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LESSONS LEARNT FROM THE DEVELOPMENT OF IMMUNOTHERAPY

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DISCLOSURES

Details of the DOI for all authors are listed at the end of this presentation

ABBREVIATIONS

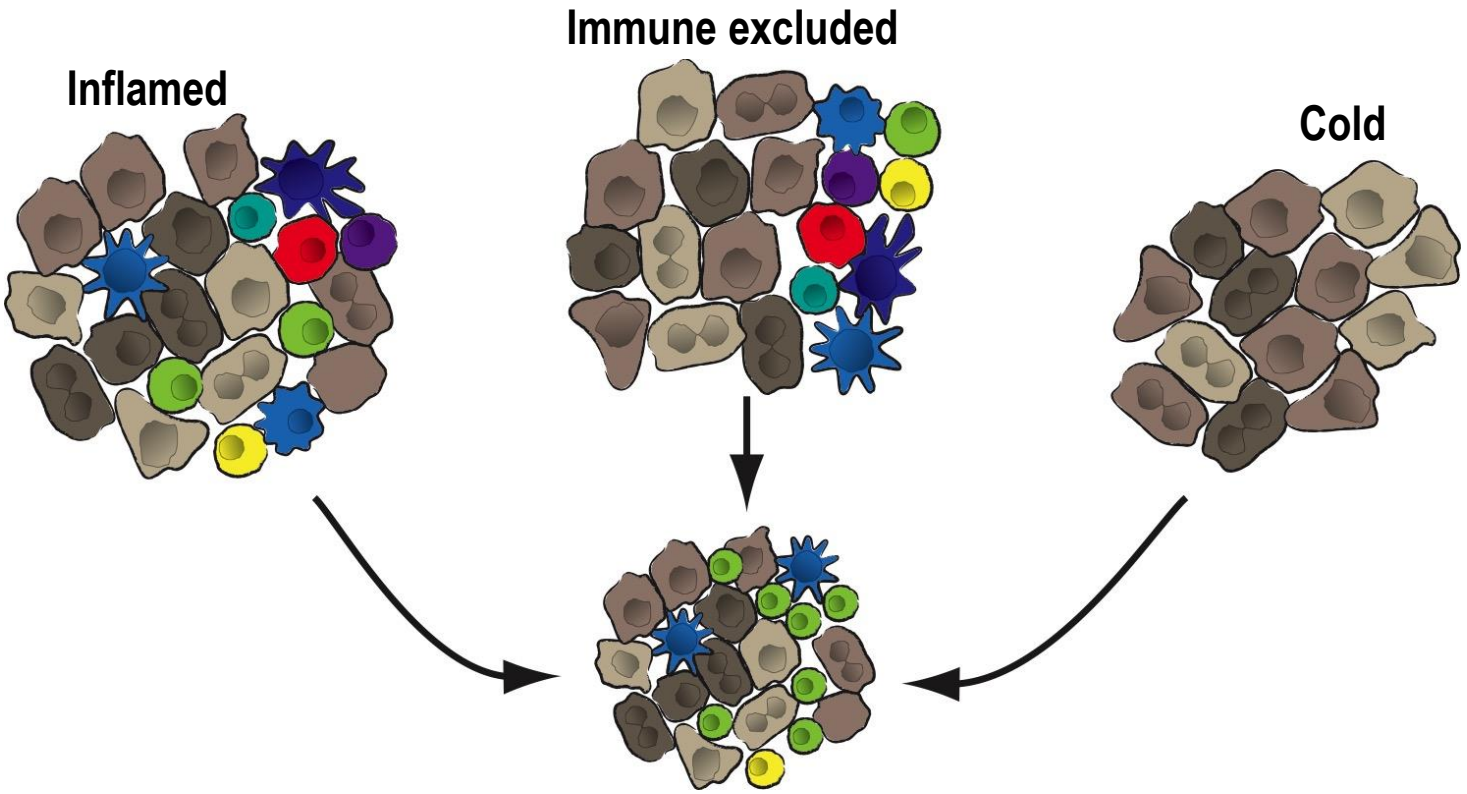
Ab: antibody
CR: complete response
CRC: colorectal cancer
CRT: chemoradiotherapy
CT: clinical trials
HPD: hyperprogressive disease
ICPi: immune checkpoint inhibition
IrAE: Immune related adverse events
MSI: microsatellite instability
NSCLC: non small cell lung cancer
OS: overal survival
PFS: progression free survival
PR: partial respons
PsPD: pseudoprogression
Pts: patients
SCLC: small cell lung cancer
TIL: tumor infiltrating lymphocytes
TKI: tyrosine kinase inhibitor
TMB: tumor mutational burden
TME: tumor microenvironement
TGR: tumor growth rate

OVERVIEW

- Biomarkers for anti-tumour response
- Response patterns
- Toxicity
- Combination of immunotherapy with other agents
- Clinical trial organisation
- Conclusions and perspectives

BIOMARKERS FOR RESPONSE

BIOMARKERS: MICROENVIRONMENT MATTERS

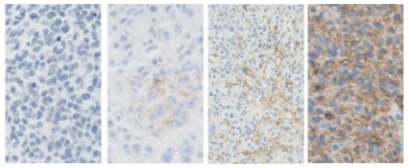


'Ideal' microenvironment: highly infiltrated with CD8 T cells that can be activated by immune checkpoint blockade

See also: Binnewies N, *et al.* Nat Med 2018, 24(5): 541-550

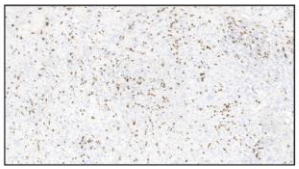
OVERVIEW OF POTENTIAL BIOMARKERS

PDL1 expression

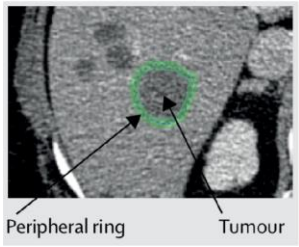


e.g. NSCLC

TIL



e.g. bladder CA



TMB

e.g. NSCLC

MSI

e.g. CRC

1) Daud AL, *et al.* J Clin Oncol, 34(34), 2016: 4102-4109, Reprinted with permission. © 2016, American Society of Clinical Oncology. All rights reserved.
2) Reprinted from The Lancet Oncology, 19(9), Sun R, *et al.* A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study, 1180-1191, Copyright 2018, with permission from Elsevier.
3) Hellman MD, *et al.* 2018, Cancer Cell 33, 843–852. Under Creative Commons Attribution (CC BY 4.0). https://creativecommons.org/licenses/by/4.0/

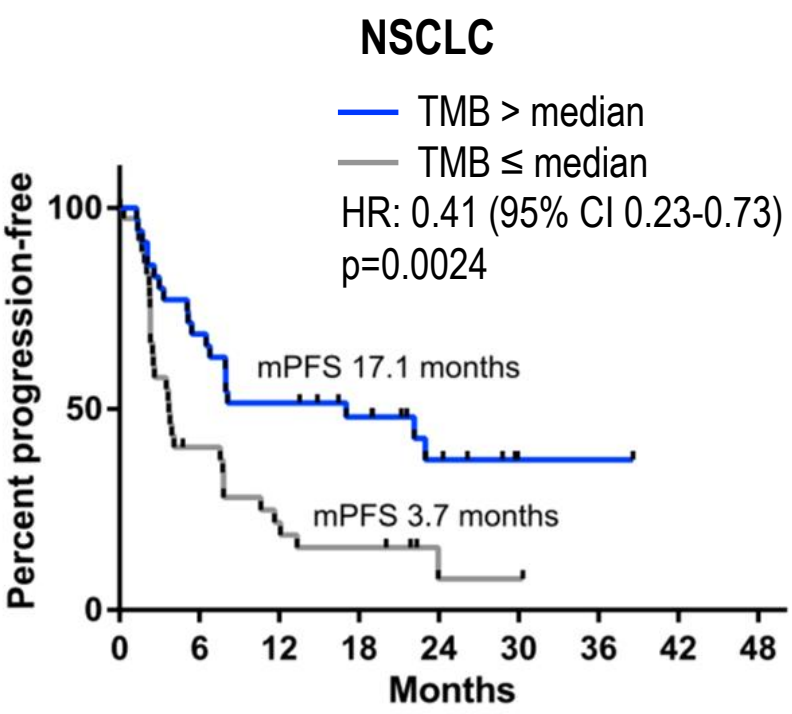
BIOMARKER: PDL1 IS CURRENTLY THE BEST WE HAVE

