ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Immunotherapy treatment duration

Experience in melanoma

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DISCLOSURES

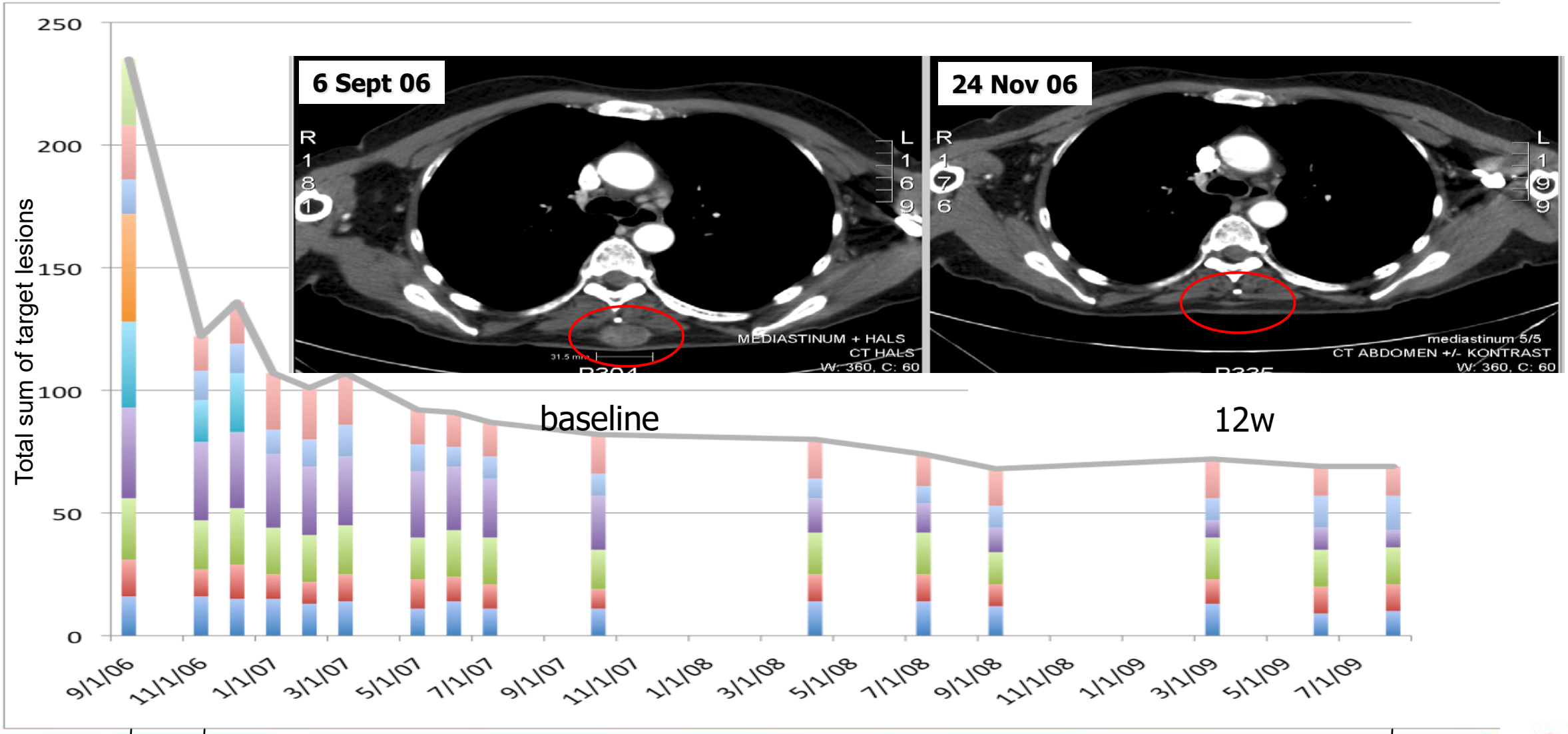
- Personal financial compensation from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and AstraZeneca for public speaking, consultancy and participation in advisory board meetings
- My institution (UZ Brussel) received research funding related to research projects conducted by my team from Pfizer, Novartis, Roche, Merck-Serono

Universitair Ziekenhuis Brussel

VUB VRIJE UNIVERSITEIT BRUSSEL

Case illustration

Long-term survival following ipilimumab treatment for stage IV-M1C melanoma

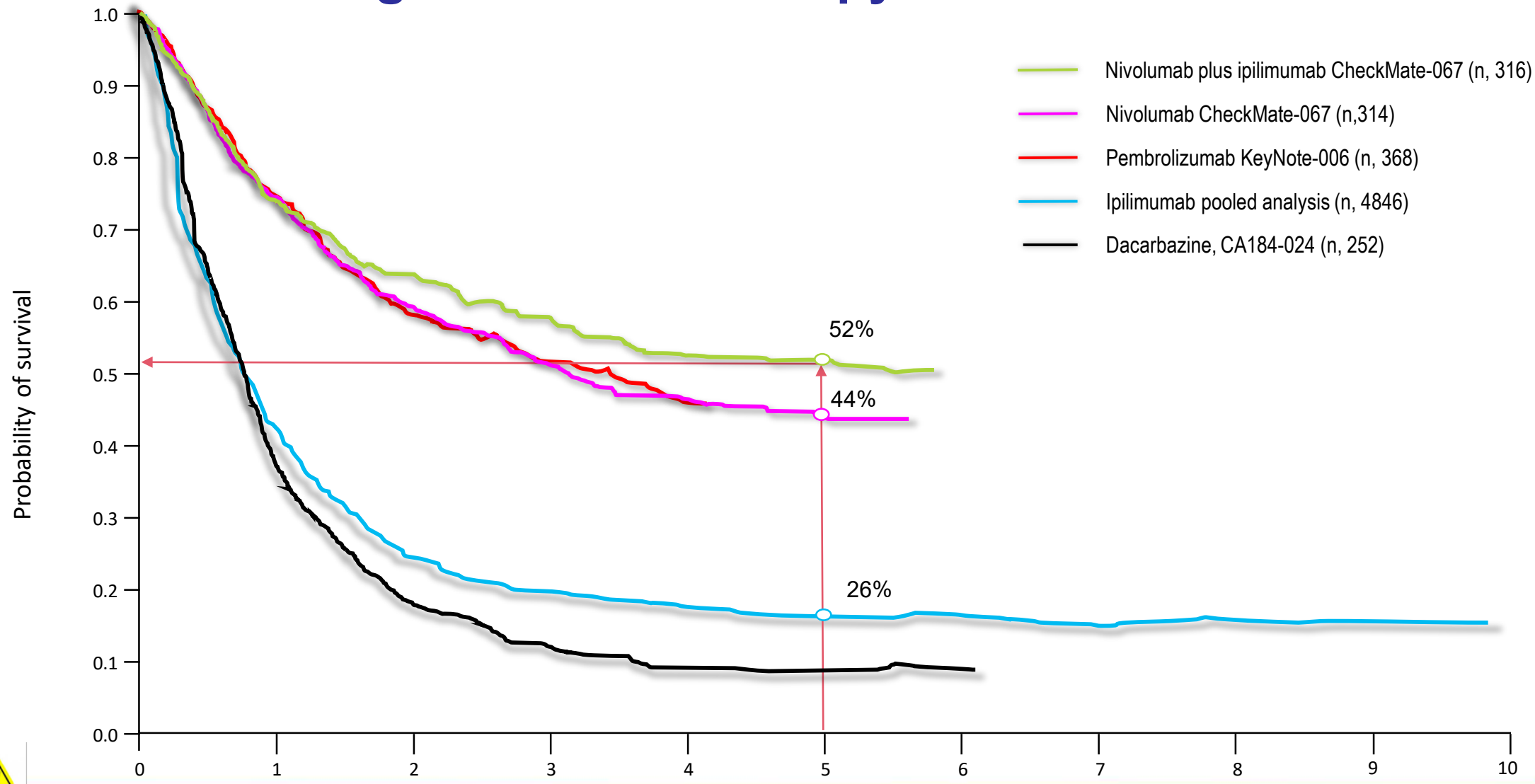



I’m 80y old now …
do I still have to
come to Brussels for
follow-up?

