INSTITUT JULES BORDET

13th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice

BSMO

Genotype-driven melanoma : what first, targeted therapies or immunotherapy ?

Is there (yet) a correct or right answer ?

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EORTC European Organisation for Research and Treatment of Cancer

ONCODISTINCT NETWORK

Stichting tegen Kanker Samen voor het leven
Fondation contre le Cancer Ensemble pour la vie

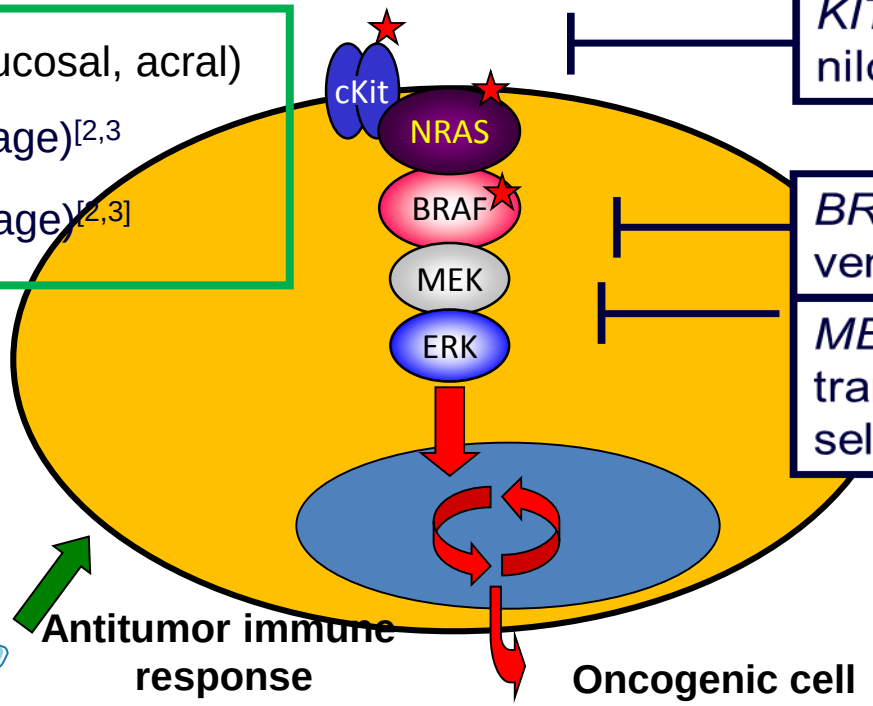
Potential targets in malignant melanoma

cKIT, NRAS, BRAF mutated in ~ 70% of melanomas, usually mutually exclusive[1]

< 5% melanomas (mucosal, acral)

~ 20% melanomas (> age)[2,3]

~ 50% melanomas (< age)[2,3]



KIT inhibitors: imatinib, nilotinib, dasatinib[4]

BRAF inhibitors: vemurafenib, dabrafenib[4]

MEK inhibitors: trametenib, cobimetinib, selumetinib, pimasertib[4]

IL-2
IFN-a
Anti-CD40
Anti-CD137
Anti-OX40

Antitumor immune response

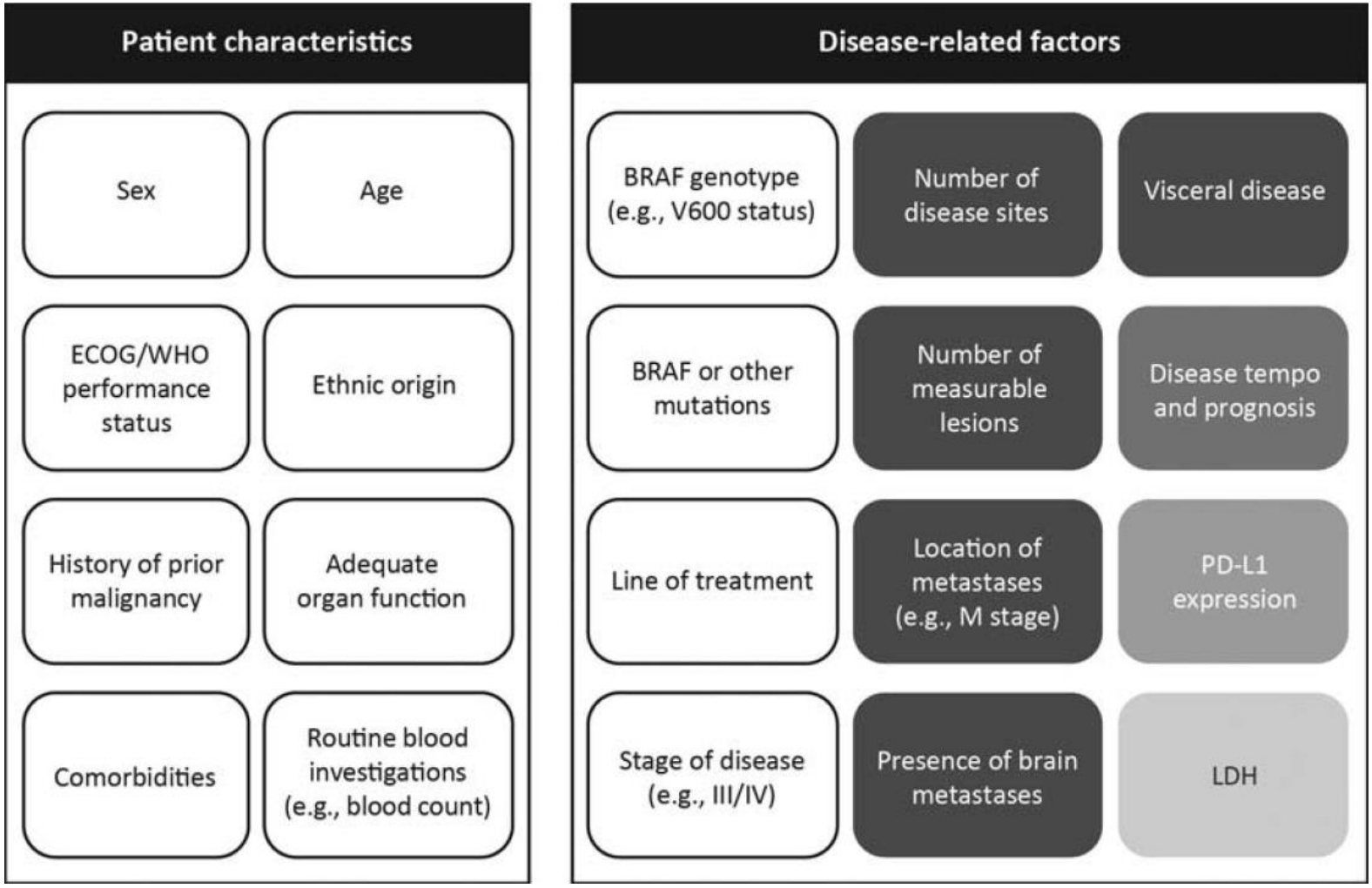
Oncogenic cell proliferation and survival

Anti-CTLA4

Anti-PD1

1. Sosman JA, et al. ASCO 2011 Educational Book. 2. Arkenau HT, et al. Br J Cancer. 2011;104:392-398. 3. Thomas N, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:991-997. 4. Nikolaou VA, et al. J Invest Dermatol. 2012;132:854-863.