- NSCLC: PDL1 is used as a biomarker for pembrolizumab but not for nivolumab
- Other tumour types: clinical value of PDL1 expression is less clear compared to NSCLC, however, important data for e.g. gastric cancer: ORR for PDL1+: 50% *vs.* 0% in PDL1- pts
- Explanation for differences:
  - Technical reasons (i.e. different antibodies, platforms, and cut-offs across studies)
  - Biological differences (expression changes over time, heterogeneity within tumour lesions, differences in immunogenicity between tumour types)

For more information see slide set of Dr Castelo-Branco

Data from Kim ST, *et al.* Nat Med. 2018, 24(9): 1449-1458
See also: Reck M, *et al.* N Engl J Med 2016; 375:1823-1833; Carbone D, *et al.* N Engl J Med 2017; 376:2415-2426

BIOMARKERS OF INTEREST: TUMOUR MUTATIONAL BURDEN (TMB) IS A NEW BIOMARKER



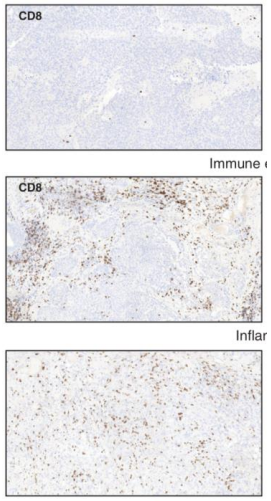
- Most evidence in NSCLC
- Assessment needs to be further defined:
  - How to assess (WES/WGS *vs.* targeted platform), Where to assess (primary tumour or met)
  - When to assess (anytime or only just prior to treatment start)
- TMB is being analysed in other tumour types (e.g. bladder Marathasian CA, *et al*. 2018, Nat Med; gastric cancer Kim S, *et al*. 2018, Nat Med, SCLC, Hellman M, *et al.* 2018, Cancer Cell...)

See also: Hellman MD, *et al*. N Engl J Med 2018; 378:2093-2104; Rizvi H, *et al*. J Clin Oncol 2018, 36(7): 633-641; Gandara DR, *et al.* Nat Med. 2018 Sep;24(9):1441-1448

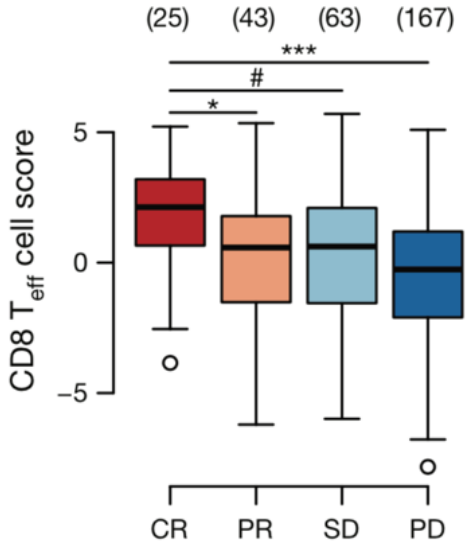
BIOMARKERS OF INTEREST: THE MORE TILS THE BETTER

Anti-PD(l)1 is reinvigorating pre-existing immunity

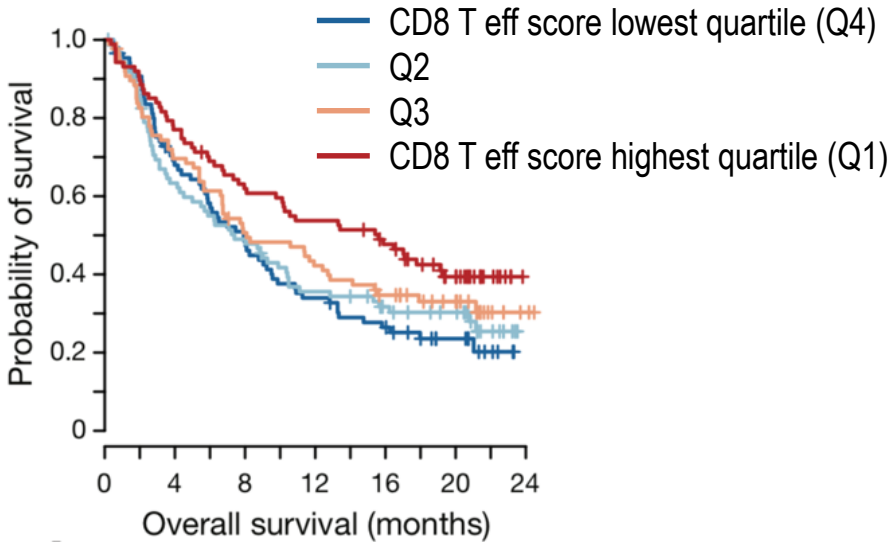
UBC treated with atezolizumab: CD8 T Cell presence is associated with more CR and longer OS



CD8 IHC staining of UBC samples



Bladder CA



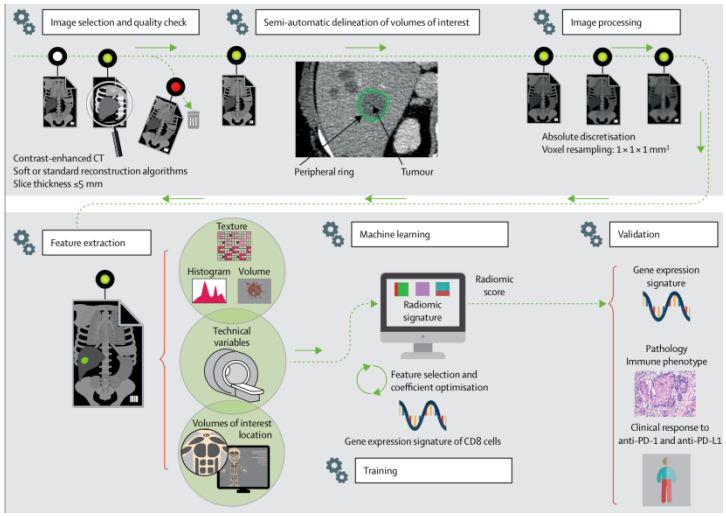
Further prospective validation is required as well as practical utility

Figure Reprinted by permission from Springer Nature, Nature, 54(7693):544–48, TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells, Mariathasan S, *et al.* Copyright 2018.
See also: McDermott DF, *et al.* Nat Med. 2018 Jun;24(6):749-757

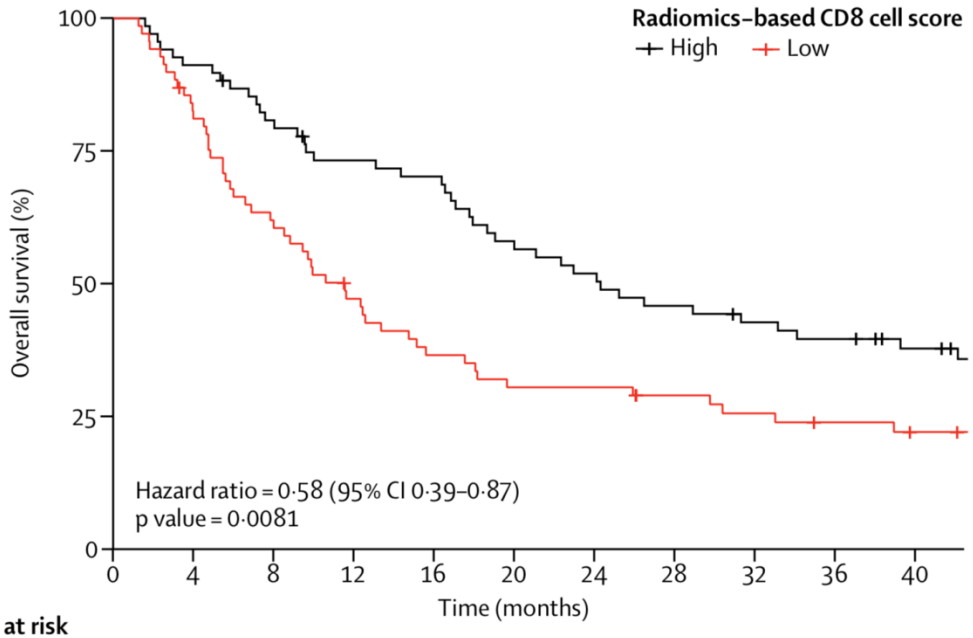
BIOMARKERS OF INTEREST: THE MORE TILS THE BETTER

