expression

Raffit Hassan[1], Anish Thomas[2], Manish R. Patel[3], John J. Nemunaitis[4], Jaafar Bennouna[5], John D. Powderly[6], Matthew H. Taylor[7], Afshin Dowlati[8], Franklin L. Chen[9], Joseph Leach[10], Ulka N. Vaishampayan[11], Claire Verschraegen[12], Jean-Pierre Delord[13], Hans Juergen Grote[14], Anja von Heydebreck[14], Jean-Marie Cuillerot[15], James L. Gulley[16,17]

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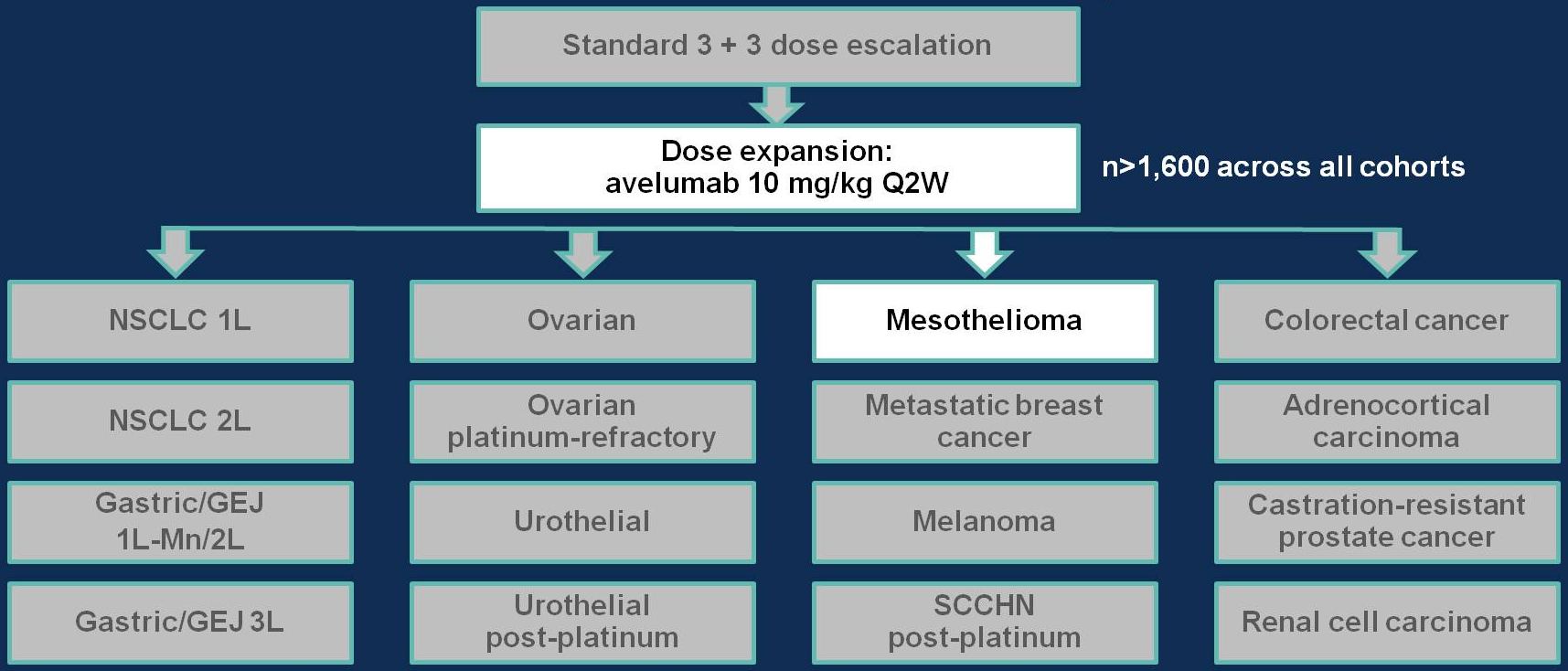
Oral Presentation at the 52nd ASCO Annual Meeting, June 3-7, 2016; Chicago, Illinois. Abstract No. 8503.

