ITMIG International Thymic Malignancy Interest Group

POST ESMO-WCLC-ITMIG

2017 OncoZON update

13 November 2017

SCLC / Mesotheliomen

Eindelijk vooruitgang ?

Gerben Bootsma

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ESMO

Disclosure belangen spreker	
(potentiële) Belangenverstrengeling	**Geen**
Voor bijeenkomst mogelijk relevante relaties met bedrijven[1]	**Bedrijfsnamen**
• Sponsoring of onderzoeksgeld[2] • Honorarium of andere (financiële) vergoeding[3] • Aandeelhouder[4] • Andere relatie, namelijk …[5]	

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Mesotheliomen:

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Malignant Pleural Mesothelioma: Challenges for New Treatment

Oral abstract session

1. **Systemic Therapy: Anti-Mesothelin antibody conjugate Phase II (Kindler et al)**
2. **Immunotherapy: Combination checkpoint inhibitors (Baas et al)**
3. **Prophylaxis: Radiation Therapy post chest wall procedures**
4. **Palliative care: Respect Meso trial (Brims et al)**
5. **Surgery: Mars II trial (E.Lim et al)**

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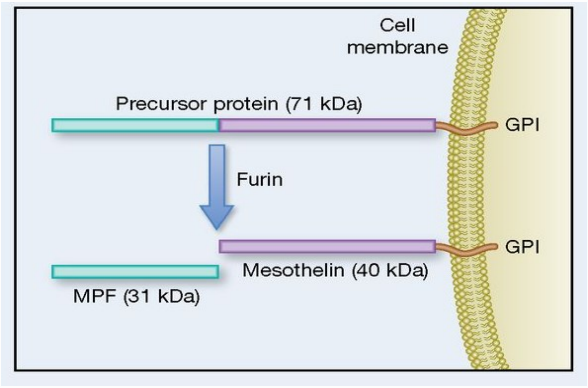
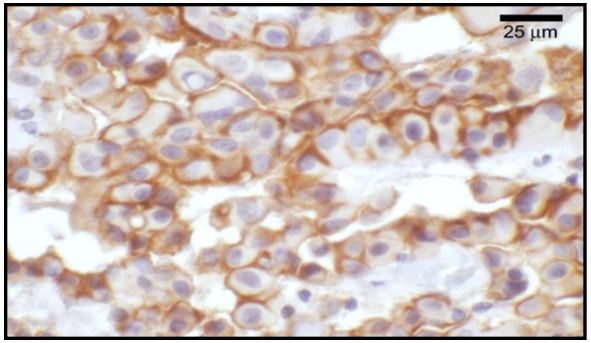
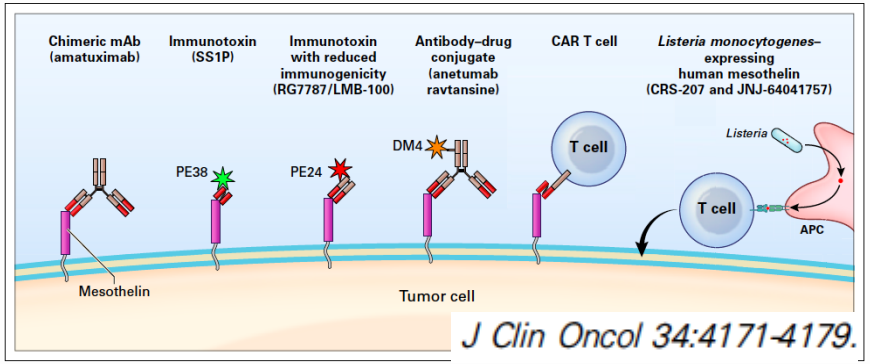
Targeting Tumor-associated Antigens: *Mesothelin*

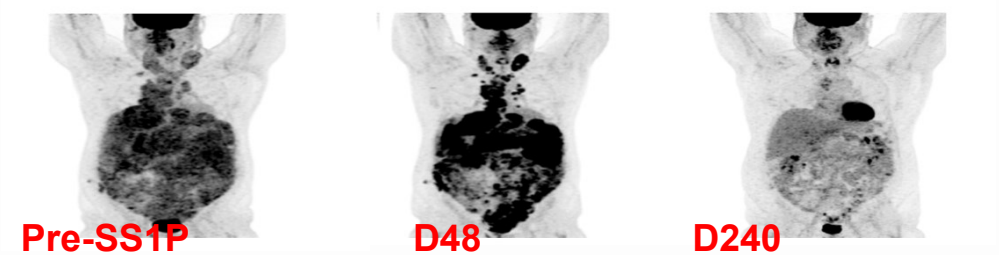




Chang K, Pastan I., PNAS 1996
Pastan I, Hassan R., Cancer Res. 2014
Hassan et al. Clin. Cancer Res., 2004
Ordonez NG. Am J Surg Pathol, 2003

- **Cell surface glycoprotein expressed in normal human tissues - mesothelial cells lining pleura, peritoneum and pericardium**
- **Expressed at high levels in epithelial MPM**





Hassan R et al., Science Transl. Medicine 2013

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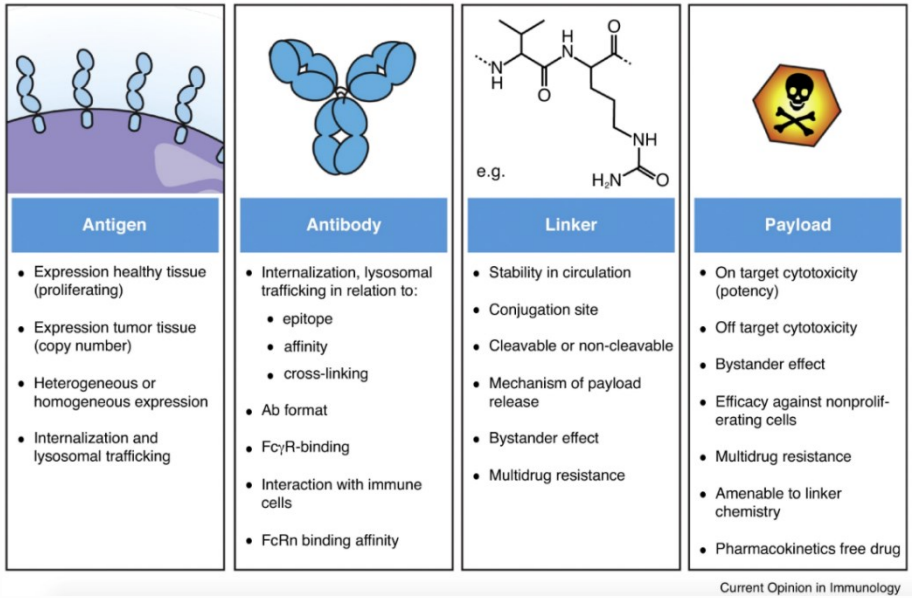
Kindler et al. Anetumab Vs. Vinorelbine Randomized Phase II Study

- **Rationale**:
- No established second-line chemotherapy for MPM
- Mesothelin-directed therapies for MPM given that the vast majority of epithelioid mesotheliomas express high levels of mesothelin on the cell surface
- Prior clinical trials of anti-mesothelin antibody therapy for MPM had demonstrated safety, even if there was not substantial efficacy
- Prior clinical trial of anti-mesothelin Mab (MORAB-009) in combination with Pem/Cis did not show benefit when compared with historical controls of chemotherapy alone.

Kindler et al. Anetumab Vs. Vinorelbine Randomized Phase II Study

- **<u>Study background:</u>**
- Anetumab ravtansine: novel drug conjugate - anti-mesothelin Mab and microtubule inhibitor DM4.
- Prior Phase I study of Anetumab ravtansine (n=16) demonstrated safety and efficacy: PR 31%; DCR -75%
- Vinorelbine reasonable control agent given prior clinical use in second- and third-line therapy of MPM with acceptable toxicity.



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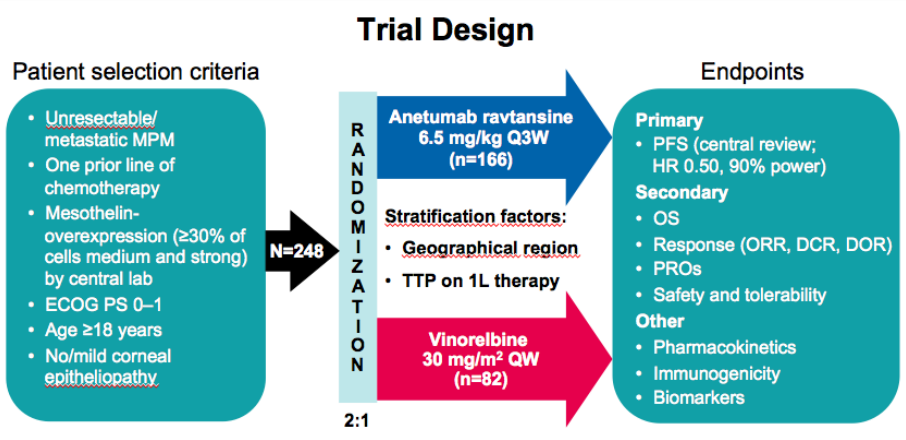
Kindler et al. Anetumab vs Vinorelbine Phase II

- Study design: Open-label, randomized, Phase II trial assessing efficacy and safety with 2:1 randomization of Anetumab to Vinorelbine.
- Inclusion: >30% "medium-strong" mesothelin expression. **No delineation of histologic subtype**
- Stratification: Geographic region and for TTP on 1L chemotherapy
-



- Primary endpoint: PFS with central radiographic review and HR 0.5, 90% power.
- Secondary endpoints: OS, RR, PRO's, safety and tolerability
- Exploratory: Pharmacokinetics; *Immunogenicity; Biomarkers*

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Kindler et al. Anetumab vs Vinorelbine Phase II

	Anetumab ravtansine (n=166)	Vinorelbine (n=82)
Male, %	74	76
Age, median years (range)	66.5 (42–84)	65.5 (46–84)
ECOG PS 0/1, %	37/63	35/65
Histology: epithelioid/biphasic, %	96/4	96/2*
TNM stage at study entry III/IV, %	35/61	31/59
TTP on 1L therapy <6/≥6 months, %	39/61	37/63
Time in months since most recent progression, median (range)	2.1 (0.3–25.1)	1.9 (0.7–12.9)

- **<u>Study design/issues:</u>**
- Nearly 50% of patients failed screening for mesothelin
- Another 20% of patients failed secondary screening
- Efficacy population is ITT; safety population is those patients who actually received drug
- Well matched by age, sex, histology, stage, TTP on 1L Rx

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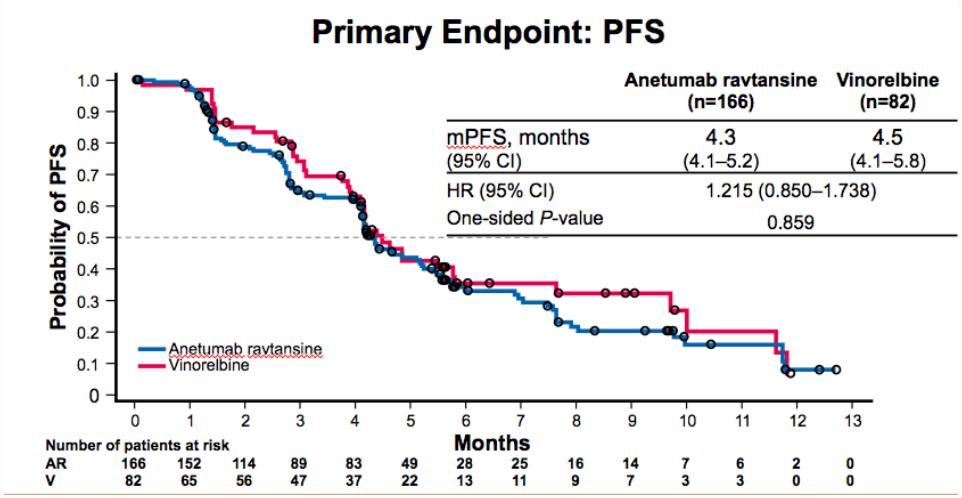
Kindler et al. Anetumab vs Vinorelbine Phase II

- **Take home message:** **No difference in PFS between treatment and control groups (HR 1.215); PFS slightly favored control group – Vinorelbine**



- No subgroups favoring treatment.
- Secondary endpoint: No difference in OS, with trend favoring control
- ORR greater in treatment group (14% vs. 5%) with similar DCR.
- Higher percentages of Grade 3/4 AE's in Vinorelbine group
- 1 treatment related death in Anetumab group
- Differences in patterns of AE's between two cohorts as expected
- Under study in other cancers

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Malignant Pleural Mesothelioma: Challenges for New Treatment

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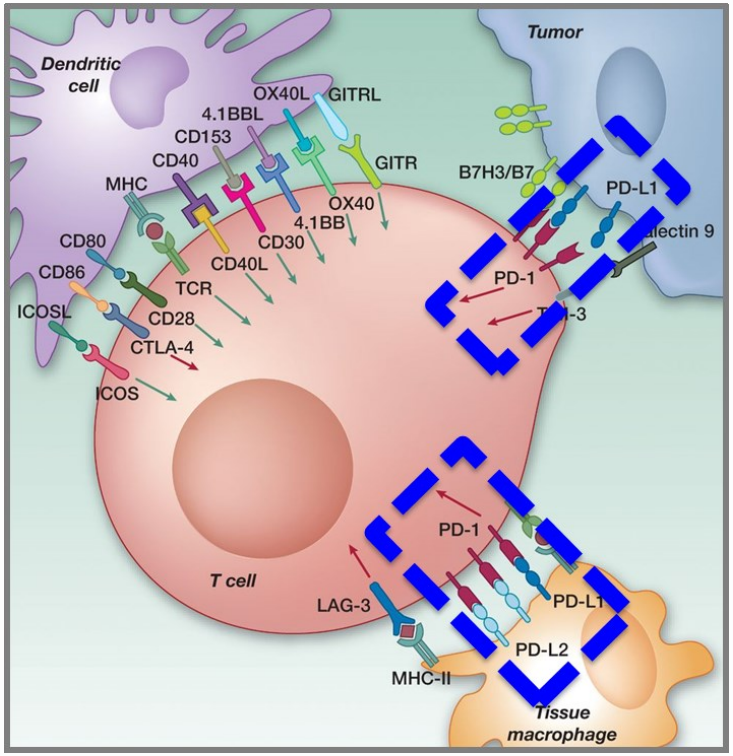
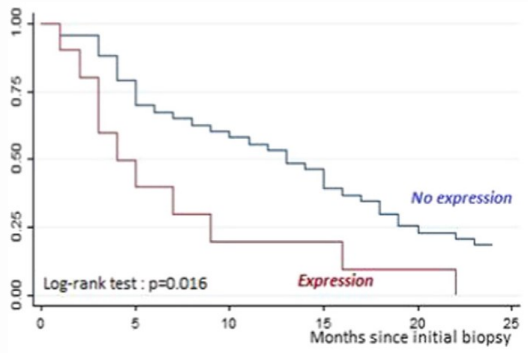
Checkpoint Inhibitors In Pleural Mesothelioma