Metastatic melanoma: the play



Oncogenic-driven melanoma other than BRAF

- **c-Kit mutated melanoma**
  - Targeted therapy ?
  - Imatinib (ORR ≤ 30%), Dasatinib,…
- **NRAS mutated melanoma**
  - Targeted therapy : MEK inhibitor

	Binimetinib vs Dacarbazine[1]	Pimasertib vs Dacarbazine[2]
mPFS HR/p value	3.0 vs 1.8 mos 0.63 (0.47-0.80) / < 0.001	13.0 vs 6.9 wks 0.59 (0.42-0.83) / 0.0022
mOS HR/p value	11.0 vs 10.1 mos 1.00 (0.75-1.33) / NS	8.9 vs 10.6 wks 0.89 (0.61-1.30) / NS

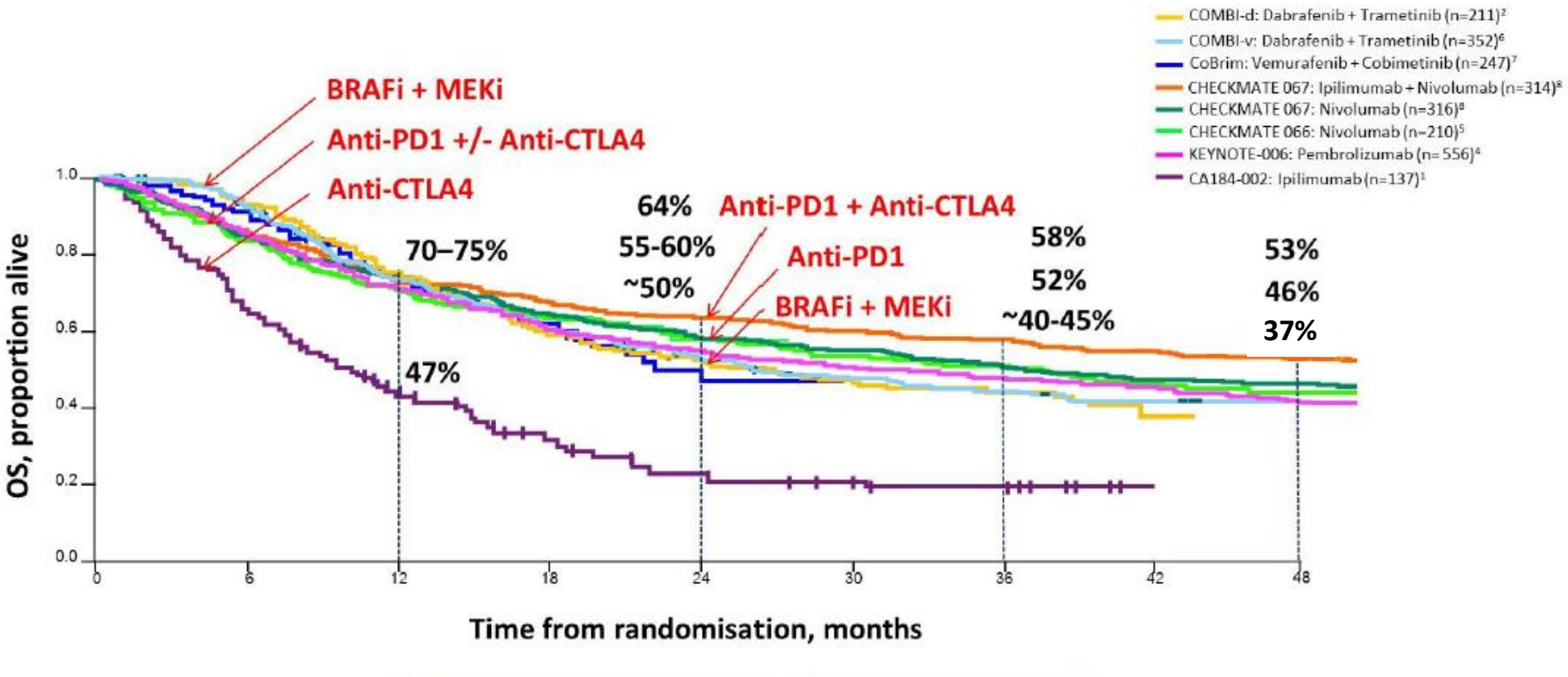
  - Binimetinib (MEKi) + Ribociclib (CDK4/6i)
  - Binmetinib + Ribociclib + Encorafenib (BRAFi): too toxic
  - Immunomodulating activity of MEK inhibitor: probably good candidate for combining MEKi + immunotherapy (anti-PD-1 ± CTLA4)

1. R Dummer Lancet Oncol 2017; 18: 435 / 2. C Lebbé ESMO 2016 / 3. JA Sosman, ASCO 2014

BRAF V600 mutated melanoma: the actors

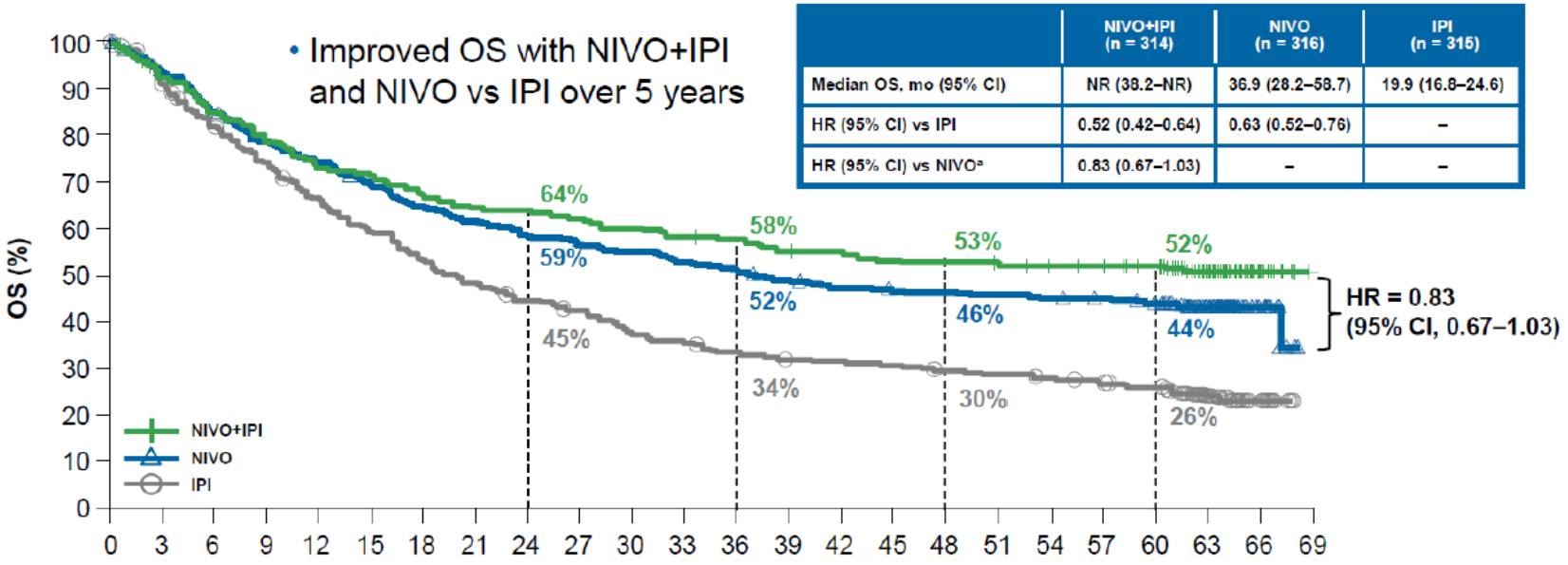
Targeted therapy		Immunotherapy	
BRAF + MEK inhibitors: Dabrafenib+ Trametinib Vemurafenib + Cobimetinib Encorafenib + Binimetinib	**Anti-CTLA4:** Ipilimumab	**Anti-PD-1:** Nivolumab Pembrolizumab	**Anti-PD-1 + anti-CTLA4:** Nivolumab + Ipilimumab Pembrolizumab + Ipilimumab
Robust and rapid onset of response Eventual progression	Less efficient	Lower initial response rate More durable long-term benefit	Slower onset of response Durable long-term benefit
	toxic	less toxic	highly toxic contra-indications
ORR: ~ 70% **PFS: 11-15 mos**	**ORR: ≤ 20%** **PFS: ≥ 6 mos**	**ORR: 40-45%** **PFS: 6-7 mos**	**ORR: ~ 60%** **PFS:**
4yrOS: ~ 40%	**4yrOS: ~ 20%**	**4yrOS: 46%**	**4yrOS: 53%**

