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www.immunoscienceacademy.be

Hot topics – Experts Panel Session

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Brussels, Belgium

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Date of preparation: December 2019

Disclaimer: Any off-label data shown are used to support the educational message of the presentation and not intended to endorse use of any drug in any way

Established activity of CPIs in:	Activity reported with CPIs in:
Melanoma	HCC
NSCLC	Cervical Cancer
RCC	Esophageal
Urothelial	Gastric / GEJ
H & N	NET (Lung)
Merkel Cell	Ovarian
MSI high	SCLC
TNBC	

Question: How to move further (adjuvant, …)?

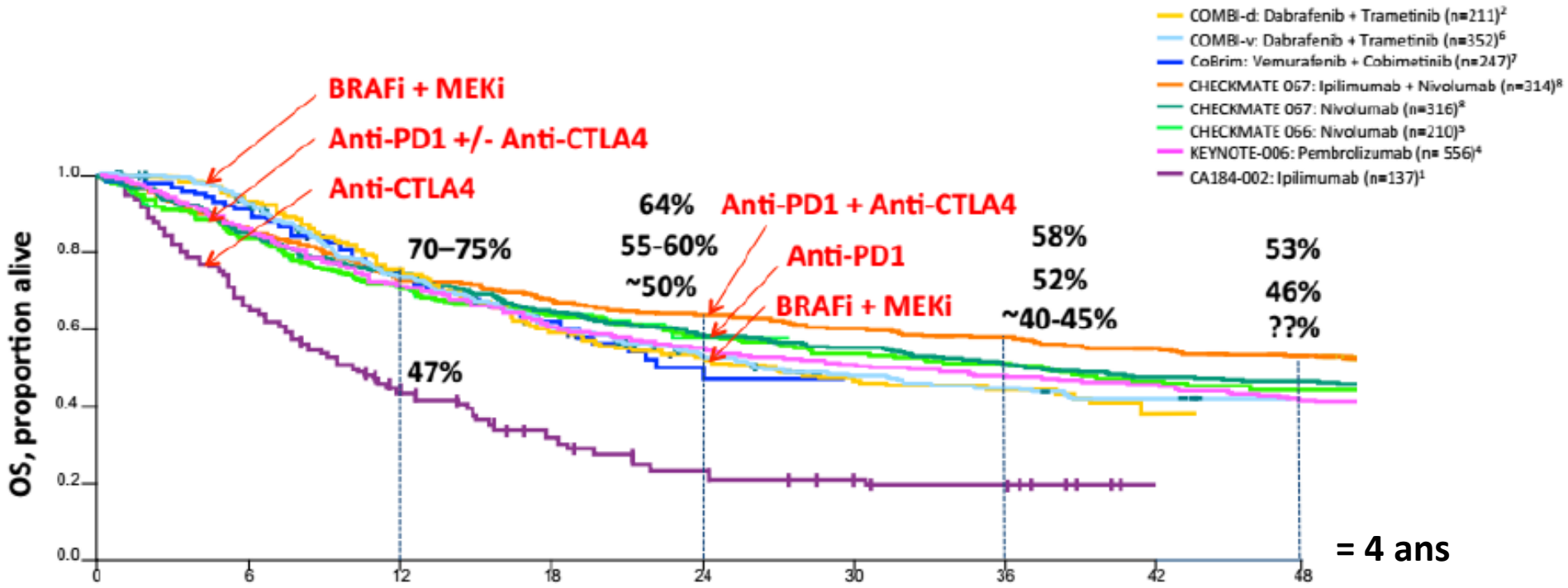
Question: How to improve the tumor activity?

No convincing activity (so far) of CPIs in:

- Prostate
- Sarcoma (all disease)
- NET (other than lung)
- Colon (outside MSI)
- Endometrium (outside MSI)
- ER+ BC
- Pancreas
- Glioblastoma
- Mesothelioma
- Germ cell tumors

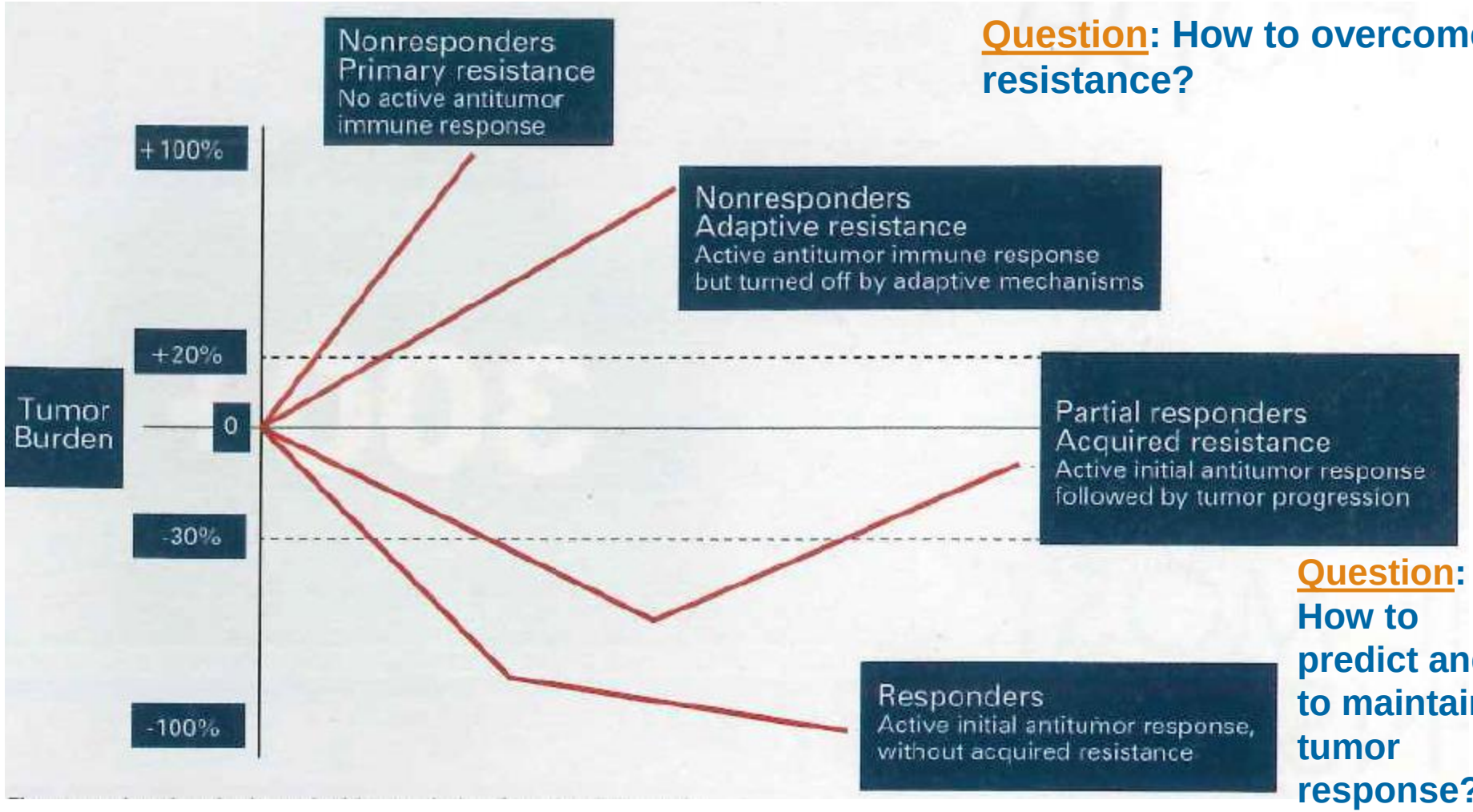
Question: How to transform these « Cold » tumors in « Hot » tumors?

Overall survival in metastatic melanoma – now we have 5 years data! : 52% of pts are alive with IPI + Nivo therapy!!



= 4 ans

Spider Plot of Clinical Scenarios Demonstrating Response and Resistance to Immunotherapy



Question: How to overcome resistance?

Question: How to predict and to maintain tumor response?

Patient’s immune response is dynamic and constantly evolving. This may be due to their own environmental and genetic factors or a result of treatment interventions, including surgery, chemotherapy, targeted therapy, radiation and immunotherapy

Experts

Expert: Dr S. Aspeslagh, UZ Brussel

Medical Oncology

Expert: Prof Dr P. Pauwels, UZ Antwerpen

Pathology

Expert: Dr. S. Rauh, CHEM Luxembourg

Internal Medicine-Onco/haematology

The views and opinions expressed in these presentations are **those** of the experts... Assumptions made are **not** necessarily reflective of the position of BMS

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Expert: Prof Dr P. Pauwels, UZ Antwerpen

Pathology

Biomarkers

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Which biomarker do you need, to decide on your treatment with immunotherapies for a lung cancer patient (non-mutation specific)?

- *PDL1*
- *TMB*
- *TIL's*
- *Interferon gamma signature*
- *Other*

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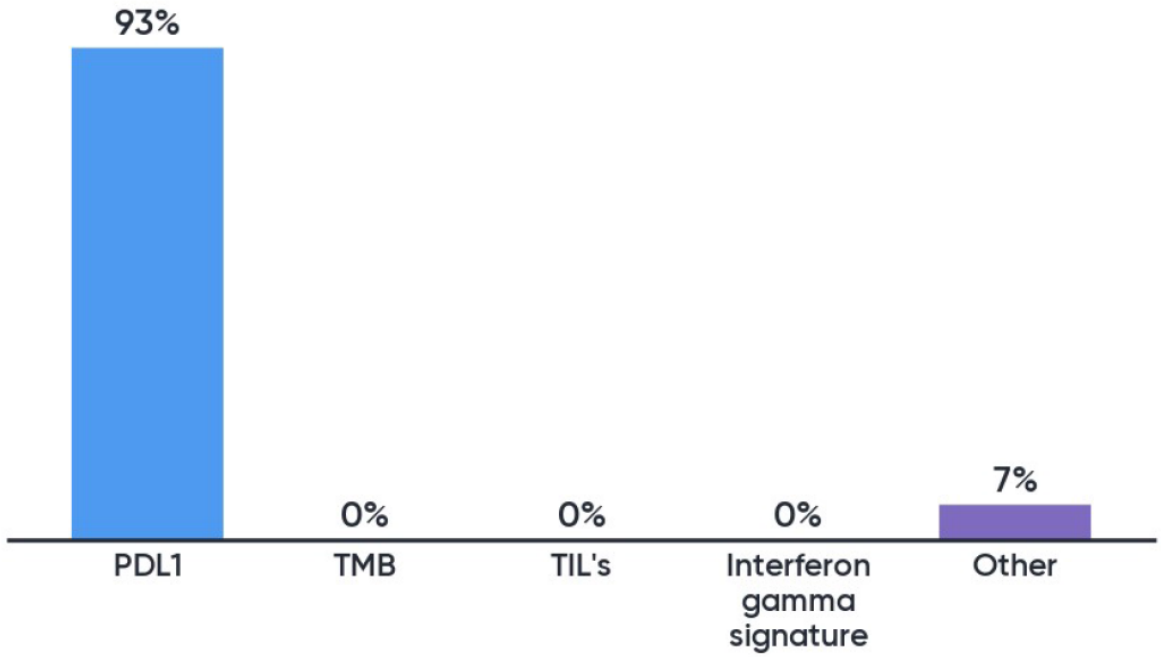
Which biomarker do you need, to decide on your treatment with immunotherapies for a lung cancer patient (non-mutation specific)?



