Casus

Maligne Pleuraal Mesothelioma MPM

24 maart 2022
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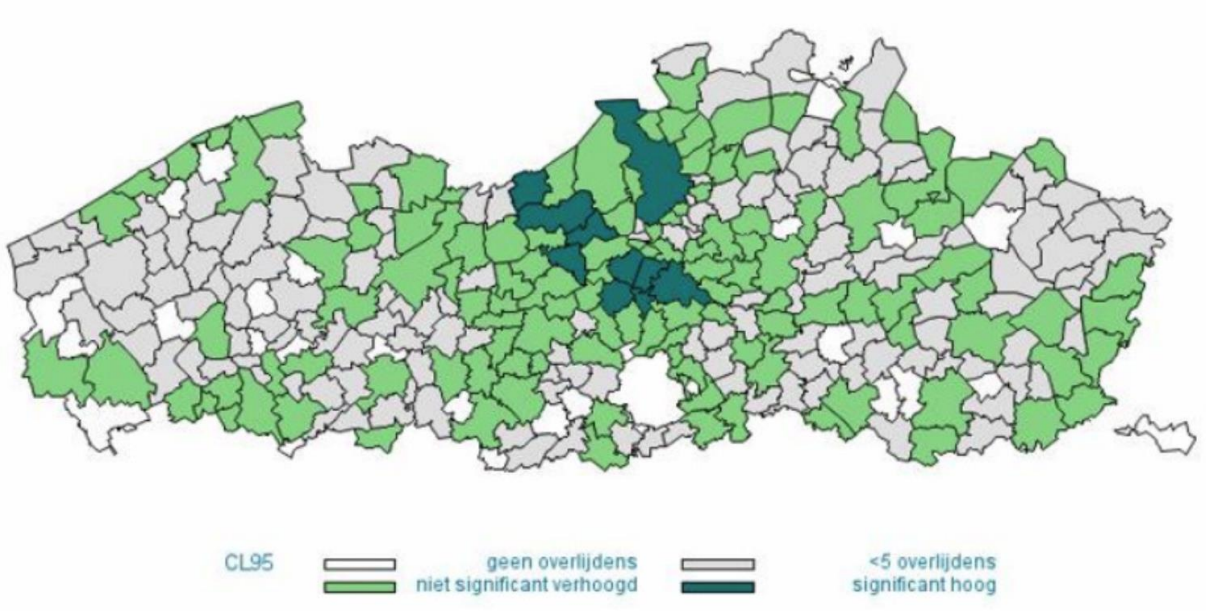
VITAZ (nieuwe naam van AZ NIKOLAAS !)



Indirect gestandaardiseerde sterfteratio (SMR) door mesothelioom (C45) in de periode 1998-2015 in het Vlaamse Gewest voor mannen, significant verhoogd voorkomen in gemeenten t.o.v. Vlaanderen (bron: Zorg en Gezondheid 2017). (Nota: De kaarten geven enkel het Vlaamse Gewest weer.)

VITAZ STERK IN ZORG

ESMO Designated Centres of Integrated Oncology and Palliative Care

UZA

TOGA Thoracic Oncology Group Antwerp University of Antwerp

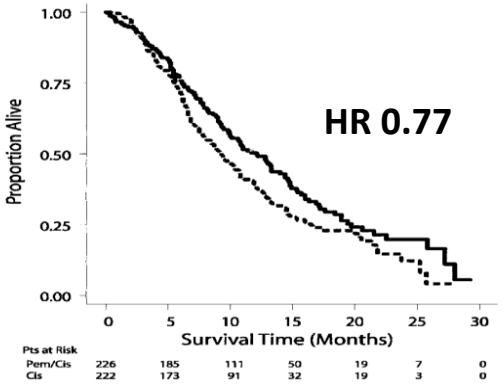
LongArtsen.be

Malignant pleural mesothelioma (MPM) is a highly aggressive cancer, with a 5-year survival rate of < 10%, mOS 18 m.

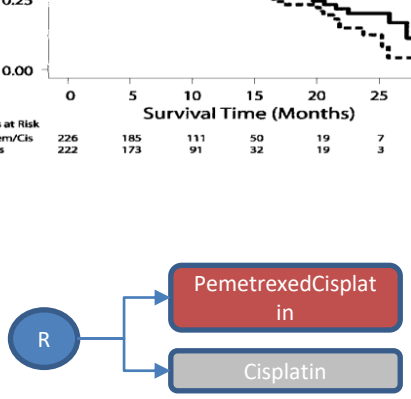
Platinum doublet chemotherapy has been the approved standard of care for 1L unresectable MPM since 2004

Epithelioid histology has been associated with better outcomes than non-epitheliod histology

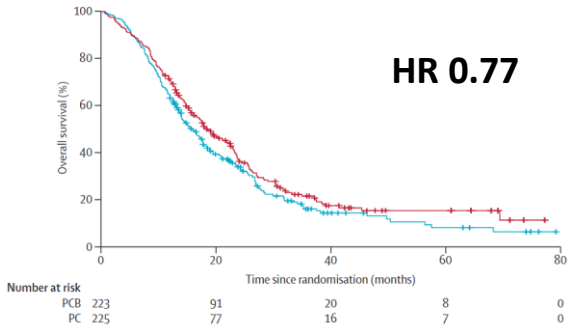
2003



HR 0.77



2016



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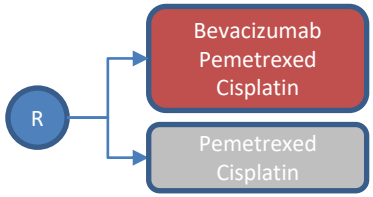
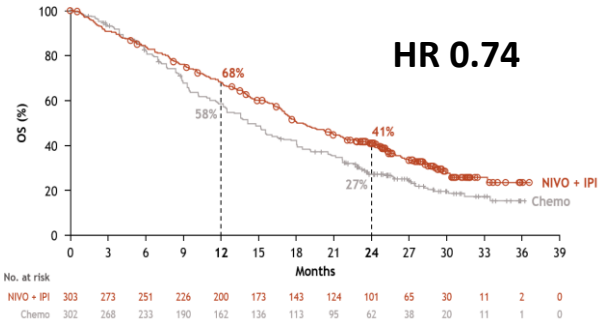