Overall survival in metastatic melanoma



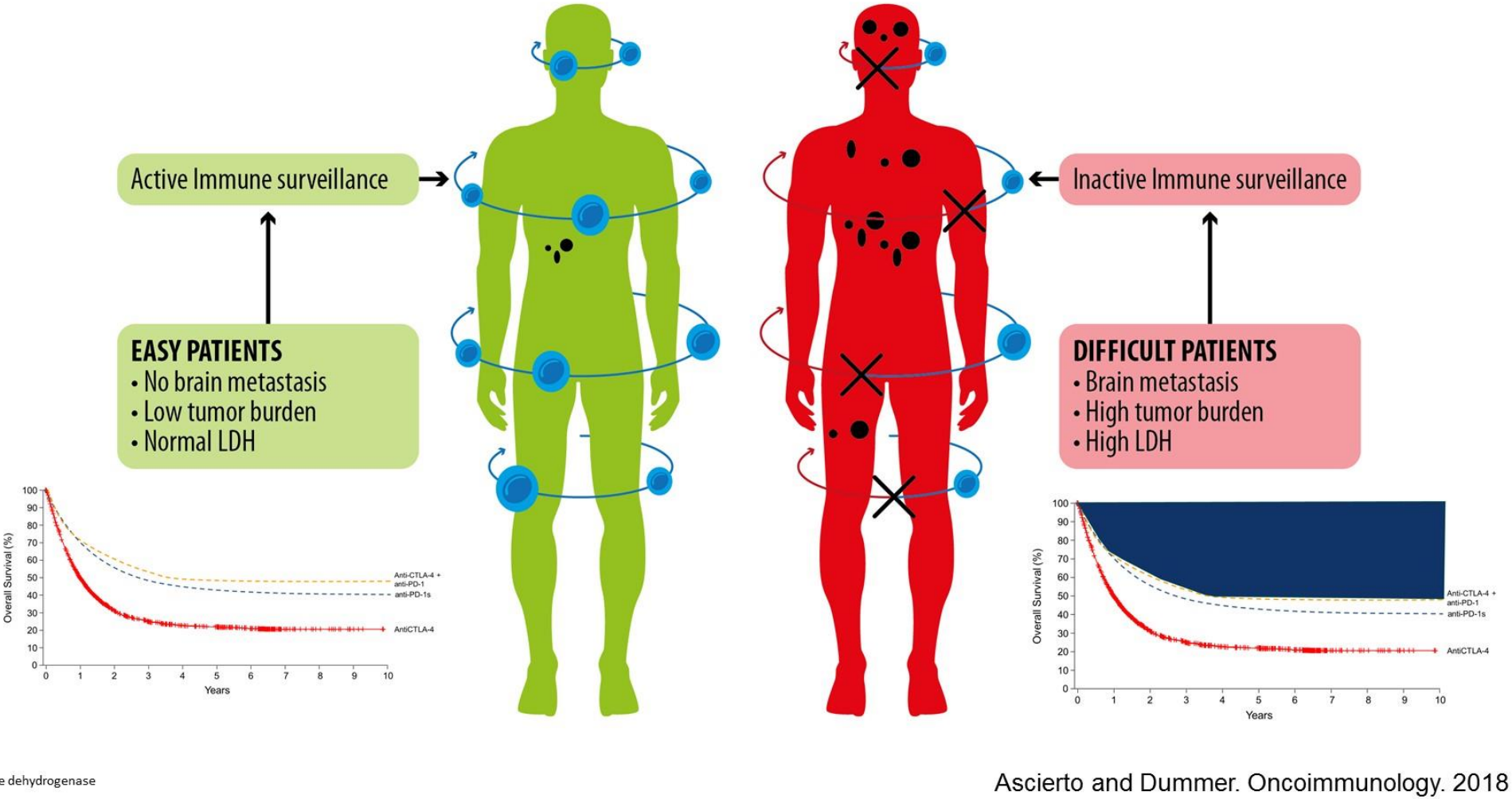
G. Long, ESMO 2018

Immunotherapy: single-agent anti-PD-1 or anti-PD-1 + anti-CTLA4 combination ?



	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–

Clinical risk factors and immune status



e dehydrogenase

Ascierto and Dummer. Oncoimmunology. 2018

Targeted and immunotherapy in brain metastases

Asymptomatic Brain Metastases	Active Brain Mets	
	Response	6-mo IC PFS
Dabrafenib + Trametinib (n=76)[1]	58%	44%
Ipilimumab (n=51)[2]	10%	-
Pembrolizumab (n=23)[3]	26%	40%
Nivolumab (n=21, drug naive)[4]	21%	21%
Nivolumab + Ipilimumab (n=27, drug naive)[4] /(n=101)[5]	56%/54%	60%/63%

1. Davies MA et al Lancet Onc 2017; 2. Margolin K et al Lancet Onc 2012; 3. Kluger H et al JCO 2019; 4. Long GV et al Lancet Onc 2018; 5. Tawbi H et al ASCO 2019

Optimal treatment selection:

currently available biomarker & physician assessment

- **Melanoma factors**
  mutational status
  LDH
  CRP
  Metastatic sites
  CNS involvement
  Tumour burden

- **Therapeutic factors**
  Onset of action
  ORR and other benefits
  Toxicities

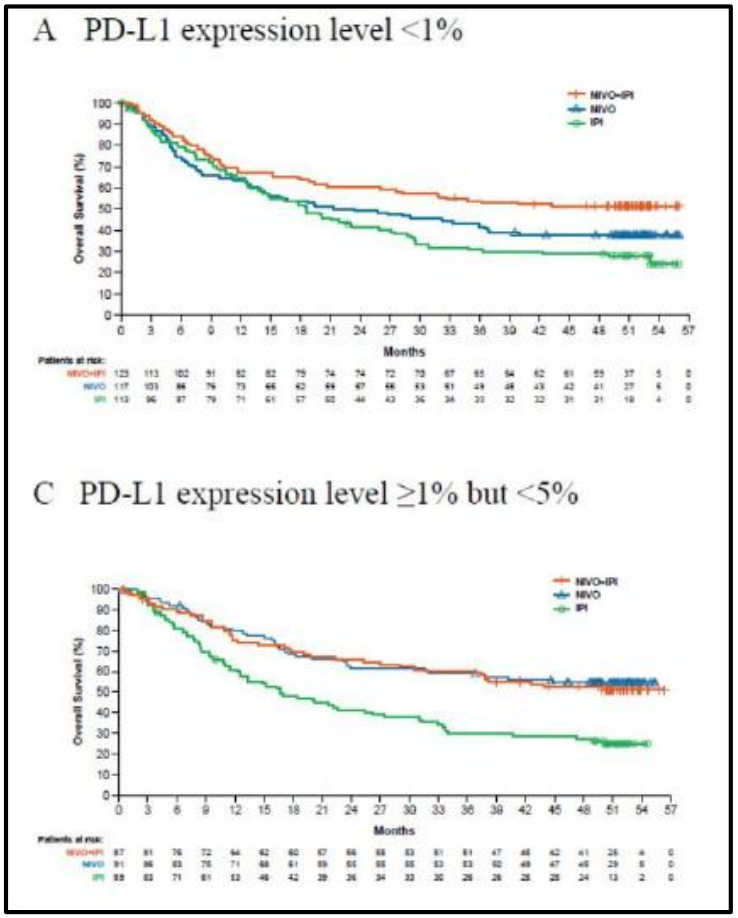
- **Patient factors**
  Performance status
  Comorbidities
  Immune function
  (Auto-immune disease, immunosuppression)
  Adherence to safe administration
  Prior therapies
  Personal preference