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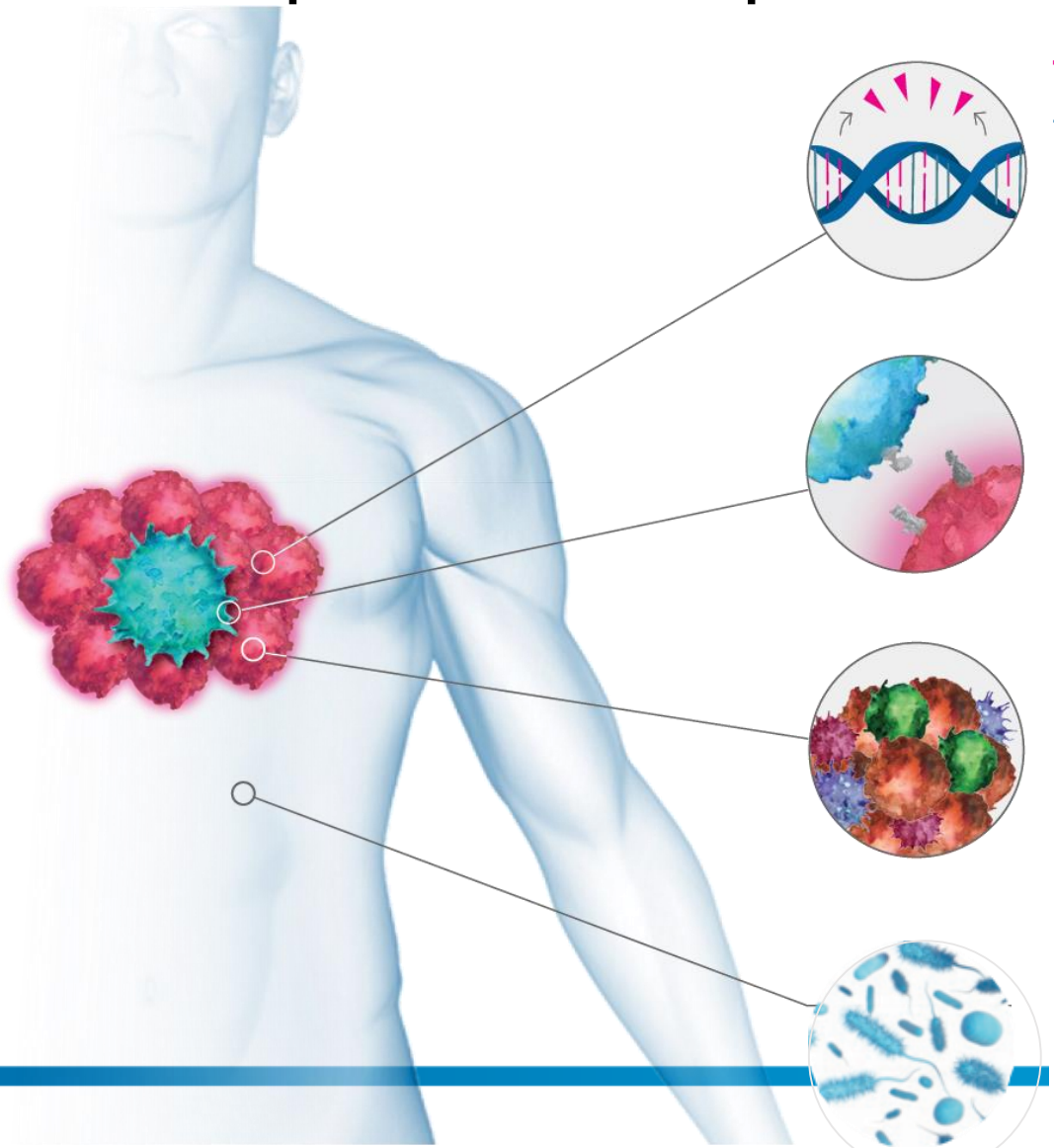
Tumor and immune biomarkers being evaluated to predict better potential responses to I-O therapy



Tumor Antigens

TMB | MSI-H/dMMR | Neoantigens

Inflamed Tumor Phenotype(s)

PD-L1 | PD-L2 | Inflammation Gene Signatures

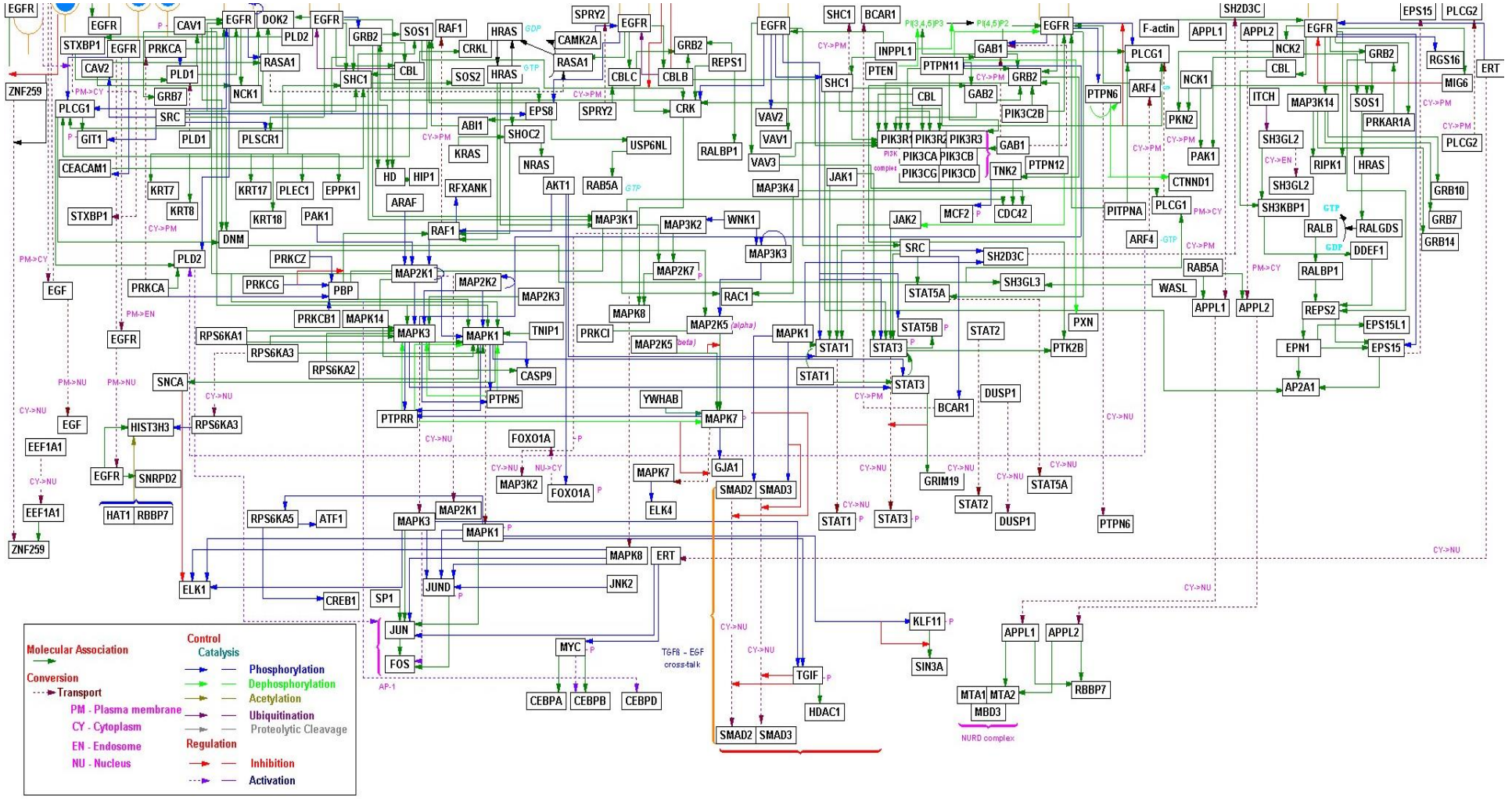
Immune Suppression

LAG-3 | Tregs | MDSCs

Host Environment

Microbiome | Germline Mutations

EGFR pathway



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Patient with smoking history and COPD is treated for a long period of time with changing doses of steroids over time.
Following the diagnosis of metastatic melanoma (BRAF - Wild type) the decision is made to start Checkpoint inhibitor therapy.

Do you expect that tumor response will be impacted by the steroids use?

- *Yes, efficacy will be impacted*
- *No, I don’t think so*
- *I don't know*

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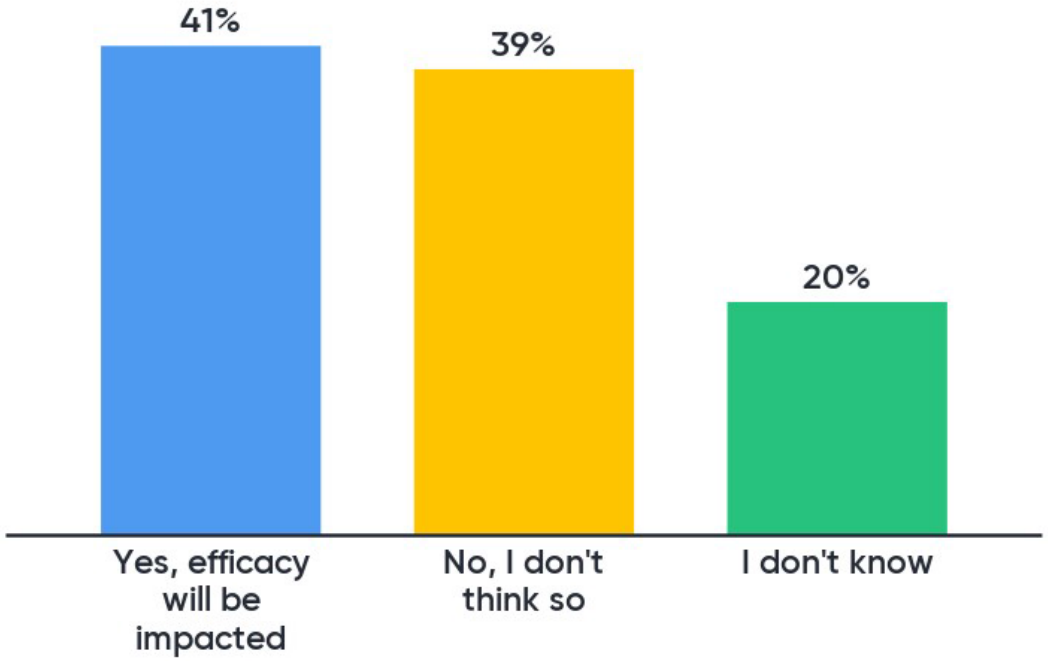
Patient with smoking history and COPD is treated for a long period of time with changing doses of steroids over time. Following the diagnosis of metastatic melanoma (BRAF - Wild type) the decision is made to start Checkpoint inhibitor therapy. Do you expect that tumor response will be impacted by the steroids use?



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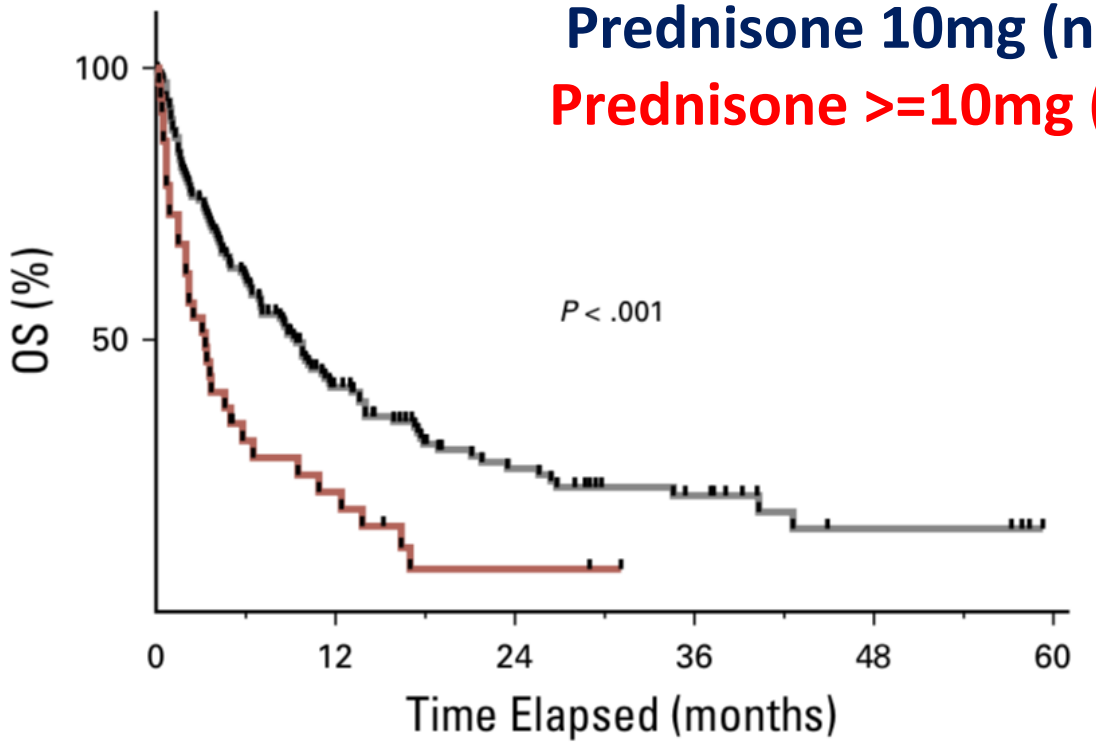
Expert: Dr S. Aspeslagh, UZ Brussel