JAVELIN Solid Tumor: an international, phase 1, multicohort dose-escalation and dose-expansion trial



GEJ, gastroesophageal junction; Mn, switch-maintenance; NSCLC, non-small-cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck

NCT01772004

Study design

Patients: key eligibility criteria	Dosing	Select assessments
• Histologically/cytologically confirmed unresectable pleural or peritoneal mesothelioma* • Progression following treatment with platinum/pemetrexed regimen* • Unselected for PD-L1 expression • ECOG PS 0-1 and estimated life expectancy ≥3 months • No prior antibody/drug targeting a T-cell co-regulatory protein (eg, anti-PD-1/PD-L1) or prior anticancer treatment within 28 days • Patients receiving immunosuppressive agents (eg, steroids) were tapered off before initiation of study treatment	Avelumab 10mg/kg IV Q2W until confirmed progression, unacceptable toxicity, or withdrawal	Best overall response (BOR) by RECIST v1.1 Safety and tolerability Progression-free survival PD-L1 expression in tumor tissue

* Inclusion criterion in the mesothelioma cohort only

Patients and treatment

Characteristics	N=53
Median age, years (range)	66 (32-84)
Sex, n (%)	
Male	32 (60.4)
Female	21 (39.6)
ECOG PS, n (%)	
0	14 (26.4)
1	39 (73.6)
Tumor histology, n (%)	
Epithelial	43 (81.1)
Mixed	6 (11.3)
Sarcomatoid	2 (3.8)
Unknown	2 (3.8)

Patients were enrolled from September 2014 to August 2015
Data cut-off: October 23, 2015

Characteristics	N=53
Median time since first diagnosis, years (range)	1.8 (0.4-31.3)
Number of prior anticancer therapy lines, n (%)*	
1	17 (32.1)
2	14 (26.4)
3	11 (20.8)
≥4	10 (18.9)
Median (range)	2.0 (1-9)

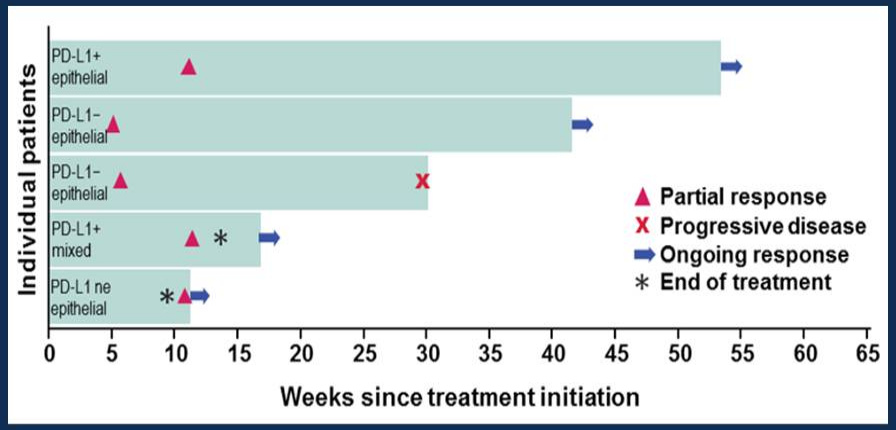
* Data for number of prior anticancer therapy lines missing for 1 patient

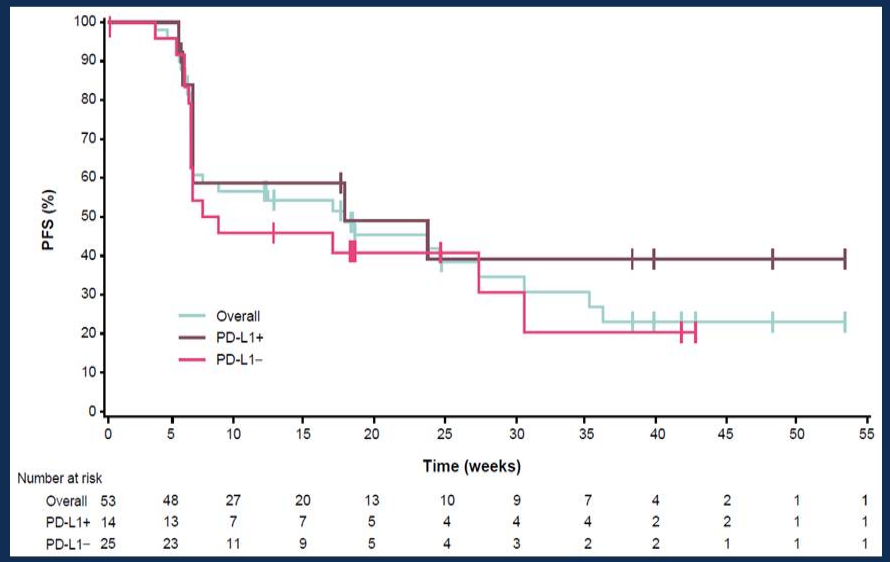
- Median treatment duration: 12 weeks (range 4-60)
- Minimum follow-up: 11.3 weeks
- 14 patients (26.4%) remain on treatment