2018


xxxxx
xxxxx
xxxxx
xxxxx
Prettige Kerstdagen
Gelukkig Nieuwjaar
Fröhliche Weihnachten
Glückliches Neues Jahr
Joyeux Noël
Bonne Année
Merry Christmas
Happy New Year

Cross-trial comparison: overall survival of advanced melanoma patients according to first line therapy ICI

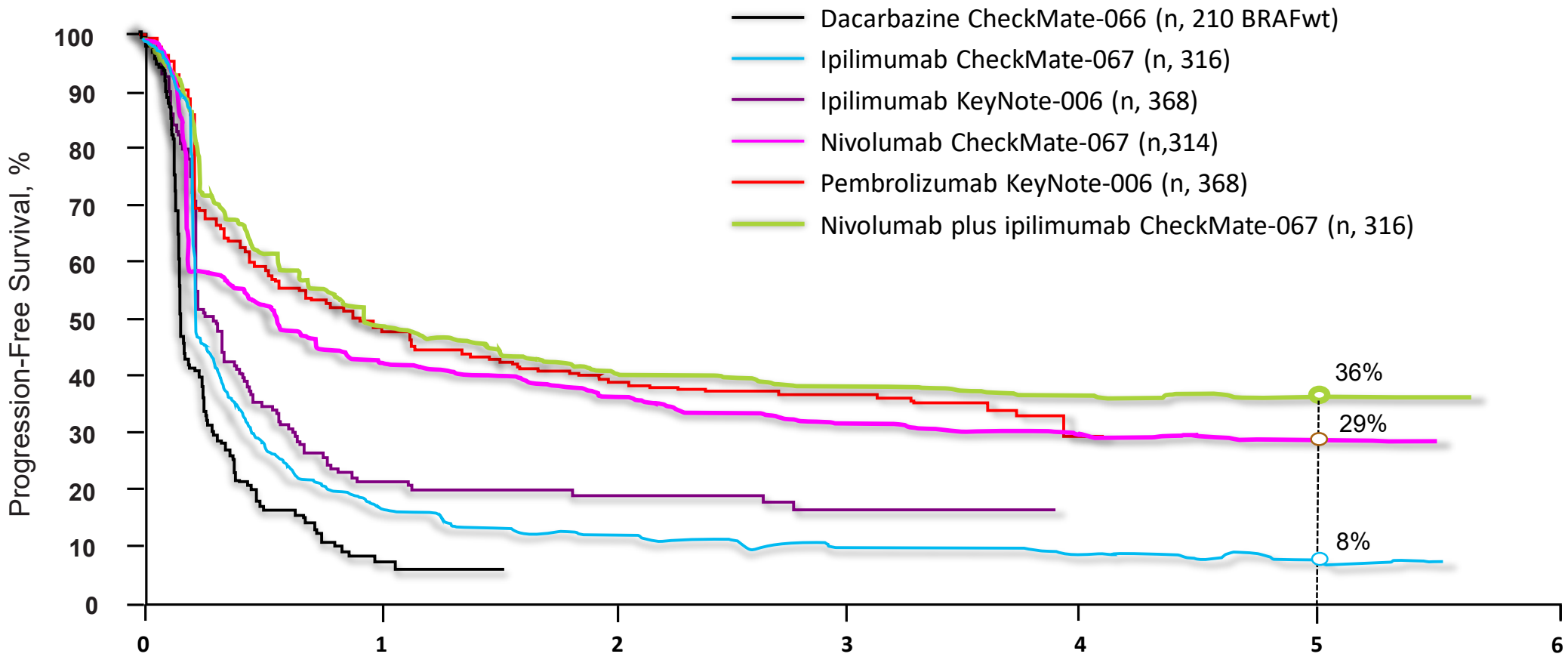


Cross-trial comparison

No adequate well-controlled head-to-head clinical trials are available.

Adapted from Rogiers A.et al. J Oncol. 2019 Apr 28;2019:5269062. doi: 10.1155/2019/5269062

Cross-trial comparison: progression-free survival of advanced melanoma patients on first line ICI therapy



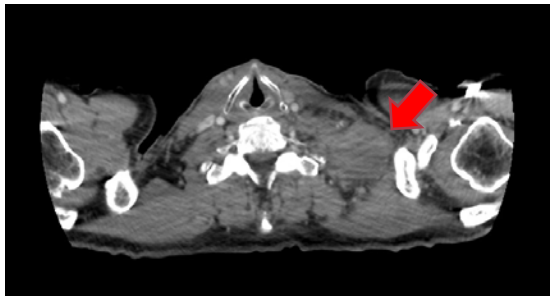
Cross-trial comparison

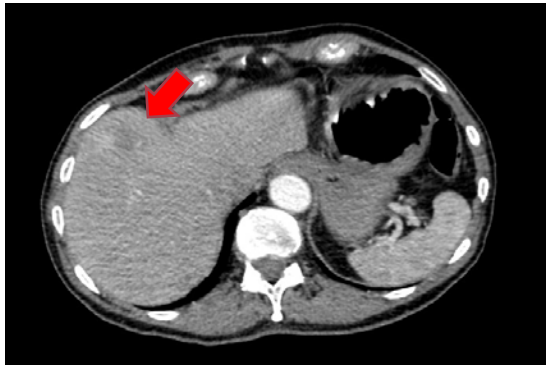
Presented by Prof Neyns at BSMO-Bordet congress on November 28, 2018.

No adequate well-controlled head-to-head clinical trials are available.

Case illustration

Long-term outcome following early discontinuation of pembrolizumab because of an irAE in a 81y old stage IV-M1c BRAFwt melanoma patient