- T-cell inflamed phenotype and PD-L1 expression observed in MPM[1-4]
- PD-L1 expression more common in non-epithelioid tumors[2-4]
- PD-L1 expression independently associated with poor prognosis
  - Median OS: 5.0 mo for PD-L1^{+} vs 14.5 mo for PD-L1^{-}



Human Pathology (2016) 52, 9–18

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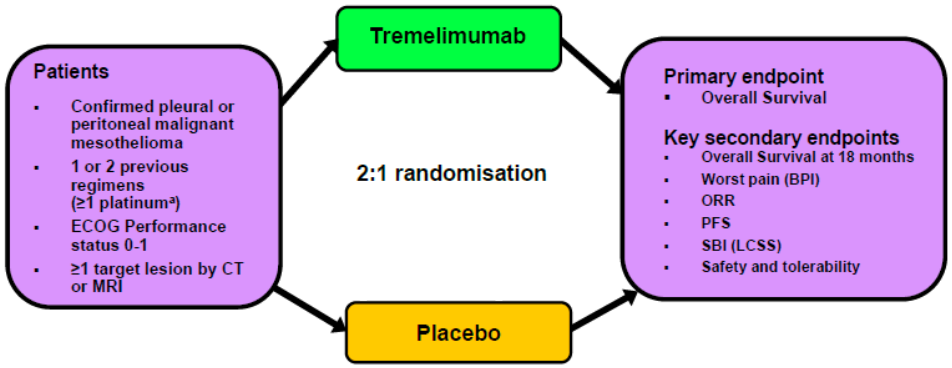
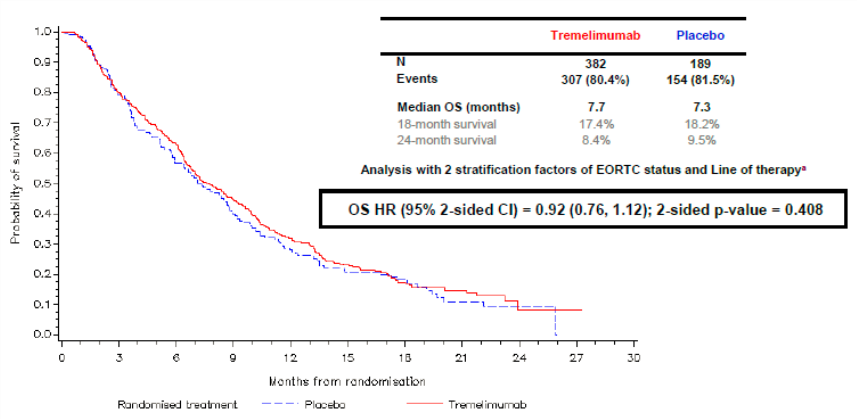
1. Kindler HL et al. Abstr. 7589 . Presented at 2014 ASCO Annual Meeting, May 30-Jun 3, 2014; Chicago, IL; 2. Cedrés S et al. *PLoS ONE. 2015;* 10: e0121071;
3. Kao SC et al. Presented at iMiG 2014, Oct 21-24; Cape Town, South Africa; 4. Mansfield AS et al. *JTO*. 2014; 9: S7-S52.

Anti-CTLA-4 Ab (Tremelimumab) alone did not improve mOS *vs.* placebo in a Phase 2b randomized trial (Determine) in MPM…





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Kindler and al, *ASCO* 2016; Alley Lancet Oncol 2017

What about I-O in MPM…

- Nivolumab has activity in pretreated MPM
- ORR consistent with prior PD-1/PD-L1 inhibitor studies.[1,2,3,4]

Summary Table: Selected PD-1/PD-L1 inhibitors in salvage MPM

Agent	NCT	Type	Population	ORR	DCR	PFS	OS	PD-L1 IHC status
Pembrolizumab (KEYNOTE-028)[1]	02054806	PD-1 inhibitor	2nd line	20%	72%	5.4 months	18 months	All patients were PD-L1 IHC (+)
Pembrolizumab[2]	02399371	PD-1 inhibitor	2nd line	21%	77%	6.2 months	NR	Did not correlate to response
Nivolumab (NivoMes trial)[3]	02497508	PD-1 inhibitor	1 prior therapy	24%	50%	3.6 months	NR	Trend for a correlations with OR
Avelumab (JAVELIN)[4]	01772004	PD-L1 inhibitor	salvage, any line	9.4%	57%	4.3 months	NR	Trend to correlate with median PFS

Oncology 18:623-630, 2017; [2]Kindler H, et al. Journal of Thoracic Oncology 12:S149-S150, 2016; [3]Quispel-Janssen J et al. Journal of Thoracic Oncology 12:S149, 2016; [4]Hassan R, et al. ASCO abstract 2016

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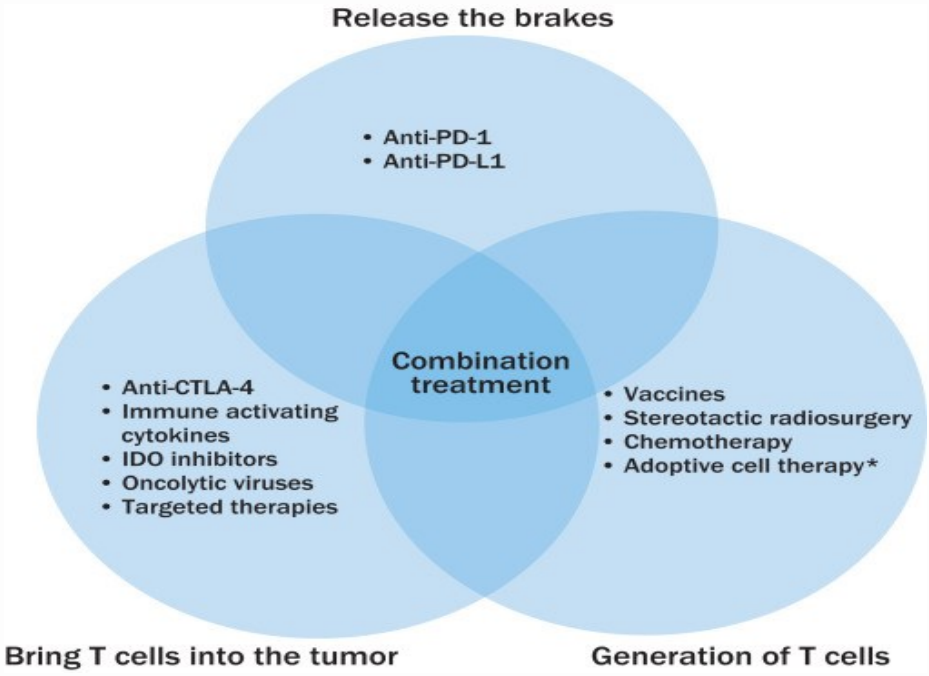
Presented by: Anne S. Tsao ASCO 2017

Combination Immunotherapy for Mesothelioma



Tremelimumab Combined With the Anti-PD-L1 MEDI4736 Antibody (Durvalumab) in Malignant Mesothelioma (NIBIT-MESO-1) [Italy]

Nivolumab Monotherapy or Nivolumab Plus Ipilimumab, for Unresectable Malignant Pleural Mesothelioma (MPM) Patients (MAPS2) [France]

Nivolumab in Patients With Recurrent Malignant Mesothelioma (NivoMes) [The Netherlands]

Combination of FAK (Defactinib) and PD-1(Pembrolizumab) inhibition in Patients With Advanced Solid Malignancies (FAK-PD1) [UK]

Atkins, Seminars in Oncology, Vol 42, Suppl 3, 2015, S12–S19

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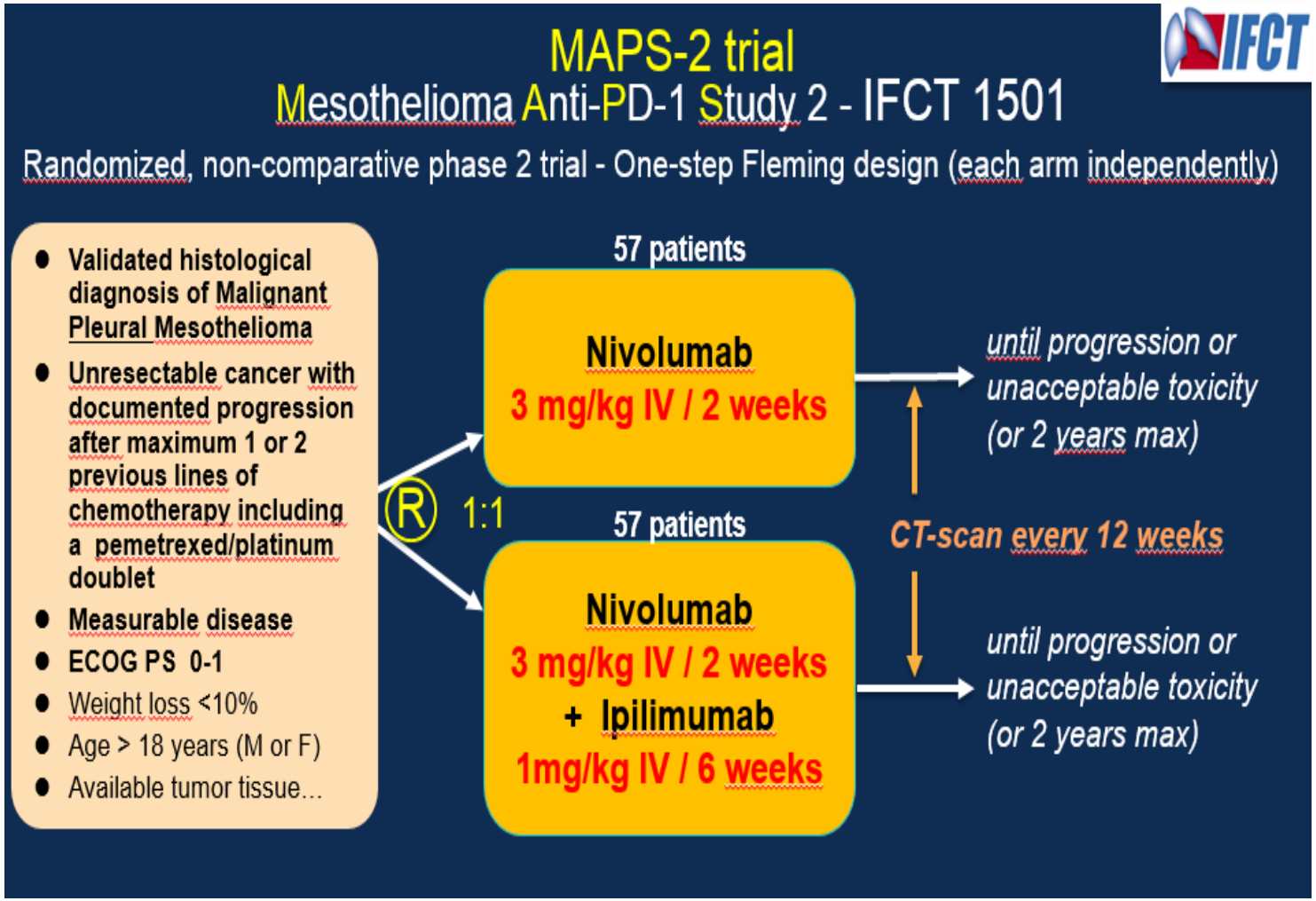
inclusie binnen 5 maanden compleet!



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Scherpereel, ASCO 2017, LBA 8507

Primaire eindpunt: DCR 12 weken
verder onderzoek DCR > 40% (independent review)

Tumor Response assessment after first 12 weeks

By a blinded, independent panel of Radiologists

in the **first 108 eligible patients**

Tumor assessment % [IC95%](n pts)	NIVO Arm (n=54)	NIVO+IPI Arm (n=54)
Objective response	18.5% [8.2-28.9%](10)	25.9% [14.2-37.6%](14)
Stable Disease	25.9% [14.2-37.6%](14)	24.1% [12.7-35.5%](13)
Disease control rate	**44.4%** [31.2-57.7%](24)	**50.0%** [36.7-63.3%](27)
Disease Progression	51.9 [38.5-65.2%](28)	42.6% [29.4-55.8%](23)
Not evaluable/not done /missing	3.7% [0.0-8.7%](2)	7.4% [0.4-14.4%](4)

First endpoint based on the statistical plan

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Let op fase II studie - Preliminaire data…

MAPS-2 trial conclusions

- Both Nivo alone Arm, and Nivo+Ipi Arm reached their 1rst endpoint in 2nd/3rd line MPM pts, increasing **meaningfully 12 weeks DCR**
- Moreover, patients from both arms of this study seem to have **prolonged median OS** than all previous reports in this setting
- Toxicity was **globally** manageable, **even if** 3 treatment-related deaths were reported in the combo arm
- Matured survival, QoL, biomarkers data, and subgroup analysis will be presented next Autumn, 1 year after accrual of the last patient

→ Immunotherapy (Nivo +/- Ipi) may provide new therapeutic options as 2nd/3rd line treatment for relapsing MPM patients

Baas et al Combination Nivolumab/Ipilimumab in 2nd/3rd line Malignant Mesothelioma

- **Study objective**
  - To investigate the combination of nivolumab + ipilimumab in patients with recurrent MPM

Key patient inclusion criteria

- Histologically confirmed MPM
- PD on or after 1 or 2 previous lines of treatment including pemetrexed + platinum
- PS 0−1

(n=38)

→ Ipilimumab 1 mg/kg q6w + nivolumab 240 mg q2w → PD/ toxicity

Primary endpoint

- DCR at 12 weeks

Secondary endpoints

- Safety, PFS, OS, ORR

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Baas P et al. J Thorac Oncol 2017;12(suppl):Abstr OA 02.02

Baas et al Combination Nivolumab/Ipilimumab in 2nd/3rd line Malignant Mesothelioma

- **Intervention:** Ipi q 6 wks; Nivo q 2 wks
- **Primary endpoint:** DCR of Nivo + Ipi
- **Secondary endpoints:**
  - Changes in tumor microenvironment on *pre- and post treatment biopsies*.
  - Toxicity
  - PFS and OS
  - % of MM patients with PDL-1 expression and distribution (?)

Study Design:

- Single-arm Simon's MiniMax 2 stage design**
- DCR of 50% at 12 weeks
- Alpha 0.02 beta -90%
- If >/= 3 responses in the first 12 patients or >/= 12 patients in the first 33, then the null hypothesis is rejected

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Baas et al Combination Nivolumab/Ipilimumab in 2nd/3rd line Malignant Mesothelioma

- **Inclusion criteria:**
  - Histologically confirmed MPM
  - Disease progression after 1-2 lines of therapy (incl Pem/Plat)
  - Evaluable disease
  - Access for fresh tumor material at baseline and at 6 weeks
  - ECOG 0,1
  - Normal organ function
  - No immune suppression
  - No ILD or history of pneumonitis.