2020



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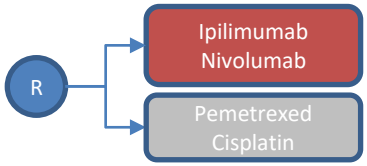
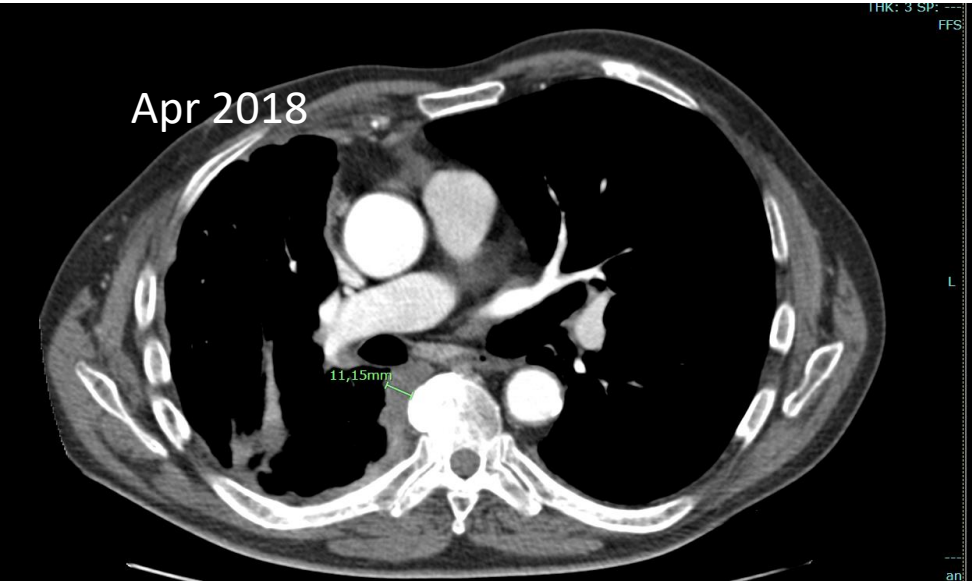
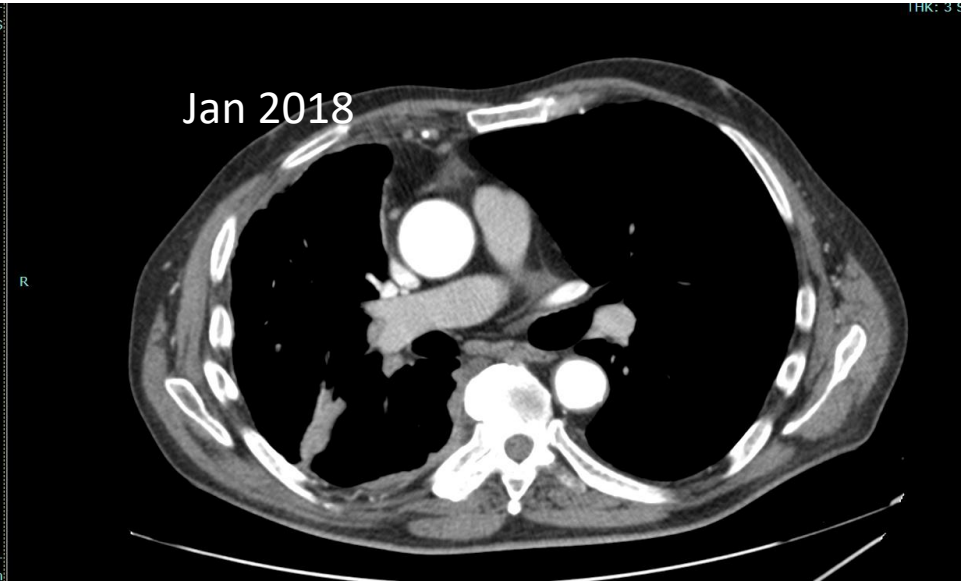


Vogelzang et al, J Clin Oncol 2003; 21(14):2636-44;: Zalcman et al, Lancet 2016; 387:1405-14; Baas et al, IASLC 2020

Casus man 74 j. augustus 2017

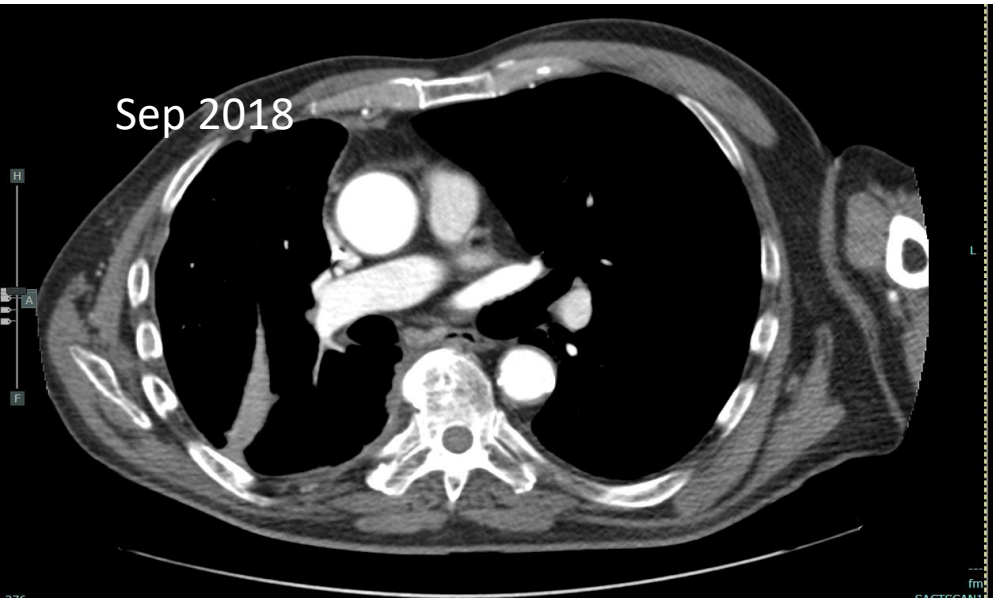
- voorgeschiedenis: 5 py ex roker; art hypertensie; gestoorde Glucose tolerantie; leverhemangiomen; BPH; feb 2015: CAP RBK/ROK
- Aug 2017: diagnose Maligne Pleuraal Mesothelioma rechts cT1N0M0
  - Geen meetbare lesies bij ct (mRecist)
- Inclusie MESODEC trial:
- Okt 2017 Leukaferese met productie van 37 Dentritische celvaccins
- Okt 2017 - jan 2018 : 4 cycli chemotherapie pemetrexed / cisplatin in combinatie met DC vaccin op d15
- Jan 2018: continuatie DC vaccin q4w
- Apr 2018 : progressieve ziekte

