CHALLENGES FOR THE APPROVAL OF ANTI-CANCER IMMUNOTHERAPEUTIC DRUGS

Challenges in evaluating relative effectiveness

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Preliminary statements

- No conflict of interest
- Bias (dermatologist)
- Reviewed documentation:
  - Published literature (melanoma, NSCLC)
  - Relevant EPARs
  - Publicly available HTA assessments

Context (1)
Targeted therapies

- Recent advances in molecular biology and genomics
  - Molecular heterogeneity of tumours
  - Identification of key molecular drivers of tumour oncogenesis and mechanisms of tumour resistance
  - shift in anticancer therapy strategies from “one-size-fits-all” approach to an individualized approach to therapy
  - development of new therapies targeted towards identified functional genetic mutations (melanoma, NSCLC, other tumours)
    - MAPK/MEK pathway activation and activating mutations in BRAF – development of BRAF and MEK inhibitors given as monotherapy or in combination to treat melanoma patients

Drug development and assessment
Targeted therapies

- Enriched designs (patients with mutation)
  - Superiority versus reference treatment
  - Targeted monotherapy versus chemotherapy
  - Combination of targeted therapies (e.g. anti BRAF + anti MEK) versus monotherapy (anti BRAF) in melanoma
- Results (melanoma):
  - high RR for targeted therapy
    - 50% monotherapy, 70% combo vs chemotherapy (5%)
  - PFS:
    - 12 months (combo), 6-7 months (mono)(resistance),
  - OS (2y)
    - D+T=25,6m vs V=18m, HR=0,66, p<0,001
- Acceptable toxicity, less skin side effects with combo

Targeted therapies

HTA assessments

Criticisms (HTA bodies)

- No double blind
  - Difficult if investigator's best choice as comparator
- Added benefit assessment based on mortality (OS), morbidity and HRQoL
  - OS data necessary to support added benefit
  - Less added benefit of only PFS data (some HTA agencies)
  - Data on other patient-relevant endpoints necessary (pain, insomnia, appetite loss, diarrhoea, fatigue…)
- Interim analysis not recommended, especially on PFS

Targeted therapies
HTA Challenges

No real challenge

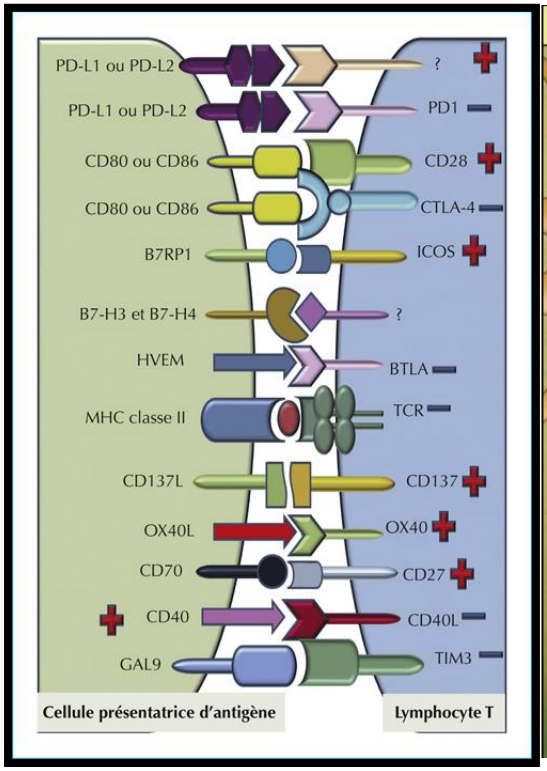
- Binary reasoning (mutation – or +)
- Companion tests validated
- EMA and HTA guidelines on co-development drug-biomarker apply
- Study designs: enriched (in most cases)
- Superiority to reference treatment