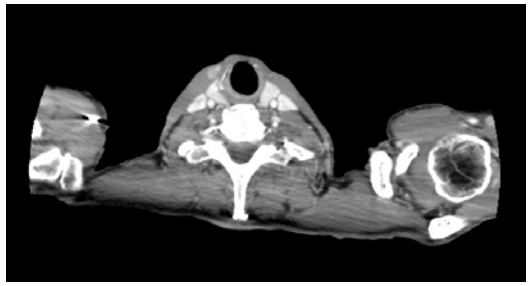
KN006

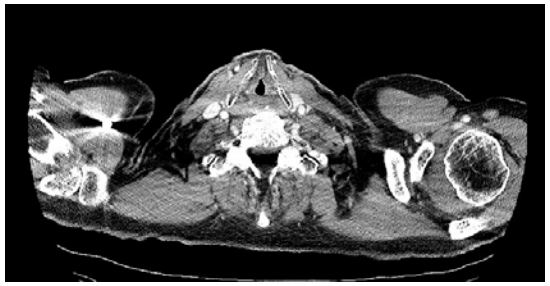
pembrolizumab

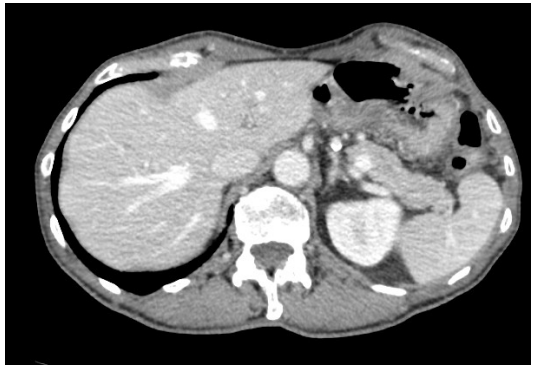
24/1/2014
14/2/2014

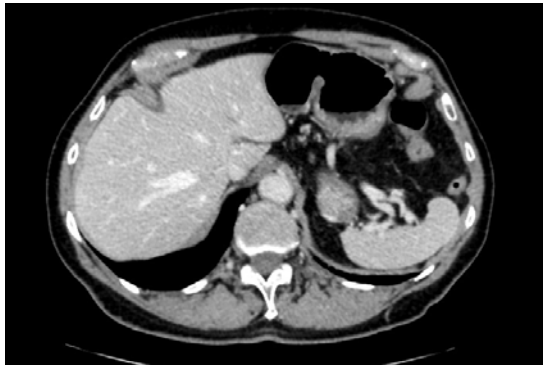
28/3/2014
PNP* grade 2

pembrolizumab









LDH 2690 U/L (ULN 618)
CRP 34,1 mg/l (ULNN <5)

LDH 364 U/L
CRP <0,5 mg/l

13/1/2014 —*3 months*→ **18/4/2014** —*4,5 years*→ **14/06/2018**

* PNP polyneuropathy

Pooled analysis: nivolumab + ipilimumab in patients who *did* or *did not* discontinue treatment because of AEs during induction

Pooled patients randomly assigned to nivolumab plus ipilimumab (N = 409; 407 treated)
CheckMate 067 (n = 314 randomly assigned; 313 treated)
CheckMate 069 (n = 95 randomly assigned; 94 treated)

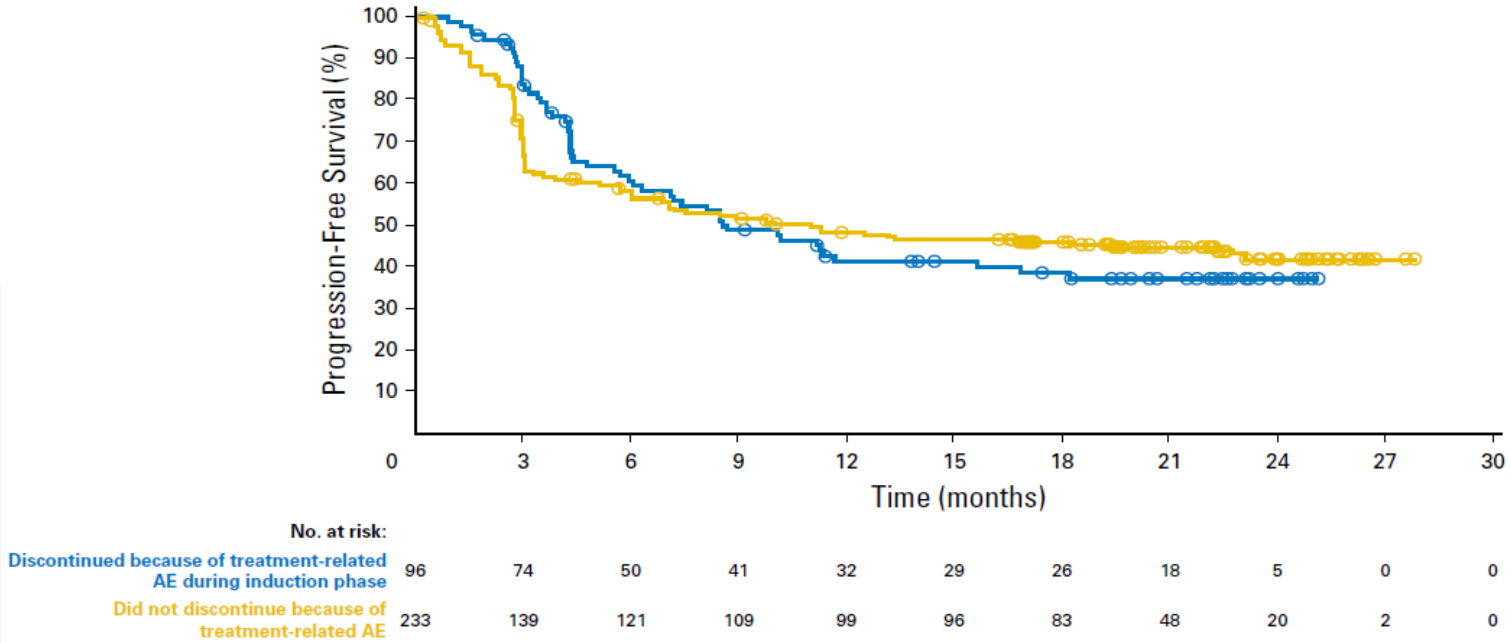
Patients who discontinued because of an AE at any time* (safety analyses; n = 176)

Did not continue study treatment	(n = 176)
Disease progression	(n = 1)
Study drug toxicity	(n = 173)
AE unrelated to study drug	(n = 1)
Not reported	(n = 1)

Patients who discontinued because of an AE during the induction phase† (efficacy analyses; n = 96)

Treated patients who did not discontinue because of an AE (n = 231)

Did not continue study treatment	(n = 150)
Disease progression	(n = 97)
Study drug toxicity	(n = 1)
Death	(n = 4)
AE unrelated to study drug	(n = 18)
Patient request	(n = 14)
Withdrew consent	(n = 4)
Maximum clinical benefit	(n = 7)
Poor/noncompliance	(n = 1)
No longer met study criteria	(n = 1)
Other	(n = 3)



Minimum 18-month follow-up, median 21.3-month follow-up

Reproduced from Schadendorf D et al. *J Clin Oncol.* 2017;35:3807-3814

AE = adverse event; CI = confidence interval; DC = patients who discontinued due to an AE during induction; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; no DC = patients who did not discontinue due to an AE; PFS = progression-free survival.

Reproduced from Schadendorf D et al. *J Clin Oncol.* 2017;35:3807-3814

Outcome of advanced melanoma patients stopping treatment in the absence of disease progression

	Study	Patient #	Reason for stopping therapy	FU post treatments stop (months)	PFS%
PD-1 inhibitor	Phase I Nivolumab[6]	17	Other than PD during response	≥ 4	71%
	Phase I Pembrolizumab (Keynote-001)[1]	67	Confirmed CR	10	97%
	Phase III Pembrolizumab (Keynote-006)[2]	103	After 2 years of therapy (protocol defined)	34.2	78.4%
	anti-PD1-Real World[3]	185	Other than PD or AE	18	78%
BRAF-/MEK-inhibitors	Cohort-study[4]	12	Other than PD	6.6	50%
	Cohort-study[5]	12	Other than PD	3	50%

References

[1] Robert, JCO 2017; [2] Robert, *Lancet Oncol* 2019; [3] Jansen, Annals of Oncol 2019;[4] Carlino, *Br J Cancer* 2016; [5] Tolk, *Mel Res* 2015; [6] Topalian et al JCO 2014

Outcome of advanced melanoma patients stopping treatment in the

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee

U. Keilholz[1*], P. A. Ascierto[2], R. Dummer[3], C. Robert[4,5], P. Lorigan[6], A. van Akkooi[7], A. Arance[8], C. U. Blank[9], V. Chiarion Sileni[10], M. Donia[11,12], M. B. Faries[13], C. Gaudy-Marqueste[14], H. Gogas[15], J. J. Grob[14], M. Guckenberger[16], J. Haanen[9], A. J. Hayes[17], C. Hoeller[18], C. Lebbé[19,20], I. Lugowska[21], M. Mandalà[22], I. Márquez-Rodas[23], P. Nathan[24], B. Neyns[25], R. Olofsson Bagge[26,27,28], S. Puig[29,30,31], P. Rutkowski[32], B. Schilling[33], V. K. Sondak[34], H. Tawbi[35], A. Testori[36] & O. Michielin[37]

> ***Recommendation 6.4.*** Stopping targeted therapy followed by observation in patients with clinical benefit (CR, PR or SD) outside of a clinical trial is not recommended.