Baseline Characteristics (N=38)*

		N			N
Gender	Male	30	Histology	Epithelial	32
Age	Median	65		Biphasic	2
	Range	37-78		Sarcomatoid	4
ECOG PS	0	11			
	1	25	Line of Rx	2nd	32
	2	2		> 3rd (3-5)	6

Enrollment Overview:

- Predominantly Males
- Mostly ECOG 1
- Mostly Epithelial
- Primarily in 2nd line

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- 29/38 had paired biopsies

Baas et al Combination Nivolumab/Ipilimumab in 2nd/3rd line Malignant Mesothelioma

- **Key results**

Response	Patients (n=27)
PR, n (%)	7 (27)
SD, n (%)	13 (48)
DCR, n (%)	20 (74)
PFS, days	144
Ongoing, n/N	15/27

  - Toxicity profile was favourable
    - 4 patients[a] reported treatment-related SAEs
- **Conclusions**
  - The combination of ipilimumab + nivolumab showed robust activity as 2L/3L treatment in unselected patients with MPM
  - Data are superior to nivolumab alone

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[a]2 patients had >1 SAE

Baas P et al. J Thorac Oncol 2017;12(suppl):Abstr OA 02.02

What about I-O in MPM…

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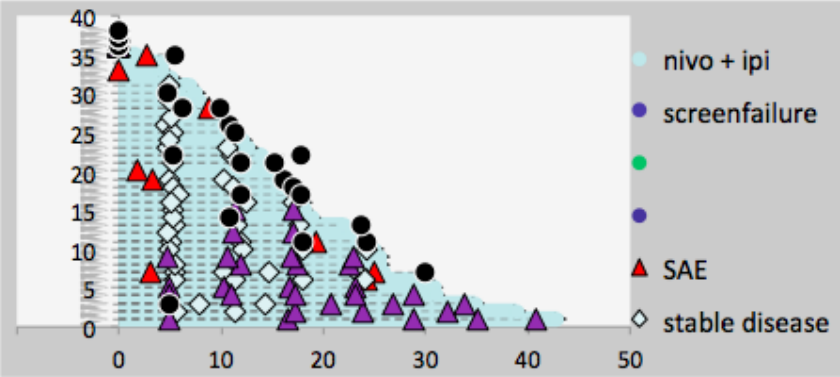
Baas et al Combination Nivolumab/Ipilimumab in 2nd/3rd line Malignant Mesothelioma



Toxicity	Grade 2	Grade 3/4	SAE	Relationship
Infusion reaction	13			
Diarrhea/colitis	4		1	probable
ALAT/ASAT		1		
Dyspnea	2	2	2	probable
Erythema	3	1		
Pruritis	5			
Pleural effusion	2	2	3	definite
Delirium		1	1	unlikely
IO metabolism (T4)	3			
Renal	1			

- Toxicity: 7/38 had SAE
  - *Pneumonitis? 4 pleural effusion (2 Gd 3-4); 4 dyspnea (2 Gd 3-4)*

- 29/38 had paired biopsies

  exploratory research volgt!

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Baas et al Combination Nivolumab/Ipilimumab in 2nd/3rd line Malignant Mesothelioma

- **Take home message:**
  - **Combination of Nivolumab/Ipilimumab appears to be active in 2nd/3rd line in MPM (> Nivolumab alone)**
  - Generally favorable toxicity profile, although 4/38 had Grade 3-4 pulmonary complications
  - Unanswered questions:
    - Histological subtype specificity? *Few non-epithelial tumors*
    - Tumor-related biomarker data?: *PDL-1 status pending*
    - Biomarkers of response to anti-CTLA-4 Mab?
    - Need biomarkers for single vs. dual CPI treatment in MPM

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Malignant Pleural Mesothelioma: Challenges for New Treatment

Oral abstract session

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Role of RT in Procedure-Tract Metastasis in Malignant Pleural Mesothelioma

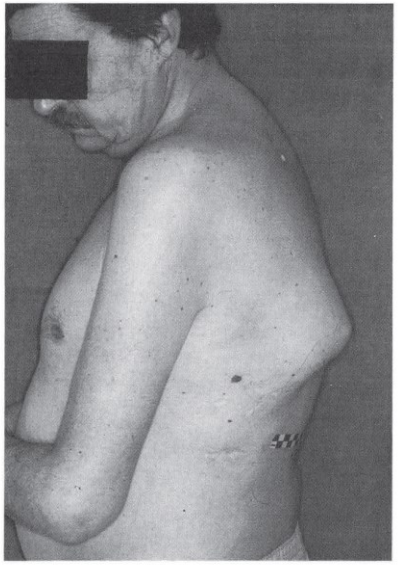

FIGURE 1. Large parietal tumor invasion developed on a needle tract after simple thoracentesis.

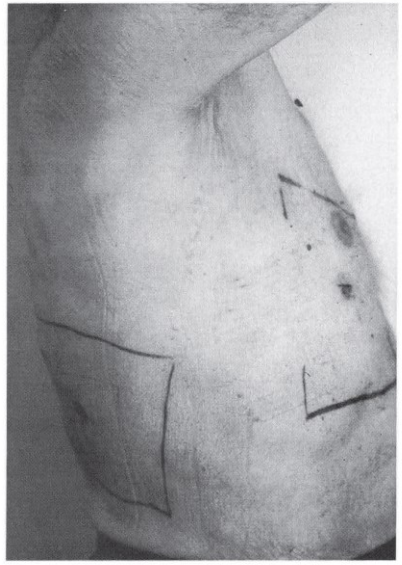

FIGURE 3. Example of irradiation fields: one for thoracoscopy scar and the second for previous needle puncture tracts (on the back).

- Three prior small randomized controlled trials assessing efficacy of RT in reducing procedure-tract metastases (PTMs) with conflicting results and substantial variation in PTM incidence.
- No world-wide consensus on benefits and recommendations of prophylactic RT in this setting.

Boutin, CHEST 1995; 108:754-58

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SMART (UK): Radiotherapy Prophylaxis vs Delayed RT for Procedure-Tract Metastasis in MPM

Conclusions:

- No significant difference was seen in procedure tract metastasis (PTM) incidence in the immediate and deferred RT groups (p=0.14)
- Prophylactic RT to large-bore pleural intervention sites does not confer benefits in terms of PTM, chest pain, QOL, analgesia use, or survival
- *Unknown If this data applies to all pleural interventions in MPM*

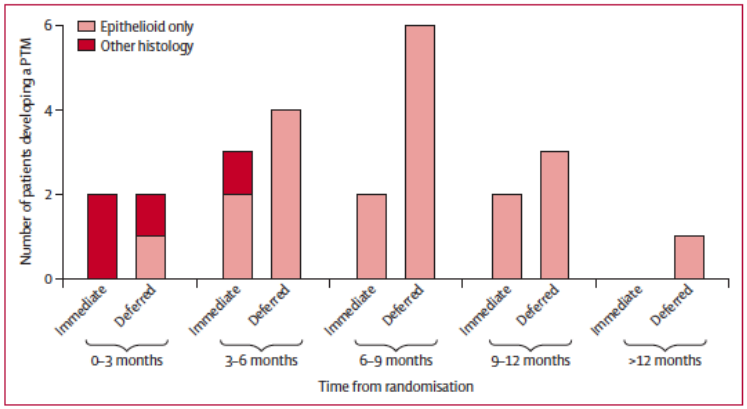

Figure 2: Time to development of PTM, by treatment group and histological subtype
PTM=procedure-tract metastasis.

Lancet Oncol 2016; 17: 1094–104

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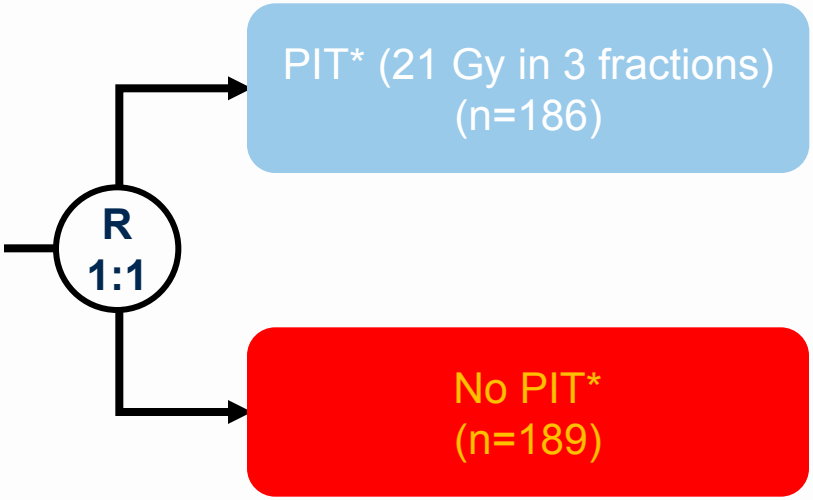
OA 02.03: Prophylactic Irradiation of Tracts (PIT) in Patients with Pleural Mesothelioma: Results of a Multicentre Phase III Trial – Bayman N, et al

- **Study objective**
  - To investigate the efficacy of prophylactic irradiation of tracts (PIT) in reducing the incidence of chest wall metastases (CWM) following a chest wall procedure in MPM

Key patient inclusion criteria

- MPM
- Within 42 days of chest wall procedure
- PS 0−2

(n=375)



Primary endpoint

- Incidence of CWM within 6 months

Secondary endpoints

- Time to CWM, radiotherapy toxicity and pain from CWM

*Chemotherapy could be given after PIT (experimental arm) or randomisation (control arm) at the discretion of the treating clinician

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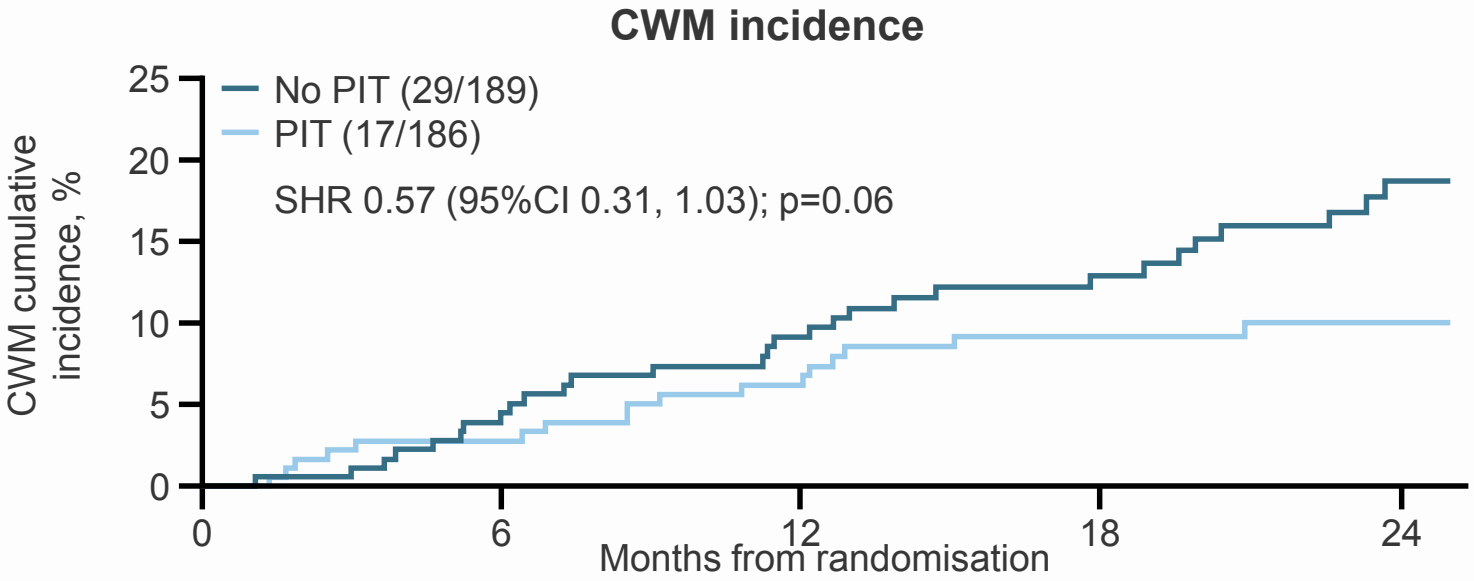
Bayman N et al. J Thorac Oncol 2017;12(suppl):Abstr OA 02.03

OA 02.03: Prophylactic Irradiation of Tracts (PIT) in Patients with Pleural Mesothelioma: Results of a Multicentre Phase III Trial – Bayman N, et al

- **Key results**



  - The cumulative incidence of CWM at 6 or 12 months was 3.2% with PIT vs. 5.3% without at 6 months and 8.1% vs. 10.1% at 12 months, respectively
  - The most common radiotherapy-related AE in the PIT arm was mild skin toxicity
- **Conclusion**
  - There was no difference in CWM between the groups; patients with MPM undergoing chest wall procedures should not be routinely treated with PIT
  - No difference in pain

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Bayman N et al. J Thorac Oncol 2017;12(suppl):Abstr OA 02.03

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5. Surgery: Mars II trial (E.Lim et al)

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02.05: RESPECT-MESO: An international randomized controlled trial to assess regular early specialist palliative care in malignant pleural mesothelioma (ISRCTN18955704)

F. Brims, S. Gunatilake, I. Lawrie, L. Marshall, C. Fogg, N. Maskell, K. Forbes, N. Rahman, S. Morris, S. Gerry, & A.J Chauhan

Respect Meso

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- **Objective:** This study was designed to examine the role of early specialist palliative care (SPC) in patients recently diagnosed with MPM
- **Methods:** Randomised, multicentre, parallel group, unblinded, controlled trial, comparing regular early SPC with standard care vs. standard care alone in 24 centers across UK and Australia
- **Outcome parameter:** HRQoL between the 2 arms at 12 weeks

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- **Results:**

- 687 Screened (declined / refused =150; ECOG PS >2 = 93)
- 174 participants randomised (SPC n=87, control n=87)
- 12 weeks: SPC n=80, control n=77

  148 (85.1%) completing primary outcome
- 24 weeks: SPC n=67, control n=68

  125 (71.8%) data for analysis

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Variable	Control	SPC	Mean difference	p=
Mean (SD) GHS QoL 12 weeks	59.5 (21.2)	60.2 (23.6)	1.8 (95% CI -4.0 to 8.5)	0.60
Mean (SD) GHS QoL 24 weeks	63.7 (19.8)	61.3 (20.8)	-2.0 (-8.8 to 4.6)	0.55
Mean (SD) GHQ-12 anxiety / depression scores 12 weeks	2.6 (3.2)	2.2 (3.0)	-0.6 (-1.5 to 0.4)	0.24
Mean (SD) GHQ-12 anxiety / depression scores 24 weeks	2.1 (2.55)	1.75 (2.5)	-0.4 (-1.2 to 0.4)	0.28
Median survival (95% CI, months)	12.6 (10.7-19.7)	11.5 (9.8-15.9)		0.51

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- **Conclusion:**

Early regular SPC for all patients with recently diagnosed MPM is not associated with beneficial changes in quality of life, as compared to palliative care review based on symptom burden and clinical judgement.