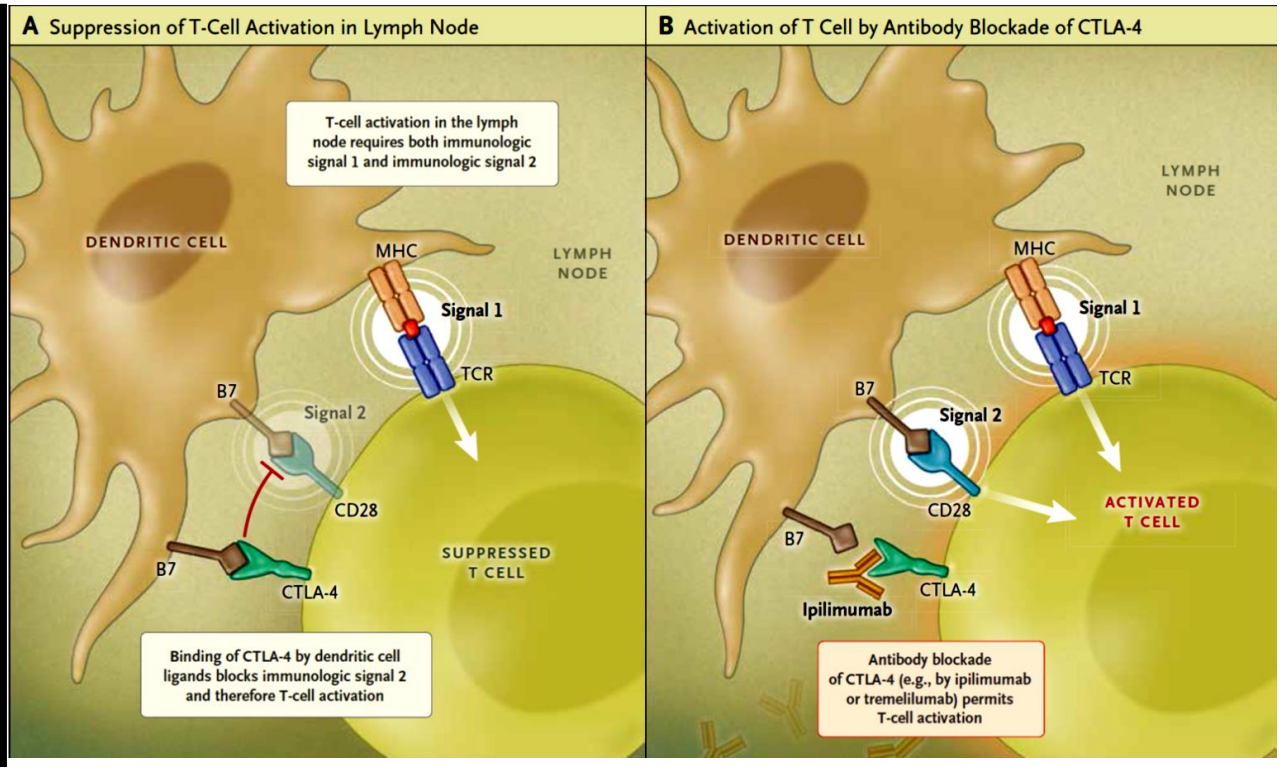
- Easy to understand treatment effectiveness and safety profile
  - RR, PFS, OS

Context (2)
Immunotherapies

- Better understanding of anti-tumour immunity (today):
  - Negative costimulatory molecules or “checkpoints” (CTLA-4, PD-1)
  - PD-1 receptor and its ligands PD-L1 and PD-L2
    - expressed on activated T-cells (CD8, CD4), activated B-cells, natural killer cells, APC and tumour cells in response to inflammatory stimuli
    - negative regulators of T-cell activity involved in the control of T-cell immune responses
    - prevent immune-mediated rejection of the tumour
  - Development of treatments targeting the PD-1/PD-L1,2 axis

Better understanding of anti-tumour immunity





New E J Med October 2015 T Ribas & al

Better understanding of anti-tumour immunity

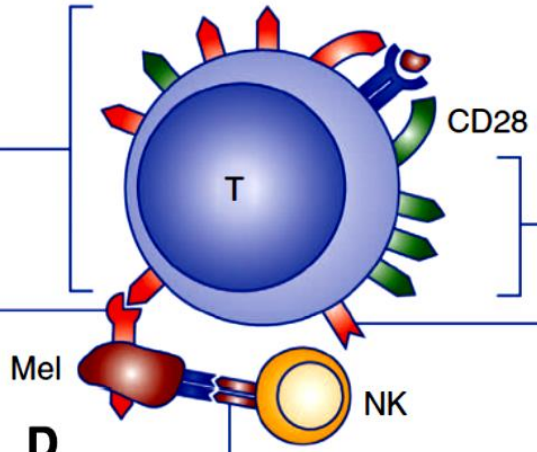
- Products in development:
  - New inhibitors of molecules blocking T cell activation
  - New agonists of T cells co-activators
  - Others

A

CD28/CTLA-Ig family	
Target	Status
CTLA-4	Approved
PD-1	Phase III accruing
BTLA	Preclinical
LAG3	Preclinical
ICOS	Preclinical