Anti-PD(l)1 is reinvigorating pre-existing immunity: Potential for radiomics

CD8 cell score determined by analysis of CT scan might predict OS upon immune checkpoint therapy



All tumour types



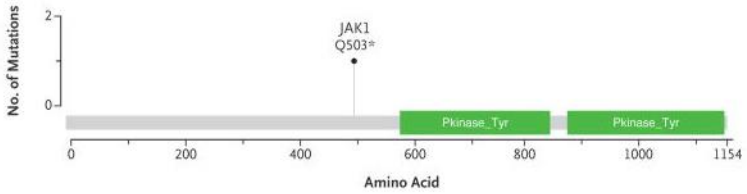
Number at risk (number censored)

High	68 (0)	62 (1)	54 (1)	48 (2)	46 (2)	37 (2)	34 (2)	30 (4)	27 (4)	25 (5)	21 (6)
Low	69 (0)	55 (0)	41 (1)	31 (2)	24 (2)	20 (2)	20 (2)	17 (2)	15 (3)	13 (3)	11 (6)

BIOMARKER: NEGATIVE ASSOCIATION WITH RESPONSE

The presence or absence of certain molecular alterations or pathways involved in the CD8 T cell anti-tumour response might be good biomarkers for determining which patients will not benefit from ICPI monotherapy

JAK1/JAK2 mutations prevent IFNγ anti-tumour response[1]

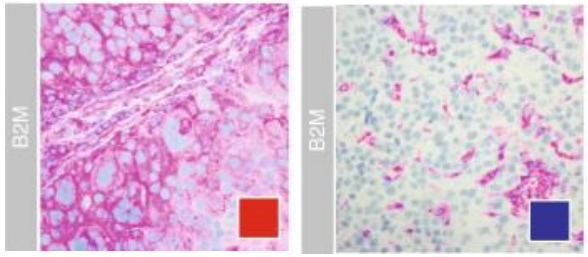


Melanoma, CRC

TGFβ expression is inversely correlated with anti-tumour response with ICPI[2]

Melanoma, UBC

Loss of B2M expression prevents CD8 T cell killing upon ICPi treatment[3]



Melanoma

1). From N Engl J Med, Zaretsky JM, et al. Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma, 375, 819–29. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. 2) Reprinted by permission from Springer Nature, Nature, 54(7693):544–48, TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells, Mariathasan S, *et al.* Copyright 2018; 3) Sade Feldmann M, *et al.* Nat Com 2017;26:1136. doi: 10.1038/s41467-017-01062-w under Creative Commons Attribution (CC BY 4.0). https://creativecommons.org/licenses/by/4.0/

See also: Shin DS, *et al.* Cancer Discov. 2017 Feb;7(2):188-201; Hugo W, *et al*. Cell. 165(1): 35–44.

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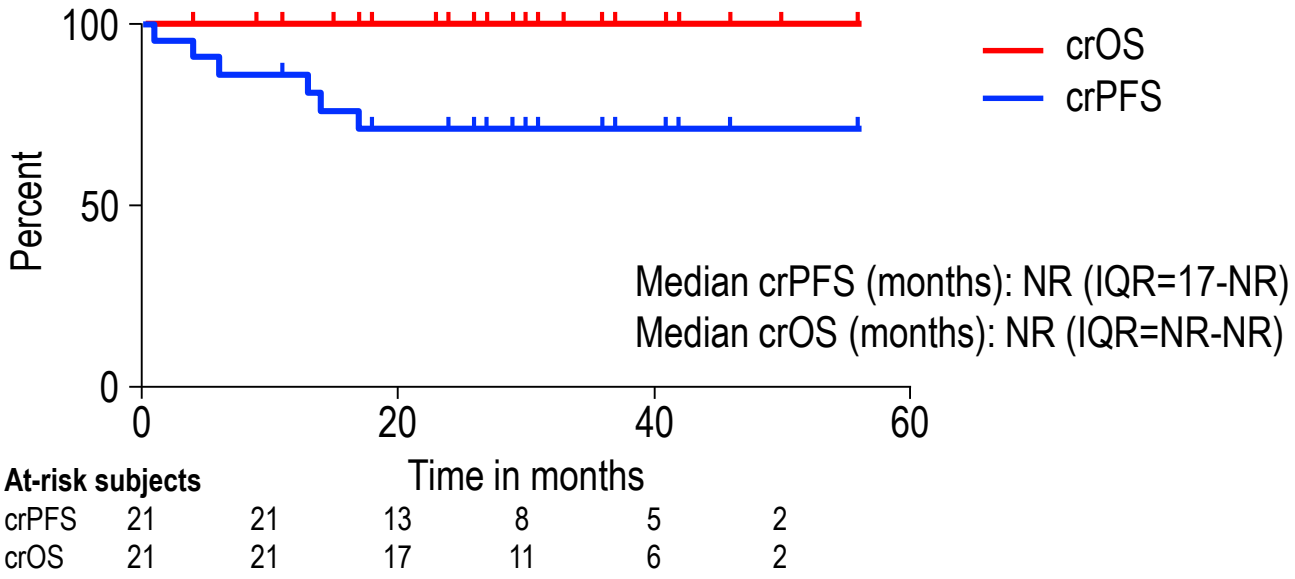
RESPONSE PATTERNS

PATIENTS HAVING A COMPLETE RESPONSE SEEM TO HAVE A LONGER OVERALL SURVIVAL

All tumour types phase I patients

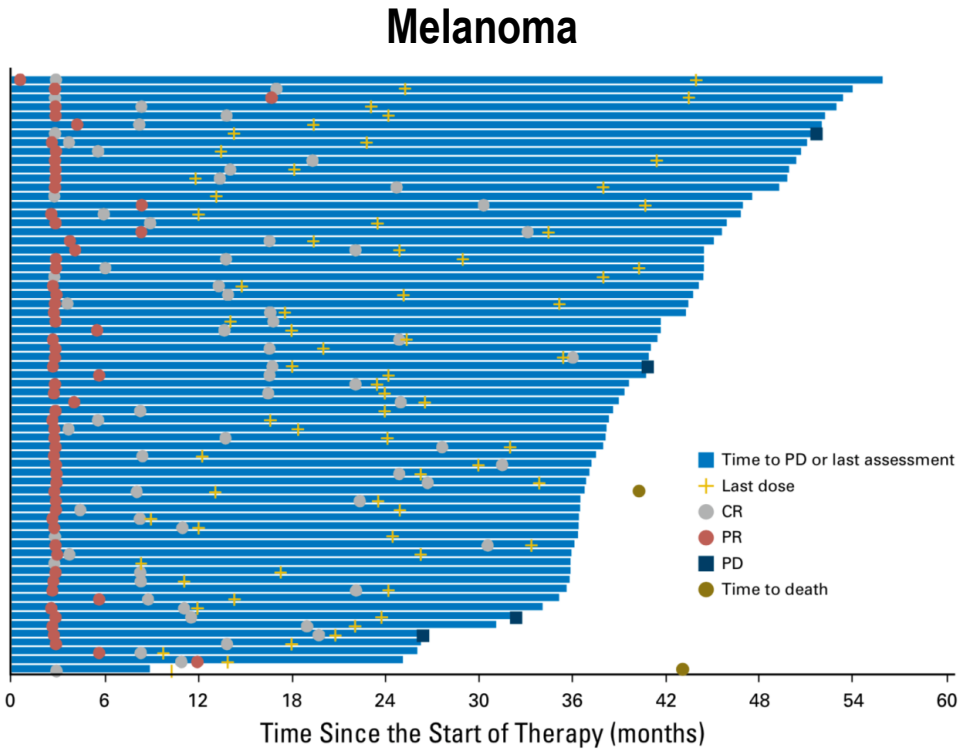
There is a striking difference in survival between partial and complete responders