Results

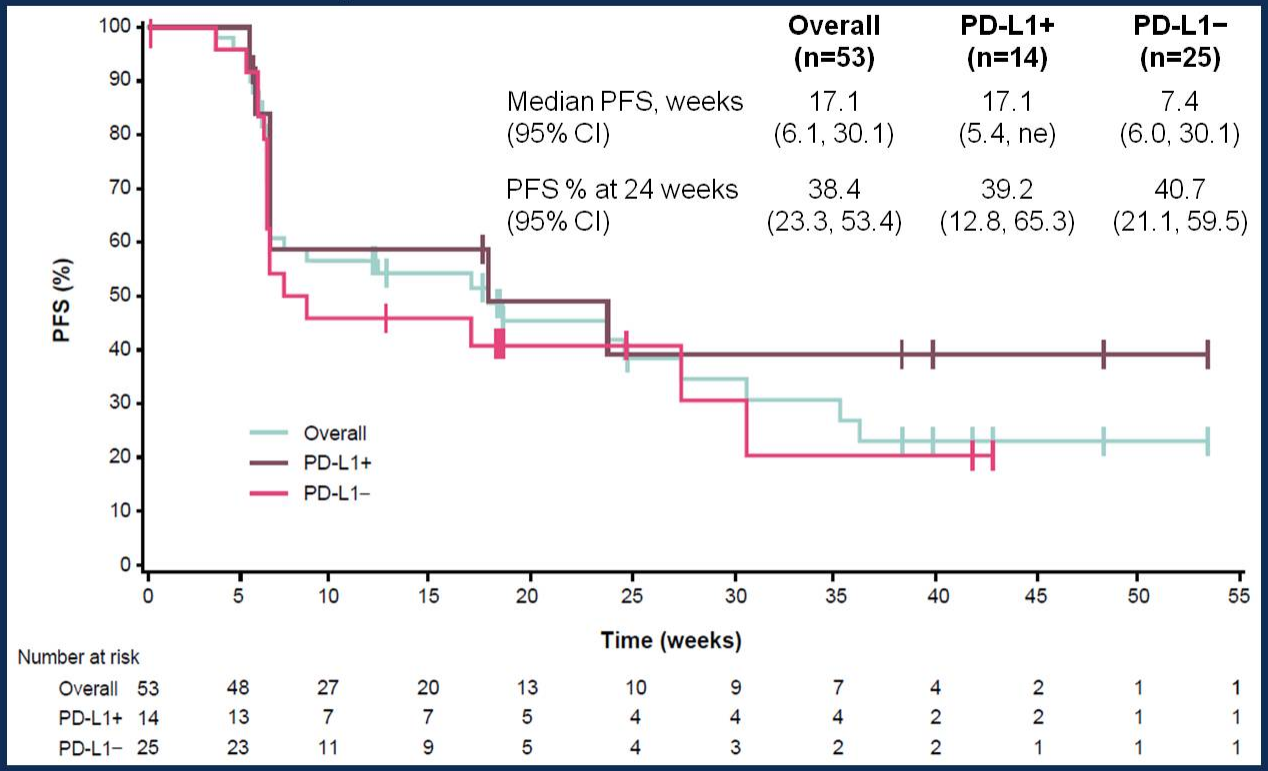
Best overall response by RECIST v1.1	n=53
Complete response, n (%)	0
Partial response, n (%)	5 (9.4)*
Stable disease, n (%)	25 (47.2)
Progressive disease, n (%)	18 (34.0)
Non-evaluable, n (%)	5 (9.4)
Overall response rate, % (95% CI)	9.4 (3.1, 20.7)
Disease control rate, % (95% CI)	56.6 (42.3, 70.2)