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Malignant Pleural Mesothelioma: Challenges for New Treatment

Oral abstract session

1. Systemic Therapy: Anti-Mesothelin antibody conjugate Phase II (Kindler et al)
2. Immunotherapy: Combination checkpoint inhibitors (Baas et al)
3. Prophylaxis: Radiation Therapy post chest wall procedures
4. Palliative care: Respect Meso trial (Brims et al)
5. **Surgery: Mars II trial (E.Lim et al)**

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02.08: Surgical selection in pleurectomy decortication for mesothelioma – an overview from screening and selection from MARS 2 pilot

Chief Investigator:
Mr Eric Lim

Centres and PIs:
Burton, Dr Manjusha Keni
Cardiff, Dr Malgorzata Kornaszewska
Clatterbridge, Dr Anthony Pope
Colchester, Dr Dakshinamoorthy Muthukumar
Derby, Dr Manjusha Keni
Leeds, Mr Richard Milton
Leicester, Professor Dean Fennell
Papworth, Dr Robert Rintoul
Peterborough, Dr Sarah Treece
Royal Gwent, Dr Alina Ionescu
Royal Marsden, Dr Sanjay Popat
Sheffield, Mr John Edwards
South Tees, Dr Talal Mansey
South Tyneside, Dr Liz Fuller
Wolverhampton, Mr Ian Morgan
Wythenshawe, Dr Paul Taylor

Independent Trial Steering Committee (TSC):
Professor Tom Treasure (Past Chair, retired)
Dr Paul Beckett
Ms Carol Tan
Professor Fergus Gleeson
Dr Pauline Leonard (Interim Chair)
Professor Fergus Macbeth

Independent Data Monitoring Committee (DMC):
Professor Linda Sharples (Chair)
Professor Peter Goldstraw (Retired)
Dr Robin Rudd
Professor Mark Britton

Papworth Clinical Trials Unit:
Ms Jane Elliott
Dr Kim Giraud
Mr Phil Noyes
Dr Belinda Lees

Sponsor:
Royal Brompton and Harefield NHS Foundation Trust

Trial Management Group (TMG):
Dr Robert Rintoul
Mr John Edwards
Mr David Waller
Mr Apo Nakas
Professor Dean Fennell
Dr Sanjay Popat

Ms Liz Darlinson
Ms Alice Holt (Observer, CRUK)
Mr Patrik Petterrson (Observer, RBH)
Mr Winston Banya
Ms Jane Elliott
Dr Belinda Lees

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Background

- Surgery “works” for mesothelioma!

- So it is said…
  - …by eminent surgeons
  - …using data from personal cohort studies
  - …occasionally with non-randomised comparisons
  - …sometimes within meta-analyses of cohort studies

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Background

- We assume surgical results are representative of a (unselected) cohort of patients with mesothelioma and hence why good outcomes are reported:
  - on their own
  - compared with medical therapy
  - within systematic reviews (of cohort studies)

- What is the estimated proportion of patients who
  - have sufficiently early stage
  - able tolerate initial chemotherapy
  - remain fit
  - are willing to receive surgery

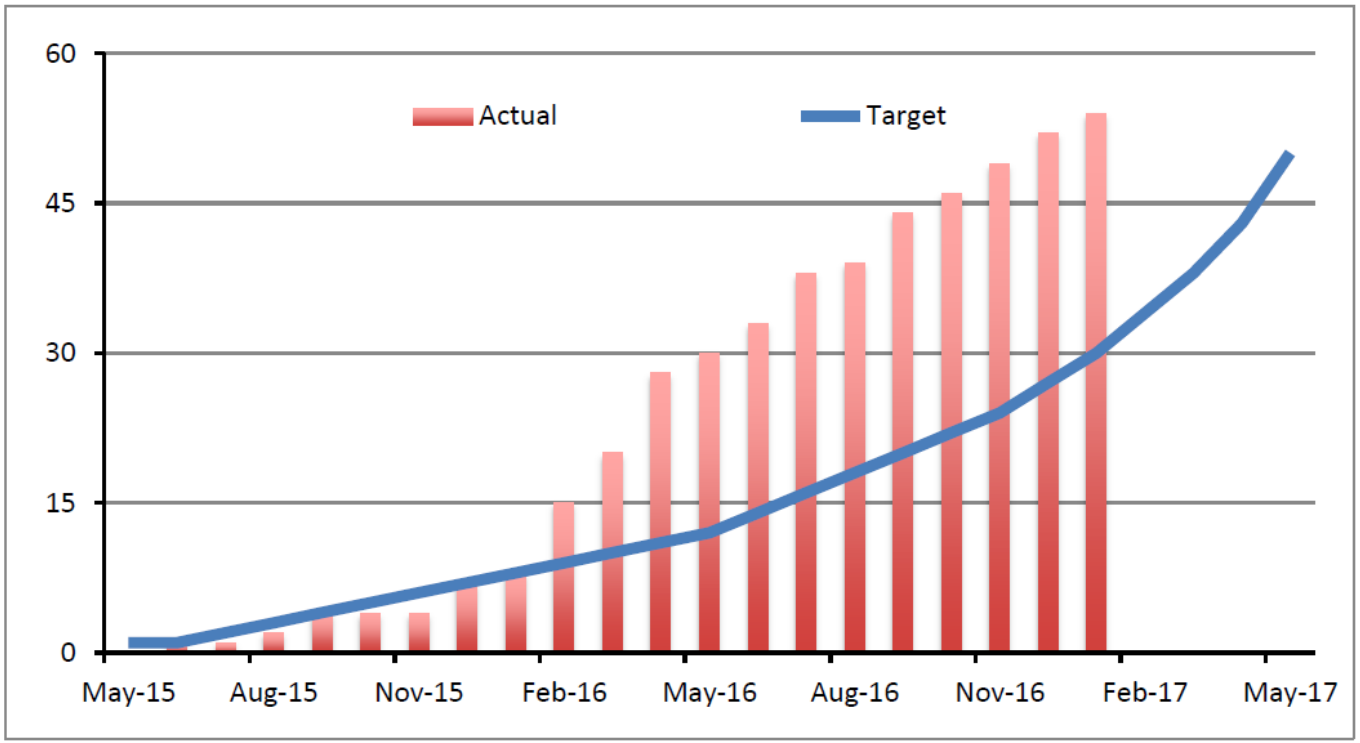
  … to make it for inclusion into the surgical cohort studies we see in published work?

MARS 2 pilot (a feasibility study)

- UK multicentre RCT study to determine if it is feasible to recruit into a randomised trial comparing
  - (extended) pleurectomy decortication versus
  - no (extended) pleurectomy decortication
- …as part of multimodality management of patients with malignant pleural mesothelioma

- Feasibility defined as the ability to
  - randomise 50 patients within the first 24 months from May 15 (Dec 16)
  - or the ability to recruit 25 patients in any 6 month period (Nov 16)

Accrual to 16 Jan 2017



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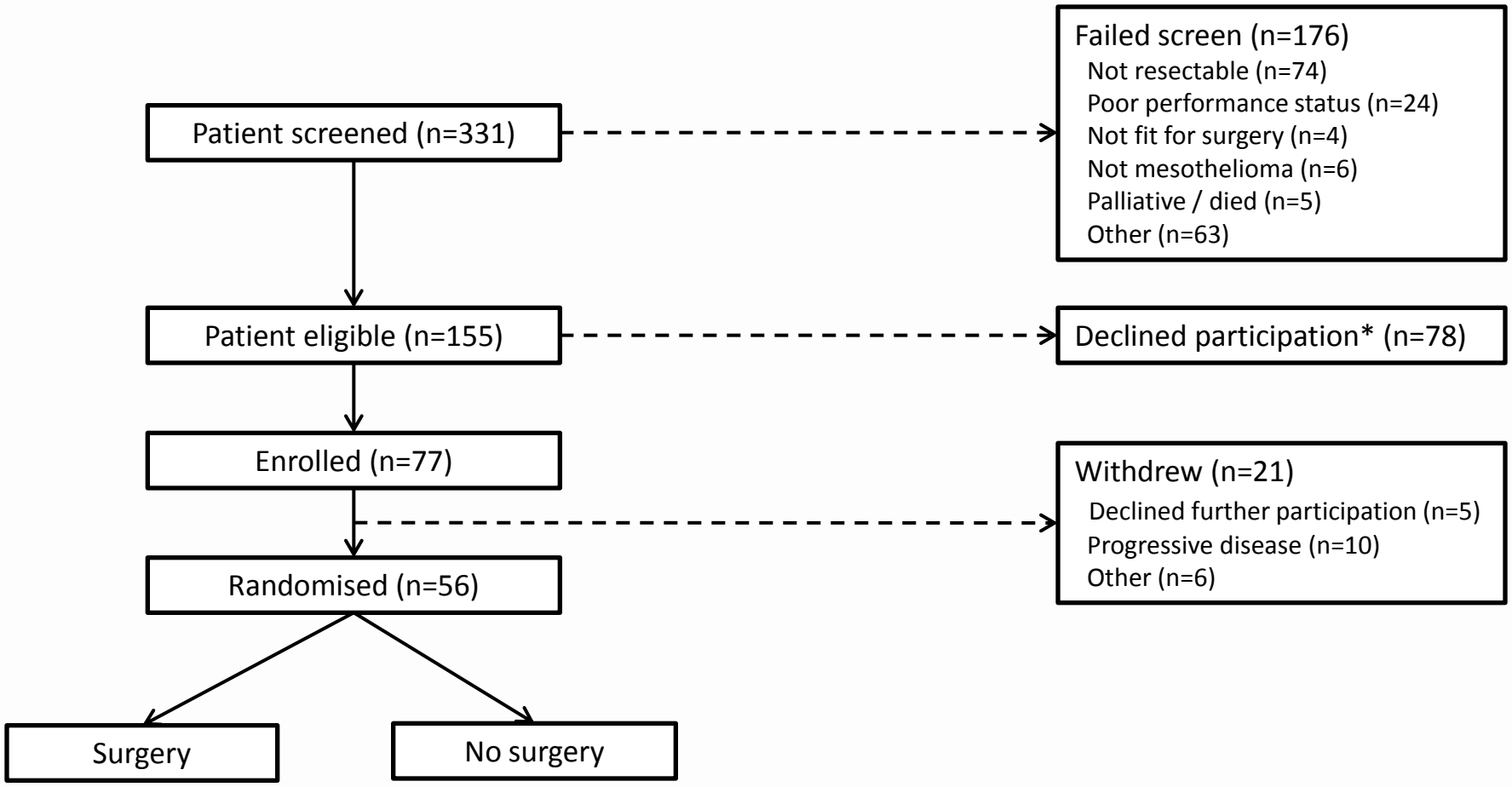
Flow diagram Dec 2016



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Inferences

- Half of patients screened for surgery were eligible 155/331 (47%)
- Final randomised pool was 56/331 (17%)

- After initial 2 cycles of chemotherapy 21/77 (27%) are unable to progress on the treatment pathway

- Best case scenario 34% of patients will receive surgery (73% of 47%)
- Worst case scenario 17% of patients will receive surgery

Summary

- Screening data from MARS 2 pilot provided a unique insight into the detailed selection process for surgery
- Exclusions occurred at multiple points in the pathway underscore the degree of surgical selection that takes place at each point in the patient care pathway
- Clear extent of selection bias underscores the importance of evaluating the efficacy of surgery within the context of RCT (MARS 2 phase III) to derive robust and meaningful estimates of any treatment effect on overall survival

Vanaf heden open in Rotterdam:

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EORTC Lung Cancer Group

EORTC randomized phase II study of pleurectomy/ decortication (P/D) preceded or followed by chemotherapy in patients with early stage malignant pleural mesothelioma

EORTC protocol 1205-LCG

(NCT02436733)

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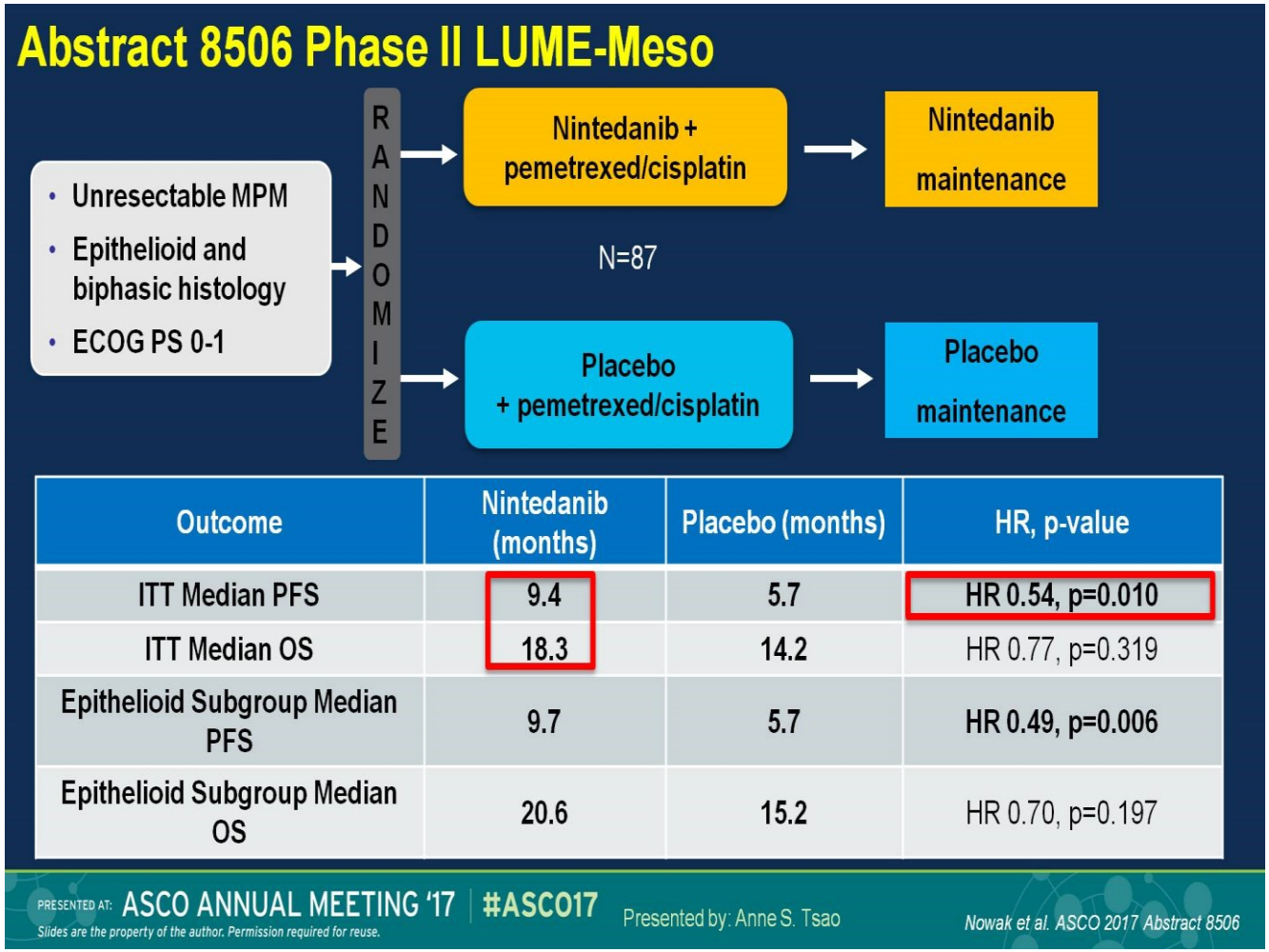
Protocol summary

Title of the Study	EORTC randomized phase II study of pleurectomy/decortication (P/D) preceded or followed by chemotherapy in patients with early stage malignant pleural mesothelioma
Objective(s)	To investigate the feasibility of immediate P/D followed by cisplatin/pemetrexed chemotherapy or deferred P/D after cisplatin/pemetrexed chemotherapy in patients with early stage malignant pleural mesothelioma.
Methodology	This is a multicenter, randomized, 1:1, non-comparative phase II trial. Patients with early stage MPM will be randomized between **ARM A**: immediate P/D followed by three cycles of chemotherapy (pemetrexed 500mg/m^2 and cisplatin 75 mg/m^2, both drugs given on day 1, every three weeks) for non-progressing patients **ARM B**: three cycles of chemotherapy (same regimen) followed by P/D, for non-progressing patients. Four weeks (±2 weeks) will be allowed between the baseline tumor assessment and the start of treatment (surgery or chemotherapy). Randomization should be done as soon as possible after baseline tumor assessment.