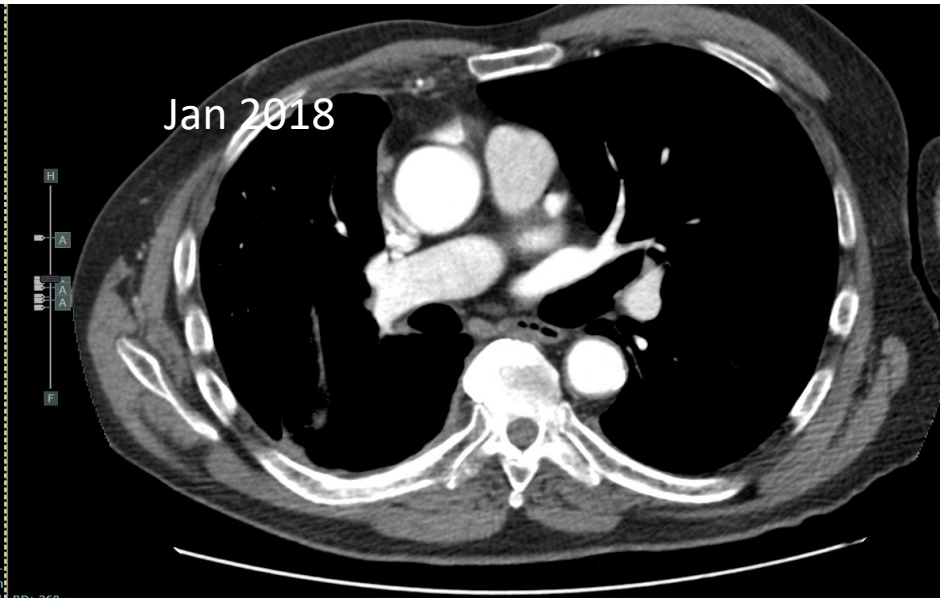




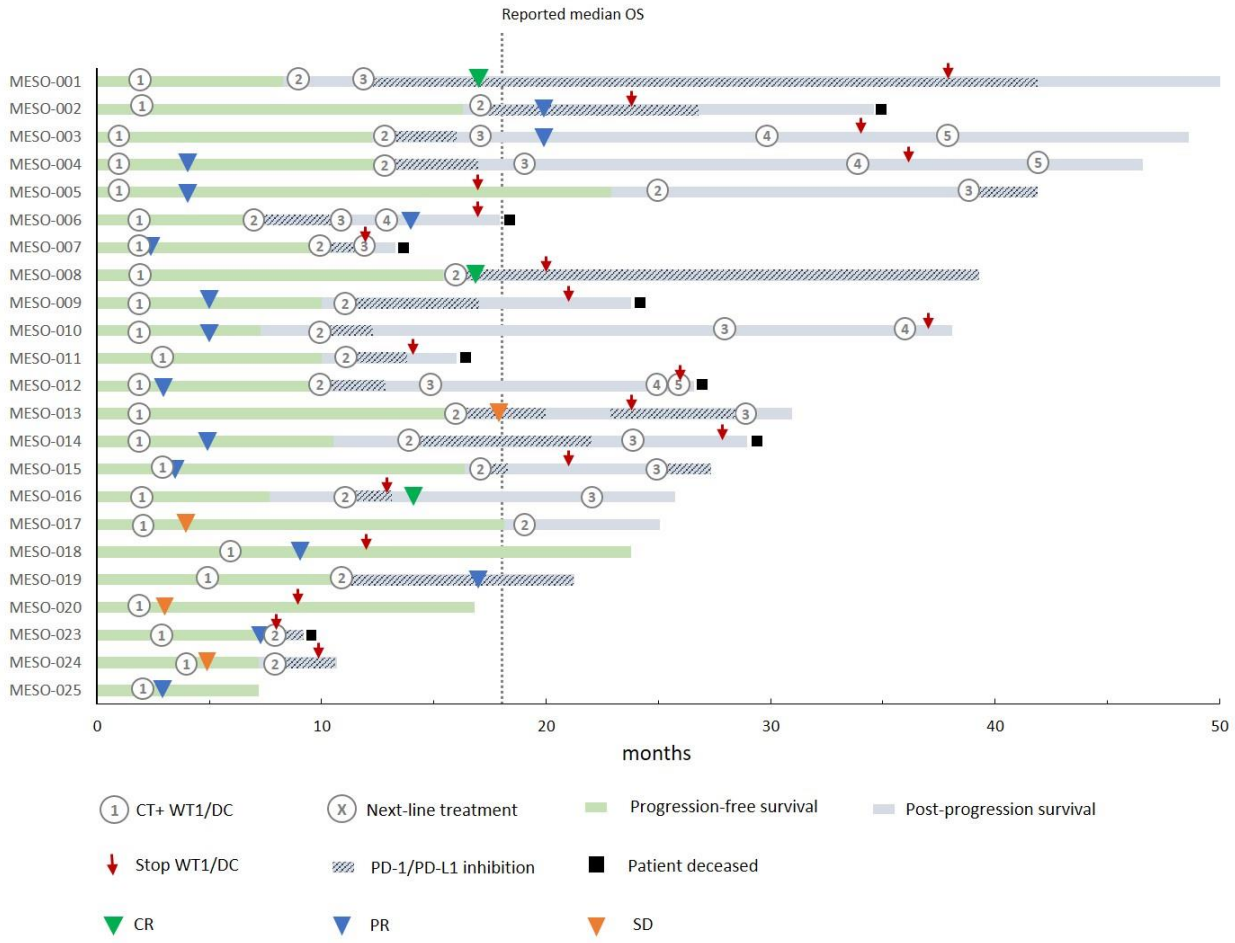
Casus man 74 j. augustus 2017

- Mei 2018 – jun 2018 : 2L Vinorelbine d1d8 q3w
  - 2cycli toegediend met Stable Disease
- Jun 2018 : staken therapie wegens intolerantie en afname PS (3)
- Aug 2018 : 3L therapie Nivolumab 3mg/kg q2w
  - MN program BMS / geen terugbetaalde indicatie
- Sep 2018 : partieel respons
- Jan 2018 : compleet repons
- Okt 2020 : laatste toediening DC vaccin
- Maa 2021 : laatste Nivolumab (66 cy)
- Jan 2022 : PS 0 / behouden CR / FU om de 6 maanden





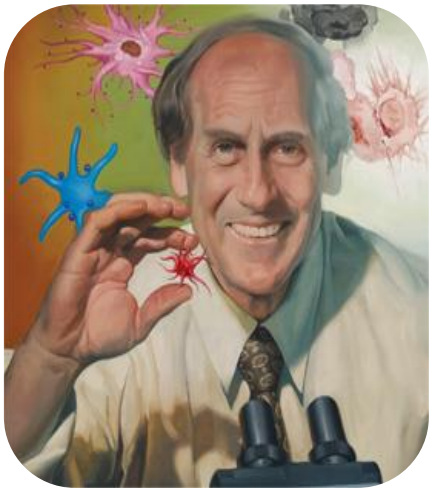
Mesodec trial : accrual update nov 21
Swimmerplot