Medical Oncology

Use of corticosteroids

Corticoids to support quality of life

F

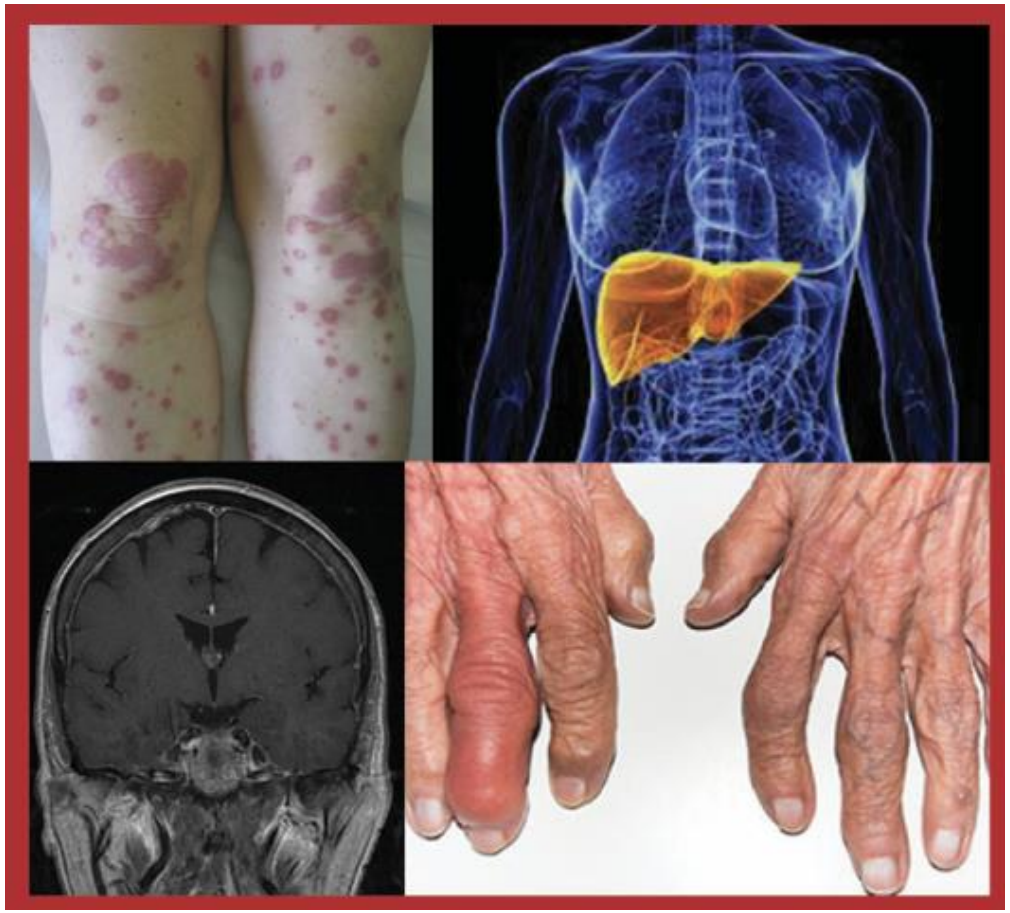


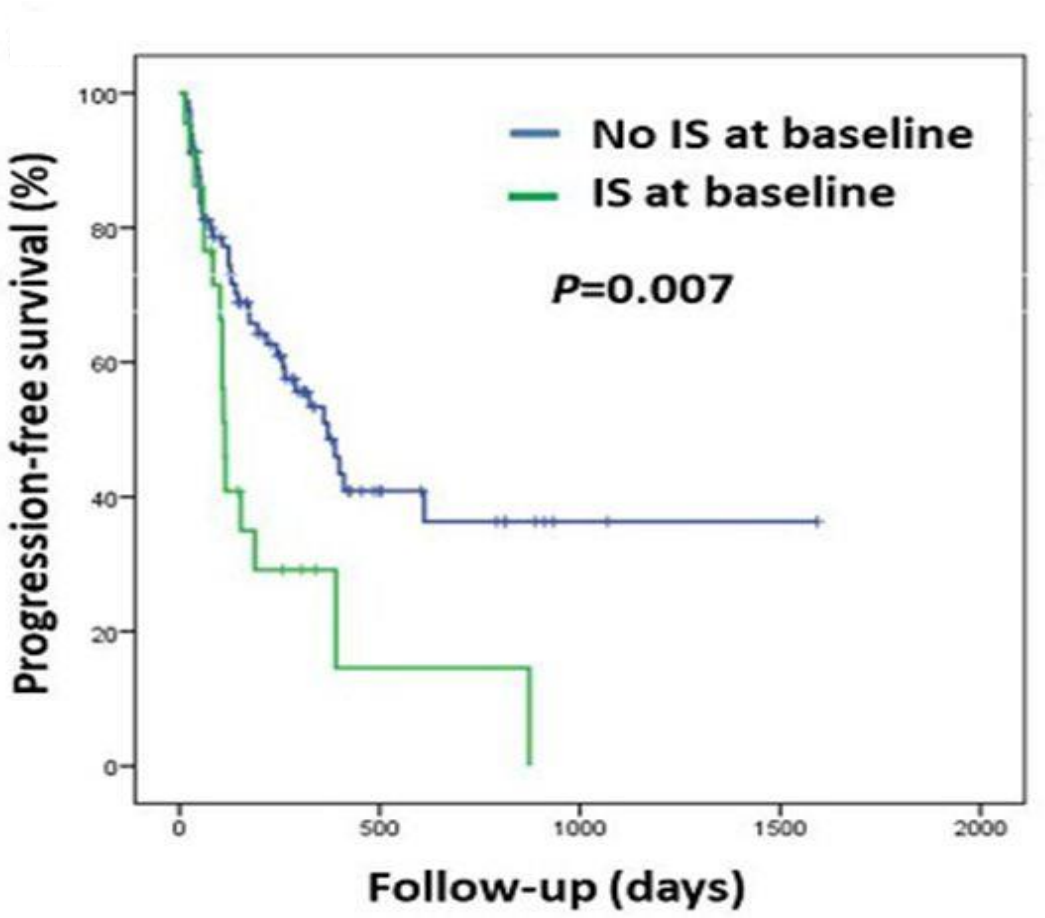
No. at risk:

< 10 mg:	148	49	23	12	4	0
≥ 10 mg:	37	7	2	0	0	0

Arbour et al JCO 2018.

Patients with preexisting autoimmune disease

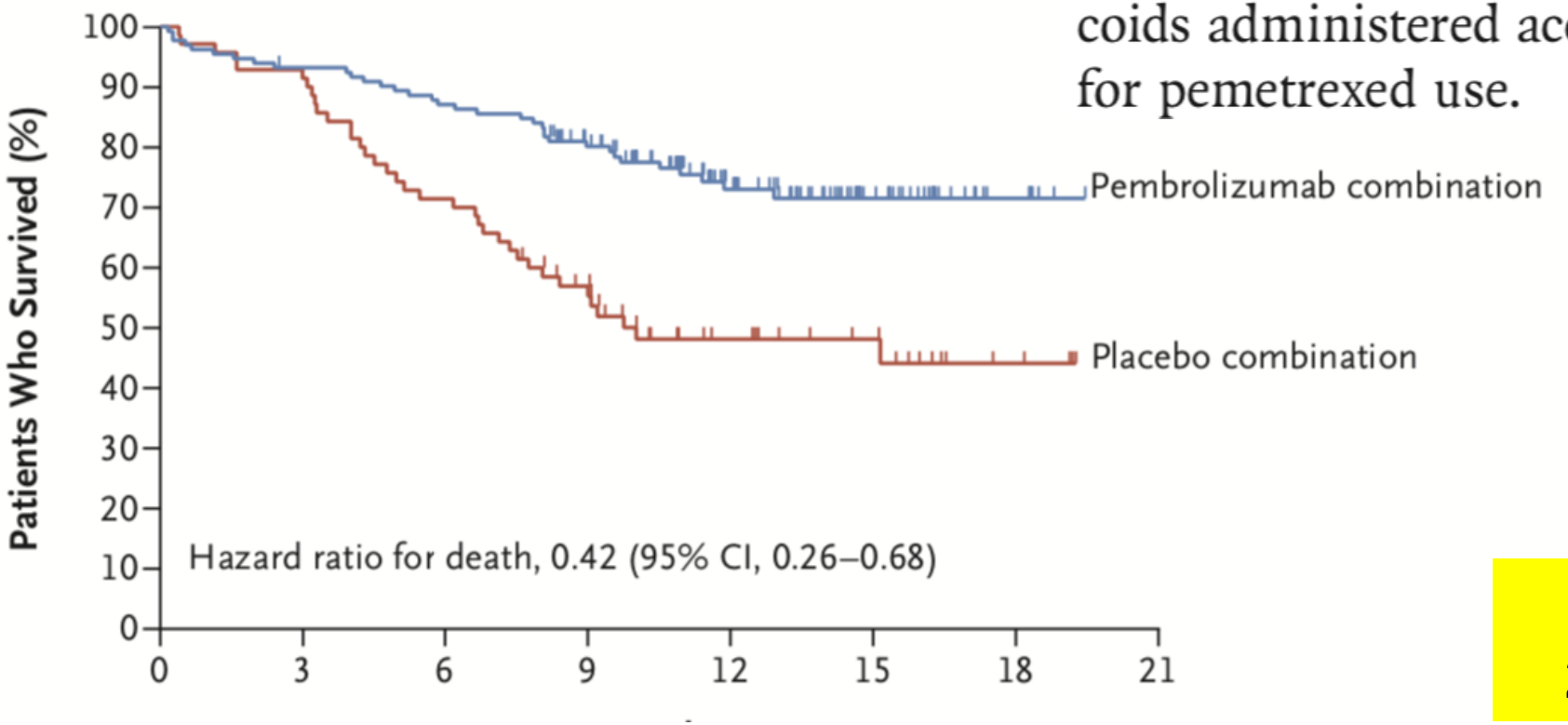




Tison A et al, 2019, Arthritis and Rheumatism

Corticoids are part of anti-tumoral therapy
Combination with chemotherapy

every 3 weeks. All the patients received premedication with folic acid, vitamin B_{12}, and glucocorticoids administered according to local guidelines for pemetrexed use.



Our centre:
20-50mg prednisolone

Gandhi et al, 2018, NEJM

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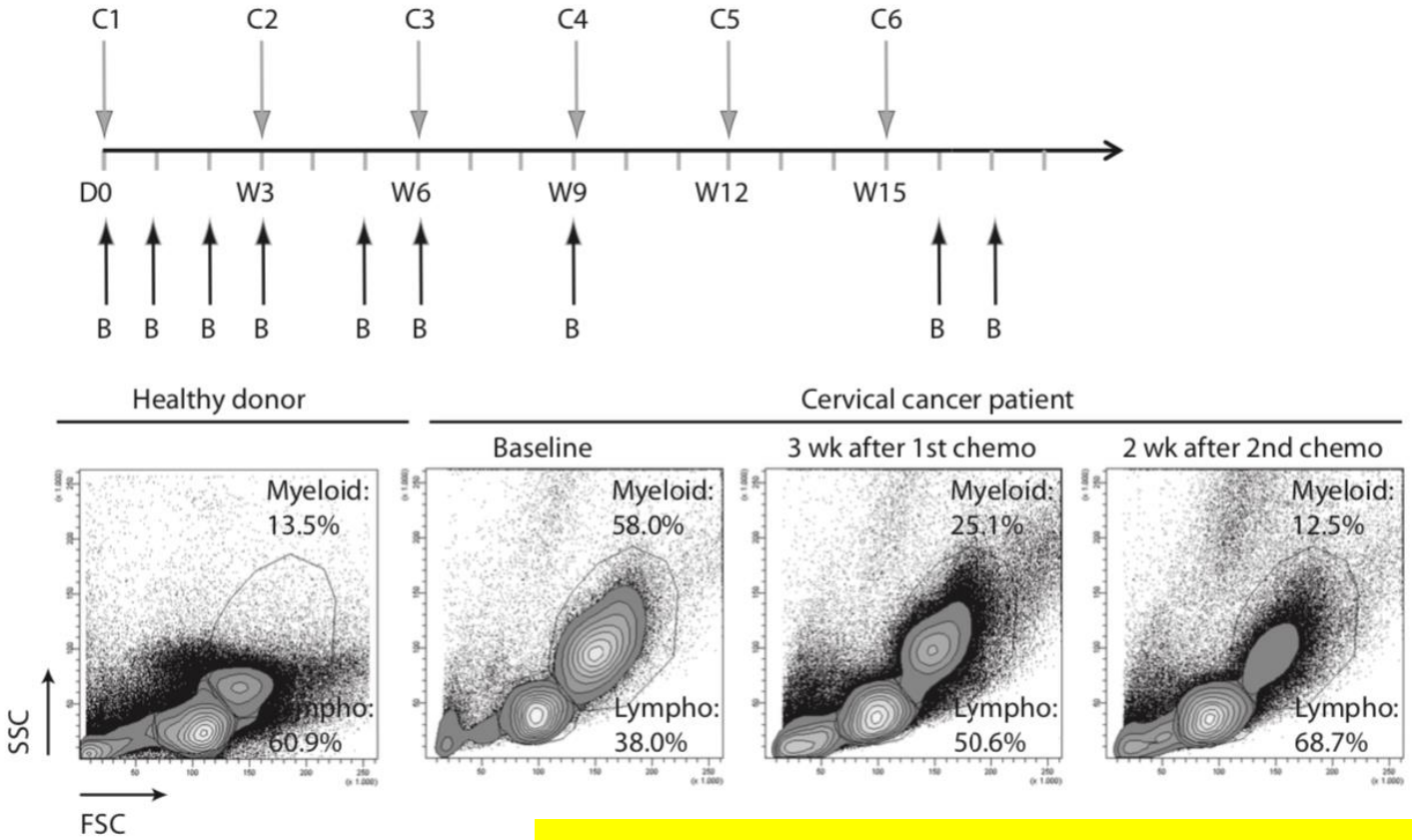
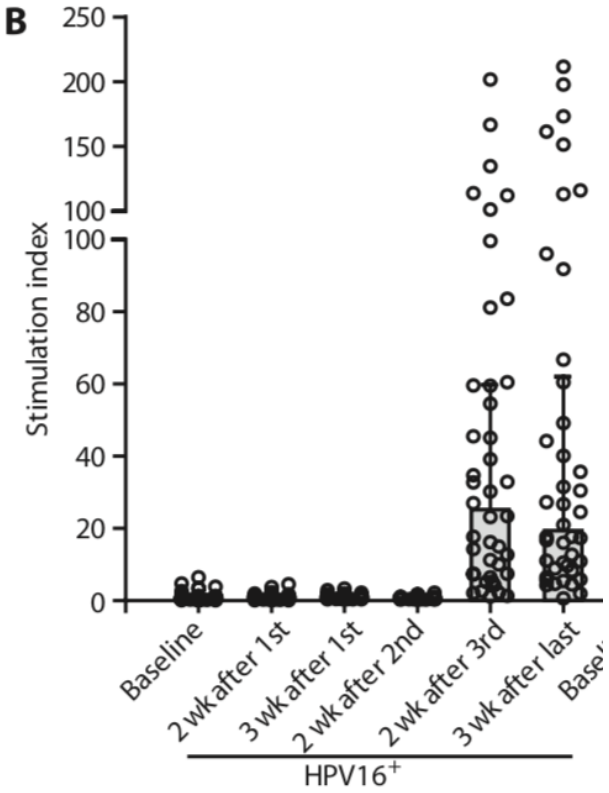
Corticoids are part of anti-tumoral therapy
Combination with chemotherapy and vaccination





Carboplatinum (AUC 6) + Taxol (175mg/m2)
+-100mg prednisolone premedication

Welters et al 2016 ScienceTranslational medicine.