Update LUME- Meso fase II trial:



Outcome	Nintedanib (months)	Placebo (months)	HR, p-value
ITT Median PFS	9.4	5.7	**HR 0.54, p=0.010**
ITT Median OS	18.3	14.2	HR 0.77, p=0.319
Epithelioid Subgroup Median PFS	9.7	5.7	**HR 0.49, p=0.006**
Epithelioid Subgroup Median OS	20.6	15.2	HR 0.70, p=0.197

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Er lijkt plaats voor Angiogenese bij MPM:

Efficacy Comparison of Anti-angiogenics + cisplatin-pemetrexed

Study Agent + Cisplatin-Pemetrexed Arm	N	histology	ORR Modified RECIST	PFS (months) Modified RECIST	OS (months)
+ Nintedanib[1]	87	0% sarcomatoid 11% biphasic	**57%**	9.4 HR 0.54, p=0.01	18.3 HR 0.78, p=0.4132
+ Cediranib[2]	20	15% sarcomatoid or biphasic	**63%**	8.6 (95% CI: 6.1-10.9)	16.2 (95% CI: 10.5-28.7)
+ Bevacizumab[3]	448	20% sarcomatoid or biphasic	**26.9%*[5]**	9.2 HR 0.61, *P* < .0001	18.8 HR 0.77, *P* =0.0167
Historical Comparison					
Cisplatin-pemetrexed alone[4]	226/456	8% sarcomatoid 16.4% biphasic	41.3%	5.7 **Time To PD** HR 0.68, p=0.001	12.1 HR 0.77, p=0.02

*6 month ORR from the phase III by investigator report only (1/3 of the cases did not have reported data); cisplatin-pemetrexed arm was 25.8%

[1]Nowak et al. ASCO 2017 Abstract 8506, [2]Tsao et al. JTO in press, [3]Zalcman et al. Lancet. 387 (10026): 1405-1414, April 2016, [4]Vogelzang et al. JCO 21: 2636-2644, 2003; [5]Personal Communication IFCT for the MAPS I study May 2017

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by: Anne S. Tsao

MA 19.03: Nintedanib + Pemetrexed/Cisplatin in Malignant Pleural Mesothelioma (MPM): Phase II Biomarker Data from the LUME-Meso Study – Nowak A, et al

- **Study objective**
  - To investigate the prognostic potential of plasma-derived angiogenic factors and genomic markers in epithelioid population of the LUME-Meso trial
- **Methods**
  - Blood samples from baseline, cycle 3 and PD were analysed for 58 angiogenic factors and SNPs in genes for mesothelin
- **Key results**
  - There was no clear association between biomarkers and treatment benefit
  - A potential signal for benefit was seen in OS for patients with low plasma endoglin and major homozygous VEGFR3 genotypes
- **Conclusions**
  - There was no association between biomarkers and treatment benefit
  - These analyses were limited by small sample size and will be evaluated further in a phase 3 study

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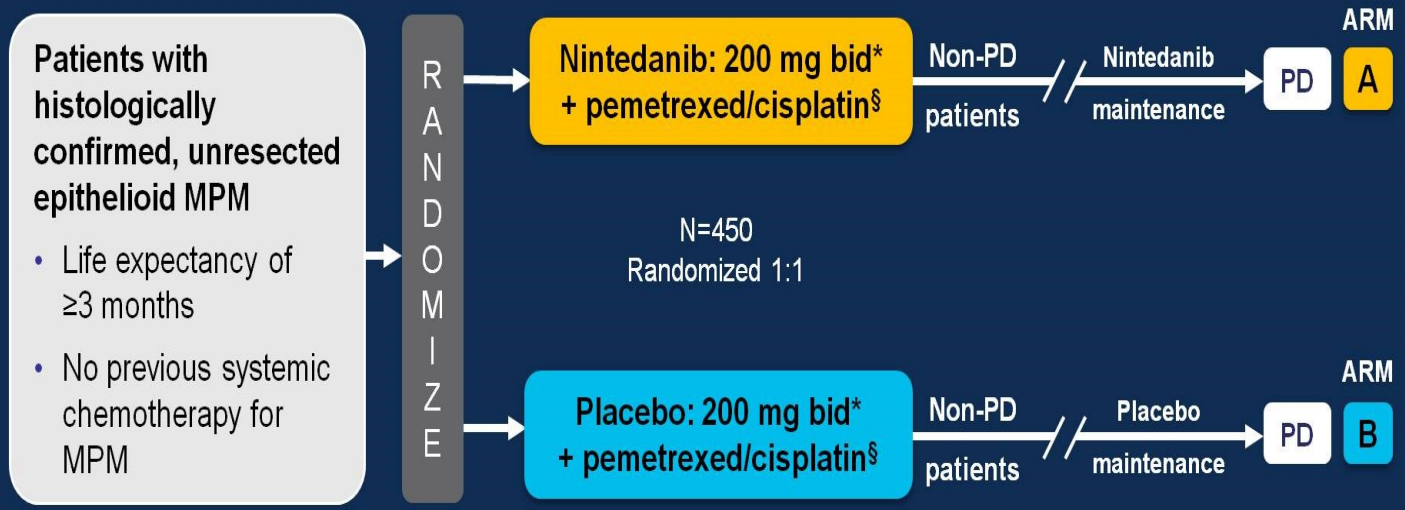
SNP, single-nucleotide polymorphism

Nowak A et al. J Thorac Oncol 2017;12(suppl):Abstr MA 19.03

Ongoing LUME-Meso Phase III: actively recruiting



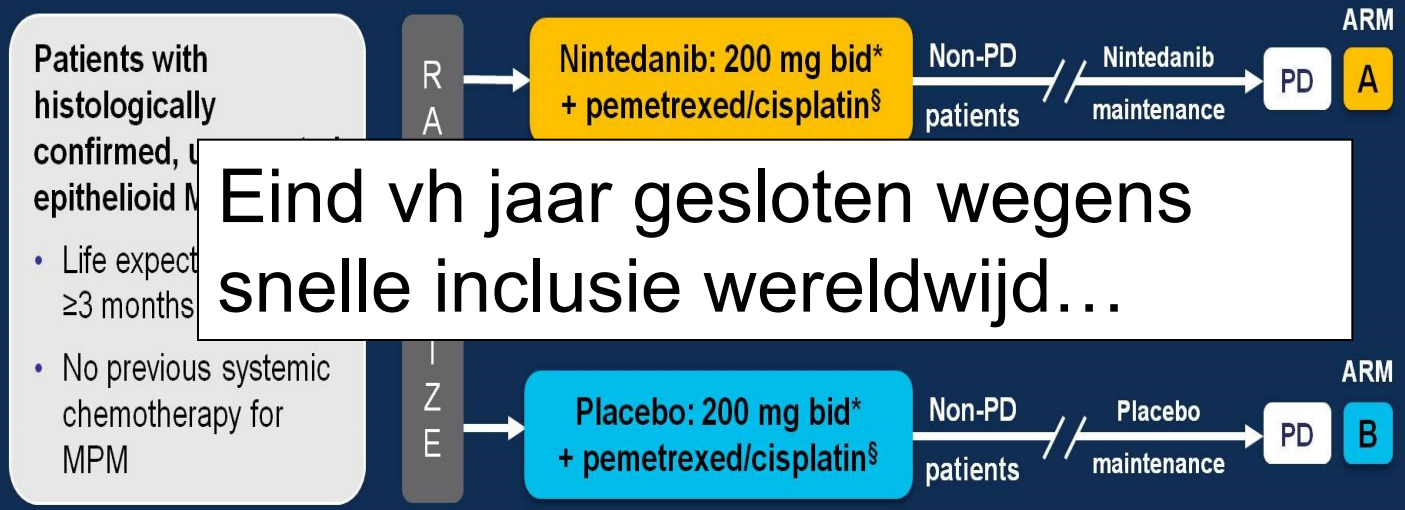
Clinical trial identifier: **NCT01907100**

Selected endpoints

Primary endpoint: PFS¶
Key secondary endpoint: OS

*On Days 2–21; §500 mg/m²/75 mg/m² i.v., every 21 days. Maximum treatment duration: 6 cycles.
¶By investigator assessment according to mRECIST.

Ongoing LUME-Meso Phase III: actively recruiting



Eind vh jaar gesloten wegens snelle inclusie wereldwijd…

Clinical trial identifier: **NCT01907100**

Selected endpoints

Primary endpoint: PFS¶
Key secondary endpoint: OS

*On Days 2–21; §500 mg/m²/75 mg/m² i.v., every 21 days. Maximum treatment duration: 6 cycles.
¶By investigator assessment according to mRECIST.

SCLC

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Slotdia Post ASCO / ESMO / WCLC 2016:

Conclusions

- Relatively minimal advances in therapeutic options for SCLC in two decades
- Genomic landscape of SCLC reveals relatively few therapeutic targets
- Recent data from immunotherapy studies provide room for optimism

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PD-L1 expression in SCLC

J Thorac Oncol. 2017 January ; 12(1): 110–120. doi:10.1016/j.jtho.2016.09.002.

PD-L1 Expression by Two Complementary Diagnostic Assays and mRNA In Situ Hybridization in Small Cell Lung Cancer

		PD-L1 IHC (Protein, TPS)					
SCLC Cohort	Antibody	<1% (n)	≥1%–<5% (n)	≥5%–<10% (n)	≥10%–<50% (n)	≥50% (n)	PD-L1 mRNA ISH (mRNA) RNA Score >2 (n)
LD-SCLC (n = 98)	SP142 (n = 95)	85.3% (81)	11.6% (11)	0% (0)	2.1% (2)	1.1% (1)	15.5% (15 of 97)
	Dako 28-8 (n = 67)	80.6% (54)	10.4% (7)	3.0% (2)	3.0% (2)	3.0% (2)	
ED-SCLC (n = 96)	Dako 28-8 (n = 87)	83.9% (73)	12.6% (11)	0% (0)	1.1% (1)	1.1% (1)	ND

- The overall prevalence of PD-L1 protein expression in tumor cells was 16.5%.
- The prevalence of PD-L1 in SCLC is lower than that published for NSCLC.

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1. Yu et al. Journal of Thoracic Oncology 2017.

ASCO 2017

Phase II study of maintenance pembrolizumab in extensive stage small cell lung cancer patients

Shirish M. Gadgeel[1†], Jaclyn Ventimiglia[1], Gregory P. Kalemkerian[2], Mary J. Fidler[3], Wei Chen[1], Ammar Sukari[1], Balazs Halmos[4], Julie Boerner[1], Antoinette Wozniak[1], Cathy Galasso[1], Nathan A. Pennell[5]

1. Karmanos Cancer Institute/Wayne State University, Detroit, MI; 2. University of Michigan, sh University Medical Center, Chicago, IL; 4. Montefiore Einstein Center nx, NY; 5. Cleveland Clinic, Cleveland, OH.

sity of Michigan, Ann Arbor, MI

Study Design

KEY ELIGIBILITY

- Extensive-stage SCLC
- CR, PR or SD following 4-6 cycles of EP/EC
- Re-staging scans within 3 weeks of Pembrolizumab
- ECOG PS 0–1
- Allowed treated brain metastases and PCI

→

CORRELATIVE STUDIES

- Tumor tissue for PD-L1 (Dako 22C3)
- Blood for CTC before cycles 1, 2 & 3 (Veridex)

→

THERAPY

- Pembrolizumab 200 mg IV every 3 weeks
- Start Pembro within 8 weeks of last chemo
- Disease assessment every 2 cycles