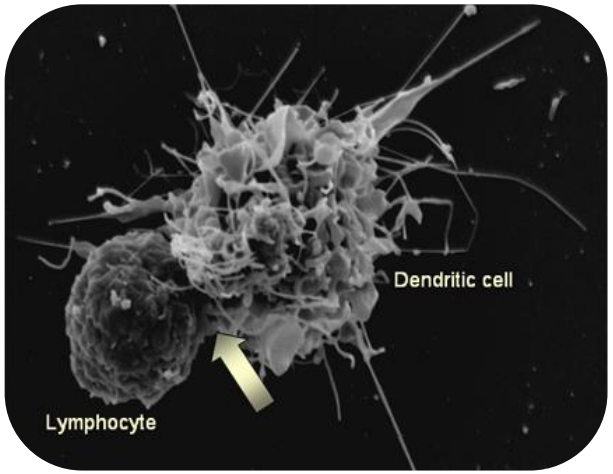


DC therapie in oncology

- 20 % toename in mediane OS
- 5-15% “objective Respons Rate”

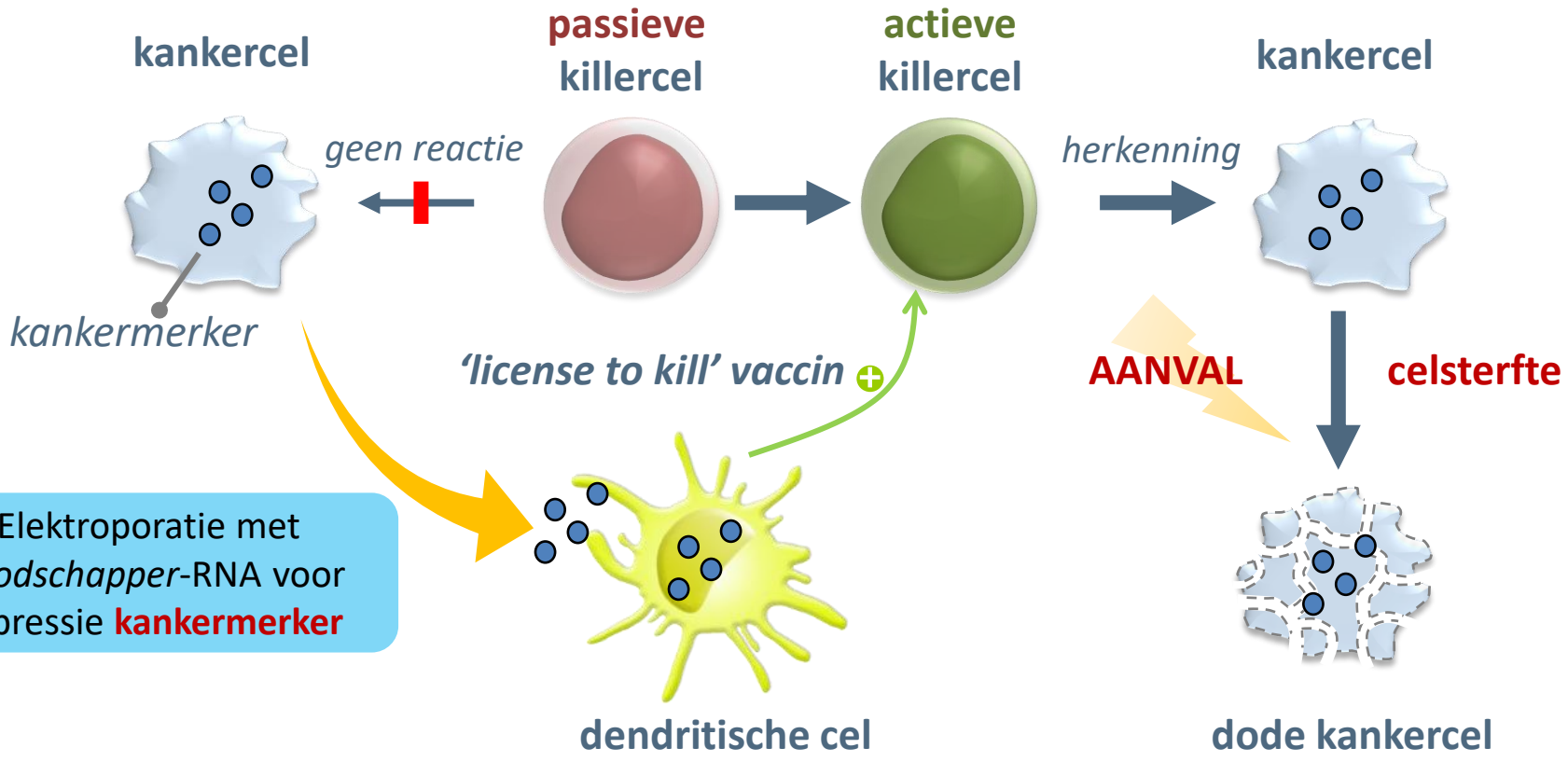
Ralph M. Steinman (1943-2011)
Nobelprijs geneeskunde 2011
Voor zijn ontdekking van de dendritische cel (1973) en zijn rol in verworven immuniteit