ESMO consensus conference recommendations

	Study			eatments onths)	PFS%
PD-1 inhibitor	Phase I Nivolumab[6]	17	response	≥ 4	71%
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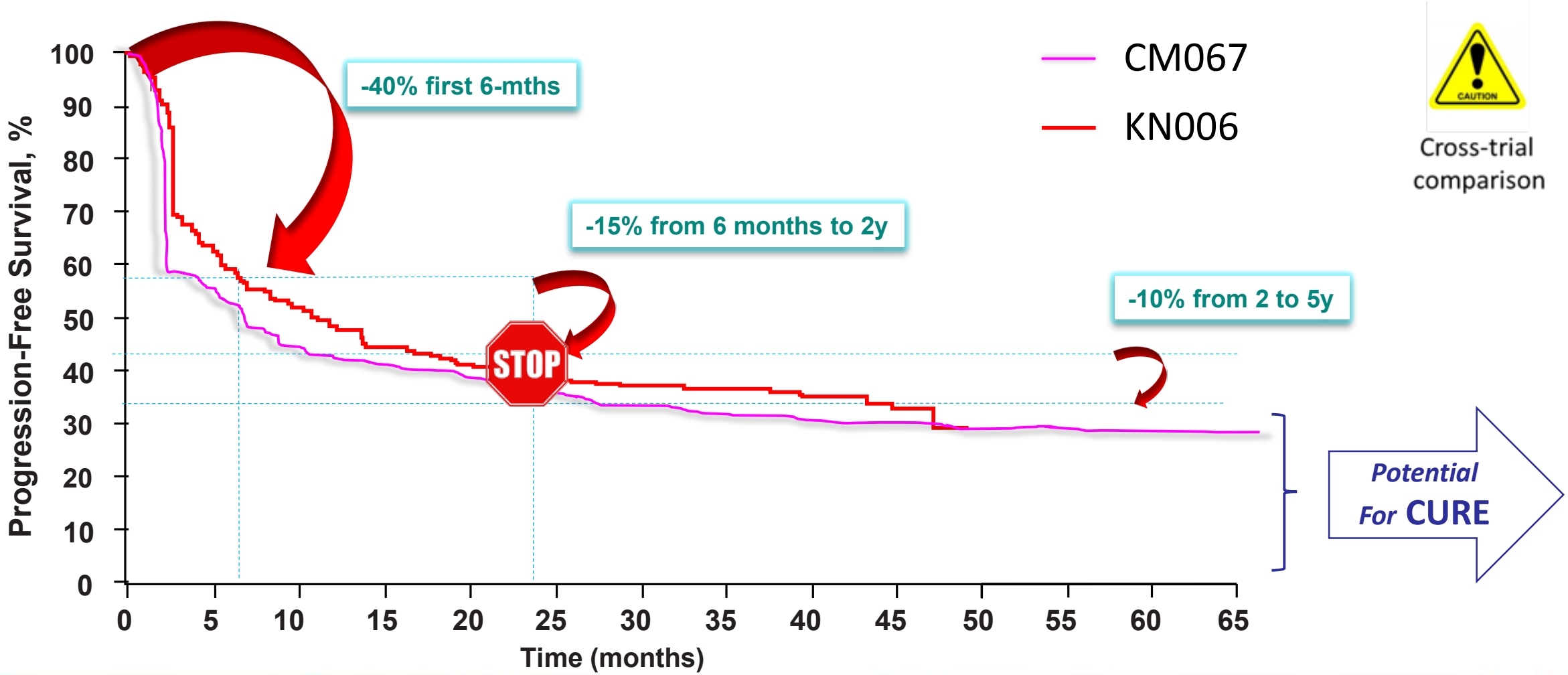
Cross-trial comparison: Overlay PFS estimates of 1L pembrolizumab (KN006) or nivolumab monotherapy (CM067)



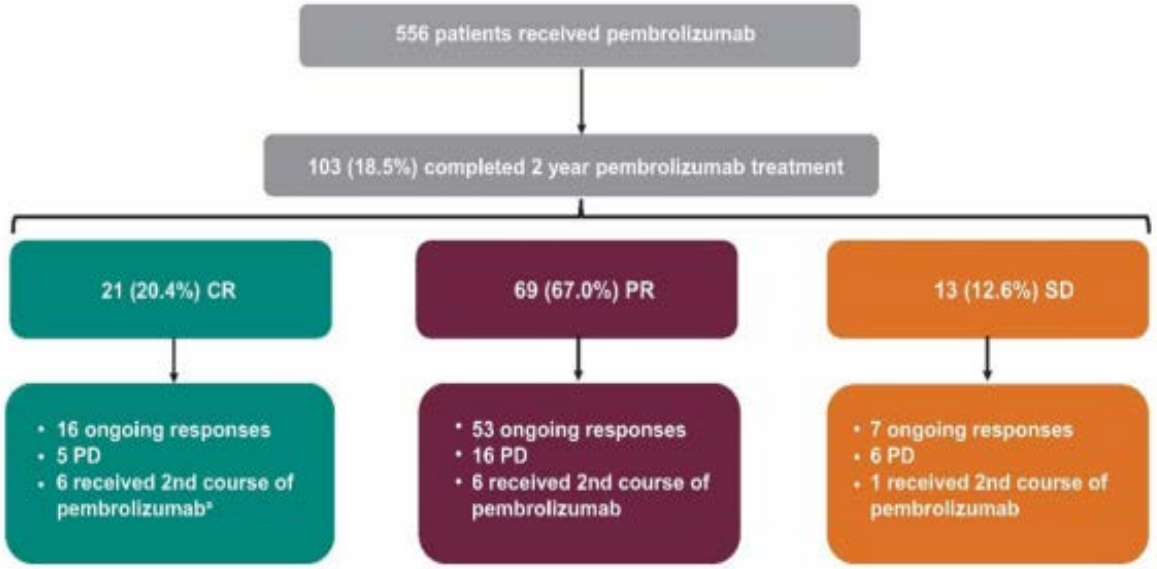
Adapted from Larkin J. et al. N Engl J Med. 2019 ;381(16):1535-1546.

Adapted from Robert C et al. Lancet Oncol. 2019 20(9):1239-1251.

No adequate well-controlled head-to-head clinical trials are available.