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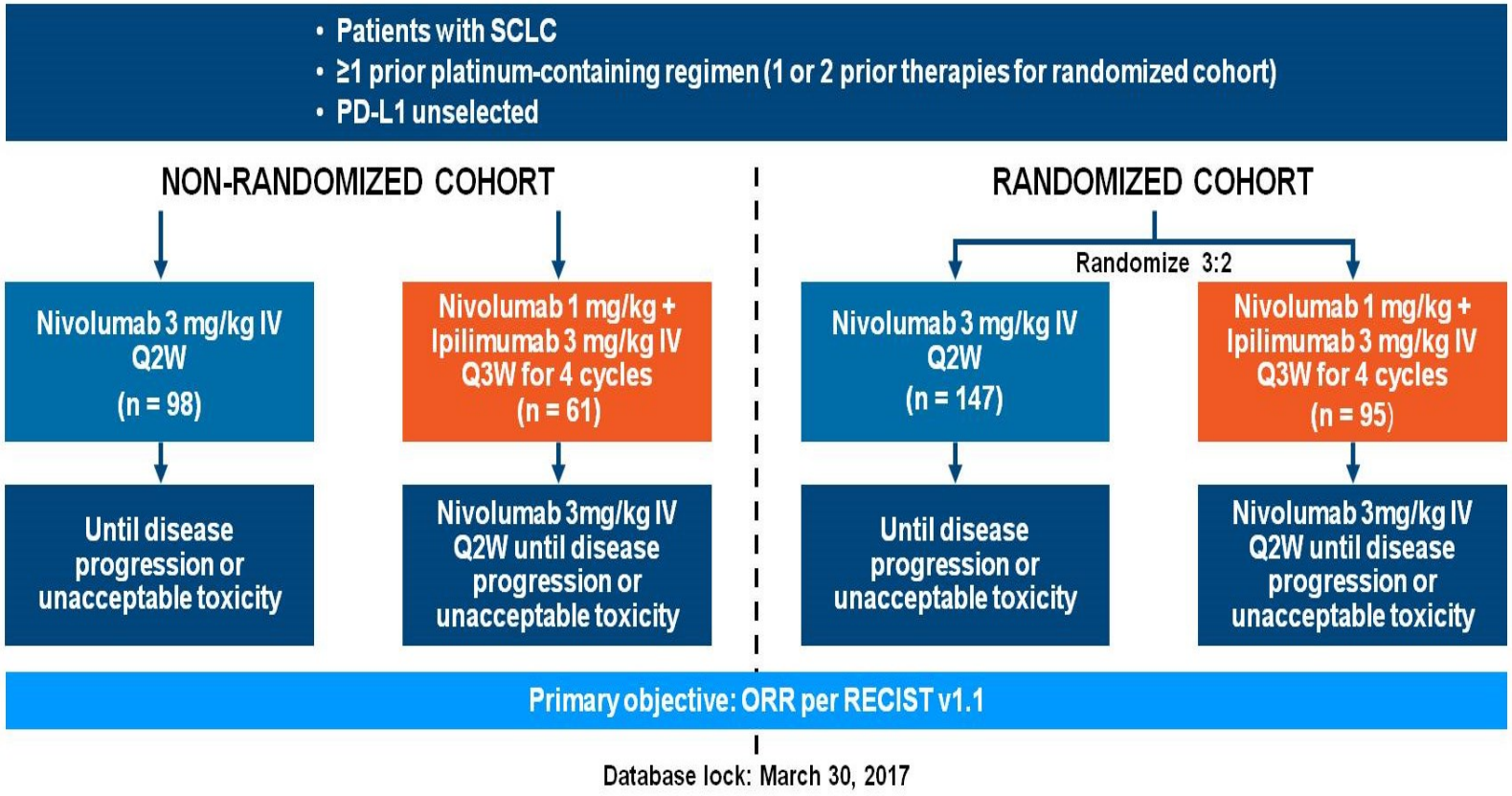
Pembrolizumab maintenance

- Niet effectief
- PD-L1 (stroma interface) predictief?
- Hoe verder: CTLA-4 remmer toevoegen?

CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC

Phase I/II CheckMate 032 Study Design



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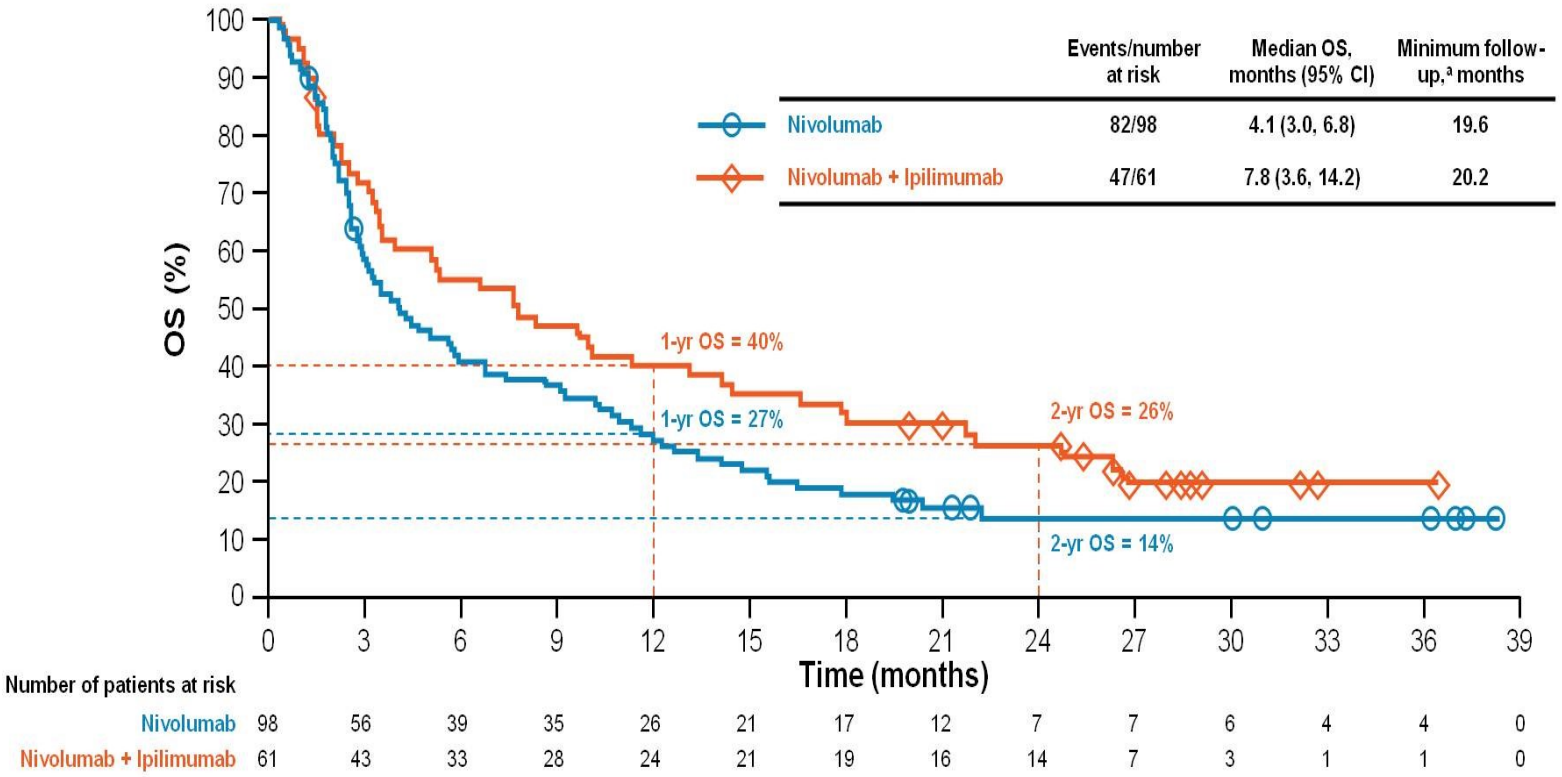
Matthew D , et al. ASCO 2017 Abstract 8503

CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
OS – Non-Randomized Cohort



	Events/number at risk	Median OS, months (95% CI)	Minimum follow-up,[a] months
Nivolumab	82/98	4.1 (3.0, 6.8)	19.6
Nivolumab + Ipilimumab	47/61	7.8 (3.6, 14.2)	20.2

[a]Between first dose and database lock; follow-up shorter for patients who died prior to database lock

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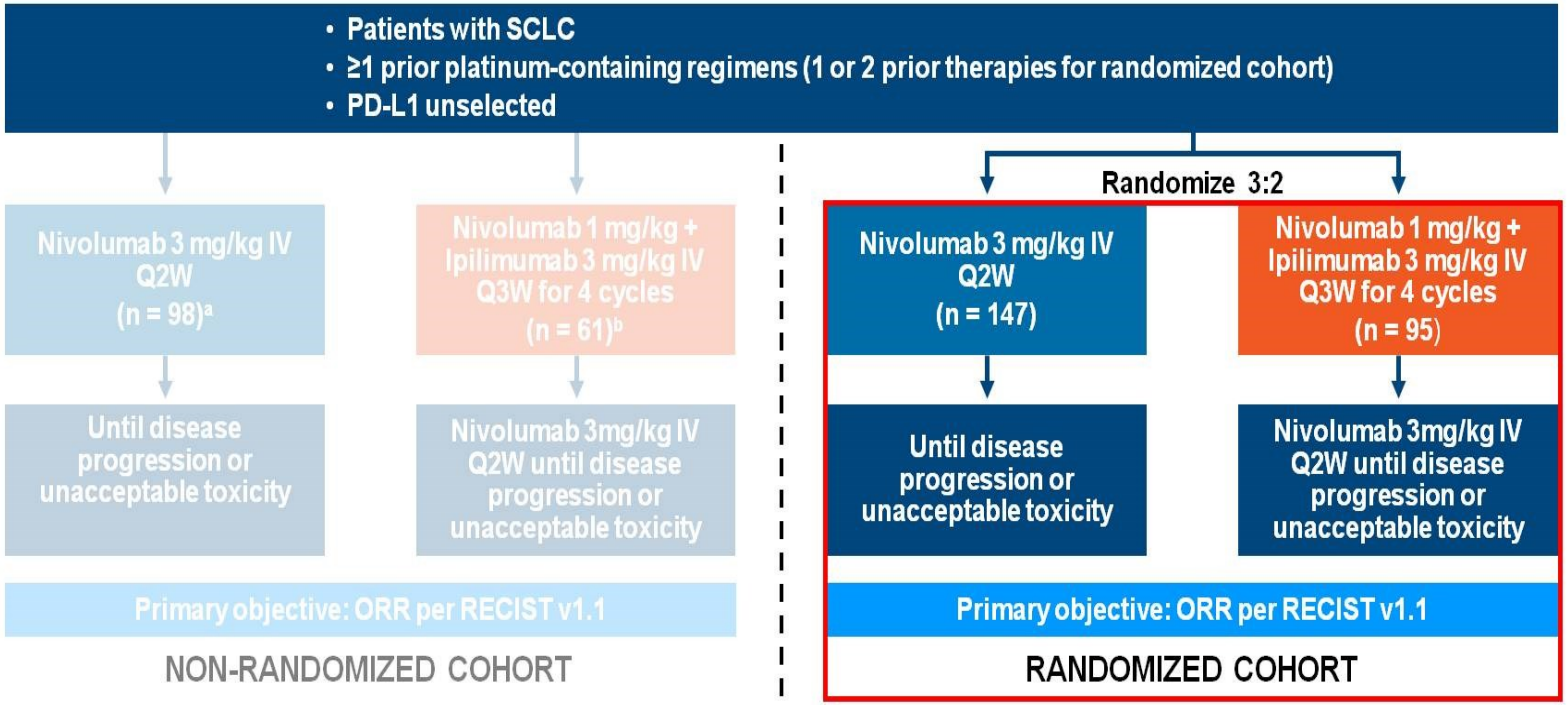
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
Phase 1/2 CheckMate 032 Study Design – Randomized Cohort

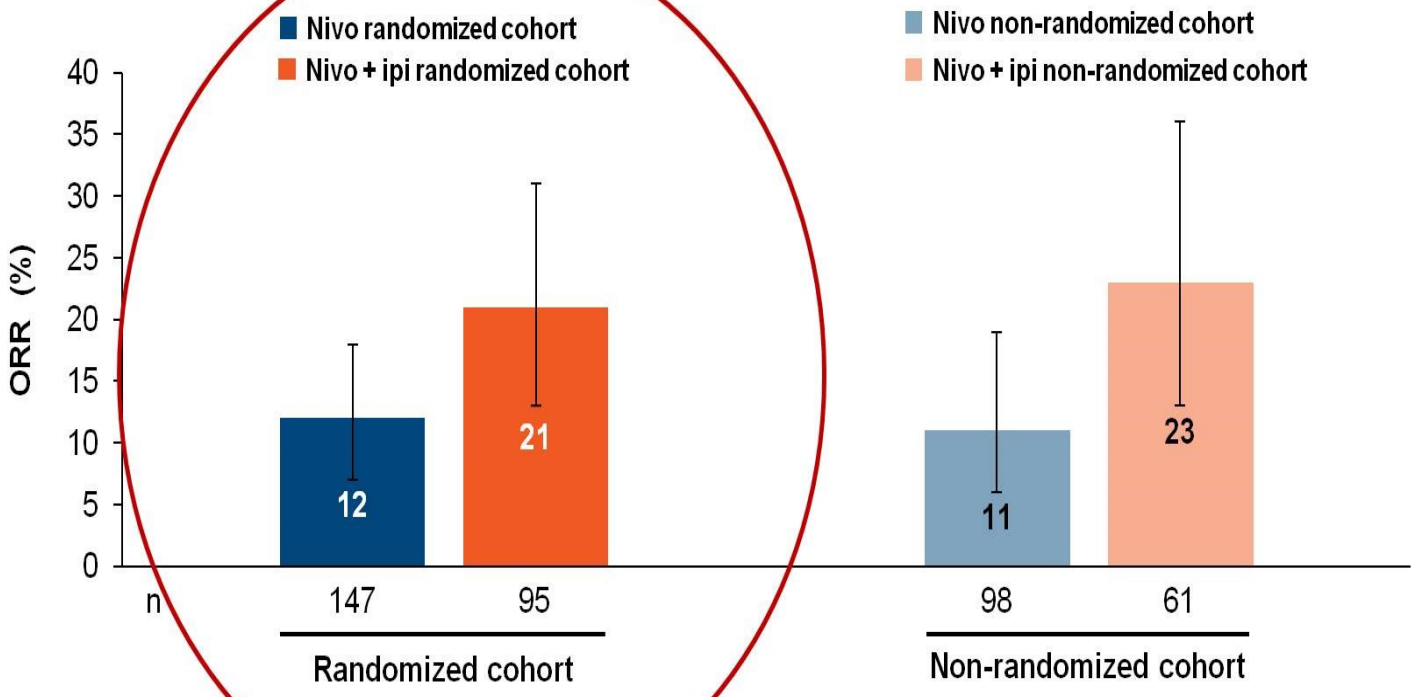


Database lock: March 30, 2017

- An interim descriptive analysis of the randomized cohort is presented
  - Median follow-up: nivolumab, 10.8 mo; nivolumab + ipilimumab, 11.2 mo

[a]Median follow-up 23.3 mo; [b]Median follow-up 28.6 mo
Follow-up was calculated as time from first dose to database lock