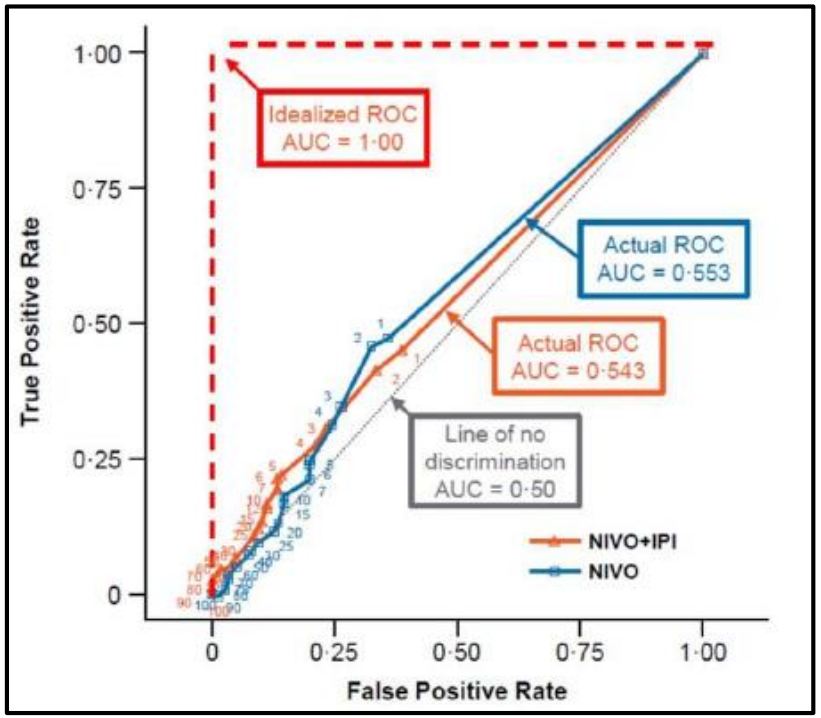
BRAF V600 mutated metastatic melanoma

Clinical scenario	Possible 1st-line choice
Low-risk, indolent disease	BRAF / MEK i or anti-PD-1
High-risk disease, no CNS involvement	BRAF / MEK i or anti-PD-1 [± anti-CTLA4 (?)]
« visceral crisis »	BRAF / MEK i
High-risk disease, CNS involvement	BRAF /MEK i or Anti-PD-1 + anti-CTLA4

Biomarkers : Checkmate 067

NIVO + IPI vs NIVO vs IPI



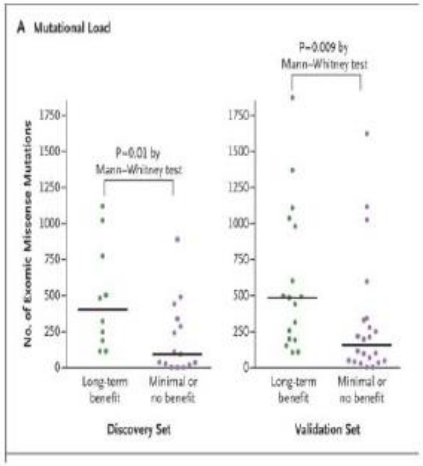


PD-L1 expression alone is a poor biomarker of overall survival

Hodi et al., Lancet Oncol, 2018; 19: 1480-92

Biomarkers of response to immune checkpoint inhibitors

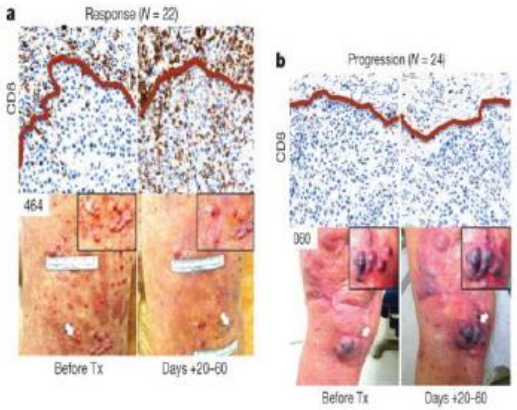
Mutational load



- Mutational load and neoantigens may help explain varied response to therapy

Snyder, et al N Engl J Med. 2014

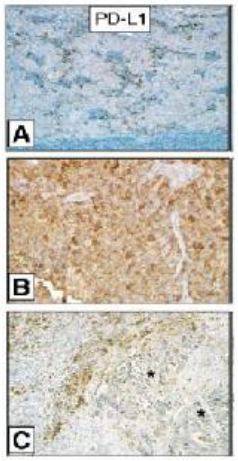
Baseline CD8⁺ T cell density / distribution



- The density and distribution of CD8+ T cells at baseline can help predict response (baseline)

Tumeh, et al. *Nature*. 2014.

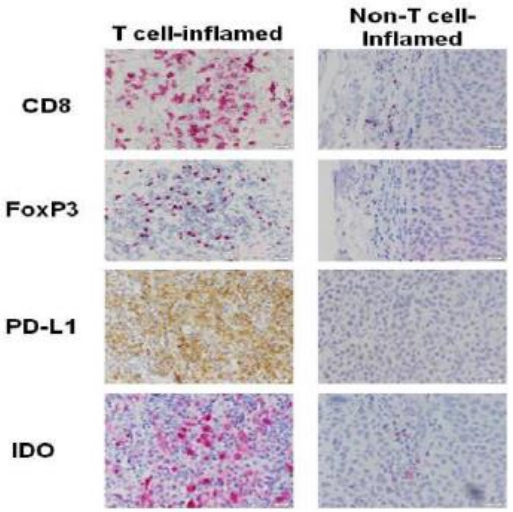
Baseline PD-L1 staining



- PD-L1 tumors are more likely to respond to checkpoint blockade

Taube et al. 2014.

T cell-inflamed tumors

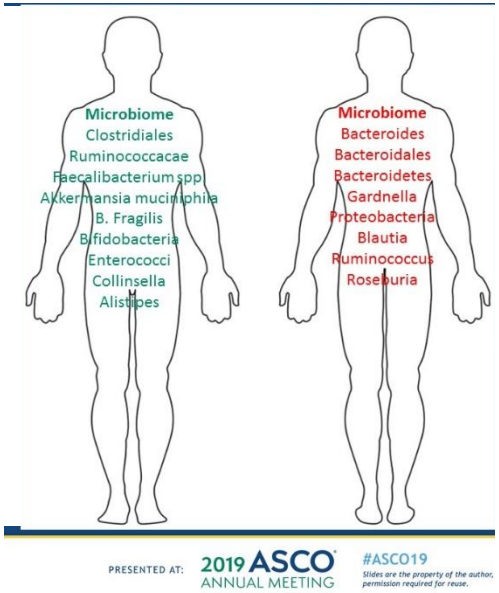


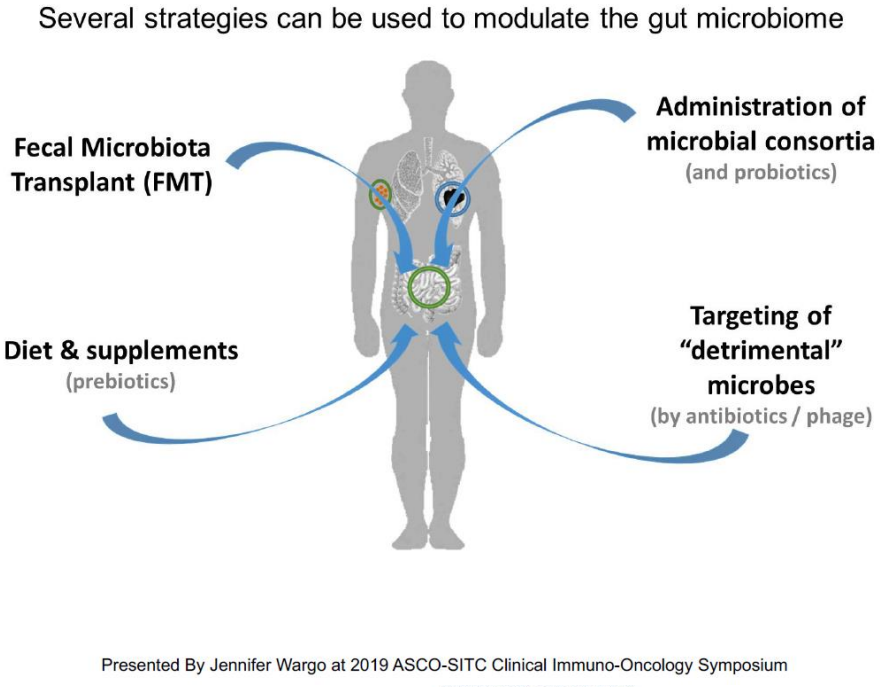
- T cell "inflamed" tumors are more likely to respond to immune checkpoint blockade

Spranger et al. Science Translational Medicine 2013.