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A patient that never received steroids before and develops grade 2 irAE.
You start steroids.

1. Do you think timing to start steroids is of importance?

- *Yes*
- *No*
- *I don't know*

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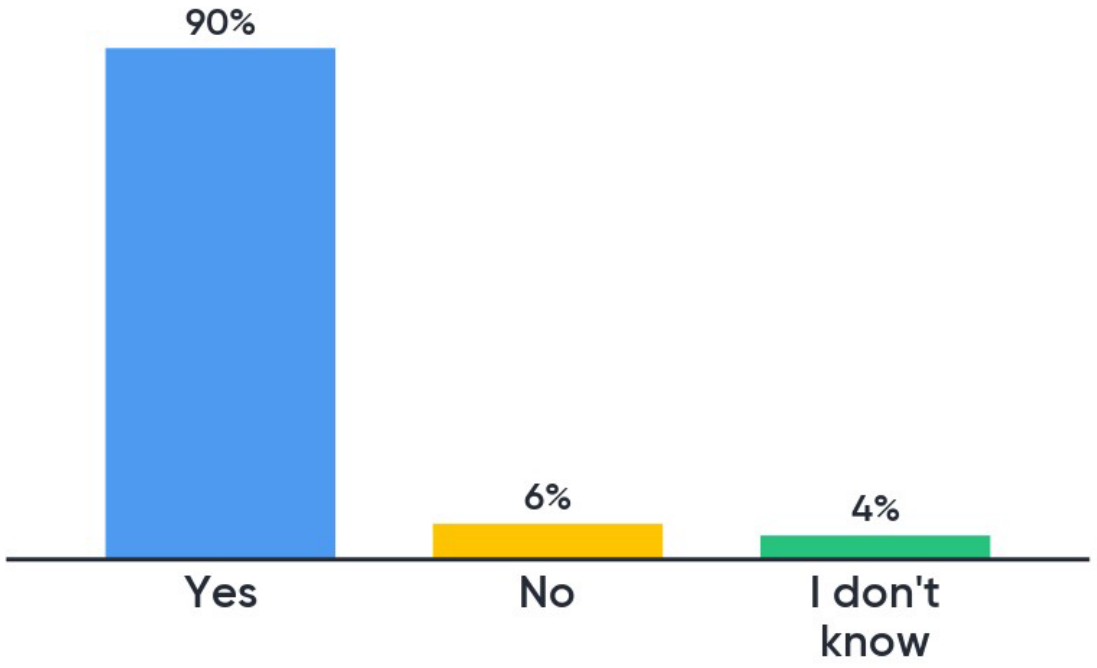
A patient that never received steroids before and develops grade 2 irAE. You start steroids.

1. Do you think timing to start steroids is of importance?



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A patient that never received steroids before and develops grade 2 irAE.
You start steroids.

2. Will you adapt dose over time?

- *Yes*
- *No*
- *I don't know*

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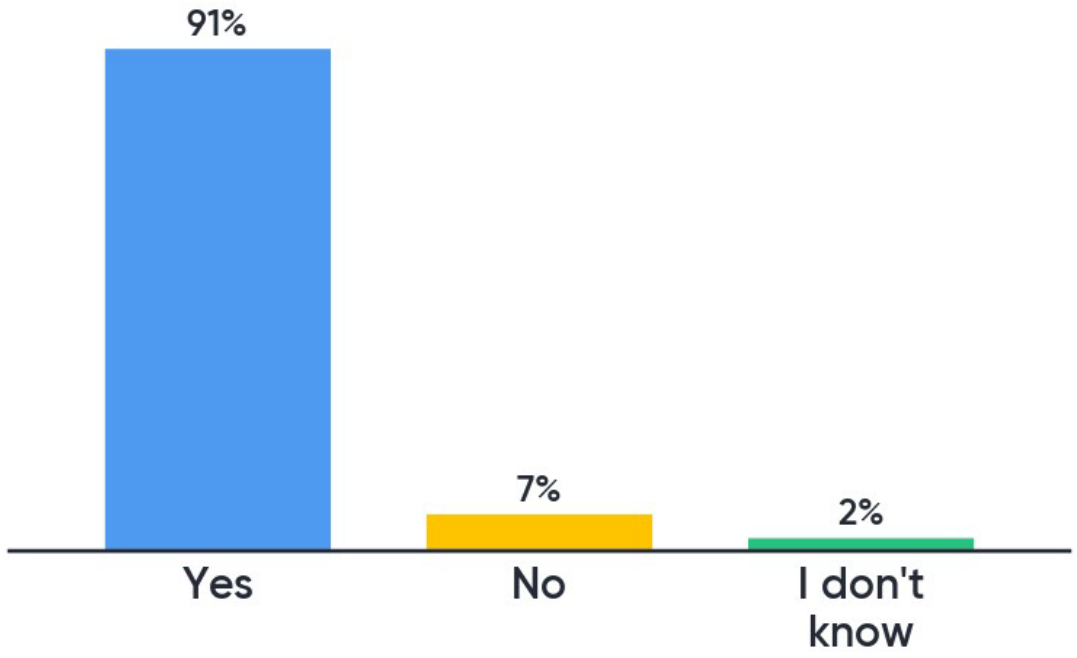
A patient that never received steroids before and develops grade 2 irAE. You start steroids.

2. Will you adapt dose over time?



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A patient that never received steroids before and develops grade 2 irAE.
You start steroids.

3. Do you think that duration of steroids use influences therapy ?

- *Yes*
- *No*
- *I don't know*

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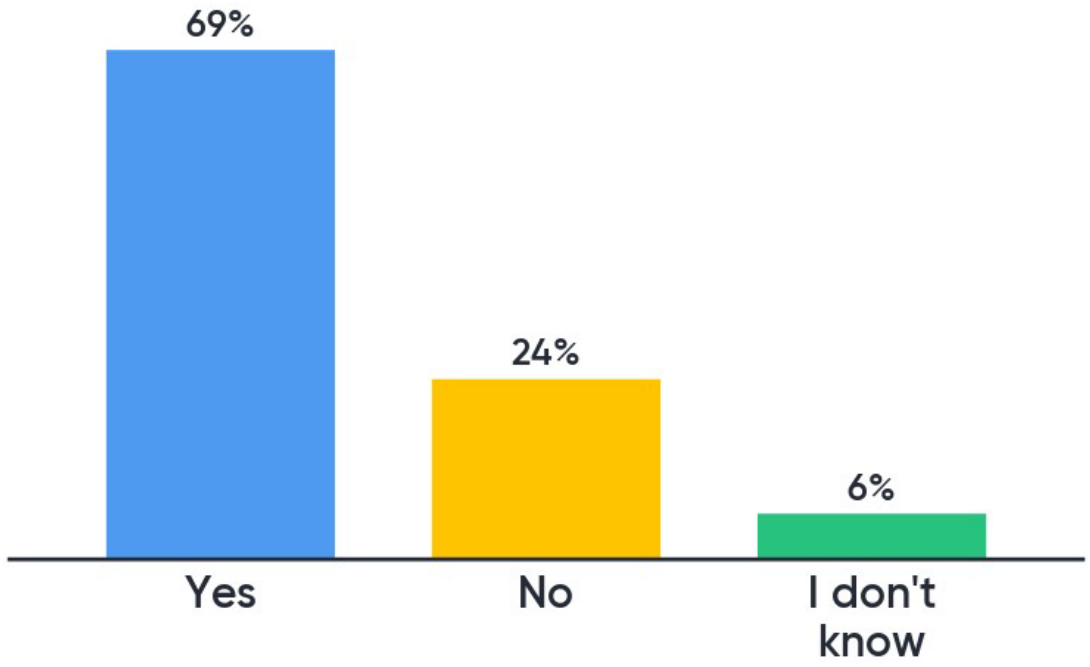
A patient that never received steroids before and develops grade 2 irAE. You start steroids.