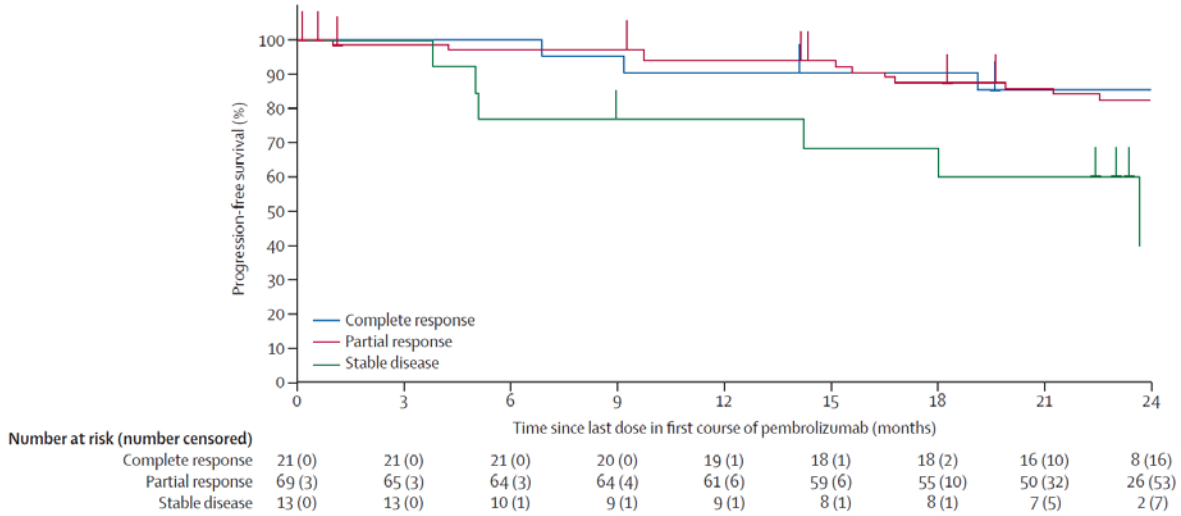
Disposition of patients who completed protocol-specified 2 years of pembrolizumab

median follow-up 34 mo after stopping pembrolizumab



PFS from last dose to PD or death in patients who completed 2 years of treatment

(n = 103)

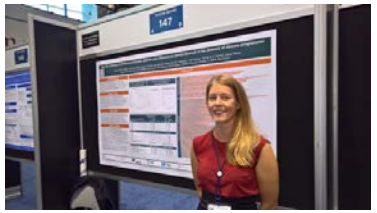


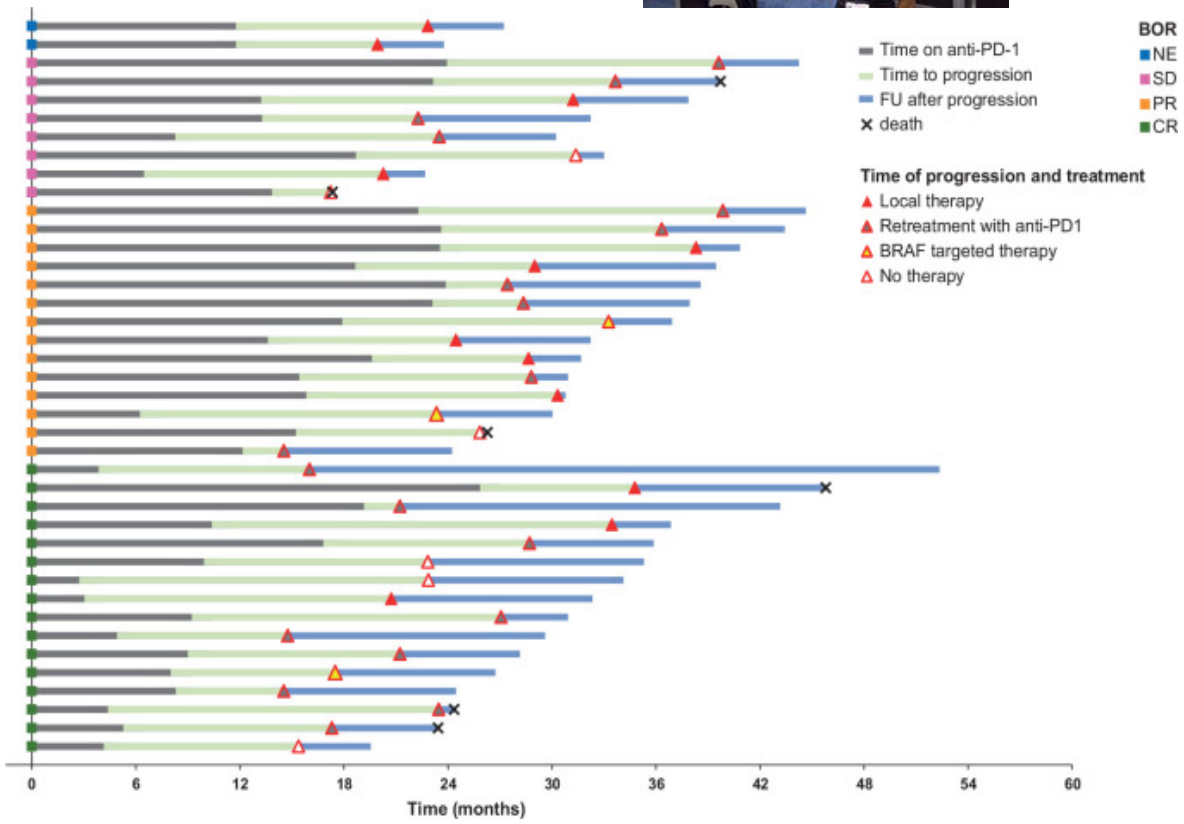
Reproduced from Robert C. et al. Lancet Oncol. 2019 20(9):1239-1251

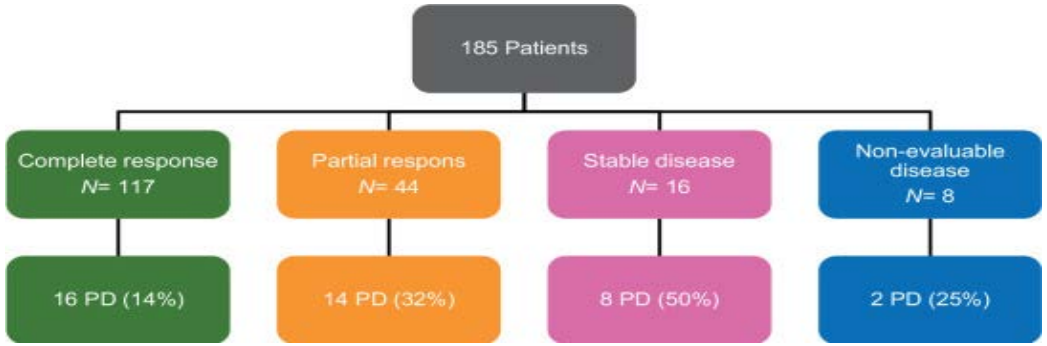
Best Response	n	Estimated PFS (95% CI)
CR	21	85.4% (61.3–95.1)
PR	69	82.3% (70.3–89.8)
SD	13	39·9% (8.1–71.4)

Reproduced from Robert C. et al. Lancet Oncol. 2019 20(9):1239-1251

Real life data from advanced melanoma pts discontinuing anti-PD1 in the absence of PD or treatment limiting toxicity at 14 hospitals across Europe and Australia