Jenifer Wargo, 2018 ASCO Annual Meeting

Influence of the microbiome





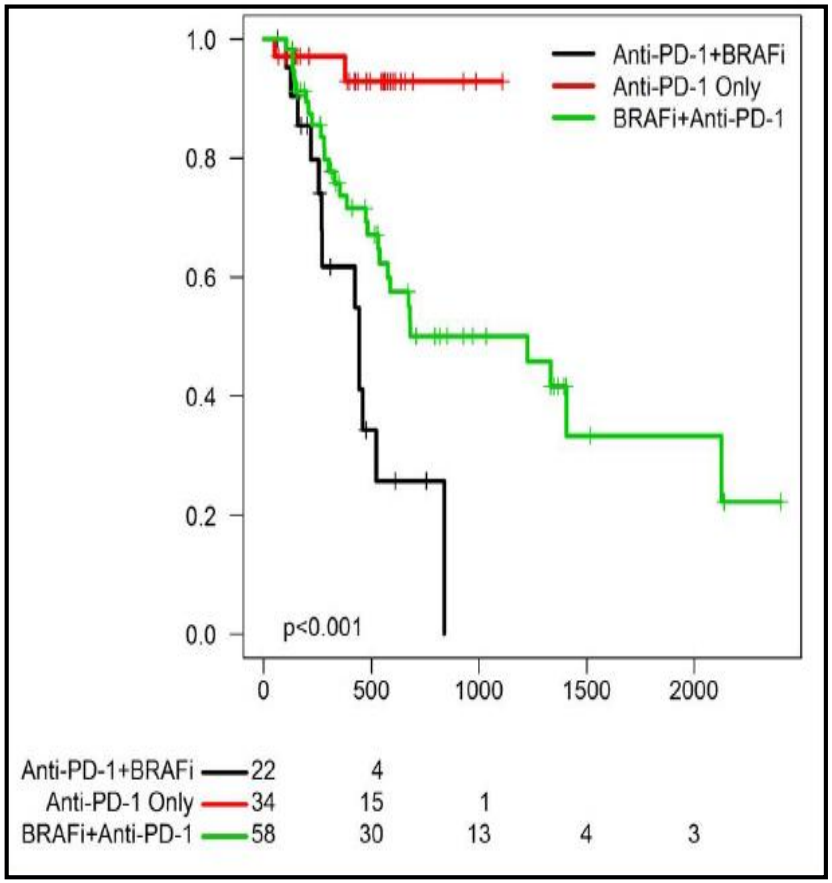
Jason Luke, 2019 ASCO Annual Meeting

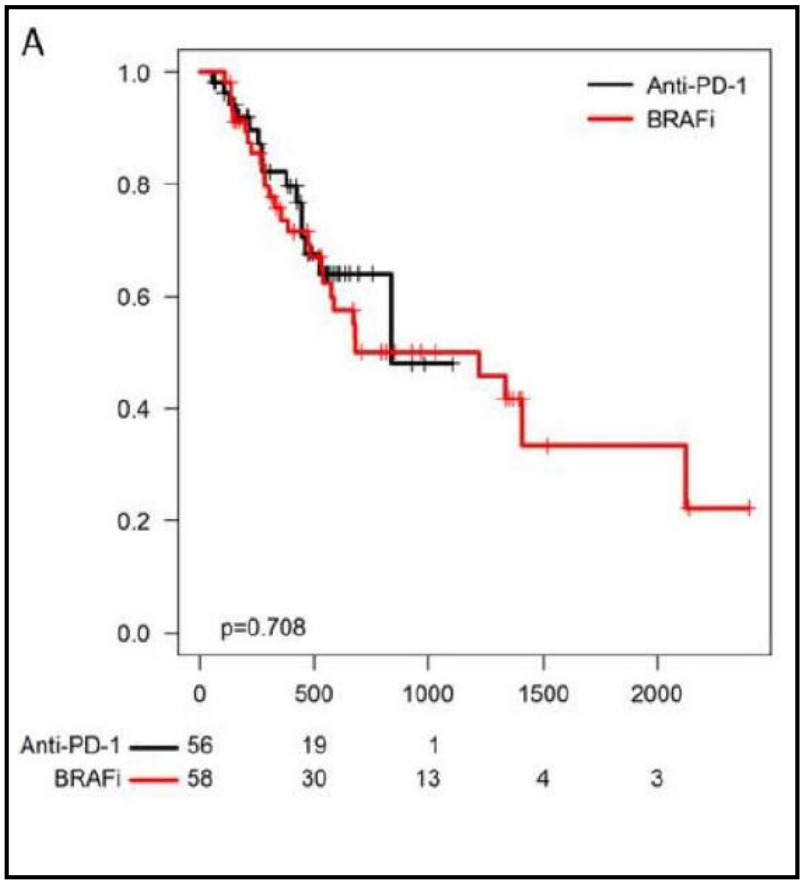
Biomarkers bottom-line

- PD-L1 expression is not a good biomarker for response to immunotherapy.
- Tumor mutational load may also be important
- as well as exploration of the microenvironment.
- Insight of microbiome about tumour immuno-responsiveness and risk of toxicity.

- As of today,
  no valid biomarkers available to assist in treatment selection, prediction of response to therapy or potential toxicity.

Something to think about …



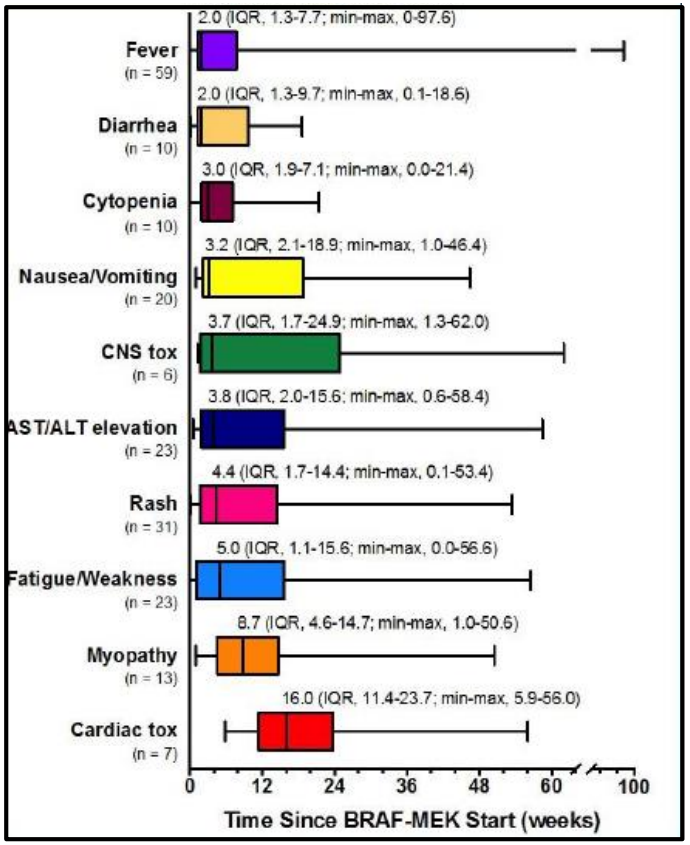


1. Patients who do well with anti-PD-1 therapy before BRAF-targeted therapy have the best outcome
2. Patients who do poorly with anti-PD-1 therapy before BRAF-targeted therapy have the worst outcome (suggestion of shared mechanisms of resistance)
3. Patients with BRAF-targeted therapy before anti-PD-1 therapy have intermediate outcomes. (suggestion IO post BRAF/MEKi is effective in some)