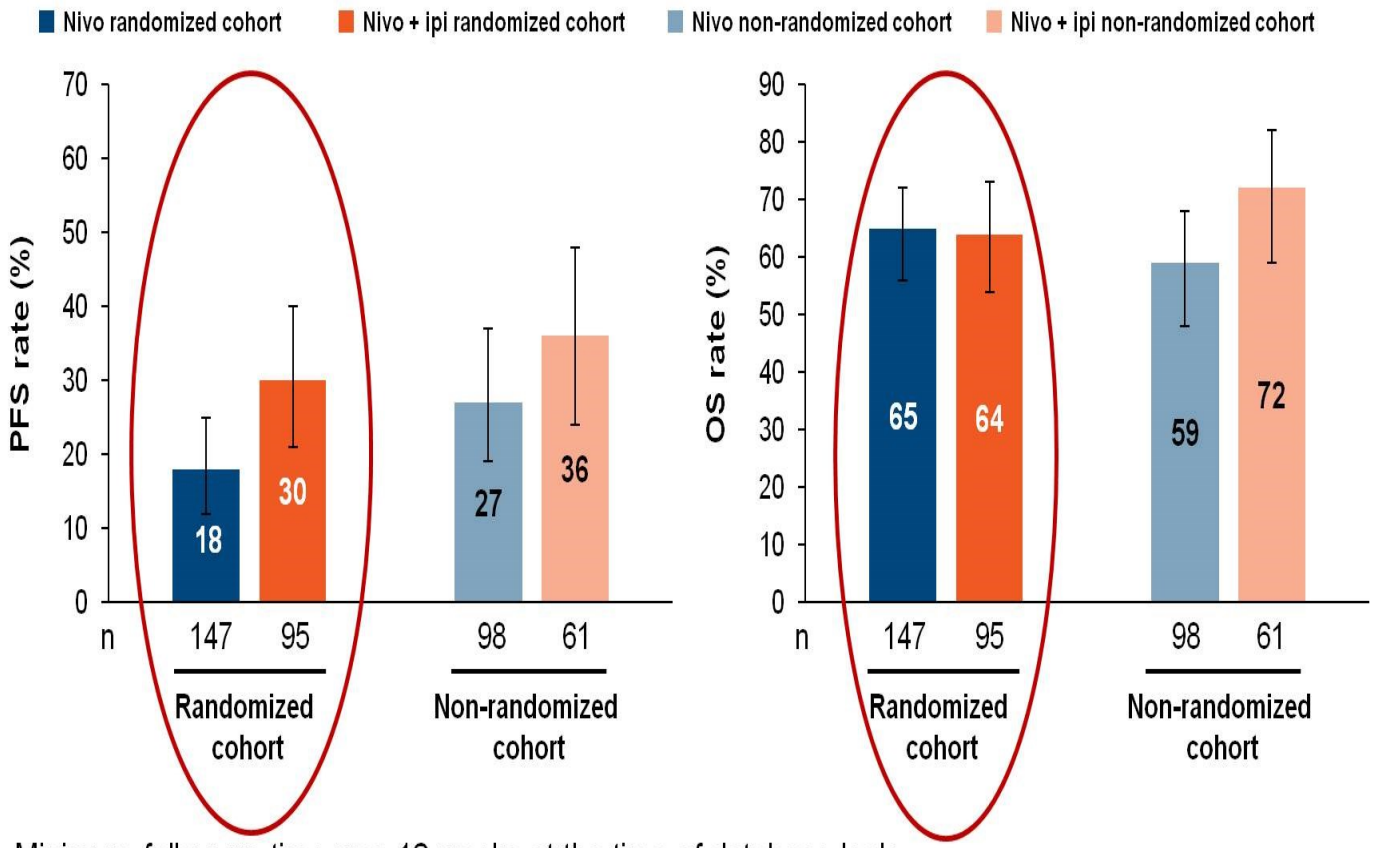
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
Summary of Response per BICR



- CRs were achieved in 2 patients in the randomized cohort (nivolumab, n = 1; nivolumab + ipilimumab, n = 1)
- Median time to response in the randomized cohort was comparable to that in the non-randomized cohort
  - Nivolumab, 1.5 mo; nivolumab + ipilimumab, 1.4 mo

Error bars indicate 95% CIs; 95% CIs are as follows – nivo (randomized): 7, 18; nivo + ipi (randomized): 13, 31; nivo (non-randomized): 6, 19; nivo + ipi (non-randomized): 13, 36
CR = complete response; ipi = ipilimumab; nivo = nivolumab

CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
3-month PFS[a] and OS Rates



- Minimum follow-up time was 12 weeks at the time of database lock

Error bars indicate 95% CIs; [a]Per BICR; PFS = progression-free survival

CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC Summary of Safety – Pooled Cohorts

	Nivolumab (n = 245)		Nivolumab + Ipilimumab (n = 156)	
	Any grade, %	Grade 3–4, %	Any grade, %	Grade 3–4, %
Any TRAEs	**55**	**12**	**73**	**37**
TRAEs leading to discontinuation	**3**	**2**	**13**	**10**
Select TRAEs by category				
Skin	16	<1	36	6
Endocrine	8	0	21	3
Hepatic	6	2	12	6
Gastrointestinal	5	0	24	8
Hypersensitivity/infusion reaction	5	0	1	0
Pulmonary	3	2	4	3
Renal	1	<1	1	0
Grade 3–4 select TRAEs that resolved, %[a]	45		78	

- Median time to resolution of grade 3–4 select TRAEs ranged from 1.8 wk (gastrointestinal events) to 16.3 wk (hepatic events) in the nivolumab + ipilimumab arm and from 3.4 wk (pulmonary events) to not reached (renal and hepatic events) in the nivolumab arm
- There were a total of 5 treatment-related deaths[b]
  - 4 with nivolumab + ipilimumab (due to myasthenia gravis, pneumonitis, seizures/encephalitis, and autoimmune hepatitis)[c]
  - 1 with nivolumab (due to pneumonitis)

TRAE = treatment-related adverse event; [a]Percentage of total number of grade 3-4 select TRAEs across categories (nivo + ipi, n = 40; nivo, n = 11); [b]In addition, there was one death in the nivo + ipi arm for which both disease progression and colitis were felt to be contributing factors; [c]A previously reported death due to renal failure was subsequently determined to not be related to treatment

NCCN Guideline for Nivolumab + Ipilimumab

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY* (1 of 3)

Systemic therapy as primary or adjuvant therapy:

- Limited stage (maximum of 4–6 cycles):
  - Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[1]
  - Cisplatin 80 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]
  - Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[3]
  - During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
  - The use of myeloid growth factors is not recommended during concurrent systemic therapy plus radiotherapy (category 1 for not using GM-CSF).[4]

- Extensive stage (maximum of 4–6 cycles):†
  - Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[5]
  - Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[6]
  - Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[7]
  - Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[8]
  - Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[9]
  - Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[10]
  - Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[11]

Subsequent systemic therapy:‡

- Clinical trial preferred.

- Relapse ≤6 mo, PS 0-2:
  - Topotecan PO or IV[12-14]
  - Irinotecan[15]
  - Paclitaxel[16,17]
  - Docetaxel[18]
  - Temozolomide[19,20]
  - Nivolumab ± ipilimumab[21,22]
  - Vinorelbine[23,24]
  - Oral etoposide[25,26]
  - Gemcitabine[27,28]
  - Cyclophosphamide/doxorubicin/vincristine (CAV)[12]
  - Bendamustine (category 2B)[29]

- Relapse >6 mo: original regimen[30,31]

Consider dose reduction or growth factor support for patients with PS 2

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Ongoing Checkpoint inhibitor studies in 2L+

Pembrolizumab	Atezolizumab	Durvalumab
• NCT02963090 (ph2): pembro vs Topotecan • MISP-MK3475 (ph2): plitacxel + pembro → pembro as maintenance	• NCT03059667 (ph2): atezo+chemo vs chemo (topotecan or EC rechallenge)	• NCT02701400(ph2): RT+treme+durva vs treme + durva • BALTIC/NCT02937818(ph2): Durva+Treme vs AZD1775 + carboplatin • MEDIOLA (ph1/2): Olaparib + Durva

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Clinicaltrial.gov

Ongoing checkpoint inhibitor trials in 1L setting

- NCT02402920 (ph1): pembro+RT
- KEYNOTE-011 (ph1): pembro + EC
- REACTION (ph2): EC ± pembro
- KEYNOTE-064 (ph3): pembro + EP vs Placebo + EP

- NCT02748889 (ph2): Atezo +chemo vs chemo
- NCT03041311 (ph2): trilacilcib (CDK 4/6 inhibitor) + EC + Atezo vs Placebo +EC + Atezo
- Impower 133

- CASPIAN (ph3): Durva+ Treme + EP vs Durva + EP vs EP

* EC=cisplatin/carboplatin + etoposide

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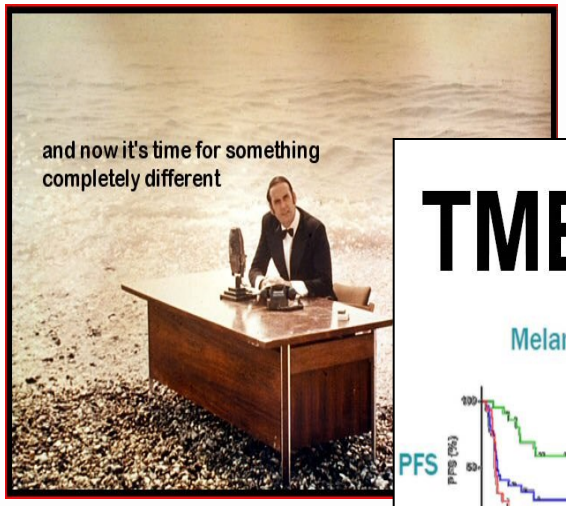
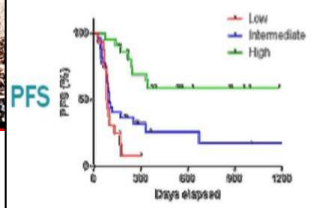
Clinicaltrial.gov



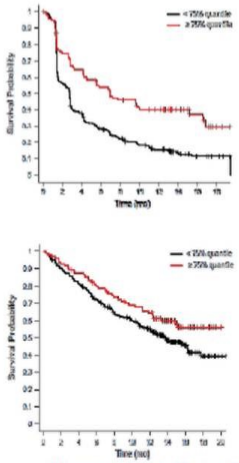
TMB is predictive of benefit to IO

Melanoma (n = 65)



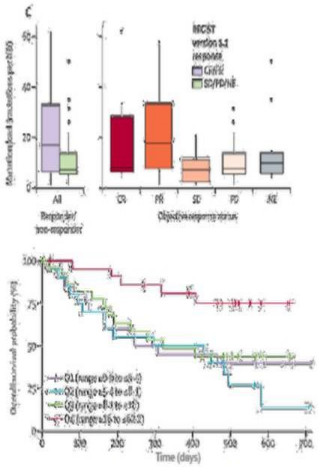
DB Johnson et al., Cancer Immunol Research, 2017

NSCLC (n = 464)



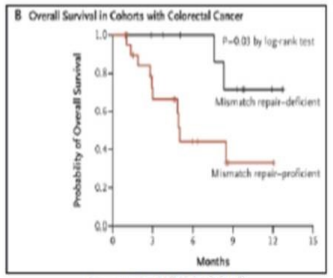
M Kowanetz et al, Annals of Oncology, 2017

Urothelial carcinoma (n = 94)



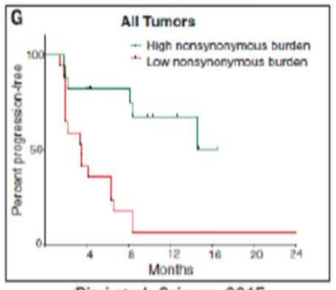
Balar AV et al. Lancet, 2017

MSI-High Colorectal Cancer



Le et al., NEJM, 2015

High TMB NSCLC



Rizvi et al., Science, 2015

- Non-synonymous missense mutations create neoepitopes for T cell recognition
- TMB correlates with degree of DNA damage (UV exposure, cigarette exposure)

Stephen P. #SY40-02 AACR 2017

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IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan

OA 07.03a: Impact of Tumor Mutation Burden on the Efficacy of Nivolumab or Nivolumab + Ipilimumab in Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 032 – Antonio S, et al

- **Study objective**
  - To determine whether high tumour mutation burden (TMB) is associated with greater benefit for treatment with nivolumab with or without ipilimumab in patients with SCLC in the CheckMate 032

- **Methods**
  - Patients from CheckMate 032 with paired tumour/whole blood samples and TMB evaluable were included (133 from the nivolumab arm and 78 from the nivolumab + ipilimumab arm)
  - Whole exome sequencing was used to determine TMB which was calculated as the total number of missense mutations in the tumour
  - Patients were divided according to three TMB tertiles based on total number of missense mutations: low 0 to <143; medium 143 to 247; and high ≥248

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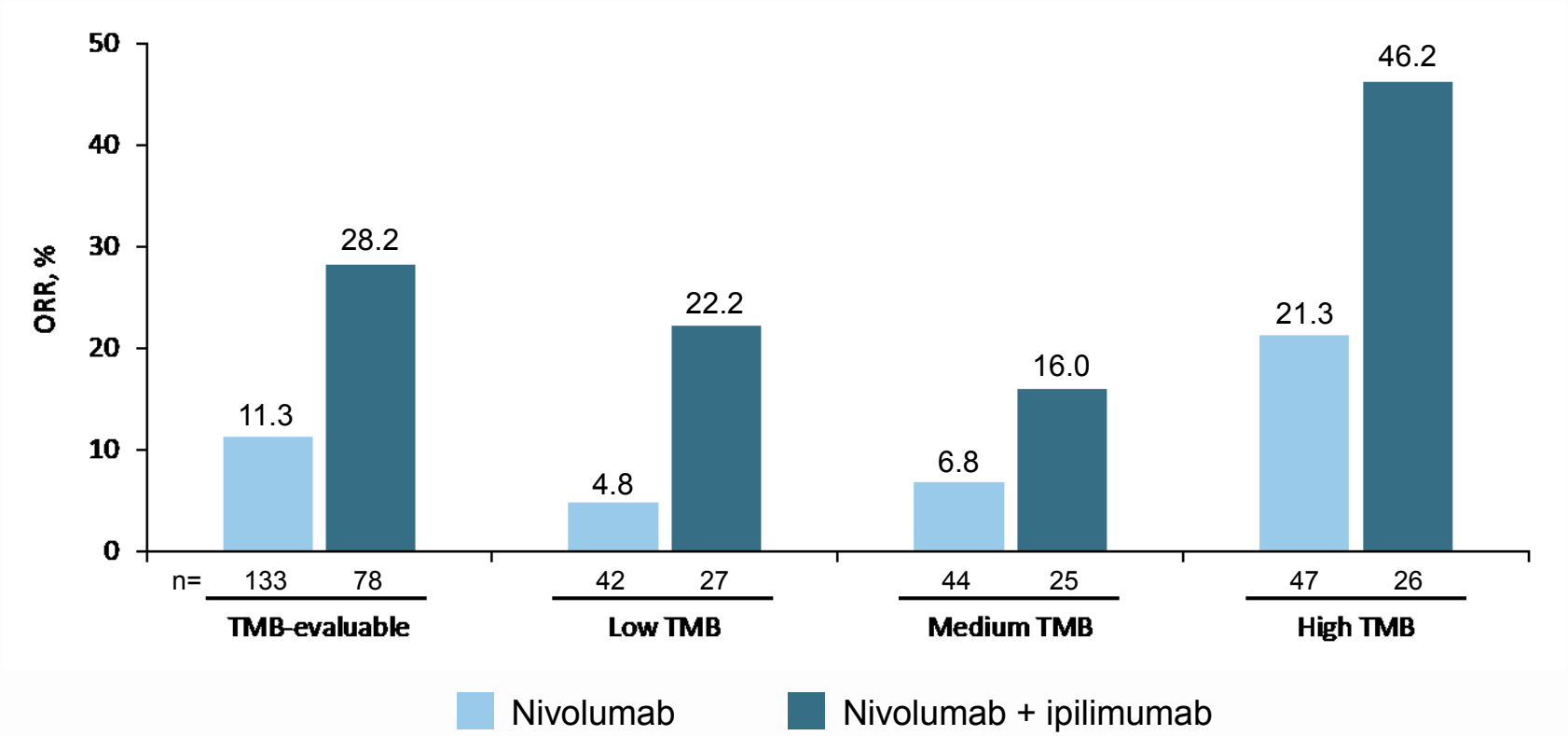
Antonio S et al. J Thorac Oncol 2017;12(suppl):Abstr OA 07.03a