B

TNF superfamily	
Target	Status
CD40	Ph I
OX40	Ph I accruing
CD137	Ph II
GITR	Ph I accruing
CD27	Ph I accruing



C

PD-1	Phase III accruing

D

KIR	Ph II accruing

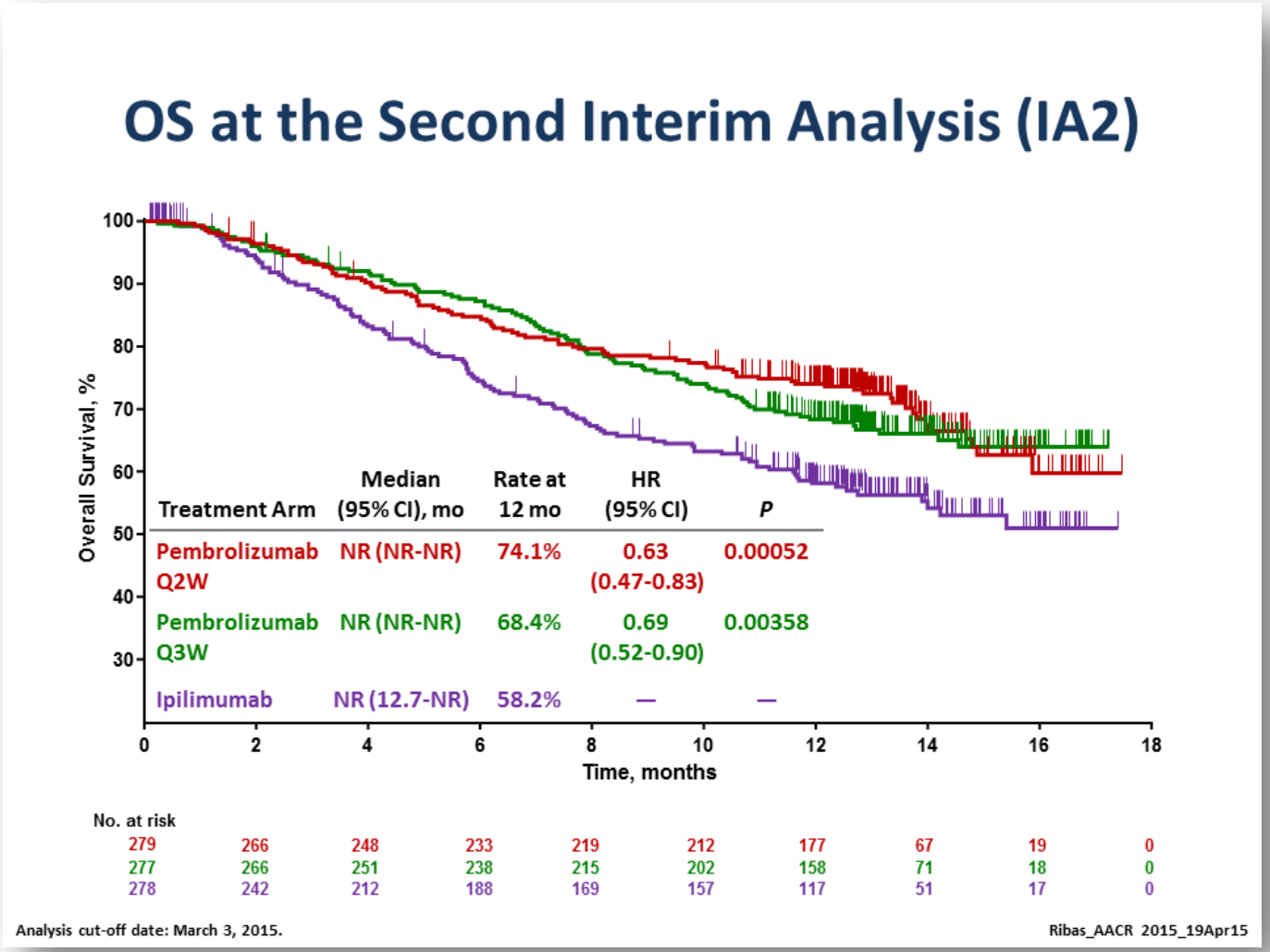
E

TIM-3	Preclinical

Immunotherapies
(melanoma, lung)