OS and PFS for CR from their first complete response

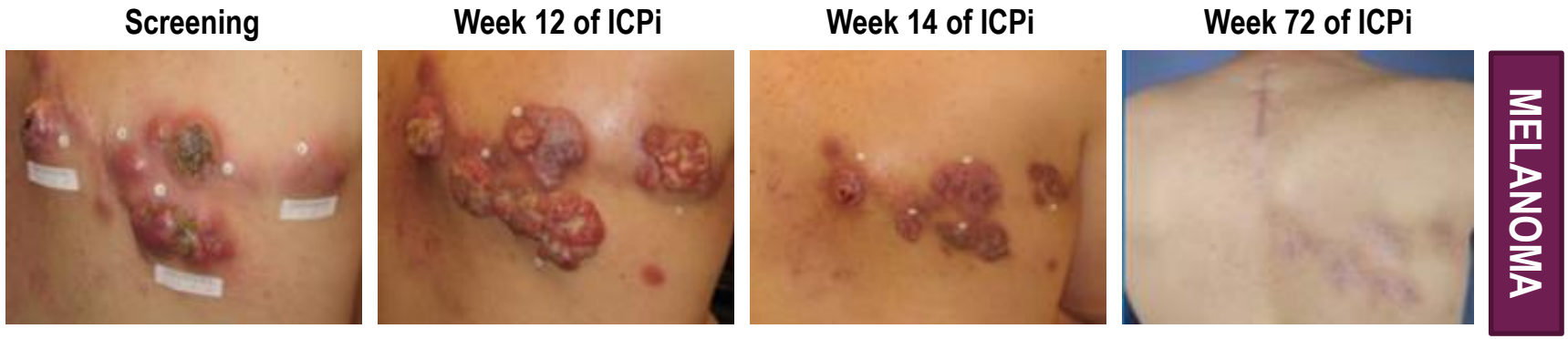


At-risk subjects						
crPFS	21	21	13	8	5	2
crOS	21	21	17	11	6	2

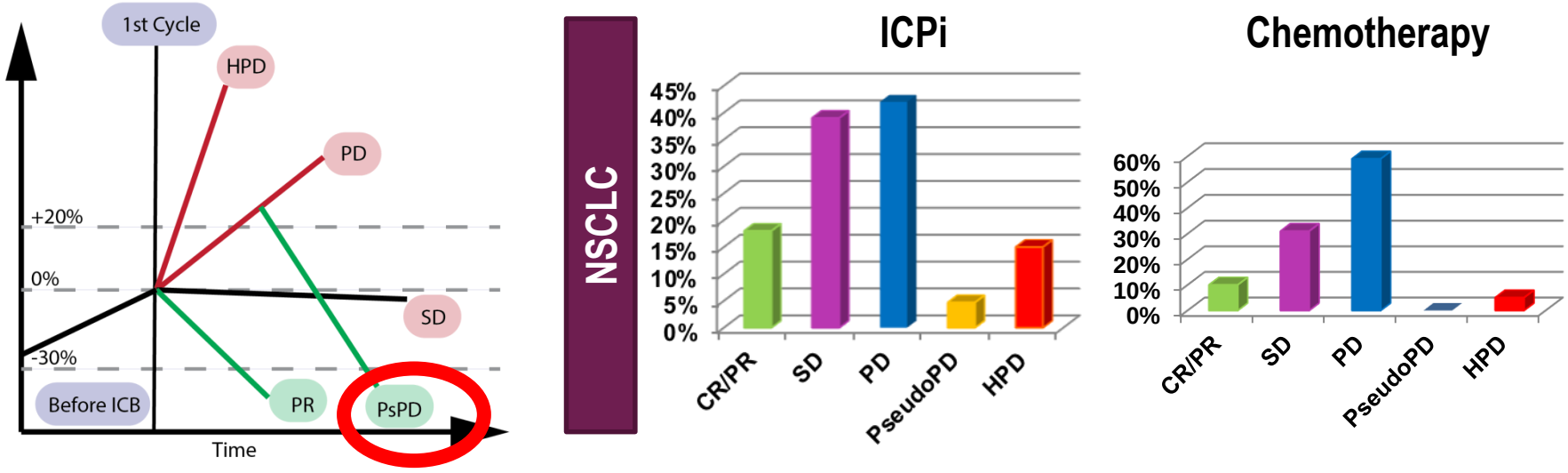
PATIENTS HAVING A COMPLETE RESPONSE ARE STILL RESPONDING 2 YEARS AFTER CESSATION OF ICPI



PSEUDOPROGRESSION (PSPD) IS RARE



Hodi et al. Abstract #3008 ASCO 2008



Robert C, *et al.* J Clin Oncol, 36(17), 2018:1668–74. with permission © 2018 American Society of Clinical Oncology. All rights reserved.

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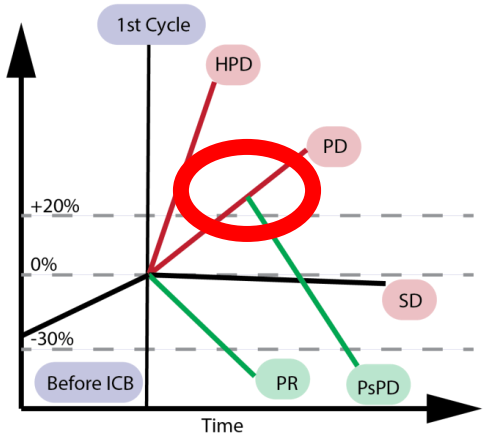
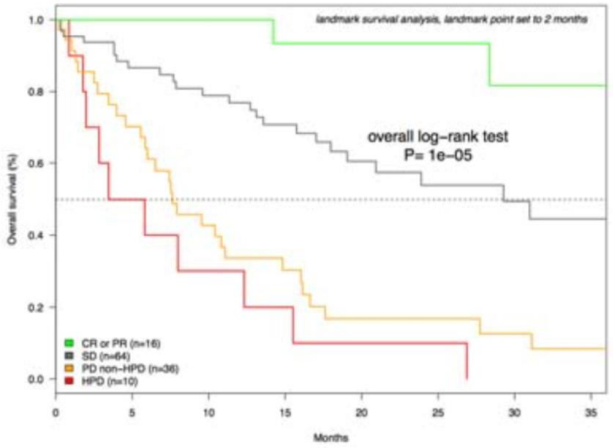
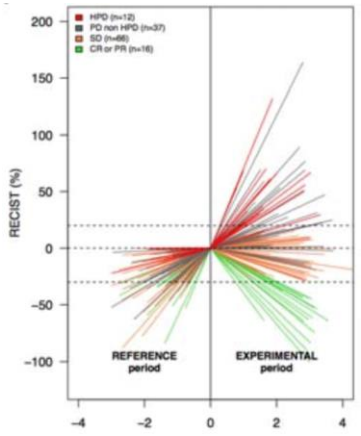
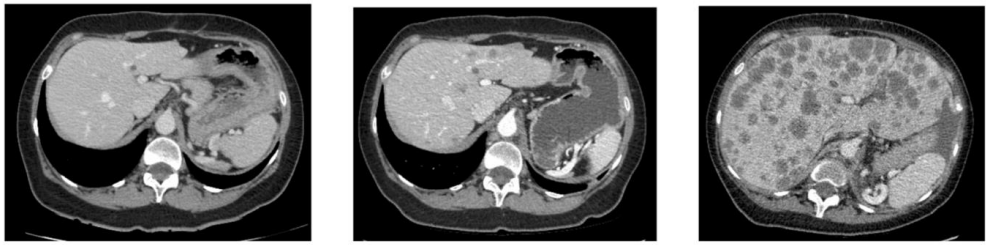
HYPERPROGRESSION (HPD) EXISTS, IT IS PROBABLY LETHAL BUT REMAINS TO BE DEFINED

Several tumour types









Before (-8 weeks) | Baseline | 1st Evaluation (+8 weeks)