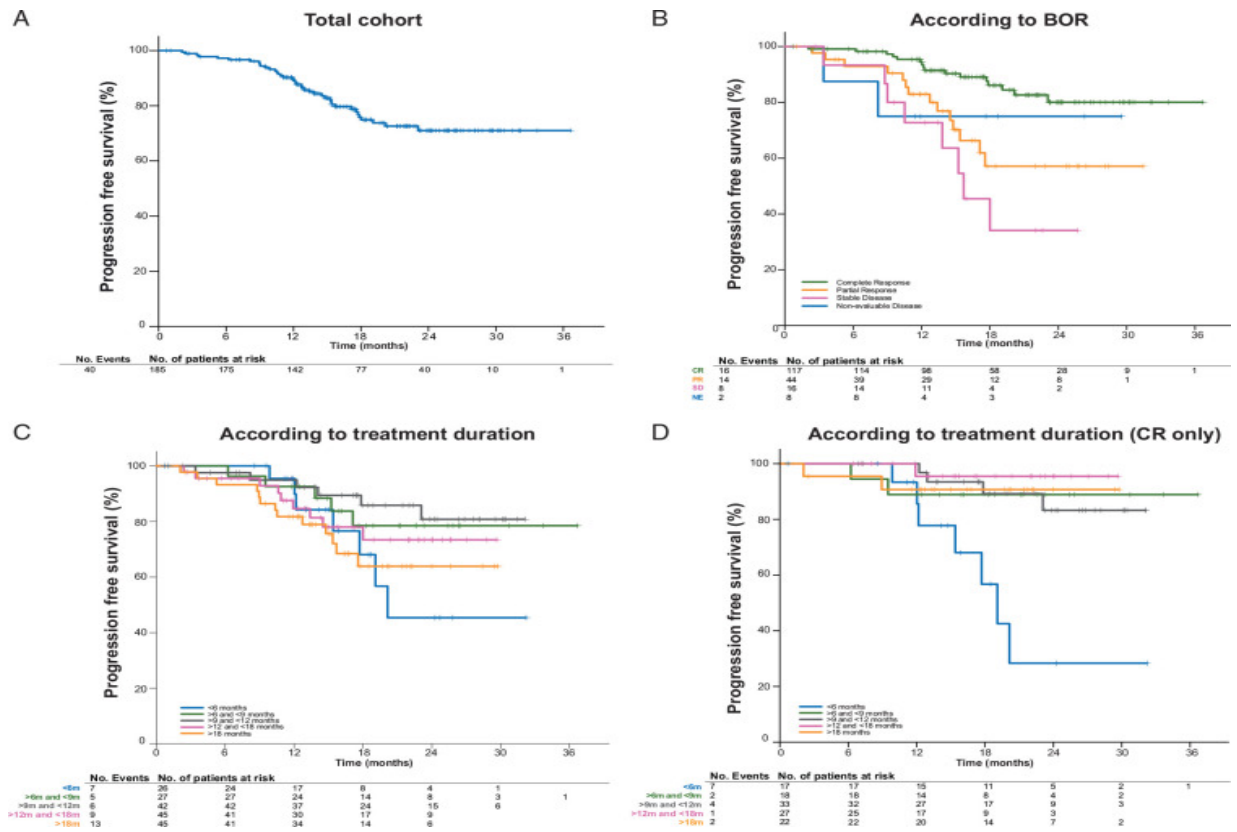






Outcome of 185 patients discontinuing treatment according to BOR and outcome after PD-1 reintroduction. Of the 185 patients who discontinued anti-PD-1, 40 patients experienced progressive disease. A PD-1 inhibitor was re-introduced in 19 patients leading to 6 renewed objective responses (32%, two patients with a CR [11%] and four patients with a PR [21%]). Abbreviations: PD-1, Programmed cell death protein 1; CR, complete response; PR, partial response; SD, stable disease; NE, non-evaluable disease; PD, progressive disease; BOR, best objective response.

Elective discontinuation should only be considered after a minimum of 6 months of treatment duration



Kaplan–Meier probability curves for progression-free survival from discontinuation of anti-PD-1. Progression free survival from discontinuation of anti-PD-1 for the total cohort that discontinued in the absence of PD or TLT (A); according to best overall (B) and according to time on anti-PD-1 therapy for the whole cohort (C) and only for patients with a CR (D). The hash marks designate patients who were censored at that time point. Abbreviations: PD-1, programmed cell death protein 1; BOR, best overall response; PD, progressive disease; TLT, treatment limiting toxicity.

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Recommendation 6.1. Patients with a CR that persists at the following radiological evaluation (at least 4 weeks after), and who have received at least 6 months of anti-PD-1 treatment, can be considered for stopping therapy.

Recommendation 6.2. Stopping treatment with anti-PD-1 therapy should be considered after 2 years of treatment in the case of PR.

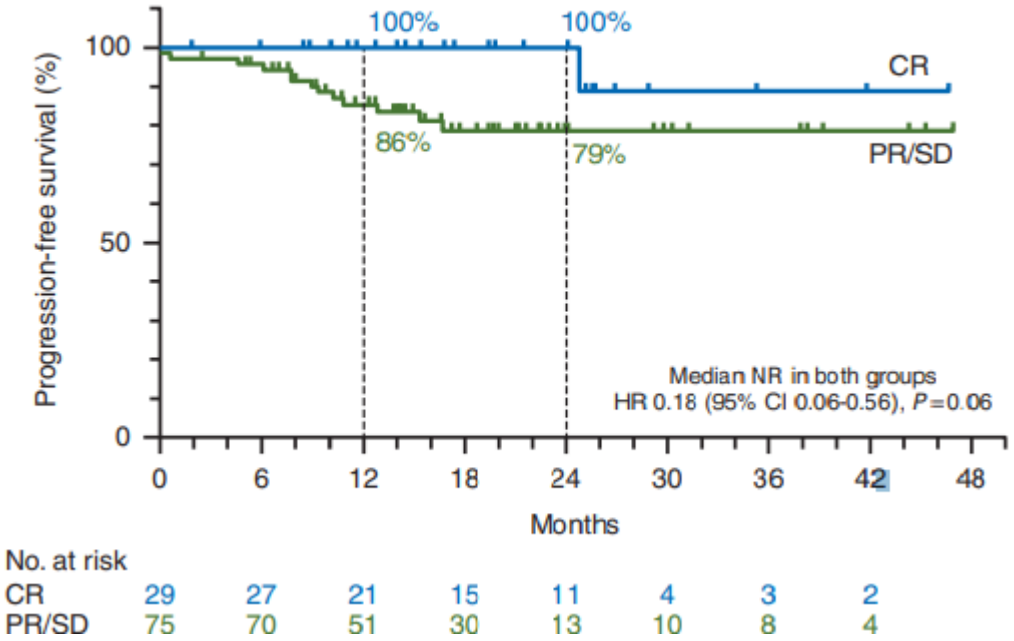
Recommendation 6.3. Stopping treatment with anti-PD-1 therapy can be considered after 2 years of treatment in the case of SD.