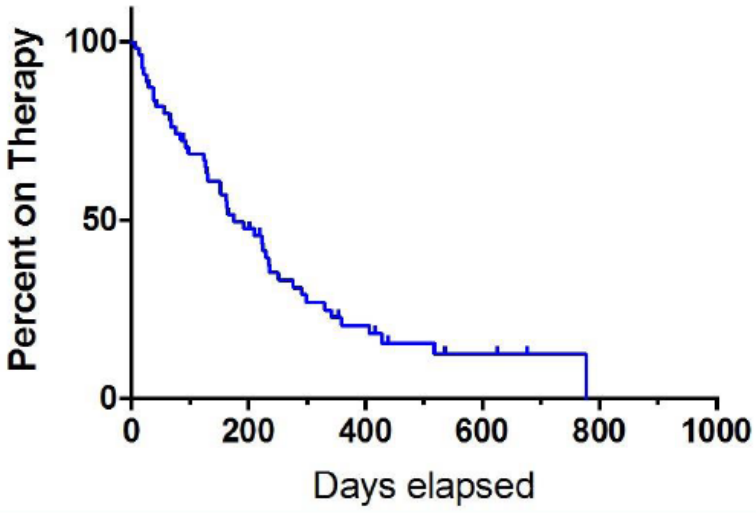
DB Johnson J Immunother 2017

BRAF targeted therapy after anti-PD1 based therapy

is toxic



and not that efficacious



Toxicity (N=78 pts)
- 83% dose modifications
- 31% hospitalisations

Activity (N=55 pts)
- mPFS: 5.8 months
- mOS: 15.6 months

Saab et al. Cancer 2019

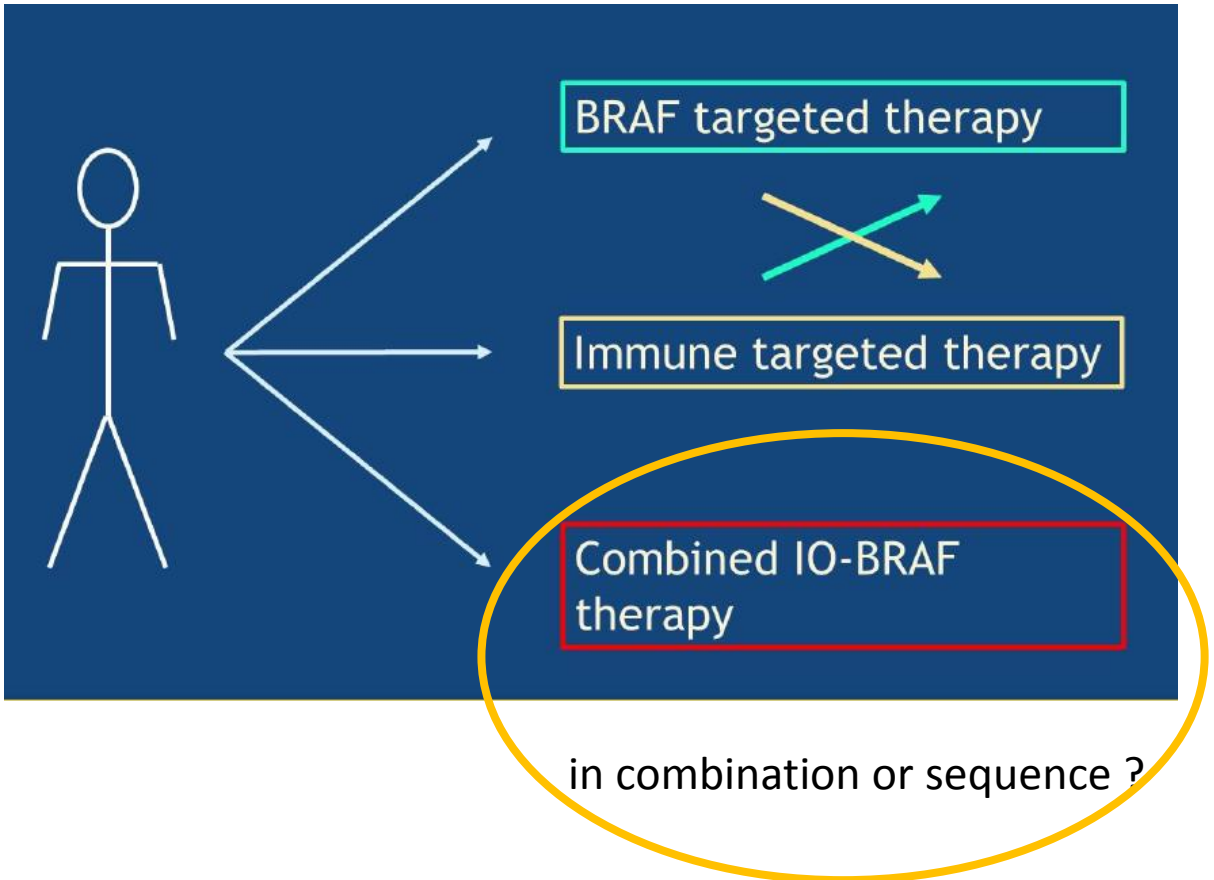
Current and future considerations

- No prospective head-to-head data comparing IT with TT in first-line therapy for BRAF mutated melanoma
- Optimal sequence still debated
- Phase III trials currently underway:
  - DREAMSEQ trial (NCT 0222478):
    Dabrafenib-Trametinib → Nivolumab-Ipilimumab vs
    Nivolumab-Ipilimumab → Dabrafenib-Trametinib
  - SECOMBIT trial (NCT 02631447):
    Encorafenib-Binimetinib → Nivolumab-Ipilimumab vs
    Nivolumab-Ipilimumab → Encorafenib-Binimetinib vs
    Encorafenib x 8 weeks → Nivolumab-Ipilimumab → rechallenge

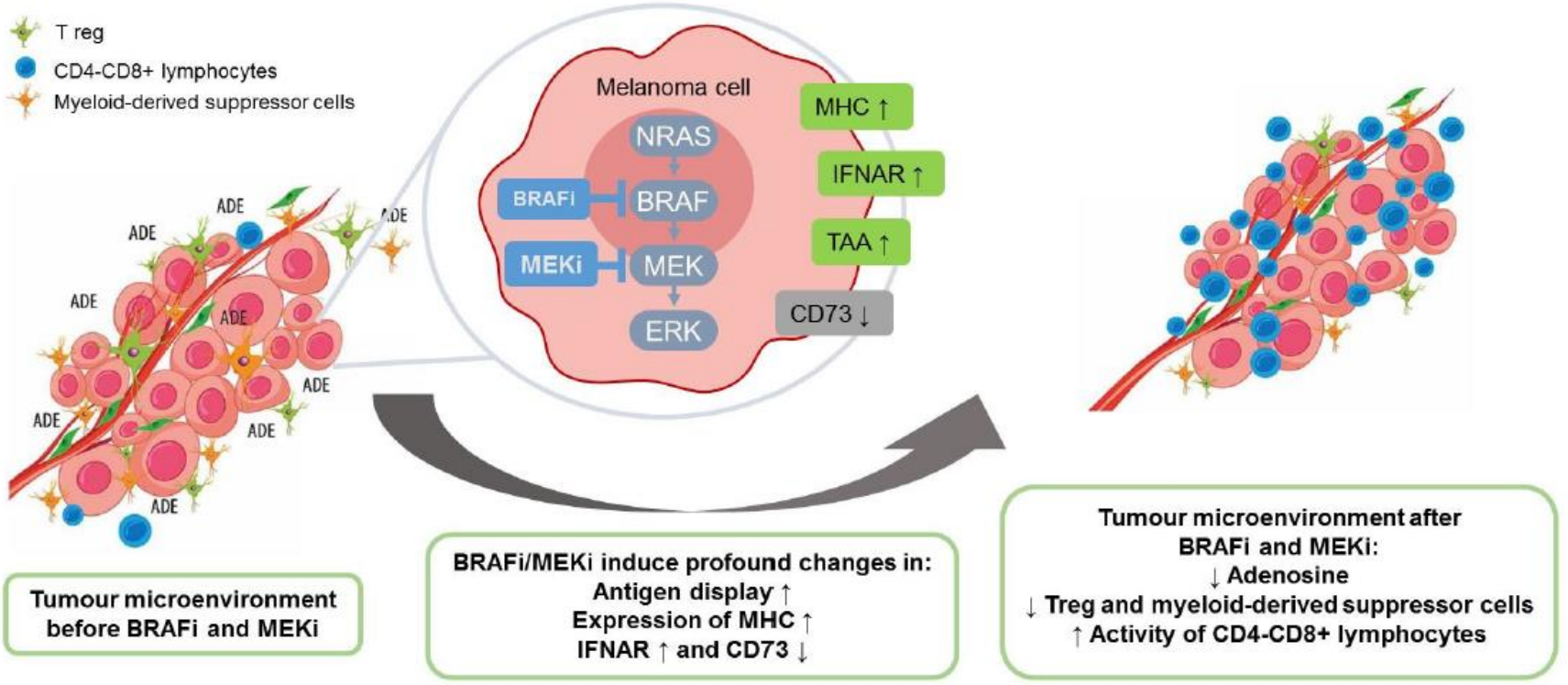
  but : what about anti-PD1 monotherapy vs BRAF/MEK inhibitors ?