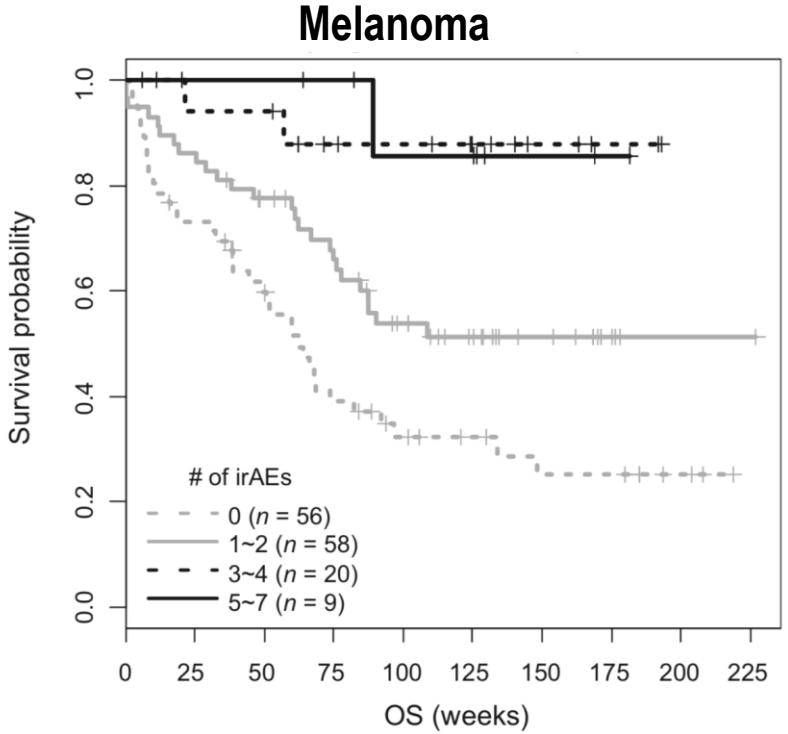
It should be discussed if HPD should be considered a severe side effect

Reprinted from Clinical Cancer Research, 2017, 23(8): 1920–8, Champiat S, *et al.* Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1, with permission from AACR.

See also: Saada Bouzid E, *et al.* 2017, Ann Oncol; Kato S, *et al.* 2017, Clin Cancer Res; Ferrara R, *et al.* 2017, Ann Oncol, Abstract; Lo Russo G, *et al.* 2018, Clin Cancer Res.

TOXICITY

AUTOIMMUNE TOXICITY MIGHT BE INDICATING ACTIVATION OF IMMUNE RESPONSE AND BE ASSOCIATED WITH OUTCOME



Reprinted from Clinical Cancer Research, 2016, 22(4): 886-894, Freeman-Keller m, *et al.* Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes, with permission from AACR.

See also: Kim H, *et al.* 2017, OncoImm; Fuji T, *et al.* 2017, Invest New Drugs; Weber JS, *et al.* JCO, 2017.

DRUG CESSATION BECAUSE OF AUTOIMMUNE EVENTS DOES NOT STOP RESPONSES

Retrospective analysis of RCC and melanoma patients treated with ICPi shows no difference in OS in patients that stopped ICPi because of toxicity

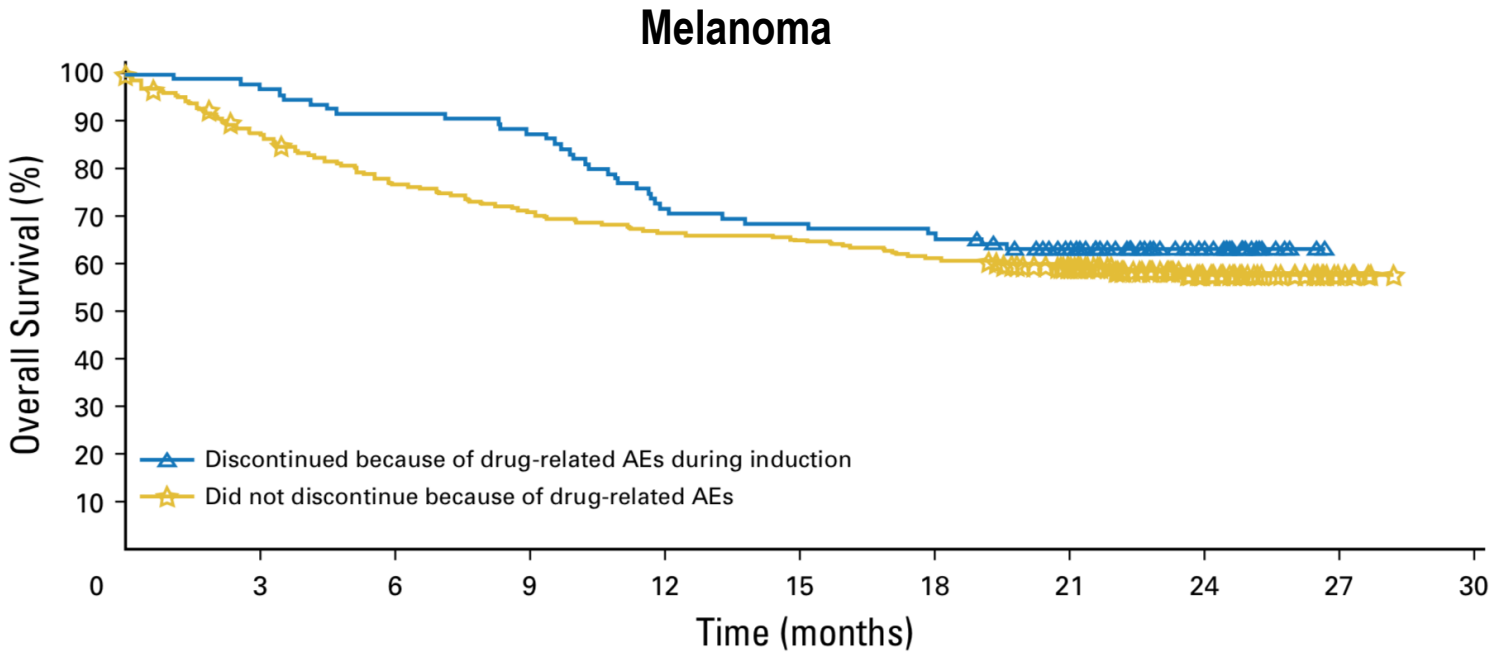


Figure from Schadendorf D, *et al.* J Clin Oncol,;35(34), 2017:3807–14. Reprinted with permission. © 2017 American Society of Clinical Oncology. All rights reserved
See also: Martini DJ, et al 2018 (RCC) ; Weber JS, *et al.* 2017 JCO.

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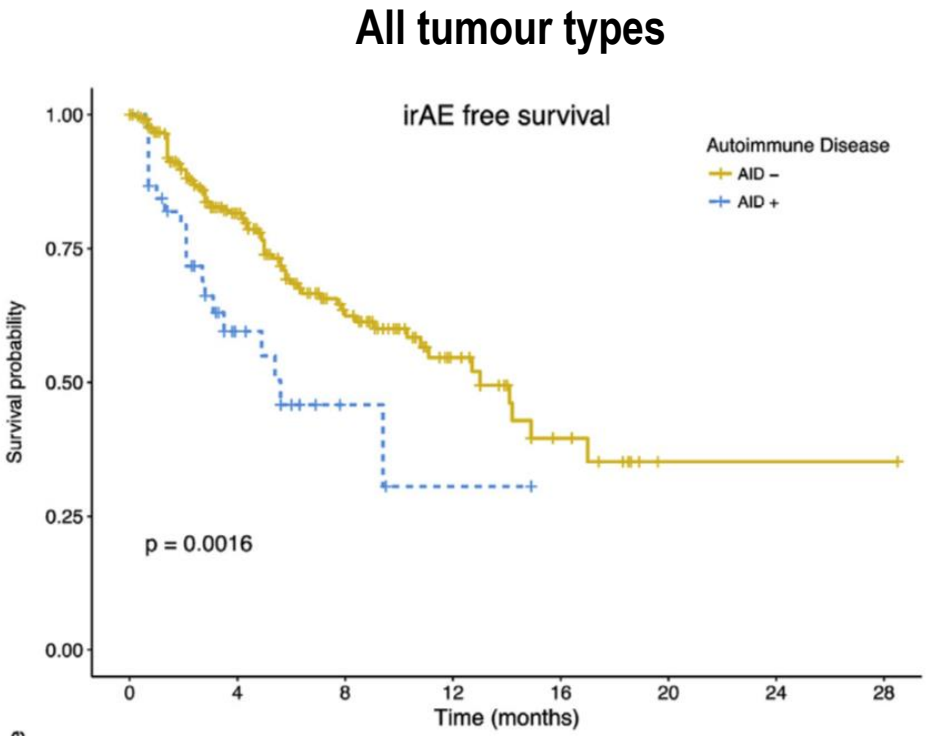
PRE-EXISTING AUTOIMMUNE DISEASE SHOULD NOT BE AN ABSOLUTE CONTRAINDICATION FOR IMMUNOTHERAPY