S. Anguille et al, Lancet Oncology 2014

Dendritische celvaccinatie



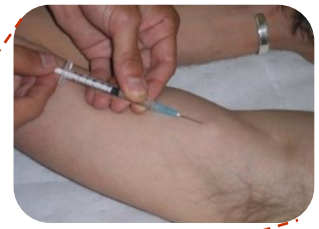
Productie cyclus dendritisch celvaccin




Binnenbrengen boodschapper RNA
kankermerker


= RNA/DC vaccin

TOEDIENING via de huid



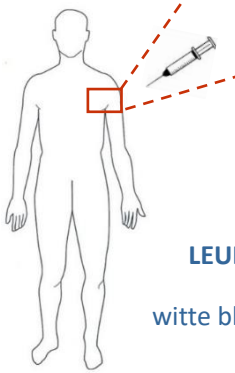
rijpe DC

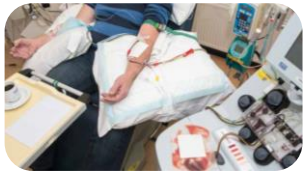
MATURATIE

onrijpe DC

DIFFERENTIATIE

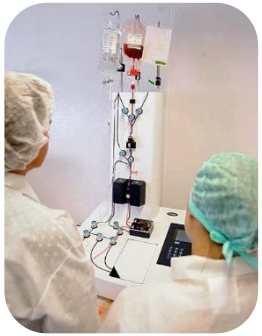
monocyt





LEUKAFERESE
Collectie
witte bloedcellen

Monocytenisolatie



Eva Lion CCRG UZA

Combinatie Checkpoint inhibitie en Dendritic cells : bij verschillende tumoren

- Mesothelioma:
  - Denim study / Mesodec trial

- Melanoma:
  - Fase I trial: 4 v 16 ptn tonen respons waarvan 2 CR
    Ribas et al., Clin Cancer Res., 2009
  - Fase II trial met ORR v 38%, waarvan 20% CR en 51% DCR
    Wilgenhof et al. JCO, 2016
  - Klinisch respons bij ptn op ipilimumab tot ziekteprogressie met DC: OS v 51% na 2 j.
    Boudewijns et al. J Immunother, 2016

- NSCLC:
  - PDC lung trial:

  An open-label, dose-escalation, phase I/II study to assess the safety, the tolerability, the immunogenicity and the preliminary clinical activity of the **therapeutic cancer vaccine, PDC*lung01**, associated or not with anti-PD-1 treatment in patients with non-small-cell lung cancer (NSCLC)

  Open for inclusion: UZL, VITAZ (AZ Nikolaas), AZ Delta, Jessa

Verschillende therapeutische toepassingen

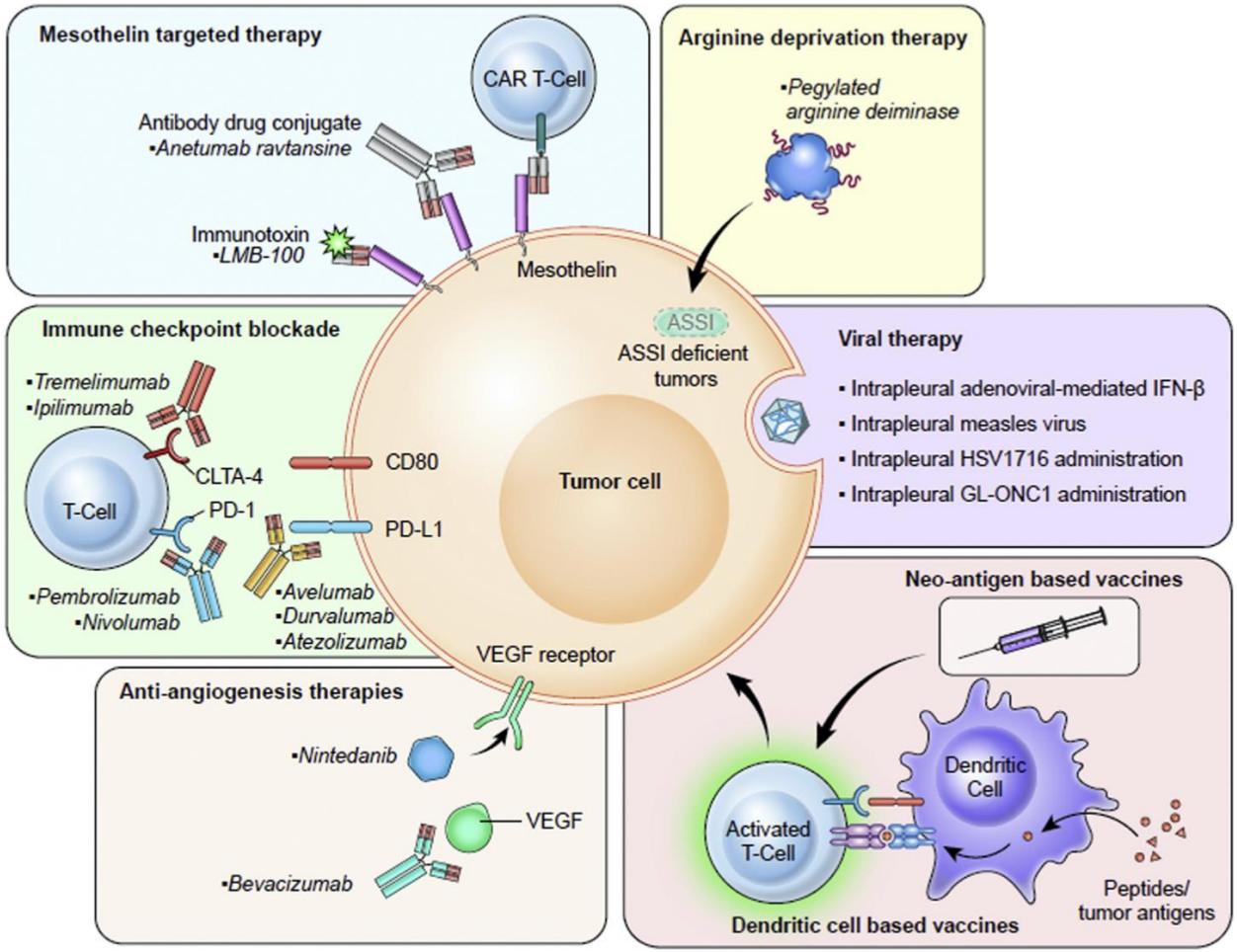
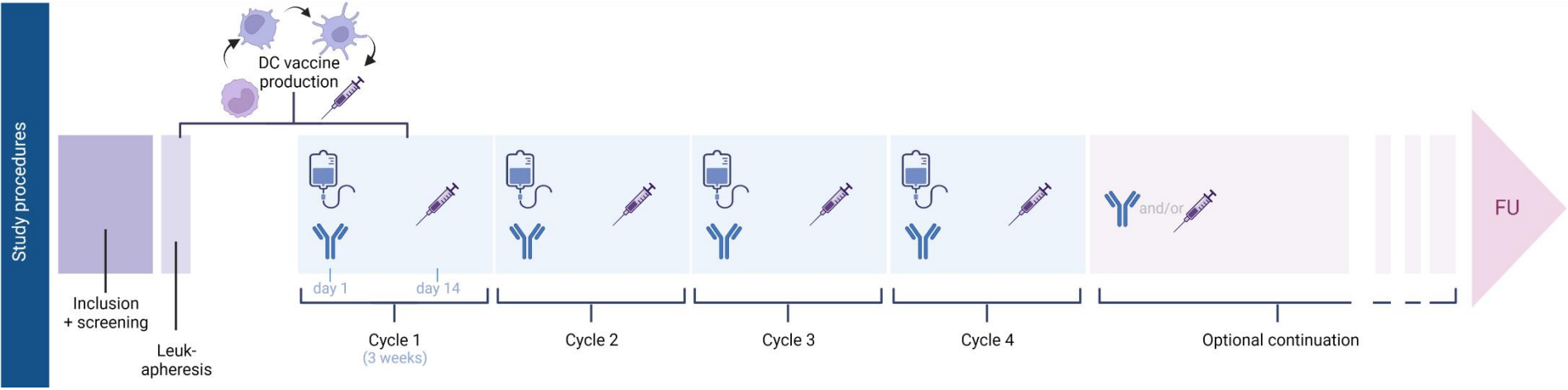