3. Do you think that duration of steroids use influences therapy ?



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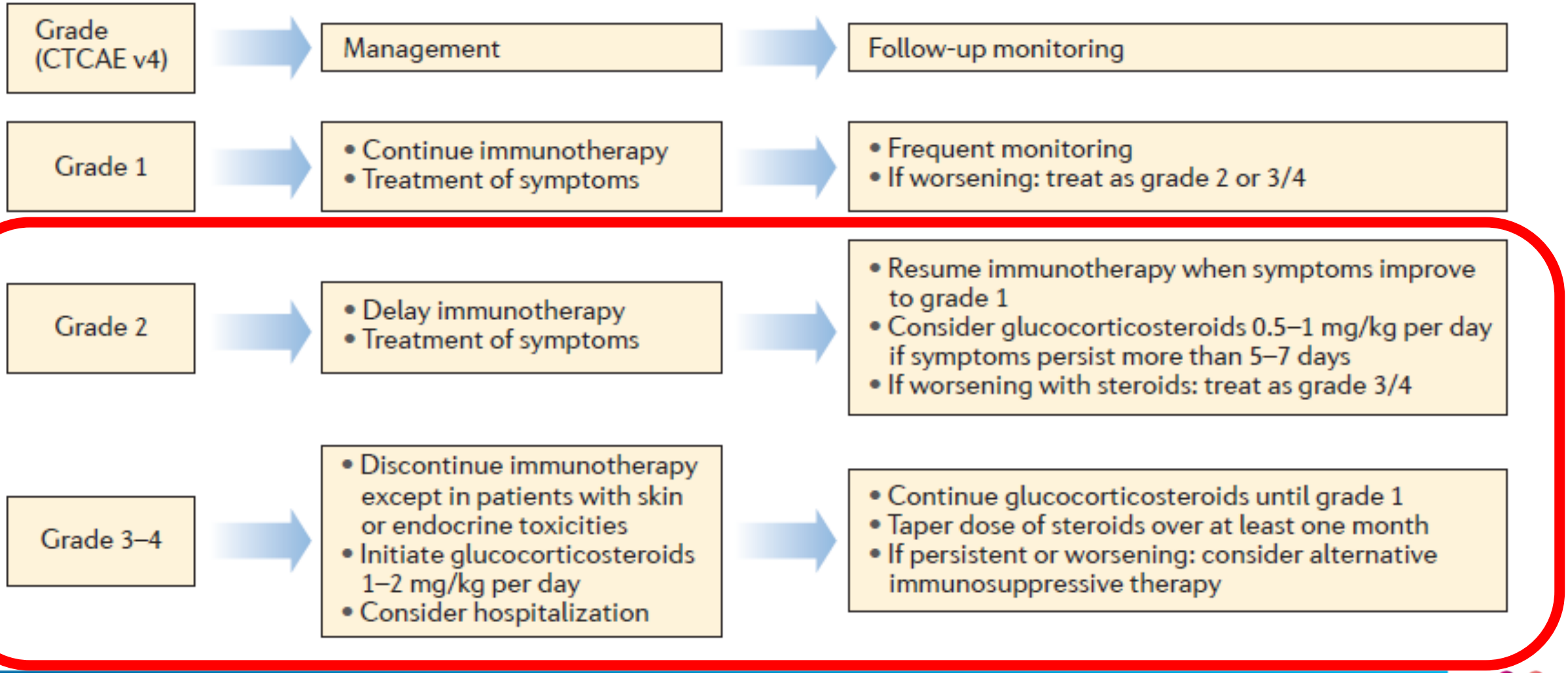
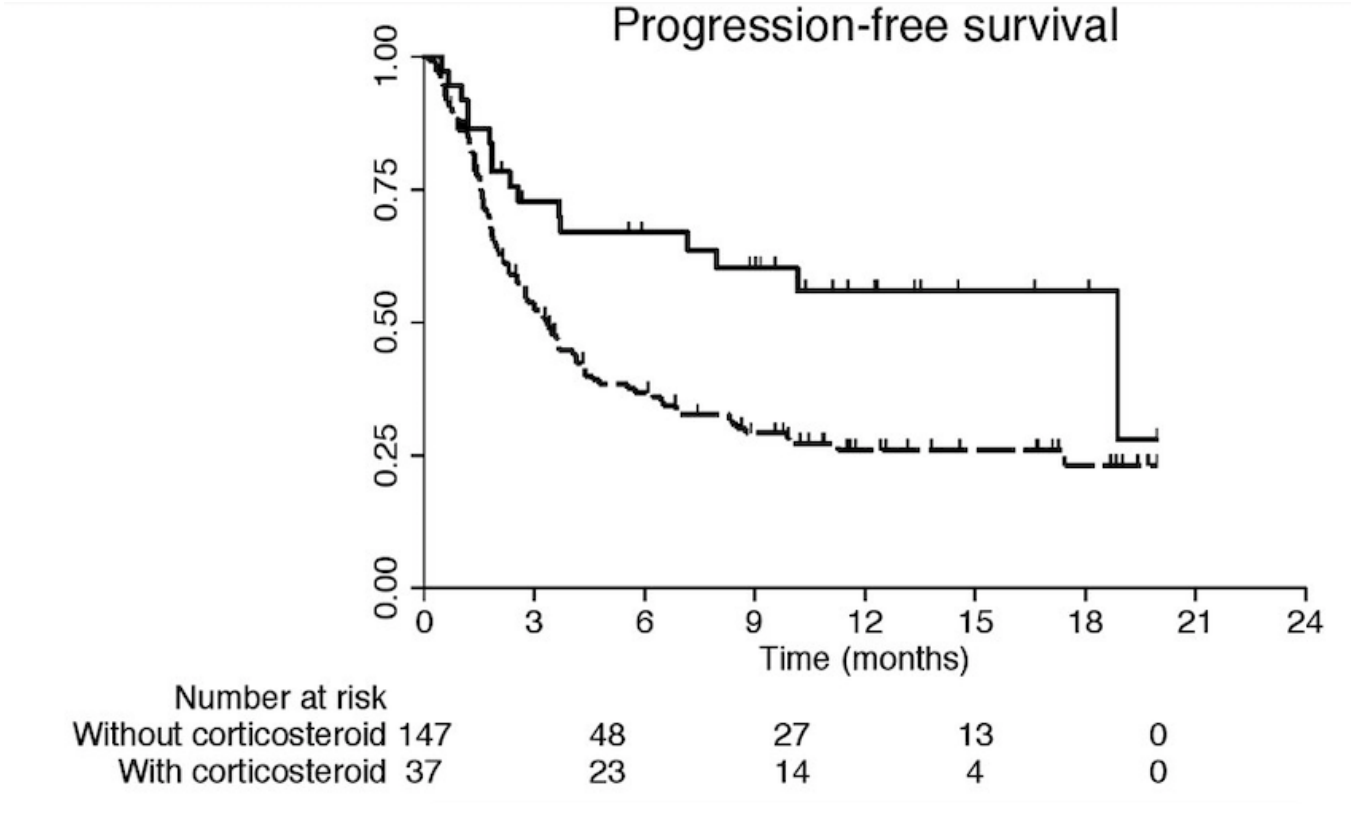
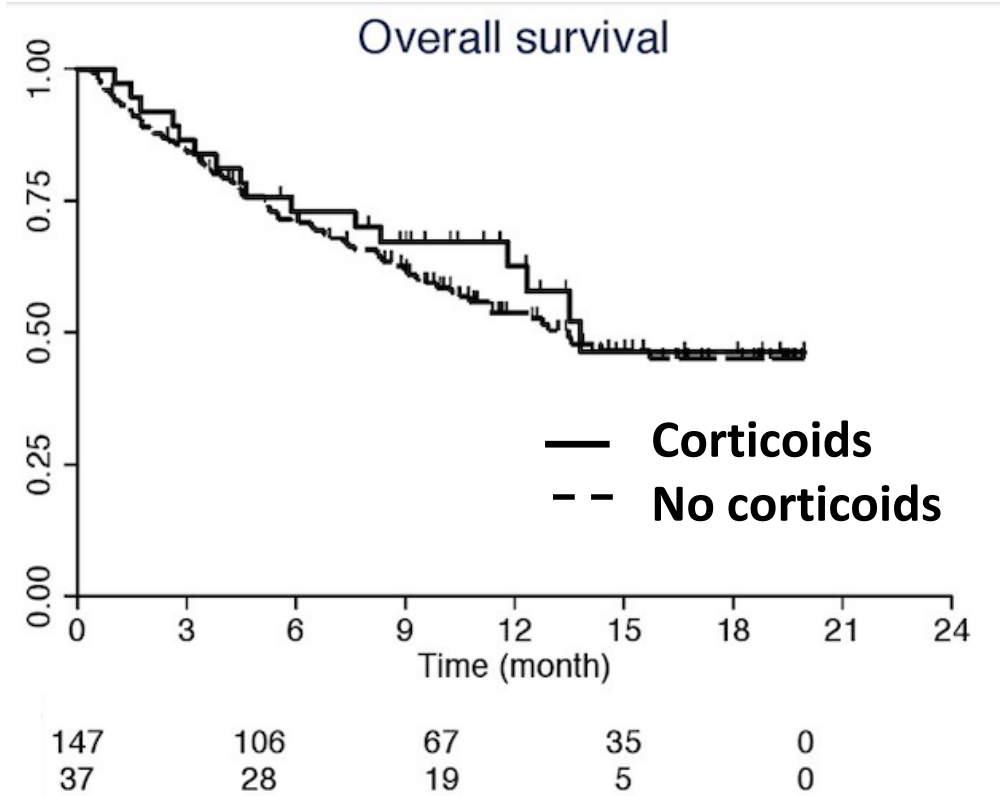
Severity of irAE



Boutros, C. et al. 2016 Nat Rev Clin Oncol 13, 473–486

Effect of corticoids given for irAE on the anti-tumour response





The effect of other immunosuppressives on cancer evolution such as TNF blockers, Leflunomide, Vedolizumab, Tocilizumab, MMF,... is rather unclear...

Higashiyama et al 2018 SITC

Not always corticoids required!

- **Hepatitis:**
  - not indicated unless signs of liver dysfunction (eg jaundice, PT drop)
- **Endocrine toxicity:**
  - only replace hormones
- **Colitis:**
  - early switch TNFα blocker if corticoid resistant
  - Future: fecal transplantation?
- **Lipase increase:**
  - no treatment if no clinical signs of pancreatitis

Conclusion

- No clear cut answer how to use corticoids combined with ICP
- **For sure**
  - Corticoids are needed for life treatening irAE
  - Giving corticoids for improvement of QOL with ICP is not a good idea
  - Pulse dose corticoids during chemo do not necessary prevent immune responses
- **To be further analyzed**
  - Dose and timing of corticoids that affects anti-tumour immune answer is unclear and might depend on tumour type, irAE subtype, patient characteristics etc

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Expert: Dr. S. Rauh, CHEM Luxembourg

Internal Medicine-Onco/haematology

Checkpoint inhibitors: How long should we treat ? Can we count on effective rechallenge

Stefan Rauh
Centre Hospitalier Emile Mayrisch
Esch LU

Bristol-Myers Squibb

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A patient with melanoma first-line treatment nivo-ipi presents partial response after 1 year of treatment. Due to grade 2 side effects treatment needs to be stopped.

What do you do?

- I re-start treatment once AE has cleared
- I don't restart treatment immediately. If patient progresses again than I will re-start
- I don't know

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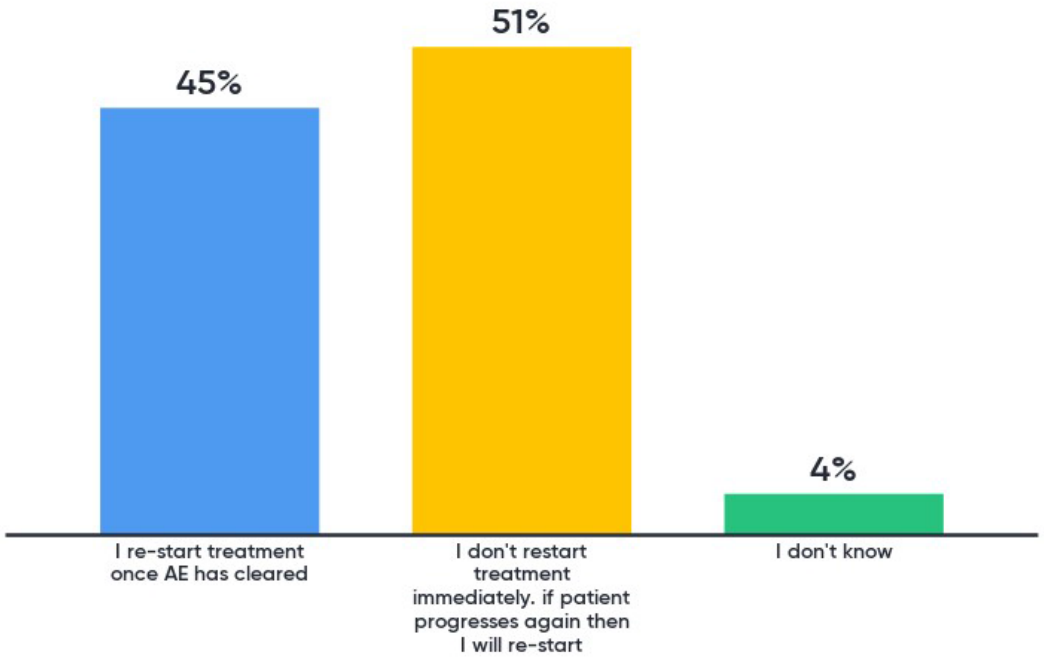
Patient with melanoma first-line treatment nivo-ipi presents <u>partial</u> <u>response</u> after 1 year of treatment. Due to grade 2 side effects treatment needs to be stopped. What do you do?



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What would you do in case this patient presented <u>complete response</u> after 1 year treatment?

- I would re-start treatment once AE has cleared
- I don't restart treatment immediately. If patient progresses again than I will re-start
- I don't know

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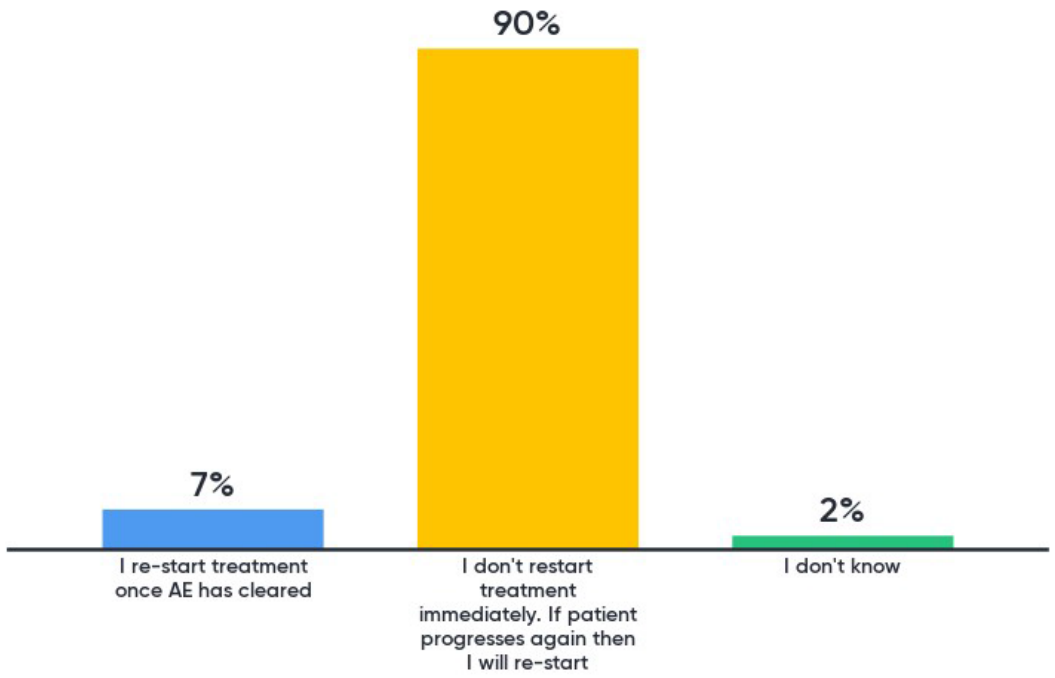
What would you do in case this patient presented <u>complete response</u> after 1 year treatment?