Retrospective analysis of patients with pre-existing autoimmunity who were treated with ICPi shows a clear difference in the OS without occurrence of IrAE.
In this study patients with pre-existing autoimmune disease experience twice a much IrAE



Reprinted from European Journal of Cancer, 91, Danlos FX, *et al.* Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease: 21-29, Copyright 2018, with permission from Elsevier.

See also: Leonardi GC, *et al.*.2018, JCO; Richter M, *et al.* 2018, Artritis and Rheum; Johnson D, *et al.* 2016, JAMA Oncol.

COMBINATION OF IMMUNOTHERAPY WITH OTHER AGENTS

IN GENERAL IMMUNOTHERAPY CAN BE SAFELY COMBINED WITH SYSTEMIC AND LOCAL THERAPY

Systemic treatments

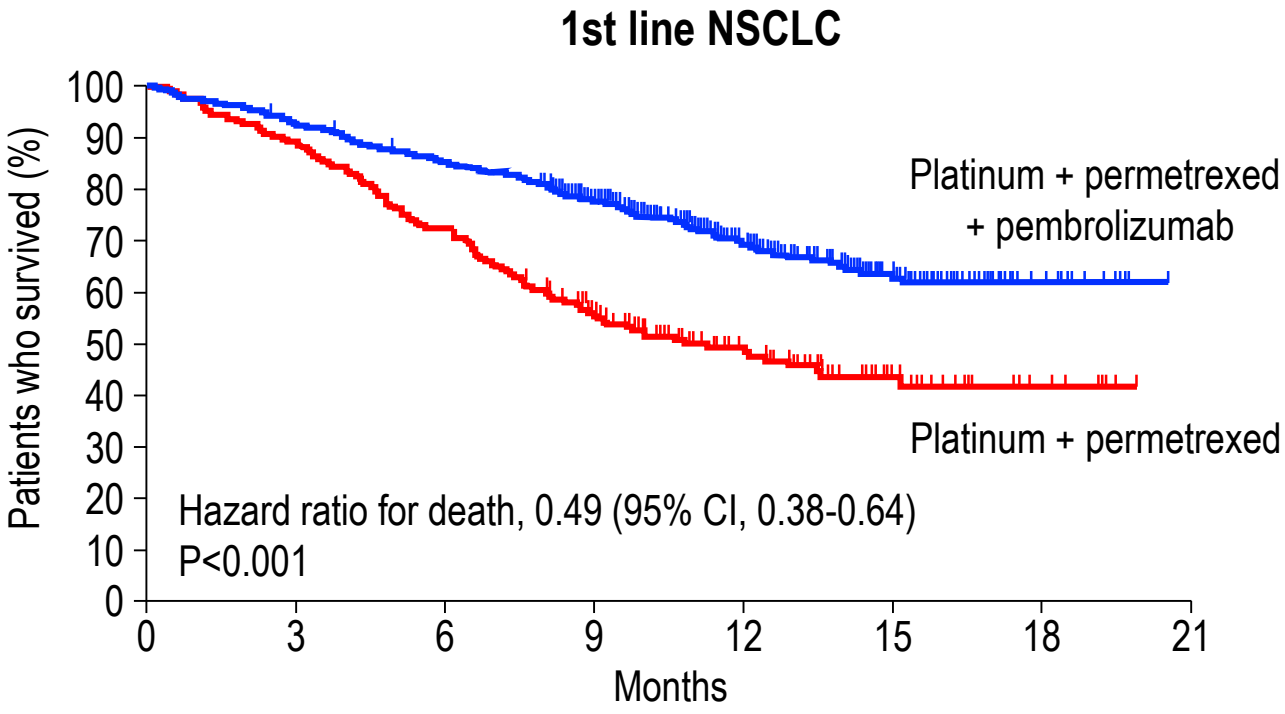
- Chemotherapy
- Targeted therapy
- Anti-angiogenic therapy
- Other immunotherapies

Local treatments

- Radiotherapy
- Surgery
- Intratumoural injection of therapeutics

IMMUNOTHERAPY + CHEMOTHERAPY

- Phase III studies confirming interest in NSCLC
- Tolerance is good: no overlapping toxicity



Gandhi L, *et al.* 2018, N Engl J Med; 378:2078-2092
See also: Langer CJ, *et al.* Lancet Oncol. 2016.

IMMUNOTHERAPY + TARGETED THERAPY

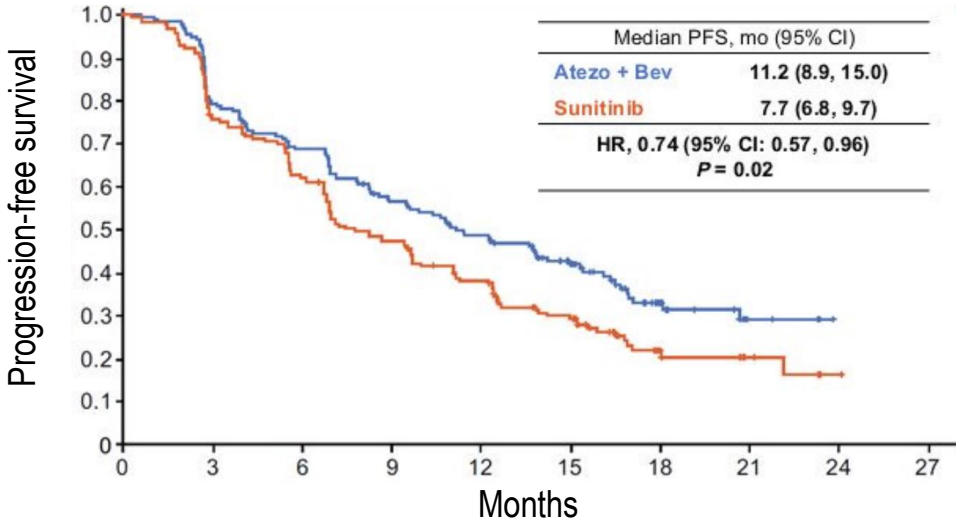
- Toxicity profile depends on combination partners
  - Vemurafenib (anti-BRAF) + ipilimumab (anti-CTLA4): study stopped for hepatitis problems
  - Osimertinib + durvalumab: stopped for pneumonitis (TATTON TRIAL: up to 64% of pts developed pneumonitis)
  - …
- Clinical interest of combining TKI + ICPI remains to be demonstrated

Data from Ribas A, *et al.* N Engl J Med. 2013;368(14):1365-6
See also: Hamid O, *et al.* 2015, SMR (melanoma).

IMMUNOTHERAPY + ANTI-ANGIOGENIC THERAPY

- Phase I/II studies demonstrating clear clinical interest good clinical tolerance: confirmation in phase III study: combination of bevacizumab with atezolizumab is superior to sunitinib in 1st line RCC (Immotion151)
- No overlapping toxicity

1st line RCC: bevacizumab + atezolizumab



Motzer RJ, *et al.* J Clin Oncol 2018;36(6_suppl): abstract 578. 2018 Genitourinary Cancers Symposium. Reproduced with permission from Professor RJ Motzer.
See also: Choueiri T, *et al.* 2018, Lancet Oncol; Mc Dermott D, *et al.* 2018, Nat Med; Huang Y, *et al.* 2018, NRI; Socinski M, *et al.* 2018, NEJM; Atkins M, *et al.* 2018, Lancet Oncol.