BRAF V600 mutated melanoma

not merely targeted therapy vs immunotherapy,
but also…



BRAF/MEK inhibitors as immunomodulating agents

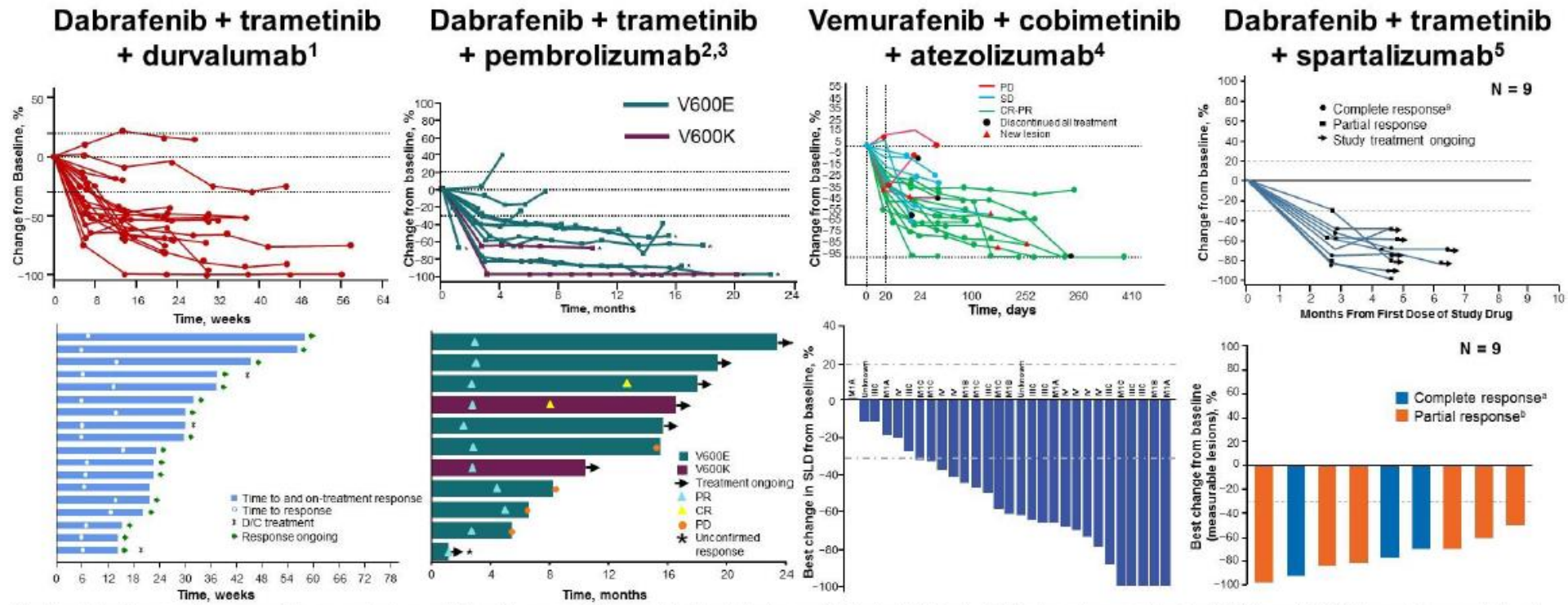


ADE, adensosine; IFNAR, interferon-α/β receptor; MHC, major histocompatibility complex; TAA, tumour-associated antigen; Treg, regulatory T cell

Image modified from Ascierto & Dummer, Oncoimmunology 2018

P Ascierto 2019 ASCO Annual Meeting

Clinical trials *combining*
BRAFi + MEKi + anti-PD(L)-1



BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. [a] Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. [b] Patients with PR and 100% change in SOD have (a) 100% change for all target lesions and (b) non-CR/non-PD response for nontarget lesions.

1. Ribas A, et al. *J Clin Oncol*. 2015; 33(suppl) [abstract 3003]; 2. Ribas A, et al. *J Clin Oncol*. 2016; 34(suppl) [abstract 3014]; 3. Ribas A, et al. *Ann Oncol*. 2017; 28(suppl 5) [abstract 1216O]; 4. Hwu P, et al. *Ann Oncol*. 2016; 27(suppl 6) [abstract 1109PD]; 5. Dummer, R, et al. *J Clin Oncol*. 2018;36(suppl 5S) [abstract 189].

PRESENTED BY R DUMMER AT AACR 2018

Courtesy of Dr Dummer

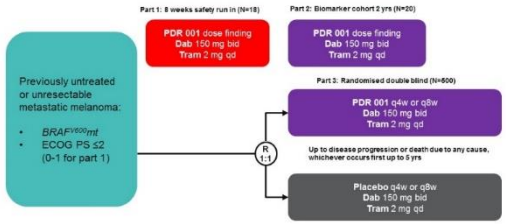
So far:

- increased toxicity
- uncertainty of long-term benefit
- randomised trials still underway
- role of sequential use ?

Combination design

NCT02967692: Phase 3 study of PDR 001 (anti-PD-1) + dabrafenib and trametinib in previously untreated BRAFv600 mutation positive patients

A randomized, double-blind, placebo-controlled, Phase 3 study comparing the combination of PDR 001, dabrafenib and trametinib vs placebo, dabrafenib (BRAFi) and trametinib (MEKi) in previously untreated patients with unresectable or metastatic BRAF V600 mutant melanoma



Primary endpoints:
- Incidence of DLTs (safety run in)
- Immune response and biomarker modulation (biomarker cohort n=20 over 2 years)
- Investigator-assessed PFS

Secondary endpoints:
- OS, ORR, duration of response, disease control rate
- QoL
- PFS and OS subgroup analysis (biomarker status)

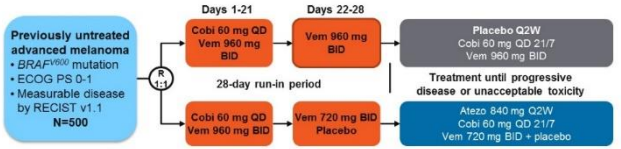
Bid, twice daily; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; qd, once daily; QoL, quality of life; ECOG-PS, Eastern Cooperative Oncology Group performance status; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomization

Clinicaltrials.gov: NCT02967692

Sequential design

IMspire150 TRILOGY: Phase 3 study of atezolizumab (anti-PD-L1) + cobimetinib + vemurafenib in previously untreated BRAF v600 mutation positive patients