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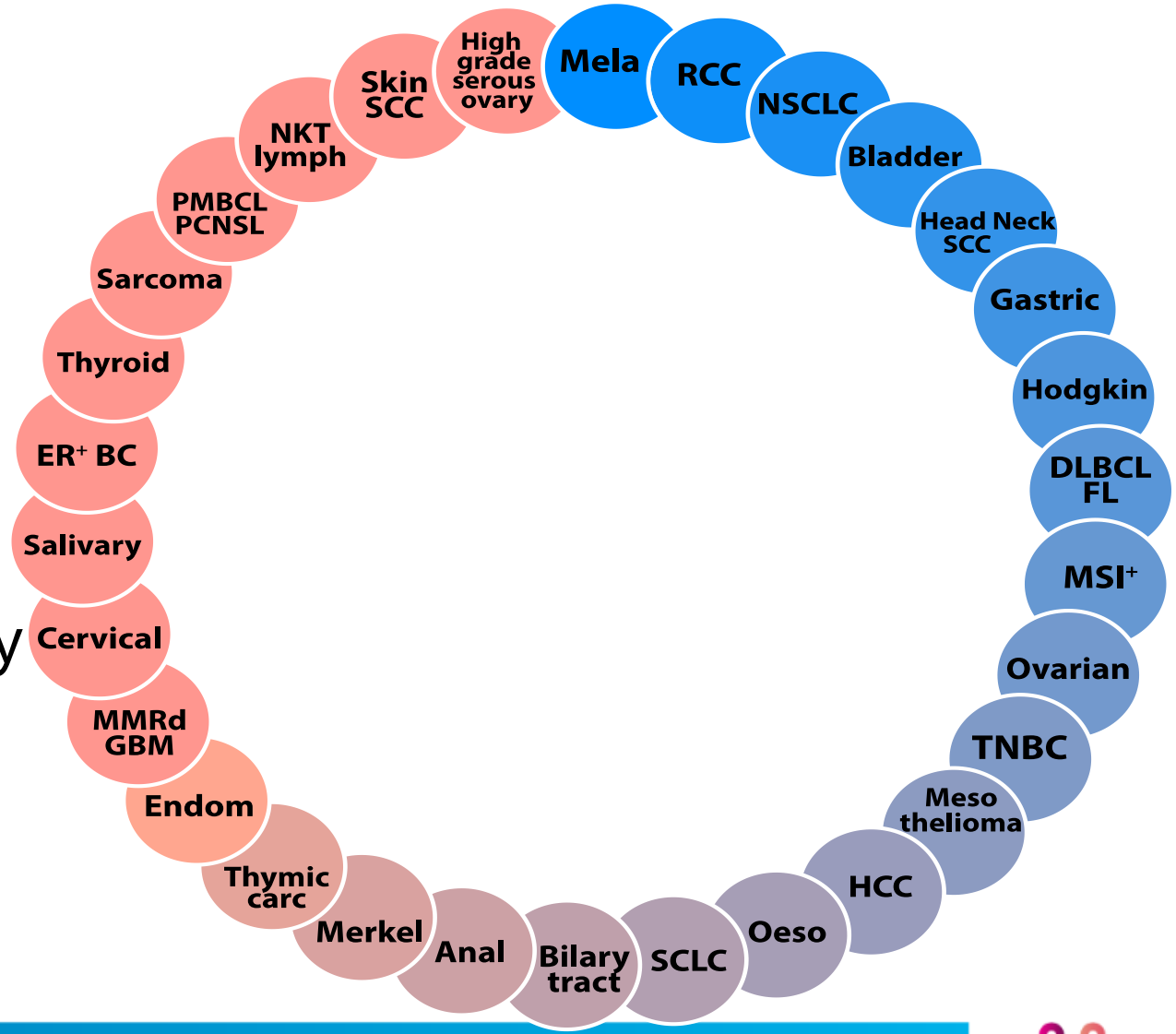
Check point inhibitors: a unique treatment

- Significant efficacy
- Active in a wide range of malignancies
- Very managable safety profile permitting long term treatment
- Immunotherapy: at present the only systemic treatment modality active beyond treatment duration

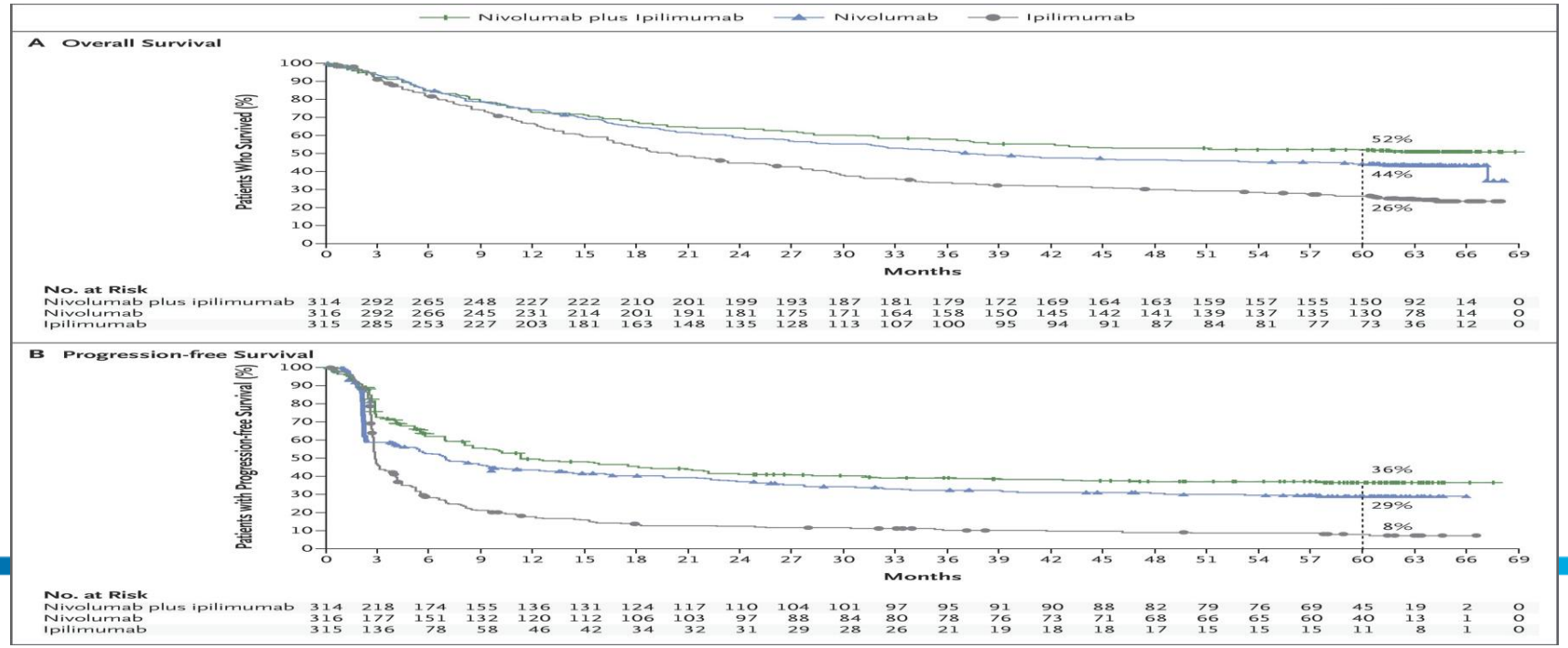


Checkpoint inhibitors: getting closer to cure patients with metastatic melanoma?

ORIGINAL ARTICLE

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

James Larkin, F.R.C.P., Ph.D., Vanna Chiarion-Sileni, M.D., Rene Gonzalez, M.D., Jean-Jacques Grob, M.D., Piotr Rutkowski, M.D., Ph.D., Christopher D. Lao, M.D., C. Lance Cowey, M.D., M.P.H., Dirk Schadendorf, M.D., John Wagstaff, M.D., Reinhard Dummer, M.D., Pier F. Ferrucci, M.D., Michael Smylie, M.D., et al.



…why should we stop treatment eventually in responders ?

- Toxicity
  - Untolerable
  - Tolerable but disturbing
- Cumbersome outpatient hospital visits
- Medical workforce limited (nurses, physicians, …)
- Financial toxicity $$$
- Local / national reimbursement regulations

Recommended treatment duration for PD1-inhibitors in metastatic melanoma : Nivolumab, Pembrolizumab

- « Treat until progression or unacceptable toxicity «

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Indicated * in Melanoma, NSCLC, RCC, Classical Hodgkin, Squamous Head and Neck, Urothelial

Duration of treatment

Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.

* ema.europa.eu, site visited dec 8th 2019

Nivolumab

U.S. FOOD & DRUG ADMINISTRATION

Treatment for: Melanoma, Metastatic, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, Hodgkin's Lymphoma, Head and Neck Cancer, Urothelial Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma, Small Cell Lung Cancer

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

fda.gov, visited dec 8th 2019

Pembrolizumab

U.S. FOOD & DRUG ADMINISTRATION

Treatment for: Melanoma, Metastatic, Non-Small Cell Lung Cancer, Head and Neck Cancer, Hodgkin's Lymphoma, Urothelial Carcinoma, Gastric Cancer, Cervical Cancer, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Renal Cell Carcinoma, Small Cell Lung Cancer, Esophageal Carcinoma, Endometrial Cancer

2.2 Recommended Dosage for Melanoma

The recommended dose of KEYTRUDA in patients with unresectable or metastatic melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for NSCLC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

24 months maximum duration listed in all solid tumors bersides melanoma

fda.gov, visited dec 8th 2019

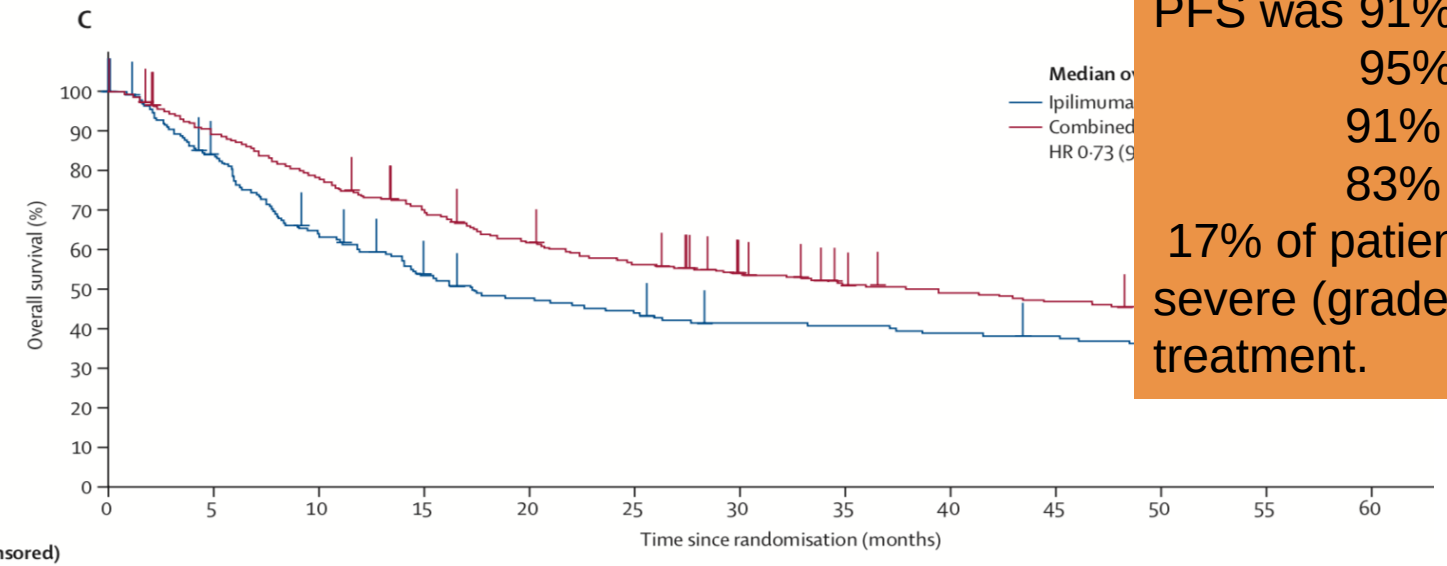
Melanoma: 2 yr treatment (pembrolizumab): 5 yr follow-up

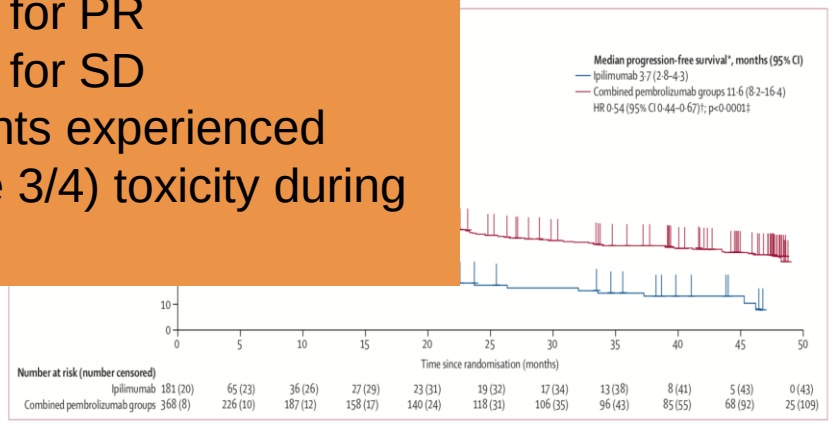
Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study

Lancet Oncol 2019

Caroline Robert, Antoni Ribas, Jacob Schachter, Ana Arance, Jean-Jacques Grob, Laurent Mortier, Adil Daud, Matteo S Carl
Michal Lotem, James M G Larkin, Paul Lorigan, Bart Neyns, Christian U Blank, Teresa M Petrella, Omid Hamid, Shu-Chih S
Nageatte Ibrahim, Georgina V Long

104 of 556 (19%) patients completed the planned course.
After following the 104 patients for a median of 9 months
PFS was 91%:
95% for CR
91% for PR
83% for SD
17% of patients experienced severe (grade 3/4) toxicity during treatment.