COMBINATION OF IMMUNOTHERAPY

- Echo 301 trial (anti-IDO + pembro): negative
- Nivolumab + ipilimumab: interesting for melanoma patients with brain mets: cave toxicity
- Nivolumab + ipilimumab (1 mg/kg): superior OS compared to sunitinib in RCC
- Many combination trials are ongoing

Long GV, *et al.* Lancet Oncol. 2018;19(5):672-681; Wolchok JD, *et al.* N Engl J Med 2017; 377:1345-1356; Motzer RJ, *et al.* N Engl J Med 2018; 378:1277-1290

IMMUNOTHERAPY + RADIOTHERAPY

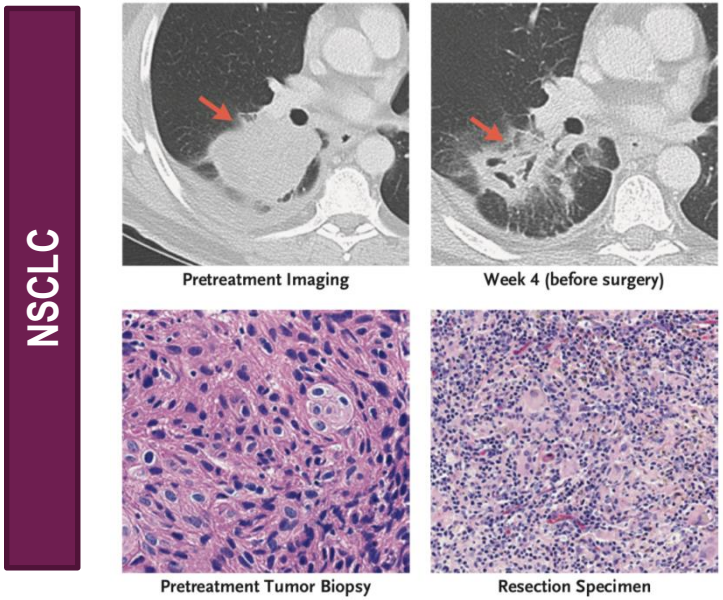
- Radiotherapy influences local and systemic immune responses
- It is feasible to combine SBRT with ICPI, no toxicity concerns
- Responses at distance of irradiated sites may be seen: abscopal effect

Data from: Luke JJ, *et al,* J Clin Oncol. 2018;36(16):1611-1618; Golden EB, *et al.* Lancet Oncol. 2015;16(7):795-803; Mohamad O, *et al.* Oncoimmunology. 2018 ;7(7):e1440168.
See also: Twyman-Saint Victor C, *et al.* 2015, Nature; Tang C, *et al.* 2017, Clin Can Res; Ngwa W, *et al.* 2018, NRC.

IMMUNOTHERAPY + SURGERY

Neoadjuvant setting: Interesting results in early CTs

NSCLC (image below), bladder CA (PURE-1), merkel cel CA (checkmate 358), melanoma, ...



Adjuvant setting: Phase III evidence

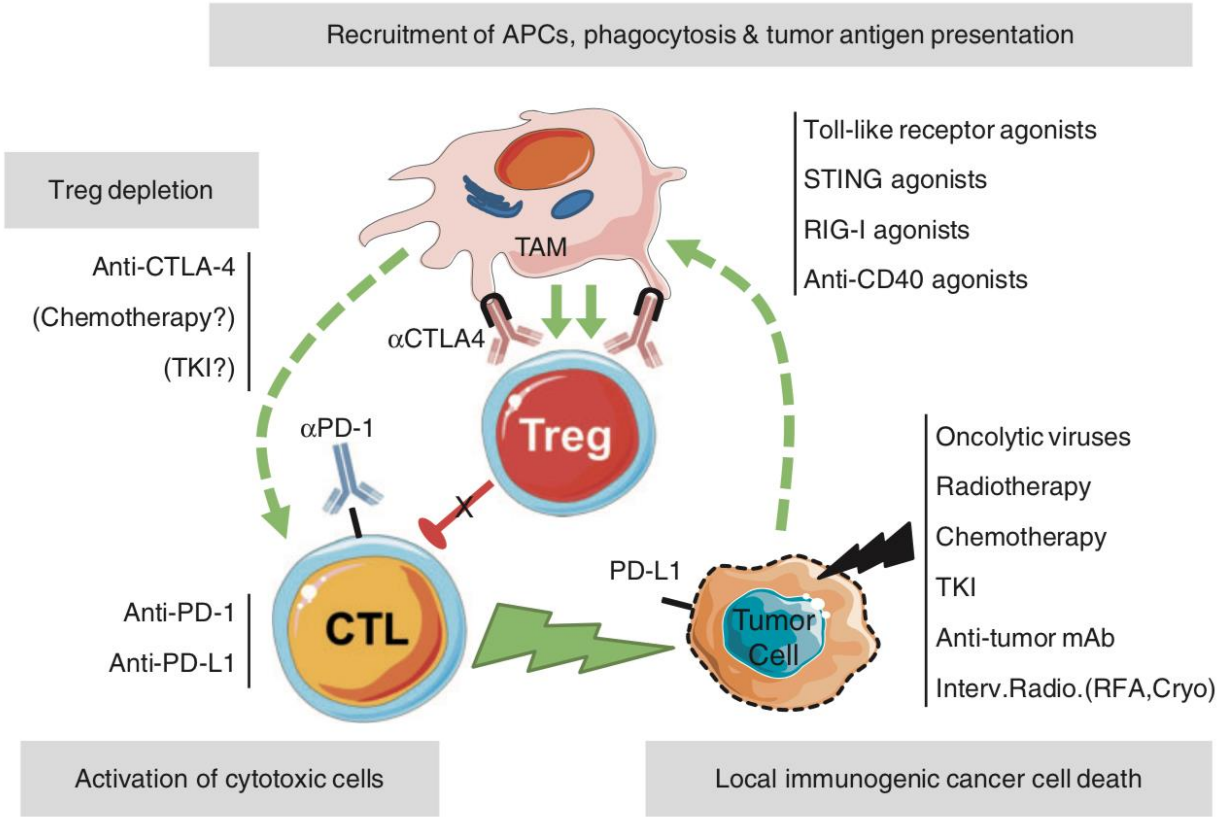
- Melanoma stage > III: nivolumab
- NSCLC treated by CRT: durvalumab (PACIFIC)

From N Engl J Med, Forde PM, *et al.* Neoadjuvant PD-1 Blockade in Resectable Lung Cancer, 378, 1976–86. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society,

See also: Amaria RN, *et al.* 2018, Nat Med; Blank CU, *et al.* 2018, Nat Med

IMMUNOTHERAPY + INTRATUMOURAL INJECTIONS

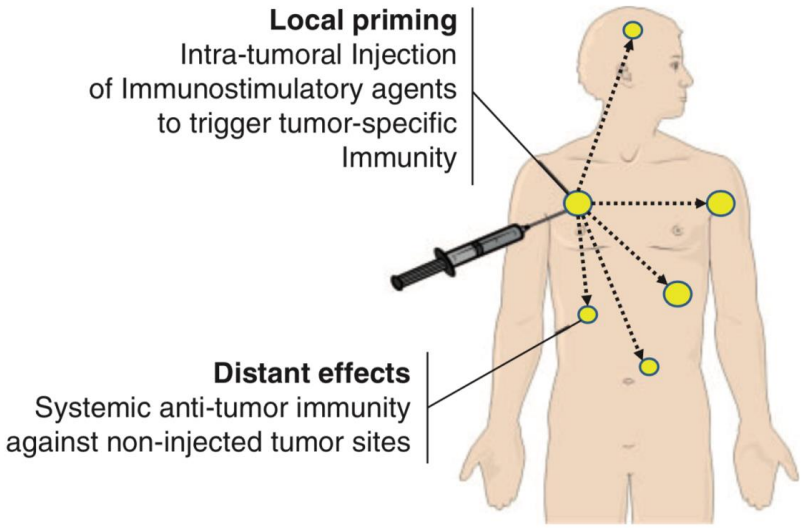
A way to modulate the tumour microenvironment (TME)



Marabelle A, *et al.* Intratumoral immunotherapy: using the tumor as the remedy, Ann Oncol 2017;28 (suppl_12). By permission of Oxford University Press/ on behalf of the European Society for Medical Oncology (ESMO).