ESMO consensus conference recommendations

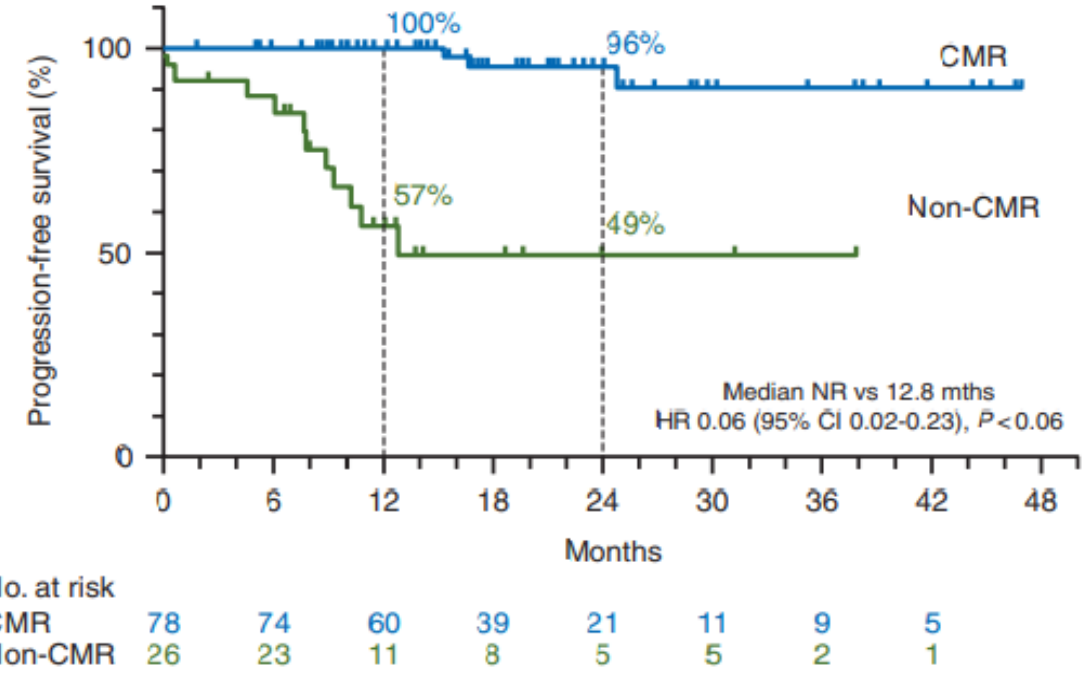
Reproduced from Jansen Y et al. Ann Oncol. 2019;30(7):1154-1161 Keilholz U. et al Ann Oncol 2020 31(11): 1435-1448

FDG-PET of value in predicting long-term outcomes ?

Progression free survival post 1-year imaging by CT response



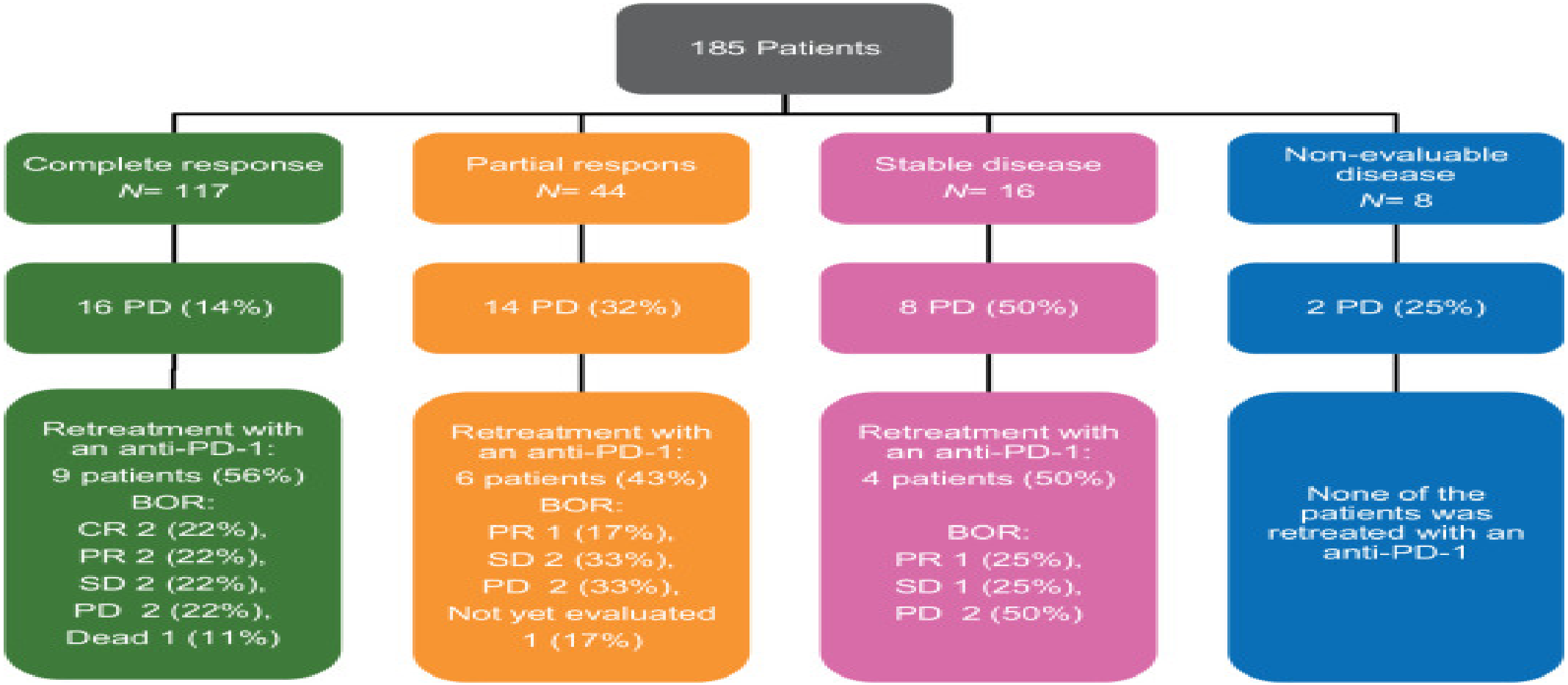
Progression free survival post 1-year imaging by PET response



- RECIST PFS post 1-year landmark was similar in patients with CR vs PR/SD, but improved in patients with CMR vs non-CMR In the 78 CMR patients, 78% had discontinued treatment and 96% had ongoing response.
- In patients with PR on CT, PFS was improved in patients with PR+CMR vs PR+non-CMR (median NR vs 12.8 months; HR 0.07 [95% CI 0.02-0.27]; p<0.01)

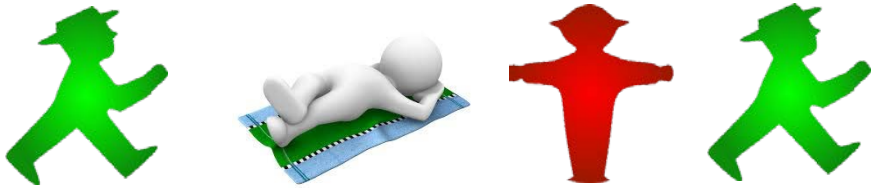
Reproduced from Tan AC et al. Ann Oncol. 2018: 29(10):2115-2120

Clinical outcome of advanced melanoma patients after discontinuation of an anti-PD-1 in the absence of disease progression or treatment limiting toxicity



Outcome of 185 patients discontinuing treatment according to BOR and outcome after PD-1 reintroduction. Of the 185 patients who discontinued anti-PD-1, 40 patients experienced progressive disease. A PD-1 inhibitor was re-introduced in 19 patients leading to 6 renewed objective responses (32%, two patients with a CR [11%] and four patients with a PR [21%]). Abbreviations: PD-1, Programmed cell death protein 1; CR, complete response; PR, partial response; SD, stable disease; NE, non-evaluable disease; PD, progressive disease; BOR, best objective response.

Melanoma: when to stop immunotherapy?