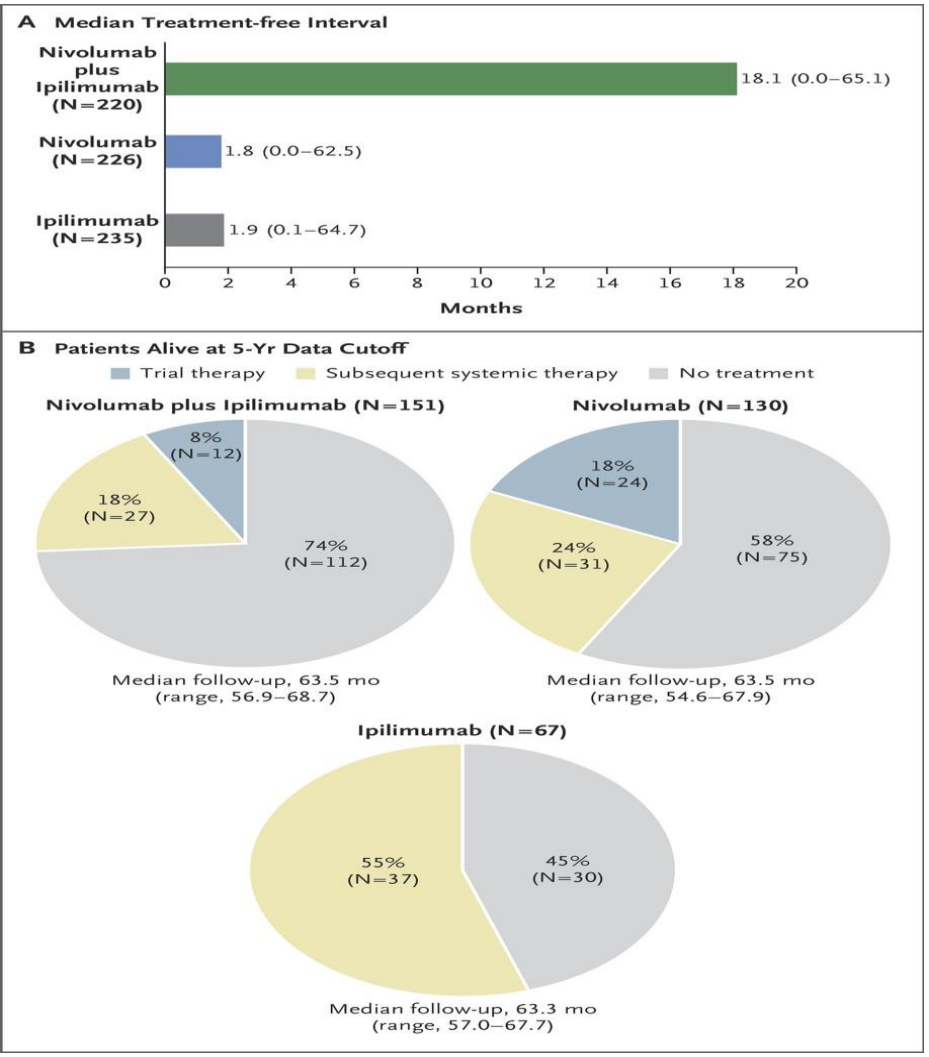


Number at risk (number censored)

Ipilimumab	181 (13)	140 (14)	105 (17)	86 (18)	76 (18)	70 (20)	64 (20)	63 (20)	60 (21)	58 (21)	52 (22)	49 (63)	8 (71)	0 (71)
Combined pembrolizumab groups	368 (4)	324 (4)	284 (7)	248 (9)	221 (9)	201 (17)	184 (22)	170 (23)	163 (23)	155 (24)	149 (29)	137 (135)	31 (166)	0 (166)

Median OS in 1st line treatment

Discontinuation due to toxicity: does it influence prognosis ?



945 patients randomized

314 Assigned to nivolumab plus ipilimumab (intent-to-treat population)

1 did not receive treatment
- 1 no longer met study criteria

313 received at least 1 treatment (safety population)

301 patients did not continue
- 90 disease progression
- 139 study drug toxicity
- 4 death
- 18 adverse events
- 27 patient request
- 3 withdrew consent
- 15 maximum clinical benefit
- 1 poor/non-compliance
- 1 no longer meets study criteria
- 3 other

12 continuing treatment

316 Assigned to nivolumab alone (Intent-to-treat population)

3 did not receive treatment
- 1 no longer met study criteria
- 1 withdrew consent
- 1 request to discontinue study

313 Received at least 1 treatment (safety population)

289 patients did not continue
- 179 disease progression
- 45 study drug toxicity
- 1 death
- 8 adverse events
- 33 patient request
- 1 lost to follow-up
- 18 maximum clinical benefit
- 1 poor/non-compliance
- 3 other

24 continuing treatment

315 Assigned to ipilimumab alone (intent-to-treat population)

4 did not receive treatment
- 2 no longer met study criteria
- 1 withdrew consent
- 1 disease progression

311 received at least 1 treatment (safety population)

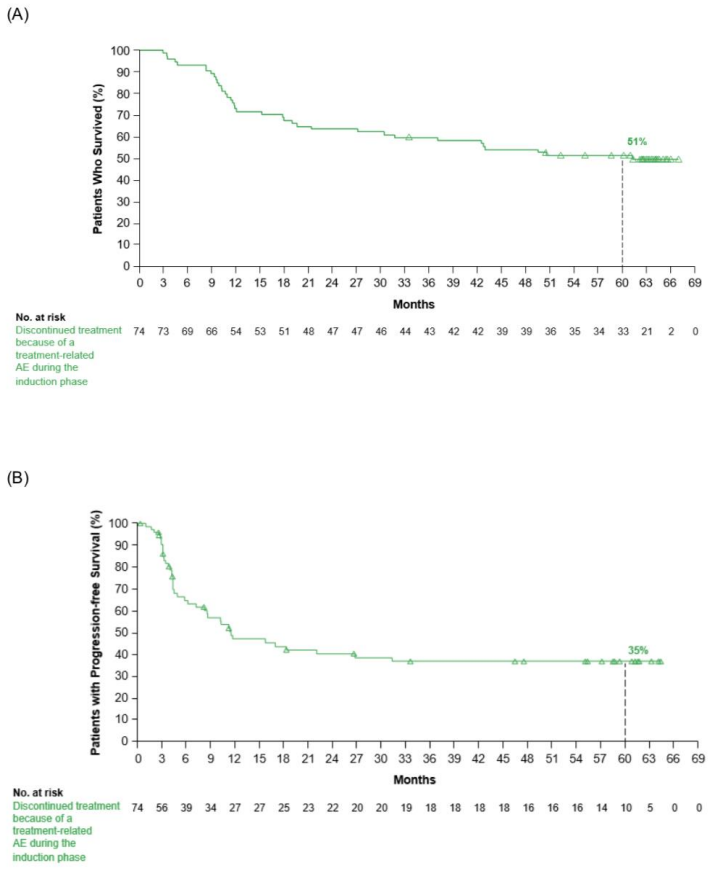
311 patients did not continue
- 224 disease progression
- 52 study drug toxicity
- 1 death
- 6 adverse events
- 13 patient request
- 1 withdrew consent
- 4 maximum clinical benefit
- 1 poor/non-compliance
- 6 administrative reasons*
- 3 other

0 continuing treatment

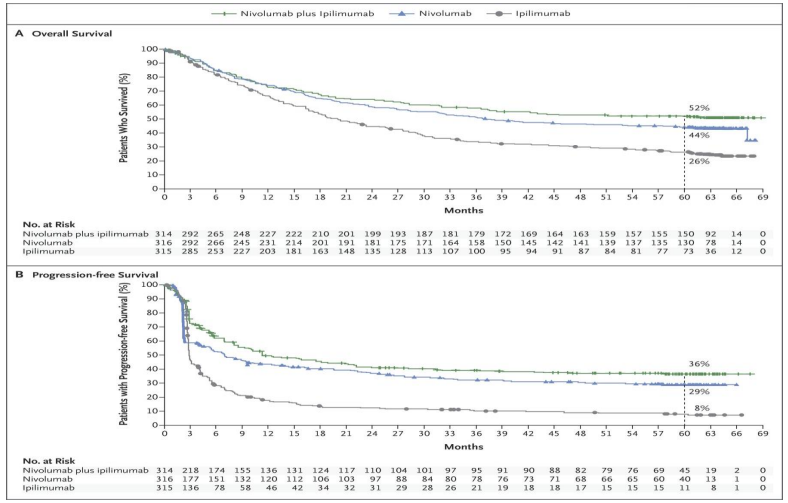
Larkin J et al. N Engl J Med 2019;381:1535-1546 + appendix

What happens in case of early discontinuation?

Figure S6. Kaplan–Meier Estimates of Survival in Patients Who Discontinued Nivolumab Plus Ipilimumab During Induction Due to a Treatment-related Adverse Event.



Compared to the entire study population:



Are these better responders due to higher sensitivity to checkpoint inhibitors?
How would all patients fare in case of early discontinuation?

Larkin J et al. N Engl J Med 2019;381: appendix

Discontinuation after complete response

VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma

Caroline Robert, Antoni Ribas, Omid Hamid, Adil Daud, Jedd D. Wolchok, Anthony M. Joshua, Wen-Jen Hwu, Jeffrey S. Weber, Tara C. Gangadhar, Richard W. Joseph, Roxana Dronca, Amita Patnaik, Hassane Zarour, Richard Kefford, Peter Hersey, Jin Zhang, James Anderson, Scott J. Diede, Scot Ebbinghaus, and F. Stephen Hodi

KEYNOTE 001
phase 1b study w multiple solid tumors (incl 655 patients w met Melanoma, 3 pembro dosages, Ipi naive and Ipi pre treated)
After CR comfirmed with 2 consecutive CT scans >/= 4 weeks and minimum 6 m treatment with Pembro: option to stop treatment after 2 further consolidation administrations

67/105 patient stopped (mainly due to patient's choice)
PFS at 2 yr 90-% whether tt cont'd or stopped

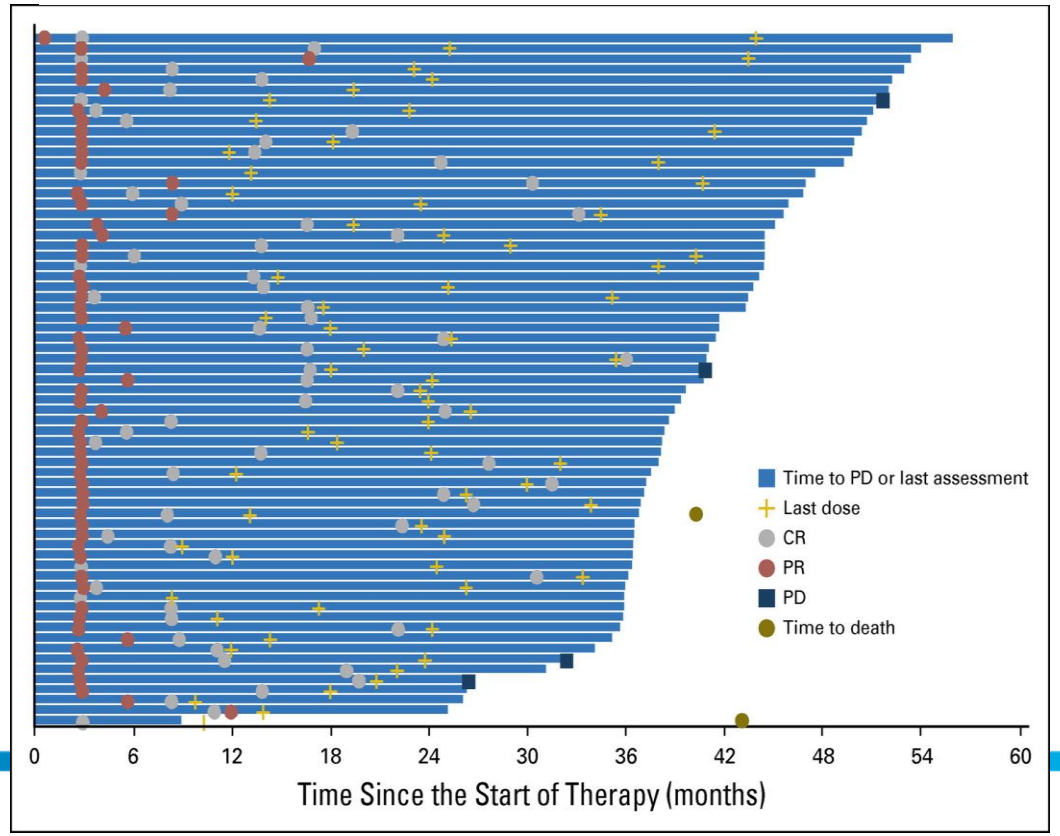
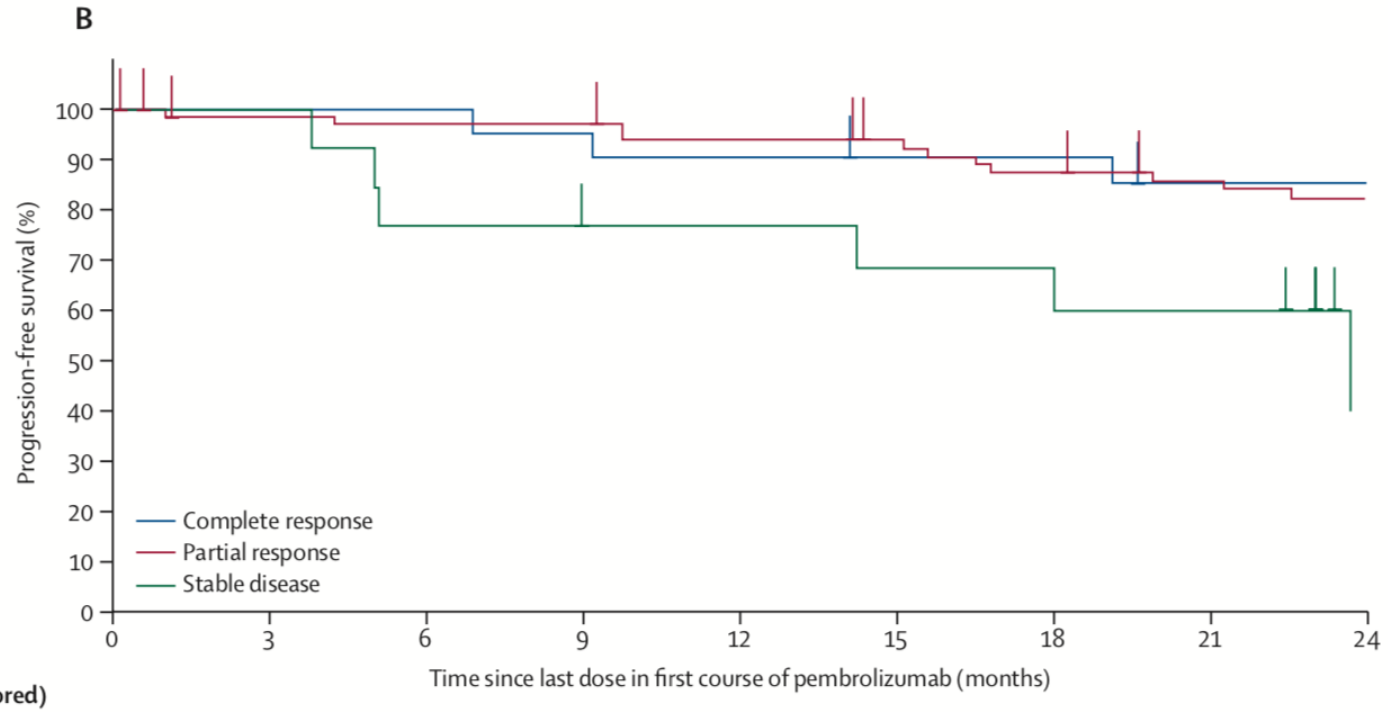