Duración media respuesta no alcanzada
rango 0+ a 42+semanas





PFS by PD-L1 expression status



ne, not estimable

Based on ≥5% threshold for tumor cell staining; 39/53 patients were evaluable for PD-L1 expression status

Treatment-related AEs

N=53	Any grade* n (%)	Grade 3-4 n (%)
Any TRAE	41 (77.4)	4 (7.5)
Infusion-related reaction†	20 (37.7)	0
Fatigue	8 (15.1)	0
Chills	8 (15.1)	0
Pyrexia	6 (11.3)	0
Decreased appetite	5 (9.4)	0
Asthenia	4 (7.5)	0
Pruritus	4 (7.5)	0

CPK, creatine phosphokinase; GGT, gamma-glutamyltransferase

* Individual TRAEs occurring in ≥7.5% at any grade are listed in the table

† Signs and symptoms of a potential infusion-related reaction (eg, fever, chills, or rigors) reported on the day of infusion were queried with investigators to ascertain whether an AE of "infusion-related reaction" should be recorded

- Most treatment-related AEs (TRAEs) were grade 1-2
- 4 patients (7.5%) had a grade ≥3 TRAE
  - Increased GGT (grade 3)
  - Decreased lymphocyte count (grade 3)
  - Colitis (grade 3)
  - Increased blood CPK (grade 4)
- 6 patients (11.3%) discontinued treatment following a TRAE
- No treatment-related deaths occurred

Estudios con inhibidores PD-1/PD-L1

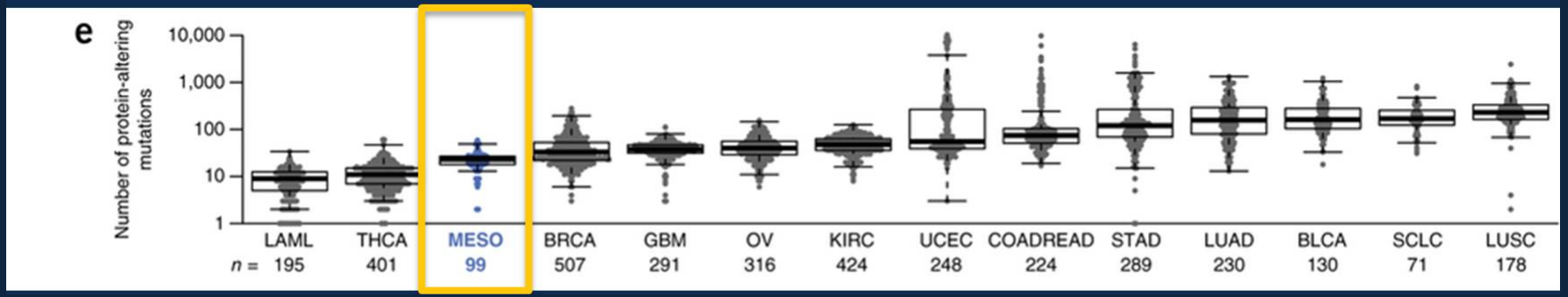
Study	Keynote-028 PD-L1+	NivoMes Unselected	Avelumab Unselected
Patient Number	25	18	53
PR	7 (28%)	5 (27%)	5 (9.4%)
SD	12 (48%)	4 (22%)	27 (47.2%)
PD	4 (16%)	9 (50%)	18 (34%)
Not assessed	2 (8%)		

- Niveles de expresion de PD-L1 en Keynote-028 no se correlacionan con respuesta
- PD-L1 positivos y negativos responden a Avelumab
- Respuesta a Avelumab no esta asociada con TIL o PD-L1
- Escaso numero de pacientes
- Criterios de selección diferentes

Conclusions

- Avelumab monotherapy had antitumor activity in patients with chemotherapy-refractory PD-L1+ and PD-L1− tumors
  - 5 patients had a partial response (ORR 9.4%), with 4/5 ongoing at last follow-up
  - Disease control rate was 56.6%
- Ongoing follow-up will further characterize durability of clinical benefit
- Avelumab had an acceptable safety profile
- This dataset is the largest study to date of patients with mesothelioma treated with an anti-PD-(L)1 antibody

Es el Mesotelioma Inmunogénico



- Relativa baja carga mutacional
- Limitada formación de Neoepitopos

Bueno et al. Nat Genetics 2016

Correlation of PD-L1 expression with immune cell infiltrates, genome-wide copy number aberrations and survival in mesothelioma.