Figure 1. Different approaches to treating mesothelioma that are currently in clinical trials. Nintedanib, in addition to targeting VEGF receptor, also targets fibroblast growth factor receptor and platelet-derived growth factor receptor. Abbreviations: CAR, chimeric antigen receptor; CTLA4, cytotoxic T-lymphocyte–associated antigen; PD-1, programmed death 1; PD-L1, programmed death ligand 1; ASS1, argininosuccinate synthetase 1; IFN-β, interferon beta; VEGF, vascular endothelial growth factor.

Scientific Advances and New Frontiers in Mesothelioma Therapeutics : Journal of Thoracic Oncology Vol. 13 No. 9: 1269-1283

Immuno-MESODEC trial

Study design |	Single arm open-label phase I/II trial
Study population |	15 treatment-naïve unresectable malignant pleural mesothelioma patients, epithelioid subtype (stage I-IV)
Study treatment |	4 cycles of: Platinum/pemetrexed-based chemotherapy + Atezolizumab (1200-1680 mg, administered i.v.) + *Wilms' tumor 1 (WT1)* mRNA-electroporated dendritic cell vaccine (8-10 x 10^6 cells, administered i.d.)



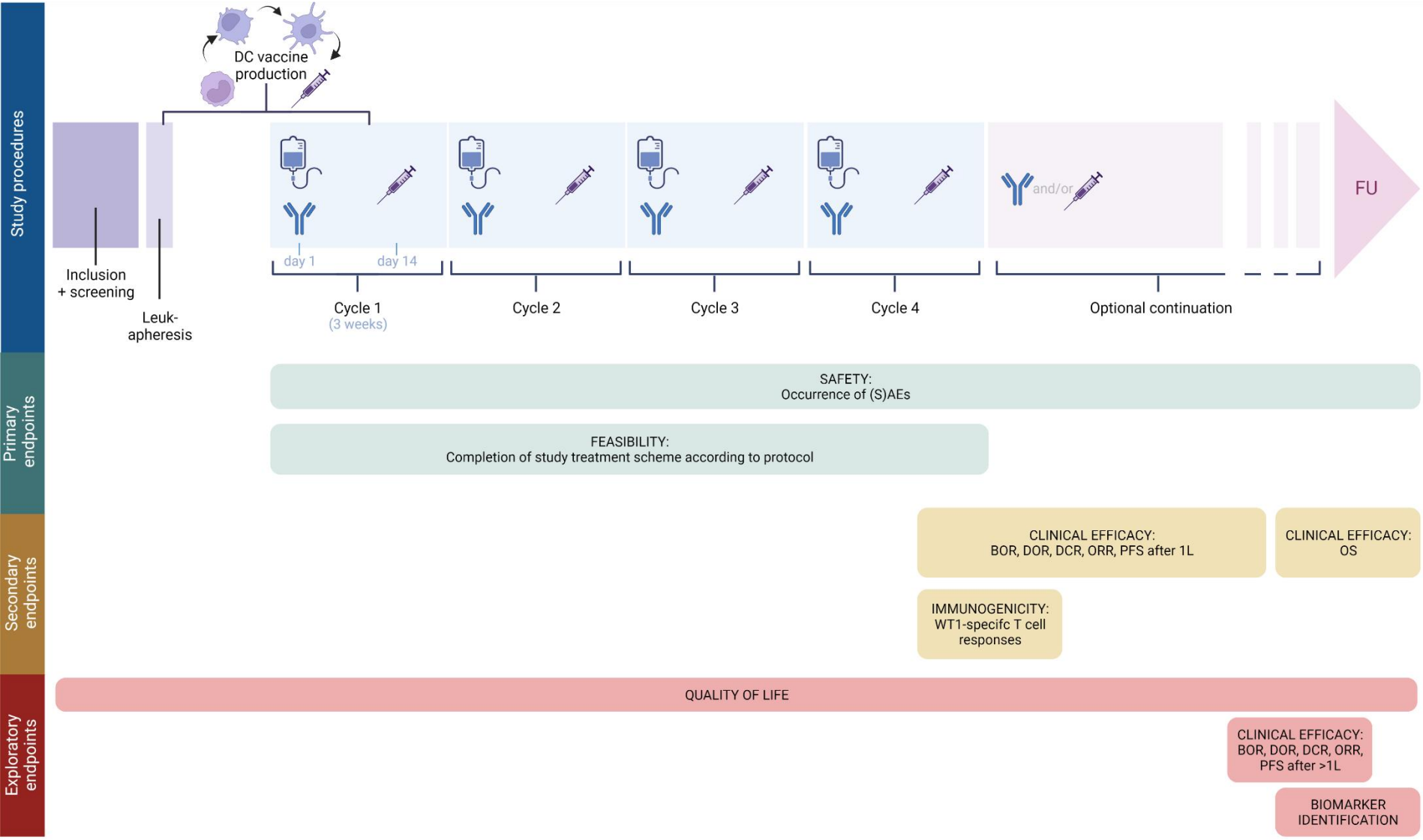
Legend:

= platinum/pemetrexed chemotherapy

= checkpoint inhibition (atezolizumab)

= dendritic cell vaccine

FU =follow-up


Study procedures
Primary endpoints
Secondary endpoints
Exploratory endpoints
DC vaccine production
Inclusion + screening
Leuk-apheresis
day 1
day 14
Cycle 1 (3 weeks)
Cycle 2
Cycle 3
Cycle 4
and/or
Optional continuation
FU
SAFETY: Occurrence of (S)AEs
FEASIBILITY: Completion of study treatment scheme according to protocol
CLINICAL EFFICACY: BOR, DOR, DCR, ORR, PFS after 1L
CLINICAL EFFICACY: OS
IMMUNOGENICITY: WT1-specifc T cell responses
QUALITY OF LIFE
CLINICAL EFFICACY: BOR, DOR, DCR, ORR, PFS after >1L
BIOMARKER IDENTIFICATION
Legend:
= platinum/pemetrexed chemotherapy
= checkpoint inhibition (atezolizumab)
= dendritic cell vaccine
FU =follow-up