Fig 2. Time to response and durability of response from the start of therapy in complete responders who discontinued pembrolizumab and proceeded to observation (n = 67). Bar length is equivalent to the time to the last imaging assessment by investigator review. CR, complete response; PD, progressive disease; PR, partial response.

…would stable disease patients have benefitted a prolonged treatment?



Number at risk (number censored)									
Complete response	21 (0)	21 (0)	21 (0)	20 (0)	19 (1)	18 (1)	18 (2)	16 (10)	8 (16)
Partial response	69 (3)	65 (3)	64 (3)	64 (4)	61 (6)	59 (6)	55 (10)	50 (32)	26 (53)
Stable disease	13 (0)	13 (0)	10 (1)	9 (1)	9 (1)	8 (1)	8 (1)	7 (5)	2 (7)

C Robert et al, JCO 36 Vol 17, 2018

…can be deliver less than 2 years treatment?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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ORIGINAL ARTICLE

Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma

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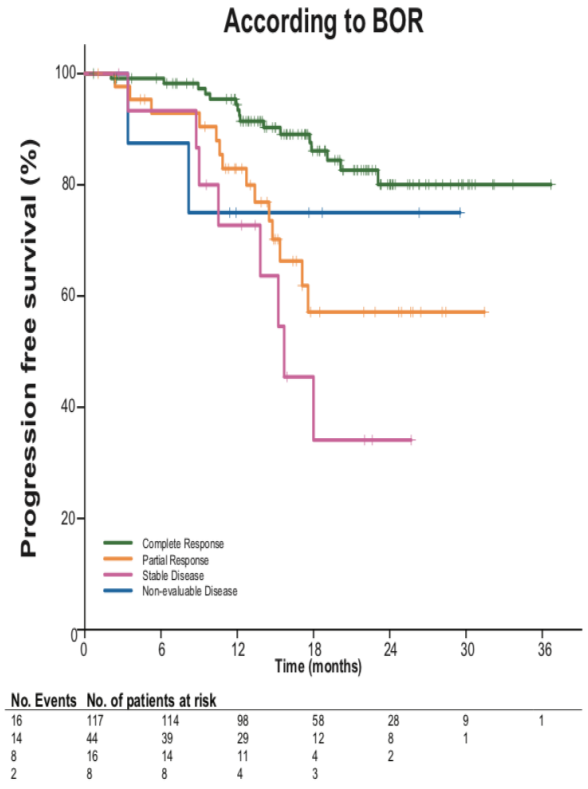
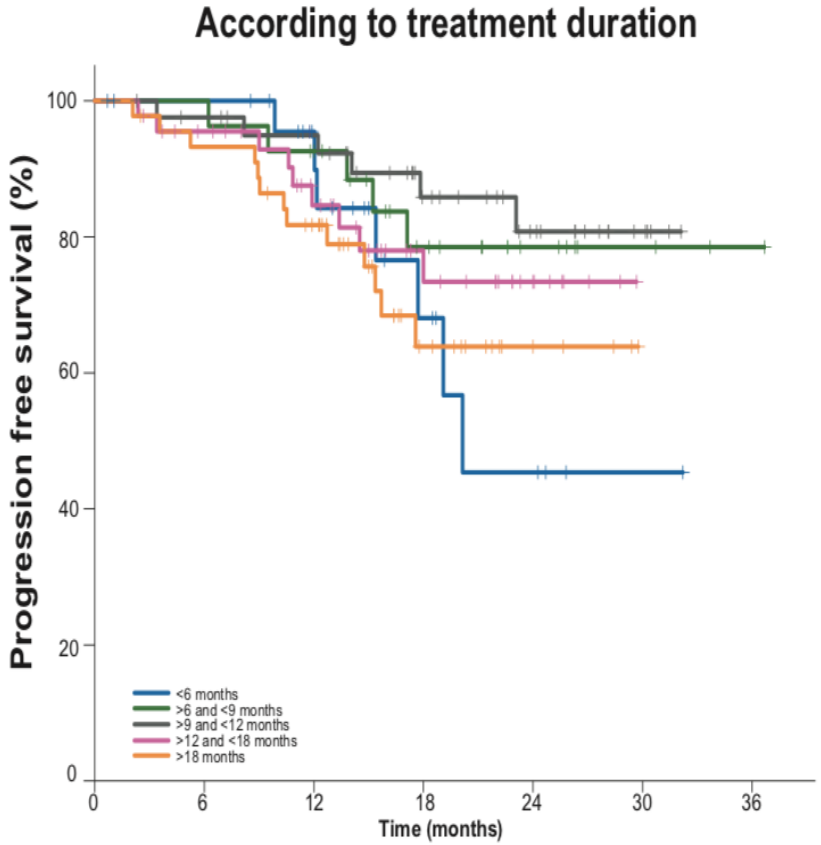
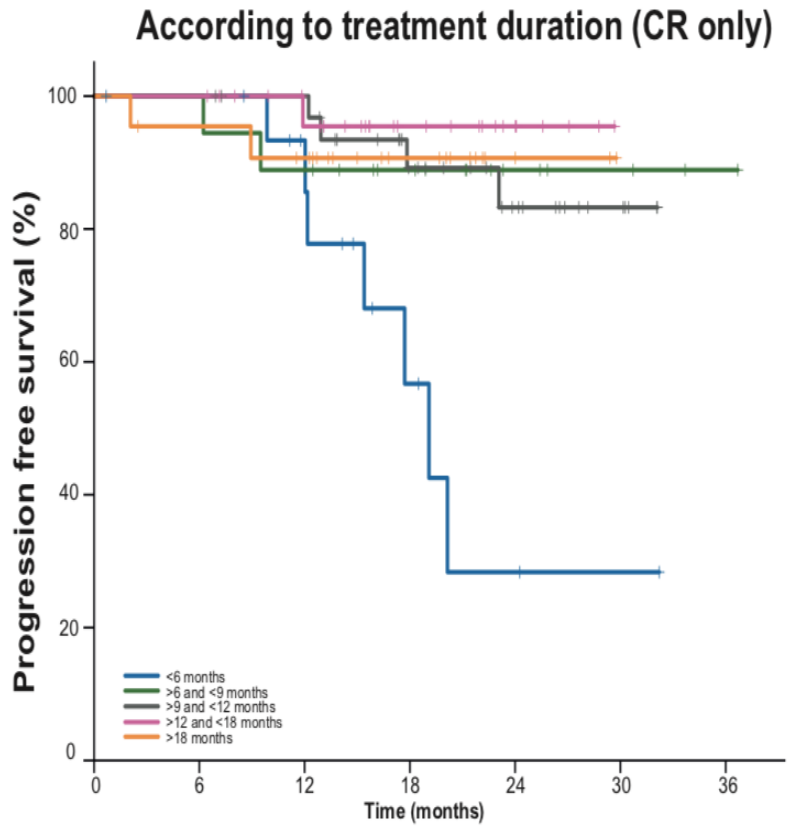
< 6 months treatment -> worser outcome







Jansen et al , Annals Oncol 30 2019

Is rechallenge an option? (stop early/safely restart if progression)

Annals of Oncology

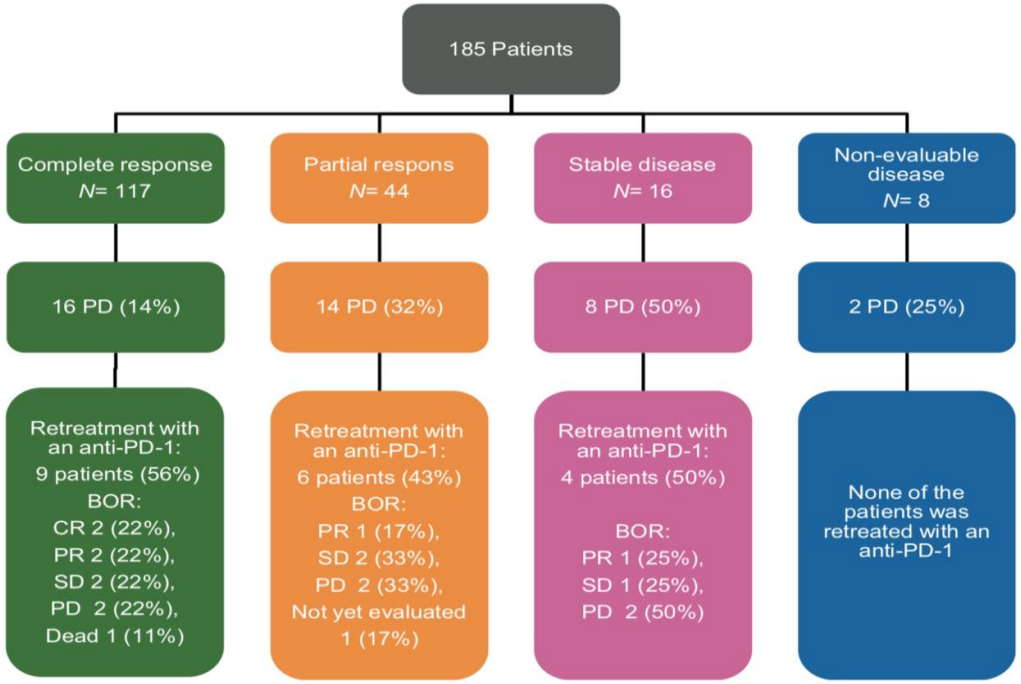


Figure 2. Outcome of 185 patients discontinuing treatment according to BOR and outcome after PD-1 reintroduction. Of the 185 patients who discontinued anti-PD-1, 40 patients experienced progressive disease. A PD-1 inhibitor was re-introduced in 19 patients leading to 6 renewed objective responses (32%, 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.

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Table 3. Outcome of patients after retreatment with anti-PD-1 therapy

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.

How much is enough ? Can we count on re-challenge? Wait for these sudy results

- STOP-GAP (NCT02821013) (Canada)
  - Intermittent vs. continuous treatment with anti-PD-1 inhibitors (n 614)
  - Primary endpoint: OS
  - Randomisation: 2 years of treatment or treatment to maximal tumour response with retreatment at the time of progression.
  - Maximal tumour response is determined by at least two radiological measurements 3 months apart
  - STOP-GAP therefore is primarily evaluating the role of re-challenge rather than the specific question of optimal treatment duration.

- DANTE trial (ISRCTN15837212; UK National Institute for Health Research (NIHR) portfolio)
  - Metastatic melanoma patients receiving anti-PD-1 therapy who are progression-free at 12 months
  - Random. to either stop (with re-challenge allowed on progression) or continue treatment as per standard use.
  - Non-inferiority trial with primary endpoint of PFS.
  - Patients are being registered in the first year of treatment with a plan to randomise 1208 patients at 12 months.

Conclusions

- Treating with checkpoint inhibitors until progression or untolerable toxicity is not feasable in a lot of cases
- 2 Years of treatment is sufficient in the treatment of metastatic melanoma
- Treating for less than 2 years may be an option especially in patients with complete remission and significant toxiciy
- Treating for less than 6 months leads to worse outcomes than longer treatment
- Stable disease – patients are most at risk for early relapse after discontinuation
- Rechallenge is an option in 1st line responders. Initial responders will not necessarily respond to rechallenge.

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