- Stopping anti-PD1 immunotherapy my be considered in advanced melanoma patients who benefit from therapy and do not experience treatment limiting toxicities with an acceptable low risk for progression within the first 3 years following treatment discontinuation
- The optimal duration of aPD-1 has not been established and may vary between patients
  - Largest body of evidence relates to an arbitrary treatment duration of 2y (KN006)
  - Real world data support shorter duration of therapy as equally safe with respect to PFS
  - CR on CT can be used as a main driver in decision making (KN001)
  - PET/CT after 1y of therapy can aid decision making in patients with PR and CMR
- Rather than prospective trials investigating arbitrary duration of therapy, predictive algorithms incorporating baseline clinical and tissue biomarkers and on-therapy response characteristics (PET/CT) may allow us to make individualized decisions on optimal treatment duration
- Retreatment at the time of PD following elective treatment discontinuation has demonstrated activity in small case series and should be considered @PD following elective discontinuation

Back-Up slides

Outcome of patients after retreatment with anti-PD-1therapy

Patient	Time on anti-PD-1 (months)	BOR 1st course anti-PD-1	Time to PD (months)	Therapy for PD	BOR 2nd course anti-PD-1	Disease status at time data cut-off
1	<6	CR	9.9	Pembrolizumab	CR	Ongoing CR[a]
2	>18	CR	2.1	Pembrolizumab	CR	Ongoing CR
3	<6	CR	12.2	Pembrolizumab	PR	PD
4	<6	CR	12.0	SRS + Pembrolizumab	PR	Ongoing PR
5	9–12	CR	17.8	SRS + nivolumab	PR	Ongoing PR
6	6–9	CR	19.2	Pembrolizumab	SD	Slow PD
7	9–12	CR	12.2	Pembrolizumab	PD	
8	12–18	CR	12.0	pembrolizumab	PD	
9	<6	CR	16.2	Pembrolizumab	died	
10	>18	PR	5.3	Pembrolizumab	PR	Ongoing PR
11	12–18	PR	2.3	Pembrolizumab	SD	Ongoing SD[b]
12	>18	PR	17.5	Pembrolizumab	SD	Ongoing SD
13	12–18	PR	13.4	Nivolumab	not yet	
14	>18	PR	12.7	Nivolumab	PD	
15	>18	PR	3.5	Pembrolizumab	PD	
16	6–9	SD	15.2	Pembrolizumab	SD	PD[c]
17	>18	SD	10.6	Pembrolizumab	SD	Ongoing SD
18	12–18	SD	9.0	Nivolumab	PD	
19	>18	SD	10.6	Pembrolizumab	PD	

Anti-PD-1 therapy was re-introduced in 19 patients leading to 6 renewed objective responses (32%, 2 patients with a CR [11%] and 4 patients with a PR [21%]). Abbreviations: PD-1, programmed cell death protein 1; CR, complete response; PR, partial response; SD, stable disease; NE, non-evaluable disease; PD, progressive disease; BOR, best objective response.

[a]Discontinued therapy after 9 cycles.

[b]Discontinued therapy after 4 cycles.

[c]Received chemotherapy for NHL.

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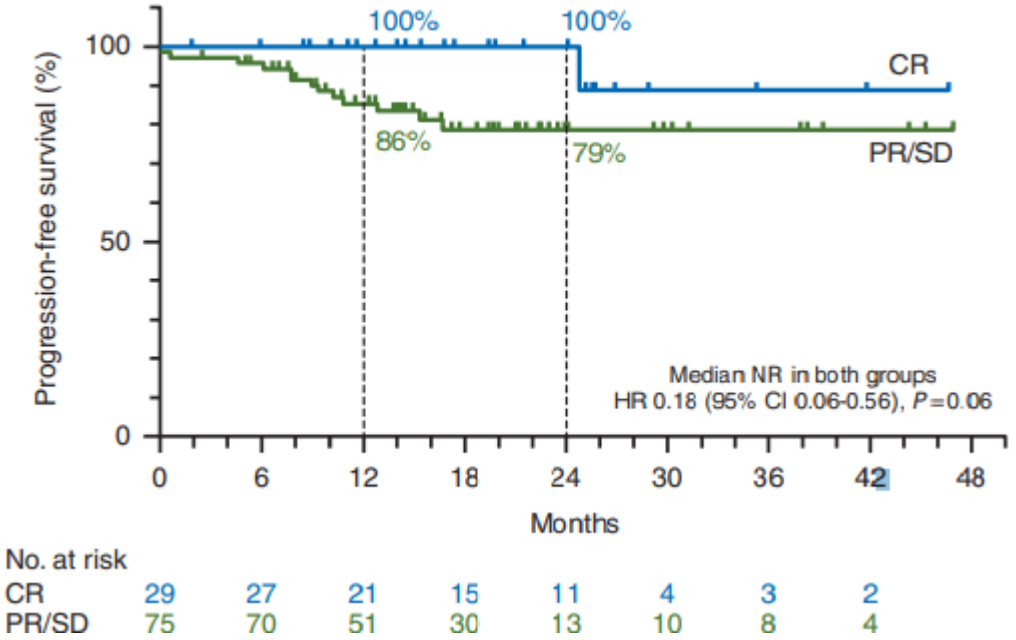
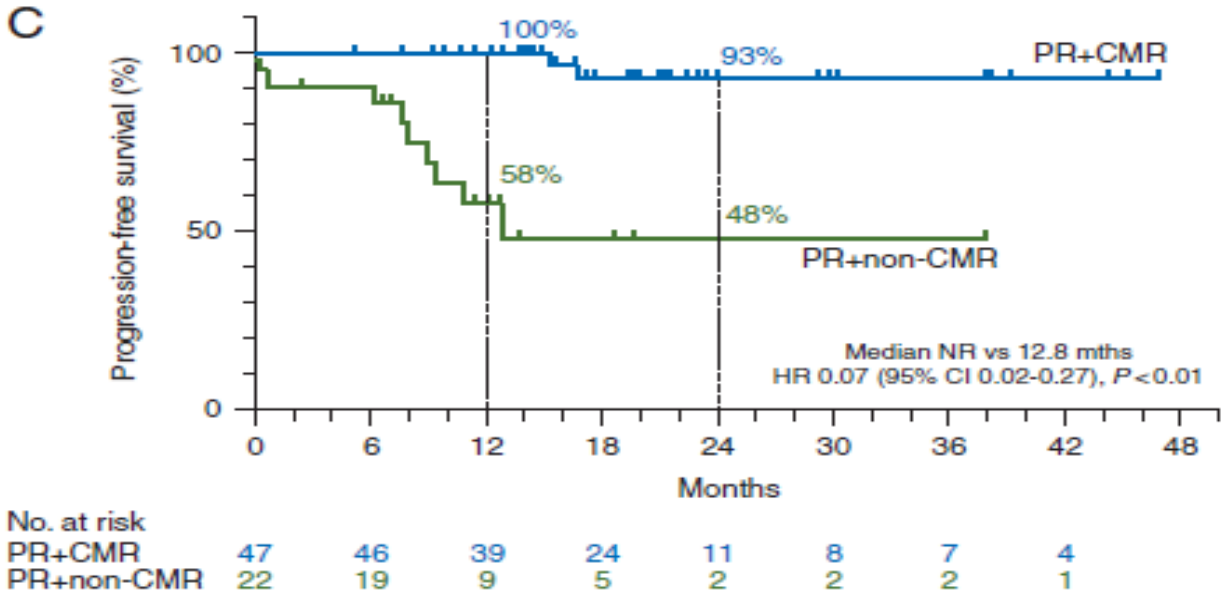
- RECIST PFS post 1-year landmark was similar in patients with CR vs PR/SD, but improved in patients with CMR vs non-CMR (median not reached [NR] vs 12.8 mths; HR 0.06 [95% CI 0.02-0.23]; p<0.01)
- In the 78 CMR patients, 78% had discontinued treatment and 96% had ongoing response.

Progression free survival post 1-year imaging by CT response



Progression free survival post 1-year imaging in patients with PR or CR



Reproduced from Tan AC et al. Ann Oncol. 2018: 29(10):2115-2120