Immuno-MESODEC trial

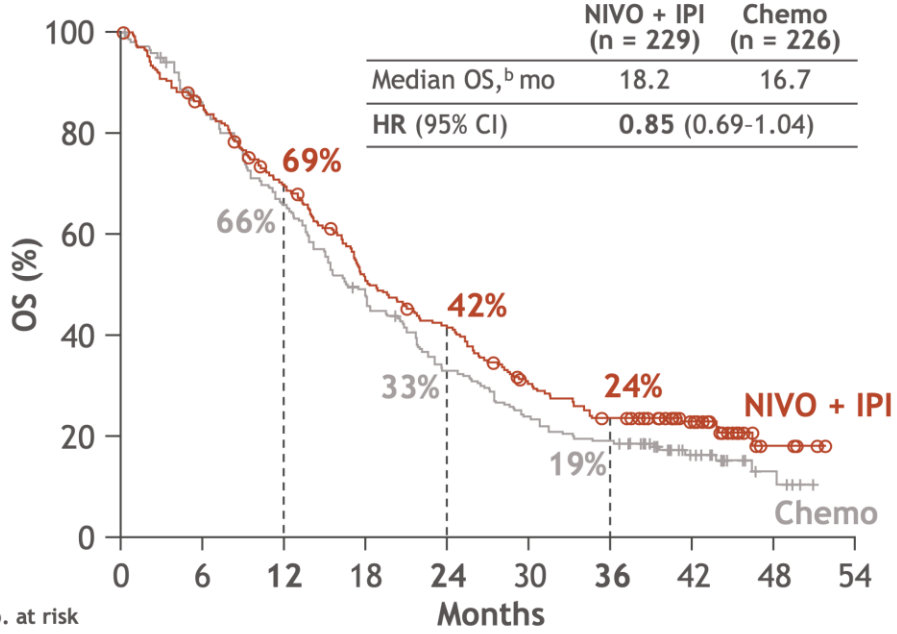
Study team |

Study financing |

3-year update: OS by histology[a]

Epithelioid

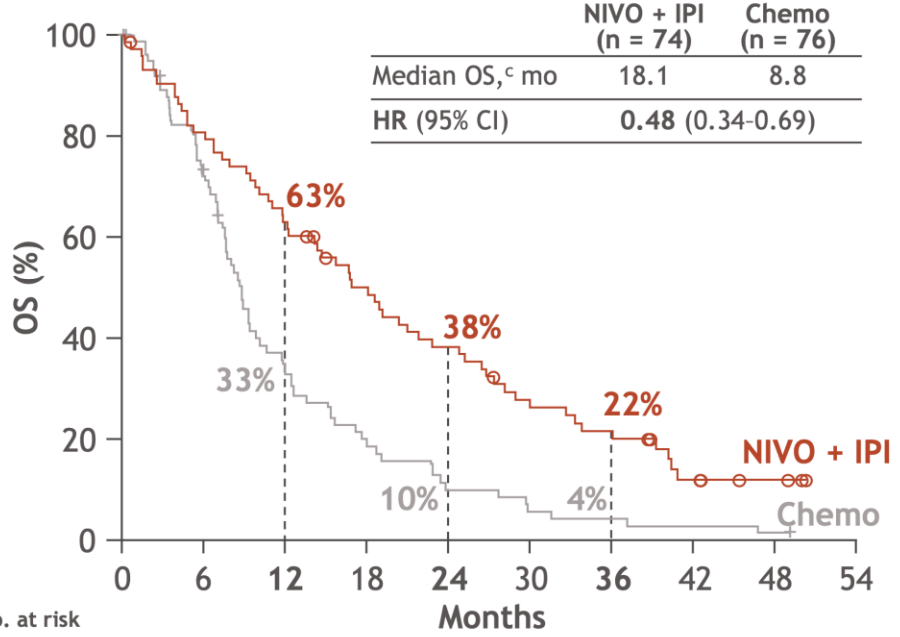
	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS,[b] mo	18.2	16.7
HR (95% CI)	**0.85** (0.69–1.04)	



No. at risk										
NIVO + IPI	229	192	154	111	90	63	48	29	4	0
Chemo	226	182	141	101	69	50	40	18	5	0

Non-epithelioid

	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS,[c] mo	18.1	8.8
HR (95% CI)	**0.48** (0.34–0.69)	



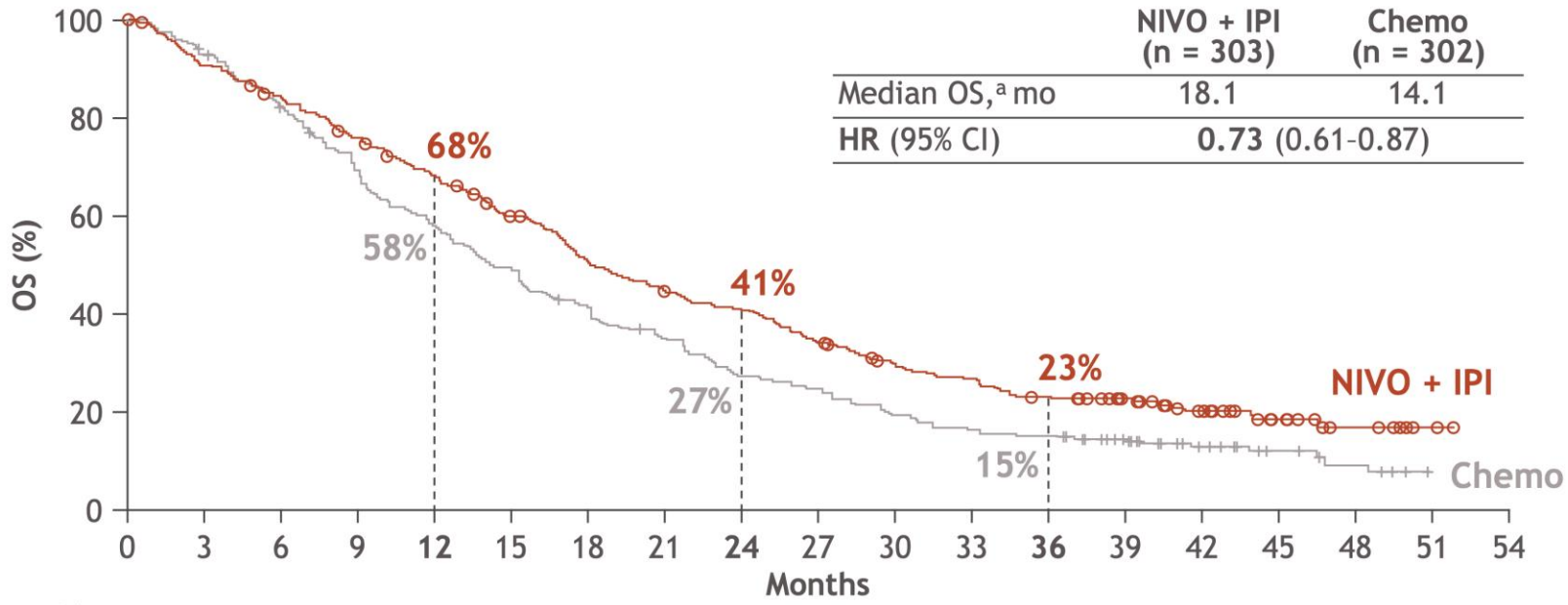
No. at risk										
NIVO + IPI	74	59	46	34	26	17	14	6	3	0
Chemo	76	52	23	13	7	4	3	2	1	0