- Phase 3, double-blinded, placebo-controlled, randomized, multicenter study to evaluate the combination of atezolizumab, cobimetinib (MEKi) and vemurafenib (BRAFi) vs placebo, cobimetinib and vemurafenib in patients with previously untreated BRAFv600 mutation-positive metastatic or unresectable locally advanced melanoma



- **Primary endpoint:**
  - Investigator-assessed PFS
- **Secondary endpoints:**
  - IRC-assessed PFS, OR
  - Investigator-assessed DOR
  - OS, 2-year landmark survival
  - Safety, PK analysis, patient-reported outcomes
  - Immune response

- 21/7, treatment for 21 days followed by no treatment for 7 days; DOR, duration of response; IRC, independent review committee; OR, objective response; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; ECOG-PS, Eastern Cooperative Oncology Group performance status; Q2W, every 2 weeks; R, randomization

- Clinicaltrials.gov: NCT02908672

IMPemBRA- study Design

Sequential design

Study cohort:
- 32 patients, 8 per arm

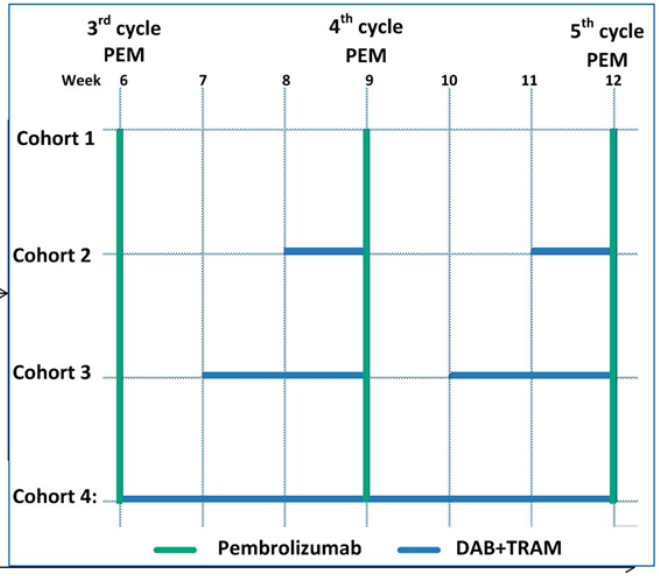
Inclusion criteria:
- Irresectable stage III or stage IV melanoma
- BRAF V600E/K positive
- Naïve for systemic therapy
- Easy accessible lesion for biopsy
- No untreated brain metastasis

Stratified according to:
LDH < ULN, >ULN, >2x ULN

PEM 200mg Q3W — R

PBMC
CT
Biopsy

PBMC
CT
Biopsy



Week 0 6 9 12 18

Primary Endpoints:
- Safety and adherence to the treatment regimen
- Immune-activating capacity of different combinations

Secondary Endpoints:
- ORR (modified RECIST) at week 6, 12, 18
- PFS

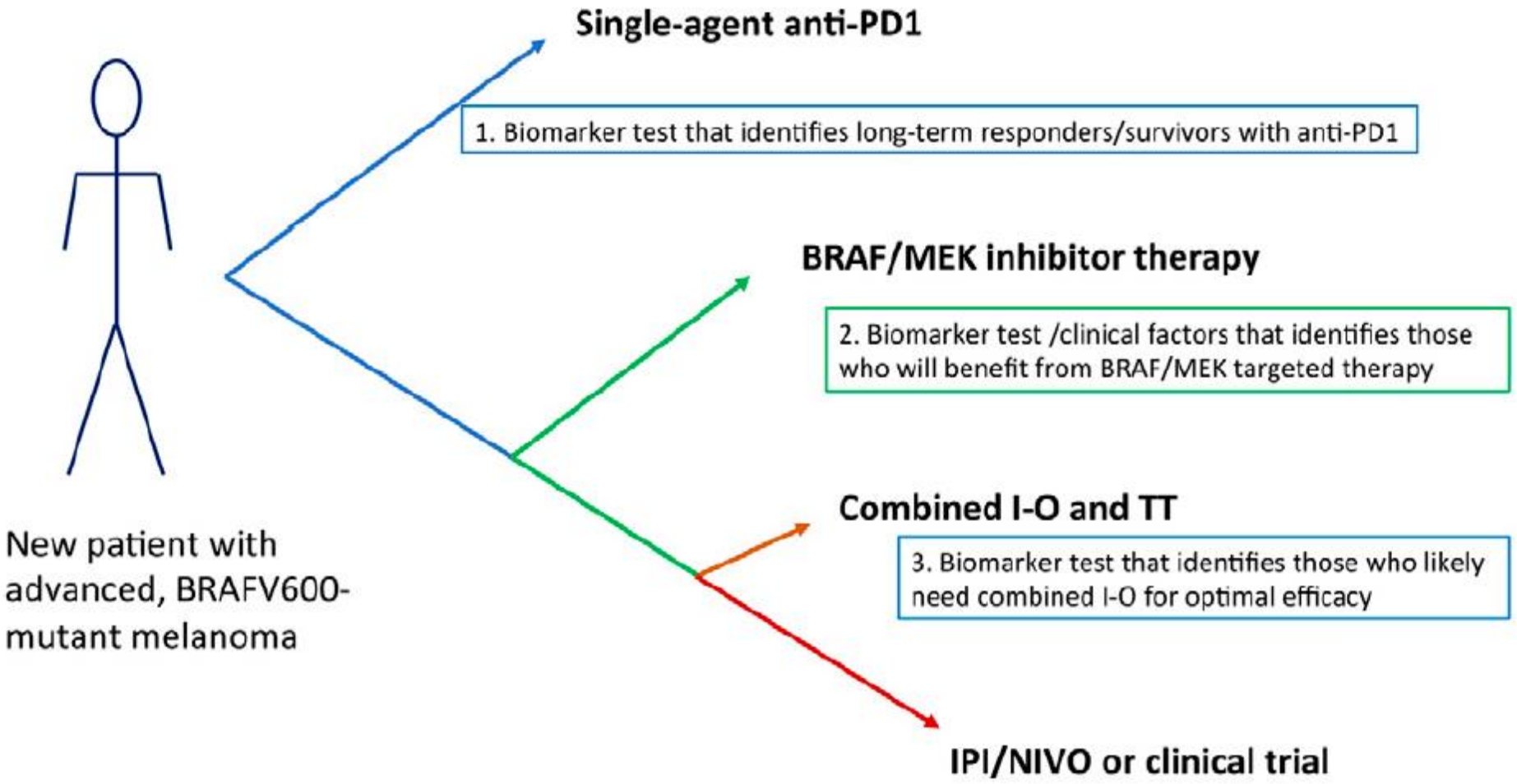
Datalock: 14/09/2018
32 patients included
29 patients randomised
26 patients completed the first 18 weeks

Rozeman et al ESMO 2018
Kindly provided by C. Blank

Combined / sequential IT and TT in BRAF V600 mutated melanoma

1. Durable benefit is seen with BRAF-targeted, anti-PD-1 monotherapy and combined anti-PD-1 + anti-CTLA4 therapies.
2. Both treatment modalities share, at least to some degree, common mechanisms of resistance and also of activity.
3. BRAF targeted therapy leads to changes in the immune microenvironment that predicts responsiveness to anti-PD-(L)1 therapy.
4. There is no prospective data regarding the optimal sequencing of BRAF-targeted therapy and anti-PD-1 based therapy (single agent or combination)
5. BRAF-targeted therapy combined with anti-PD(L)-1 is associated with significant efficacy (superior ?), but toxicity may limit its use.

The future… ?



… In the meantime,
my personal answer: clinical and biomarker trials

INSTITUT JULES BORDET

13th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice

BSMO

Genotype-driven melanoma : what first, targeted therapies or immunotherapy ?

Your answer ?

Thank you for your kind attention

EORTC European Organisation for Research and Treatment of Cancer

ONCODISTINCT NETWORK

Stichting tegen Kanker Samen voor het leven

Fondation contre le Cancer Ensemble pour la vie