Bibhusal Thapa

Abstract:**8518**

	PD-L1 neg	PD-L1 weak pos	PD-L1 high pos	P value
Number (%)	181 (58.2)	100 (32.1)	30 (9.6)	
Histology				
Epithelioid	125 (69.8)	64 (57.4)	9 (31)	<0.0001
Non-Epithelioid	54 (30.1)	40 (42.5)	20 (69)	
Median survival (months)	13.5	11.33	5.33	0.0001
CD4lo	94 (57.6)	39 (45.8)	4 (17.4)	<0.0001
CD4hi	69 (42.4)	46 (54.2)	23 (82.6)	
CD8lo	94 (58.7)	39 (43.8)	3 (10.3)	<0.0001
CD8hi	66 (41.2)	50 (56.2)	26 (89.6)	
FOXP3lo	87 (57.6)	41 (47.3)	2 (9)	<0.0001
FOXP3hi	64 (42.4)	45 (52.3)	20 (91)	

Thapa et al. ASCO 2016

- Alto porcentaje de MM expresan PD-L1(41.7%)
- Expresión alta de PD-L1 solo un 9.6%
  - No epitelioide (69%)
  - Mayor infiltrado linfocitario (CD4,CD8,FOXP3)
  - Peor pronostico (5.3m versus 13.5m)
- Ganancia en nº de copias 11.2%
- Incremento de alteraciones genómicas no correlación con expresión de PD-L1, si con peor supervivencia

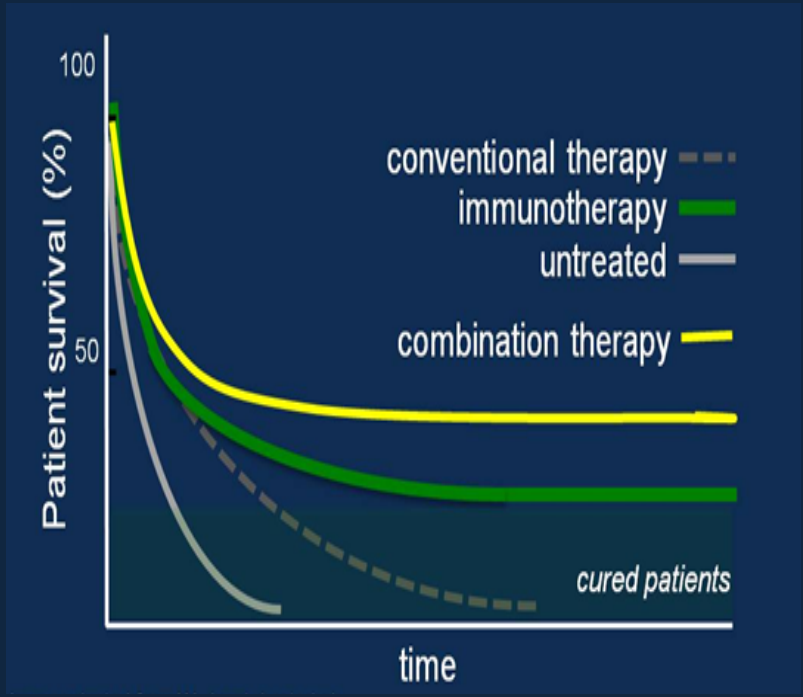
Mesotelioma

- Inhibidores de CTL-4 como agentes únicos no son efectivos en 2ª línea
- Anti PD-1 y PD-L1 son "prometedores"
- La población de pacientes en 2ª línea incluye enfermedad relativamente indolente
- Mesotelioma tienen baja carga mutacional
- Formación de neoepitopos limitada
- No existen predictores de respuesta
- Necesario completar largos ensayos

No cambios en la practica habitual

Terapias de combinación

- DREAM fase II
- - Pem/Cis + Durvalumab
- Fase II
  - Nivo vs Nivo + Ipi
- NIBIT-MESO
  - Treme + Durvalumab
- Otros
  - Combinaciones de vacunas
  - Virus Oncoliticos
  - Estrategias quirúrgicas
  - Radioterapia