Minimum follow-up: 35.5 months.

In patients with epithelioid histology, subsequent systemic therapy was received by 47% in the NIVO + IPI arm vs 44% in the chemo arm; subsequent immunotherapy was received by 4% vs 22%; subsequent chemotherapy was received by 45% vs 35%, respectively. In patients with non-epithelioid histology, subsequent systemic therapy was received by 39% in the NIVO + IPI arm vs 37% in the chemo arm; subsequent immunotherapy was received by 5% vs 20%; subsequent chemotherapy was received by 38% vs 26%, respectively.

[a]Histology per CRF; [b]95% CIs were 16.9–21.9 (NIVO + IPI) and 14.9–20.3 (chemo); [c]95% CIs were 12.2–22.8 (NIVO + IPI) and 7.4–10.2 (chemo).

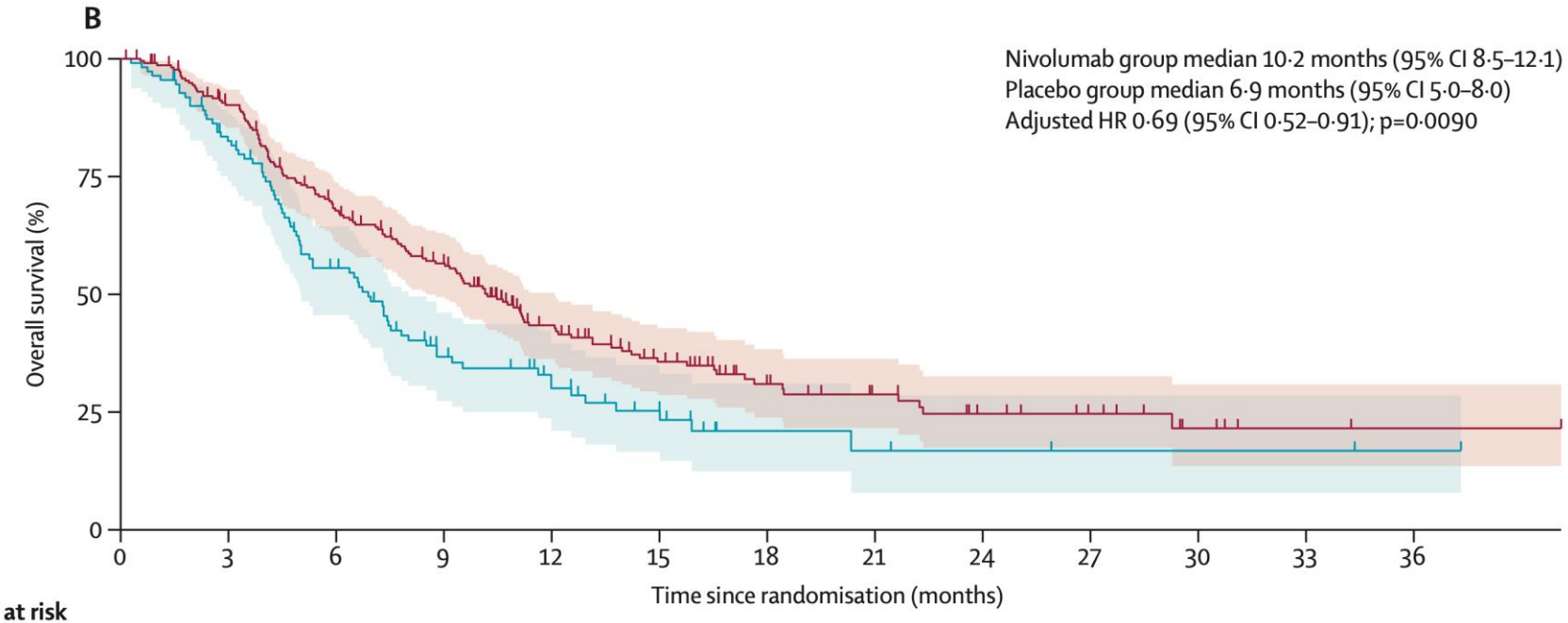
3-year update: overall survival in all randomized patients



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS,[a] mo	18.1	14.1
HR (95% CI)	**0.73** (0.61–0.87)	

Minimum follow-up: 35.5 months.
Subsequent systemic therapy was received by 45% of patients in the NIVO + IPI arm and 42% in the chemo arm; subsequent immunotherapy was received by 4% and 22%; subsequent chemotherapy was received by 43% and 33%, respectively.
[a]95% CIs were 16.8-21.0 (NIVO + IPI) and 12.4-16.3 (chemo).

Confirm trial fase III Nivolumab in 2L



Number at risk (number censored)													
Placebo group	111 (0)	88 (4)	55 (9)	31 (15)	21 (20)	13 (25)	5 (31)	4 (31)	3 (32)	2 (33)	2 (33)	2 (33)	1 (34)
Nivolumab group	221 (0)	187 (13)	137 (17)	108 (24)	67 (42)	46 (52)	29 (64)	22 (69)	15 (73)	11 (77)	5 (82)	2 (85)	1 (86)

Lancet Oncol 2021; 22: 1530–40

Risk Benefit : Ipi-Nivo versus Chemotherapy

TRAE, %	NIVO + IPI[a] (n = 300)		Chemo[b] (n = 284)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any TRAE[c]	80	30	82	32
TRAEs leading to discontinuation of any component of the regimen[c]	23	15	16	7
Serious TRAEs[c]	21	15	8	6
Treatment-related deaths	1[d]		0.4[e]	

5 % 2 %