OA 07.03a: Impact of Tumor Mutation Burden on the Efficacy of Nivolumab or Nivolumab + Ipilimumab in Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 032 – Antonio S, et al

ORR by TMB subgroup



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Antonio S et al. J Thorac Oncol 2017;12(suppl):Abstr OA 07.03a

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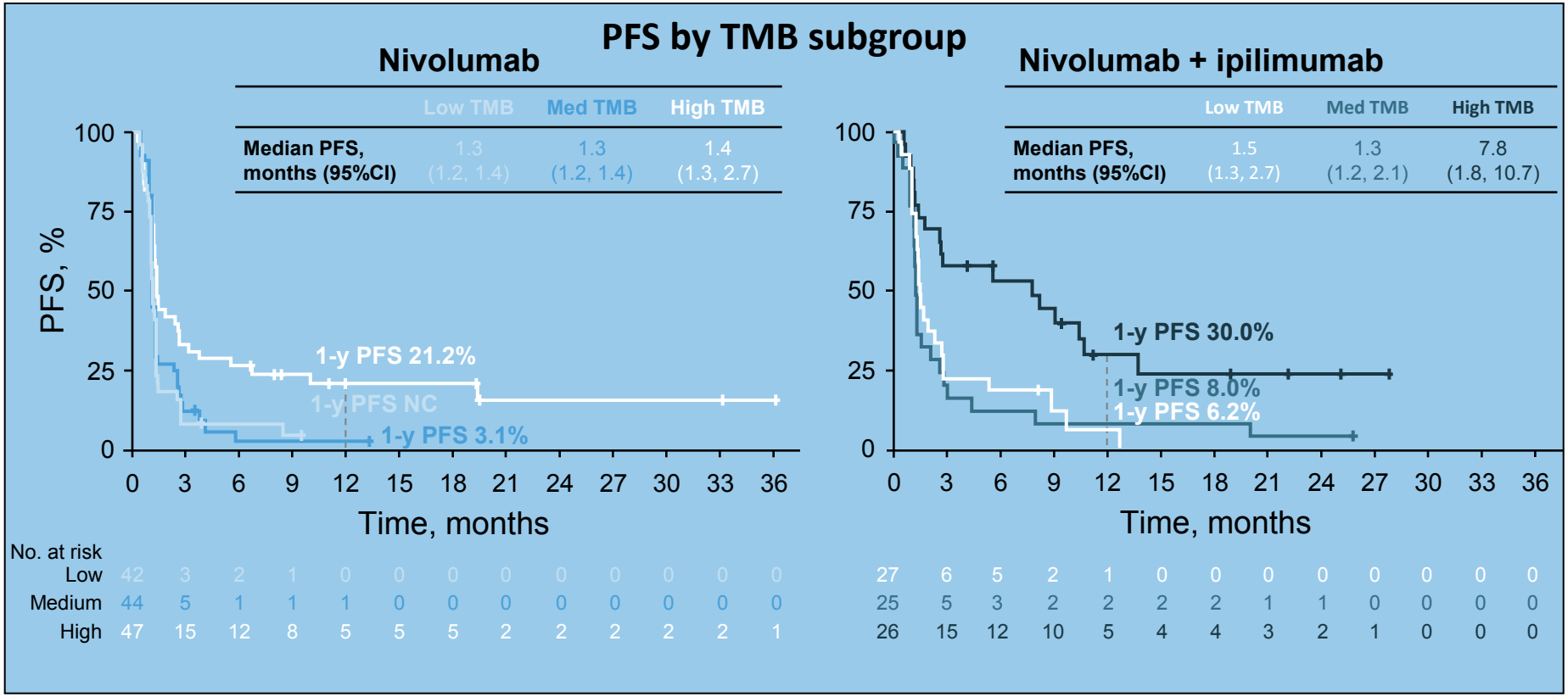

NC, not calculable

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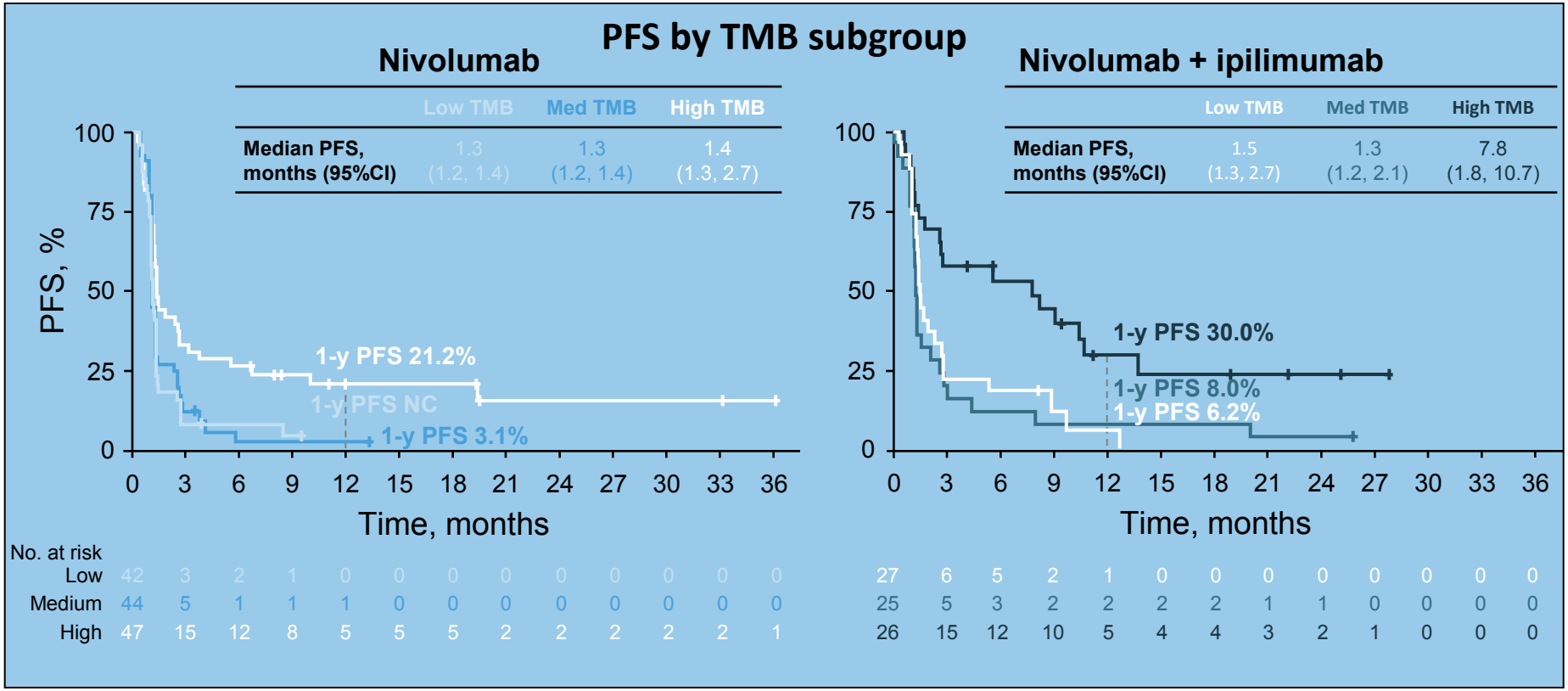
Antonio S et al. J Thorac Oncol 2017;12(suppl):Abstr OA 07.03a

OA 07.03a: Impact of Tumor Mutation Burden on the Efficacy of Nivolumab or Nivolumab + Ipilimumab in Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 032 – Antonio S, et al



NC, not calculable

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Antonio S et al. J Thorac Oncol 2017;12(suppl):Abstr OA 07.03a

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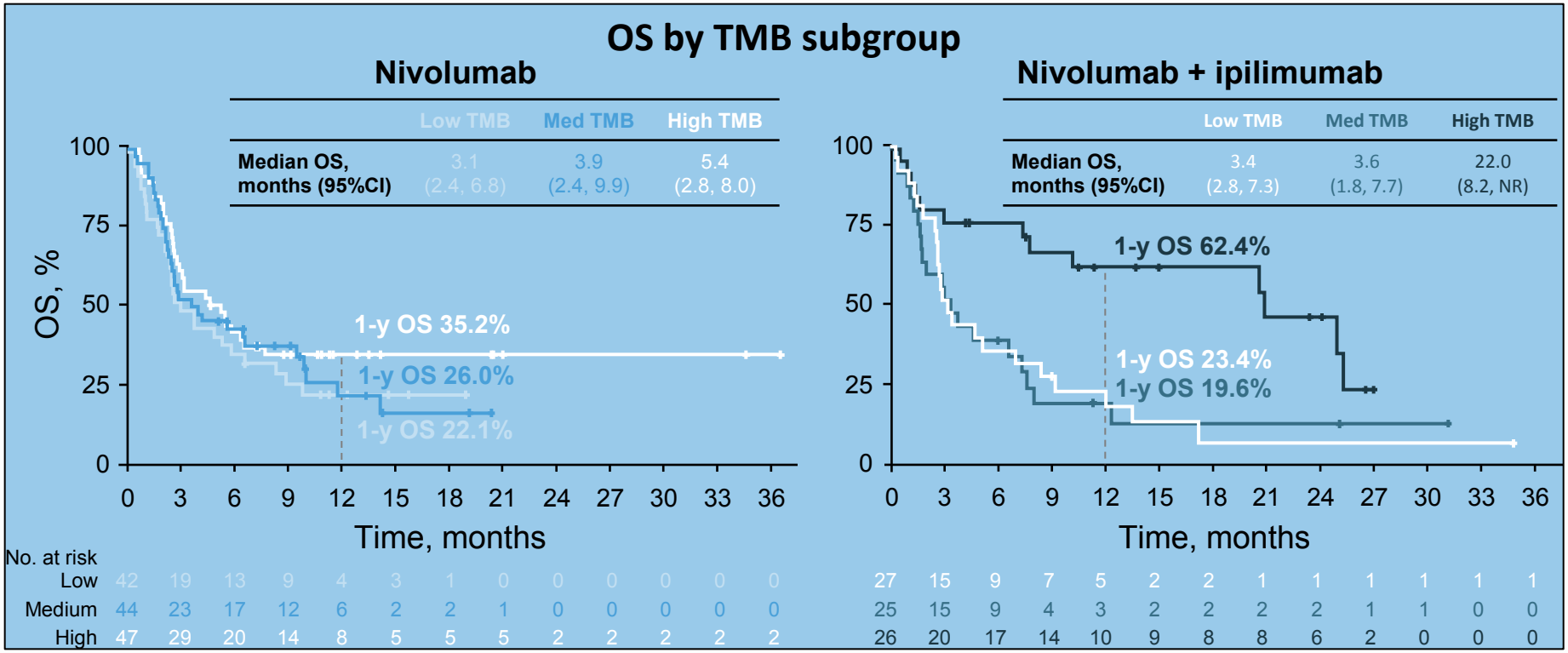

- **Conclusions**
  - Nivolumab with or without ipilimumab demonstrated improved outcomes in the high vs. low or medium TMB groups and the combination provided greater clinical benefit vs. nivolumab alone in the high TMB subgroup
  - Further investigation and optimisation of TMB as a predictive biomarker is warranted

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Antonio S et al. J Thorac Oncol 2017;12(suppl):Abstr OA 07.03a

Locaal:

ETOP/IFCT 4-12 STIMULI

A randomised open-label phase II trial of consolidation with nivolumab and ipilimumab in limited-stage SCLC after chemo-radiotherapy

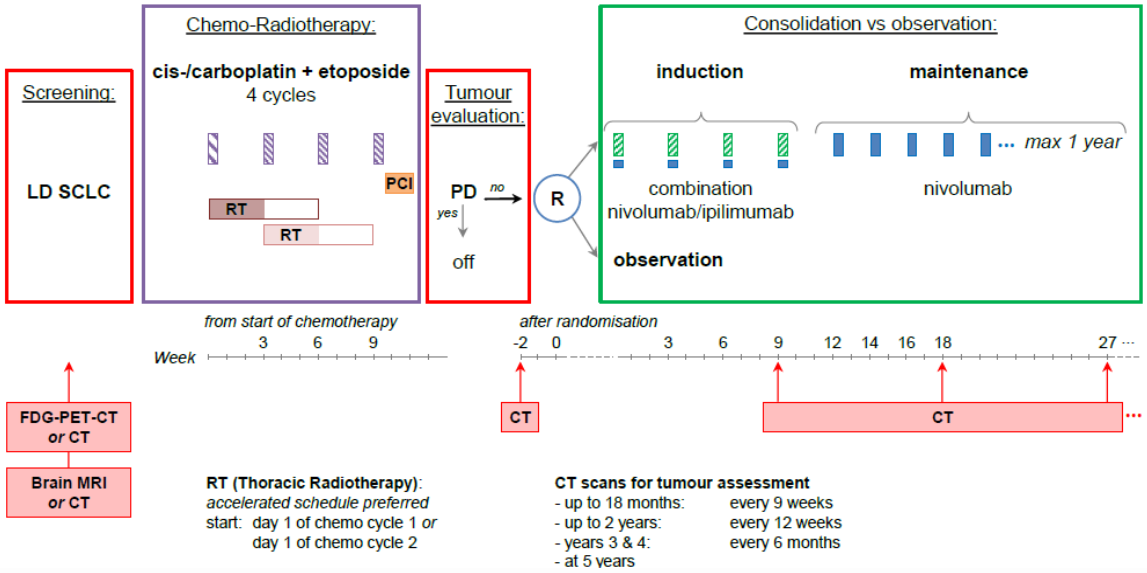
Small cell lung carcinoma Trial with nivolumab and IpiliMUmab in LImited disease

Sponsor: European Thoracic Oncology Platform (ETOP)

Pharma Partner: Bristol-Myers Squibb

Population: Radically treated limited-stage SCLC following completion of thoracic radiotherapy concomitant to chemotherapy and PCI

Design: Open-label, randomised, two-arm, phase II international multi-centre clinical trial with early interim analysis for safety



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Tijd voor Pauze - voorgerecht

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