Randomized Phase II Study of Adjuvant WT1 Vaccine (SLS-001) for Malignant Pleural Mesothelioma (MPM) after Multimodality Therapy – Updated Data

Abstract 8519

G. Zauderer[1,2], T. Dao[1], V. W. Rusch[1], M. S. Ginsberg[1], A. S. Tsao[3], R. Mehran[3], K. Panageas[1], D. A. Scheinberg[1], L. M. Krug*

[1]Memorial Sloan Kettering Cancer Center; [2]Weill Cornell Medical College; [3]MD Anderson Cancer Center, *affiliation with MSK and WCMC during this project

Supported by Department of Defense Grant W81XWH-10-1-0699 and the Meso Foundation

Contact zauderer@mskcc.org for additional info

- MPM
- WT-1 positive by IHC
- 4-12 weeks end of treatment
- KPS ≥ 70%

N= 78 patients (39 per arm)

n=19

Specific Immunotherapy x 6 (q2w):
- SLS-001 (800 µg/dose)
- Montanide (500 µl/dose)
- GM-CSF (70 µg/dose; d-2 d-0)

n=21

Control immunotherapy x 6 q2w):
- Montanide (500 µl/dose)
- GM-CSF (70 µg/dose; d-2 d-0)

Vacuna peptídica estimula CD4, CD8

Randomized Phase II Study of Adjuvant WT1 Vaccine (SLS-001) for Malignant Pleural Mesothelioma (MPM) after Multimodality Therapy – Updated Data

G. Zauderer[1,2], T. Dao[1], V. W. Rusch[1], M. S. Ginsberg[1], A. S. Tsao[3], R. Mehran[3], K. Panageas[1], D. A. Scheinberg[1], L. M. Krug*

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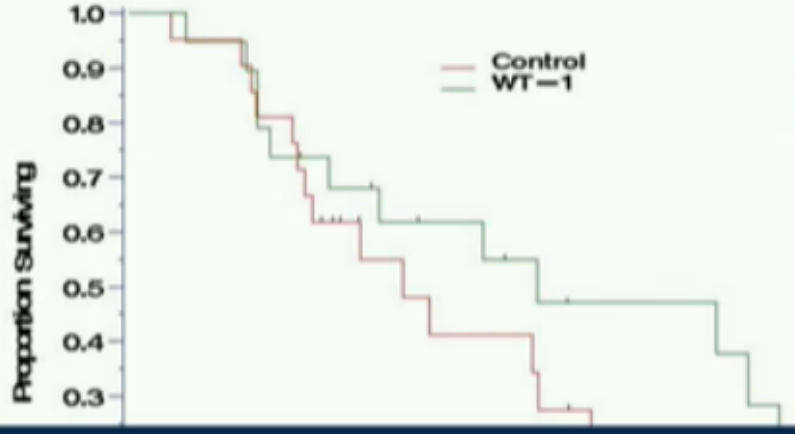
Supported by Department of Defense Grant W81XWH-10-1-0699 and the Meso Foundation