IMMUNOTHERAPY + INTRATUMOURAL INJECTIONS

- Phase I studies showing interest and good tolerance
  - Oncolytic viral therapy (talimogene laherparepvec)
    - + pembrolizumab (21 pts, phase Ib, DCR 76%)
    - + ipilimumab (Phase II)
      (n=198, ORR 39% v 18%, p =0,002)
  - Revival of TLR agonists
    - BCG (TLR 4)
    - Imiquimod (TLR7)

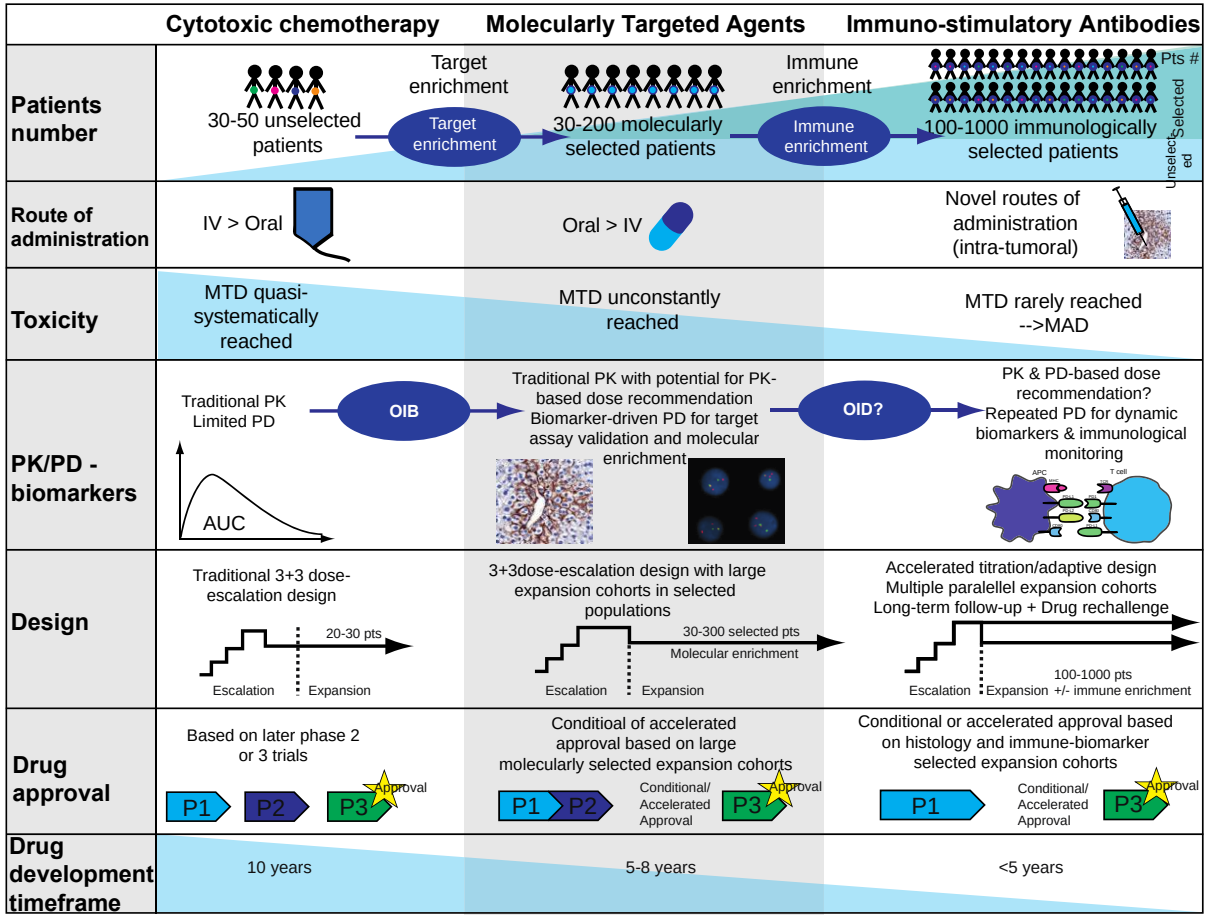


Data from: Ribas A, *et al.* 2017, Cell; Chesney J, *et al.* 2017, JCO. Twumasi-Boateng et al, 2018, NRC.

Marabelle A, *et al.* Intratumoral immunotherapy: using the tumor as the remedy, Ann Oncol 2017;28 (suppl_12). By permission of Oxford University Press/ on behalf of the European Society for Medical Oncology (ESMO).

CLINICAL TRIAL ORGANISATION

IMMUNOTHERAPY IS CHANGING THE CLINICAL TRIAL LANDSCAPE



Postel-Vinay S, Aspeslagh S, *et al.* Challenges of phase 1 clinical trials evaluating immune checkpoint-targeted antibodies, Ann Oncology 2016;27 (2):214–224. By permission of Oxford University Press/ on behalf of the European Society for Medical Oncology (ESMO).

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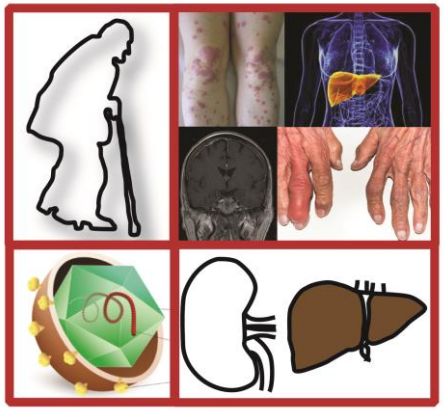
EXCLUSION CRITERIA FROM CLINICAL TRIALS NEED TO BE ADAPTED



- Brain metastasis can respond
- Hepatitis C RNA can decrease, no reactivation found
- Pre-existing autoimmune disease is not always reactivated
- Recent radiotherapy does not induce more toxicity
- Lymphopenia is not related to non-response
- Oncogeriatric patients do not seem to experience greater toxicity
- Tumour responses have been seen in patients with bad performance status (PS 2)
- Some transplant patients do not reject their graft while treated with ICPi

→ **IMMUNOTHERAPY IS THESE SETTINGS SHOULD BE THOROUGHLY DISCUSSED WITH THE PATIENT AND HIS FAMILY**

→ **PROSPECTIVE CLINICAL TRIALS SHOULD CONFIRM THESE DATA**

Data From Sun R, *et al.* 2017, EJC; Danlos F, *et al.* 2018, EJC; Herin, H, *et al.* 2018, EJC, Yoo S, *et al.* 2018, JTO; Munker S, *et al.* 2018, UEG journal; Parakh S, *et al.* 2017, BMJ.

CONCLUSIONS AND PERSPECTIVES

CONCLUSION

- Biomarkers for anti-tumour response:
  - Highly needed, PDL1 is the best we have, TMB is at its infancy
- Response patterns
  - Durable responses: hope for cure. Even in metastatic setting?
- Toxicity
  - Early identification and treatment is key
- Combination of immunotherapy with other agents
  - Seems feasible for chemotherapy, anti-angiogenic Ab and radiation, much more challenging for TKI
- Clinical trial design
  - No clear dose/response/toxicity relationship
  - More insight needed to define the optimal dose/schedule and treatment duration

FUTURE PERSPECTIVES

- Biomarkers for anti-tumour response:
  - Potential candidates: TILs, JAK1/2 mutations (cfr NSCLC, melanoma)
- Response patterns
  - Possibility to stop immunotherapy after CR (cfr melanoma).
  - Pseudoprogression and hyperprogression need to be precised
- Toxicity
  - Pharmacodynamic parameter of tumour response (cfr melanoma, NSCLC)
- Combination of immunotherapy with other agents
  - Combination with local treatments is promising
- Clinical trial organisation
  - Exclusion criteria need to be revised

THANK YOU!

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DISCLOSURES

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