Contact zauderer@mskcc.org for additional info

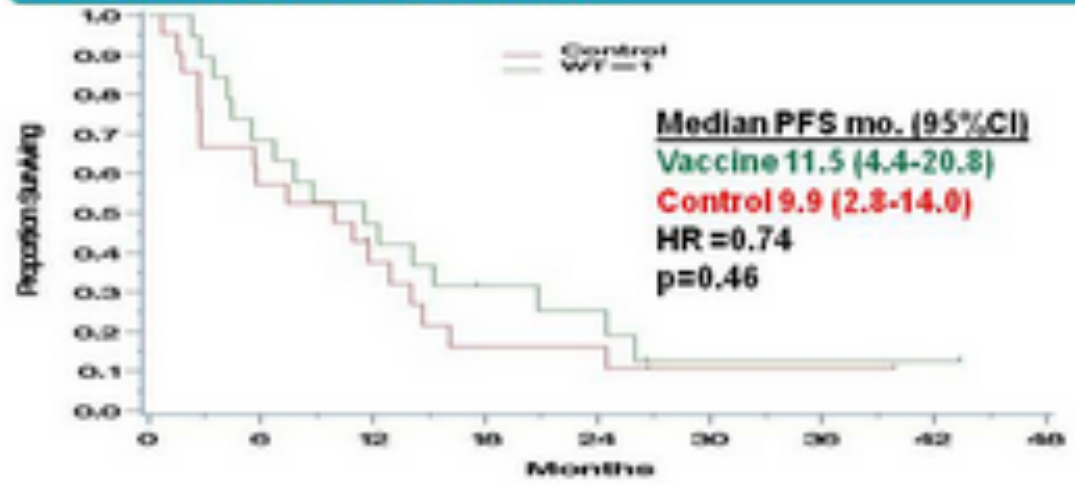
Abstract 8519

Overall Survival Stratified by Treatment Arm



Median OS mo. (95%CI)
Vaccine 24.8 (8.5-39.4)
Control 16.6 (10.2-28.1)
HR=0.51
p=0.24

Progression-Free Survival



Median PFS mo. (95%CI)
Vaccine 11.5 (4.4-20.8)
Control 9.9 (2.8-14.0)
HR =0.74
p=0.46

Carcinoma Tímico

8517: A phase II study of pembrolizumab in patients with recurrent thymic carcinoma (Giaccone)

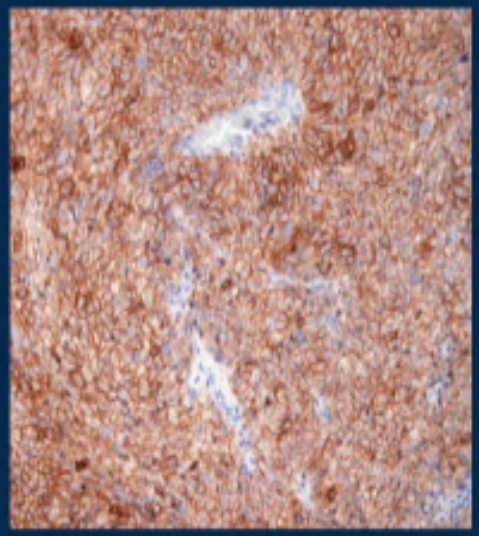
Patients with advanced or recurrent thymic carcinoma → pembrolizumab q 3 weeks

n=30

Primary Endpoint: Response Rate

Immune biomarker evaluation in Thymic Tumors

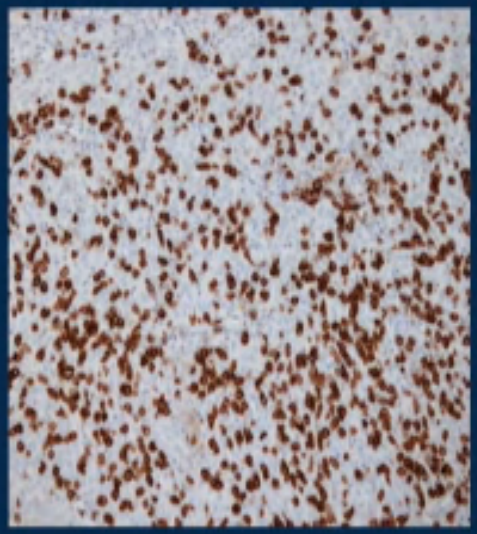
PD-L1 expression (tumor cells)
(antibody: E1L3N)



- 11/12 (94%) Thymomas PD-L1+
- 4/12 (34%) Thymic carcinomas PD-L1+

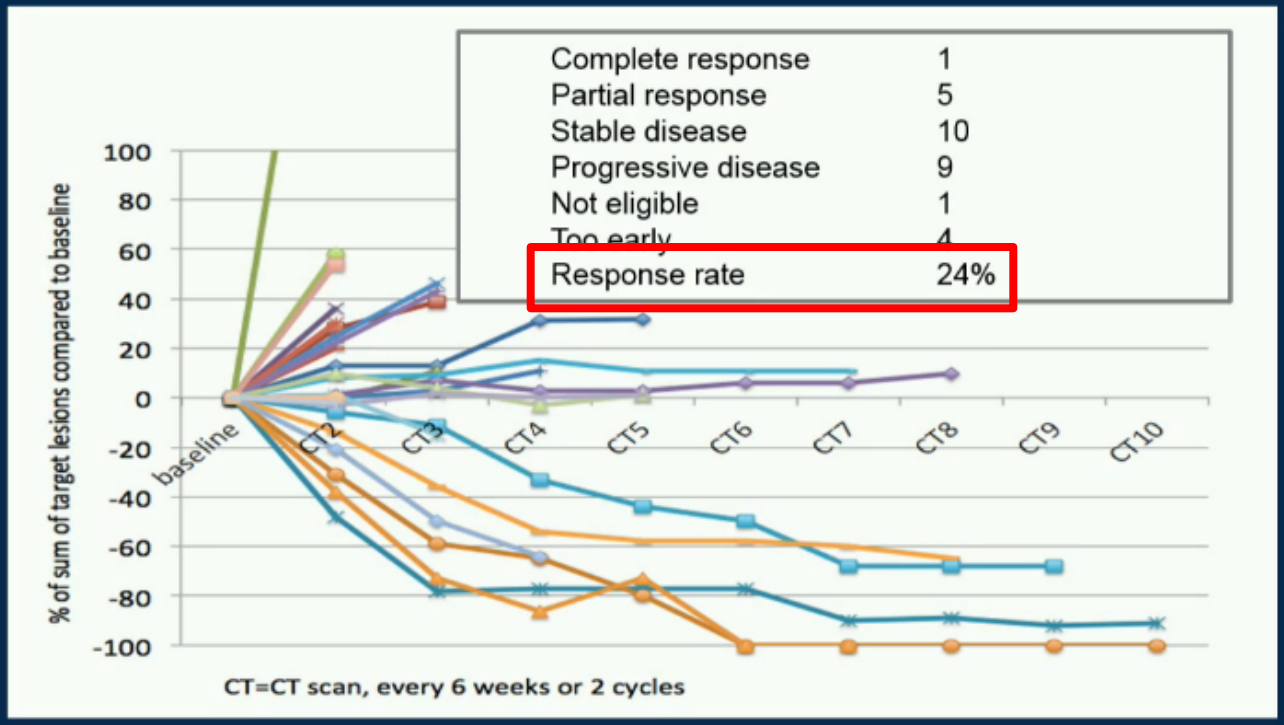
p<0.01

CD8 (+) TILs



- 24/24 had CD8 + TILs
(IHC1+= 7 IHC2+=10, IHC3+= 7)

Naidoo et al ASCO 2015



Side effects of special interest (4/30, 13%)

- Polymyositis/myocarditis
  - Developed after 2 cycles with severe asthenia, dyspnea and muscle aches. Required hospitalization, complete A-V block, pace-maker placement and steroids. Patient recovered completely.
- Diabetes mellitus type 1
  - Developed hyperglycemia grade 4, after 4 cycles. Associated with severe increase of lipase (grade 3) and amylase (grade 1) and grade 3 transaminitis. Required insulin. Did not reverse. Patient on insulin, doing well.
- Bullous pemphigoid
  - Started with severe itching after 10 cycles. Histologically diagnosed after 12 cycles. Recovered after oral steroids.
- Polymyositis/hepatitis/myocarditis
  - Developed after 2 cycles with severe asthenia, and severe muscle and joint pains. Transaminase elevation grade 4. Required hospitalization and iv steroids. Presently recovering.

Conclusiones

Ca. Células pequeñas

- Rt diaria con 66Gy no superior a 45 Gy/2veces al día
- Rovalpituzumab e Inmunoterapia resultados prometedores

Mesotelioma

- Inmunoterapia con ant CDL4 no efectivo
- Nuevos agentes en marcha prometedores
- No cambios en la practica habitual

Ca. Timico

- Inmunoterapia con Pembrolizumab 24% RG

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#ASCO16

Muchas gracias

Checkpoint Inhibitors in NSCLC

Antibody	Target	Company	Stage in development
Ipilimumab	CTLA-4	Bristol-Myers Squibb	**Phase III**
Tremelimumab	CTLA-4	MedImmune/Astra Zeneca	Phase III
BMS-936558 **Nivolumab**	PD-1	Bristol-Myers Squibb	**Approved in NSCLC (USA/EMA)**
MK-3475 **pembrozilumab**	PD-1	MSD	**Approved in PD-L1+ NSCLC (USA)**
MPDL-3280A Atezolizumab	PD-L1	Genentech-Roche	**Phase III**
Medi-4736 Durvalumab	PD-L1	MedImmune/Astra Zeneca	**Phase III**
MSB0010718C avelumab	PD-L1	Merck/Pfizer	**Phase III**