- Study design: mostly unselected designs
  - PD-1 role as predictive marker unclear
  - Subgroup analysis done (PD-1+, PD-1 -)
- Results
  - Melanoma (regardless PD-1 expression):
    - Monotherapy:
      - Rather low RR
      - Long duration of response
      - Long OS for some patients
    - Combination therapy (e.g. ipilimumab+nivolumab):
      - high RR (>50% CR+PR, regression of bulky disease), long OS, high toxicity
  - NSCLC:
    - Nivolumab (squamous NSCLC 2nd line vs docetaxel, regardless PD-1 expression): OS 9,2m vs 6m (42% vs 24% at 1y)
    - Pembrolizumab:
      - study ongoing in PD-1+ patients (50% cut off)

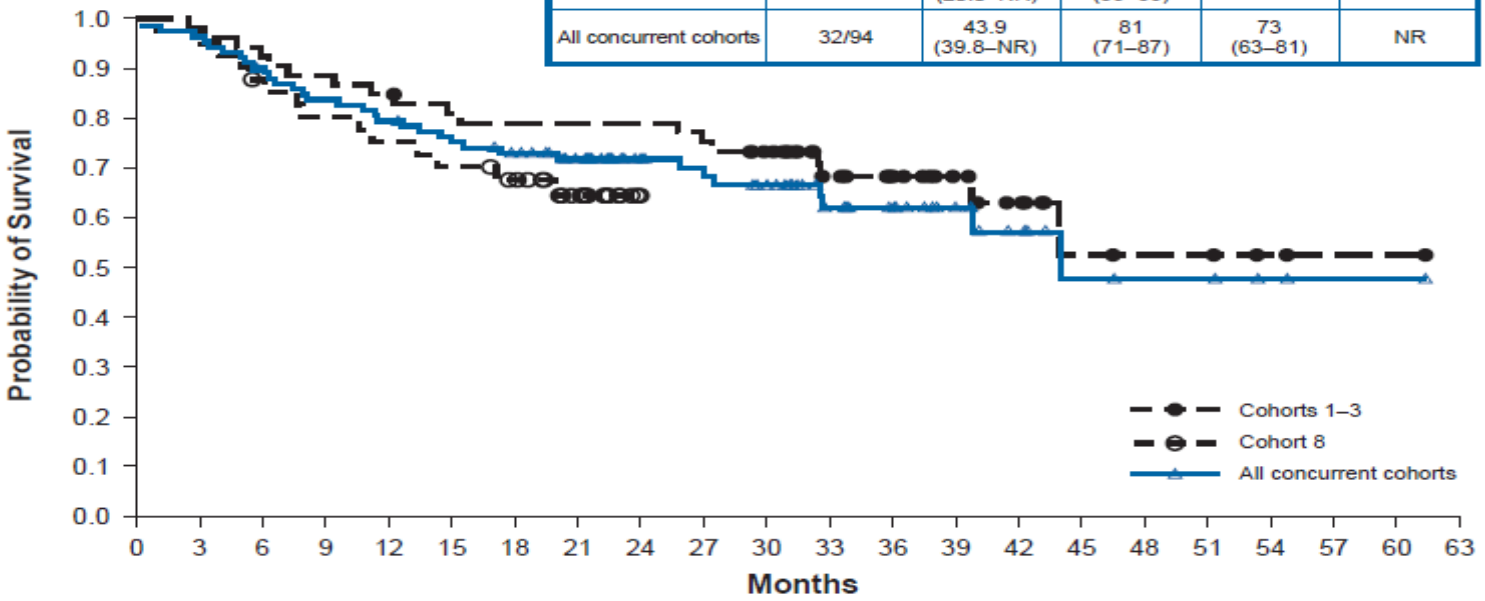
Pembrolizumab vs ipilimumab (melanoma)



Pembrolizumab: non-authorised dosage (10mg/kg)

Multi-cohort dose ranges
(ipilimumab + nivolumab)(melanoma)

	Died/treated, n/N	Median OS, mo (95% CI)	OS rate, % (95% CI)		
			12 mo	24 mo	36 mo
Cohorts 1–3	18/53	NR (39.8–NR)	85 (72–92)	79 (65–88)	68 (53–79)
Cohort 8	14/41	NR (20.0–NR)	75 (59–86)	NR	NR
All concurrent cohorts	32/94	43.9 (39.8–NR)	81 (71–87)	73 (63–81)	NR



Number of Patients at Risk

Cohorts 1–3	53	52	49	47	45	42	41	41	41	39	35	26	21	14	10	5	4	4	2	1	1	0
Cohort 8	41	40	35	32	30	28	25	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0
All concurrent cohorts	94	92	84	79	75	70	66	58	41	39	35	26	21	14	10	5	4	4	2	1	1	0

CI = confidence interval; mo = months; NR = not reached

Sznol et al SMR 2015

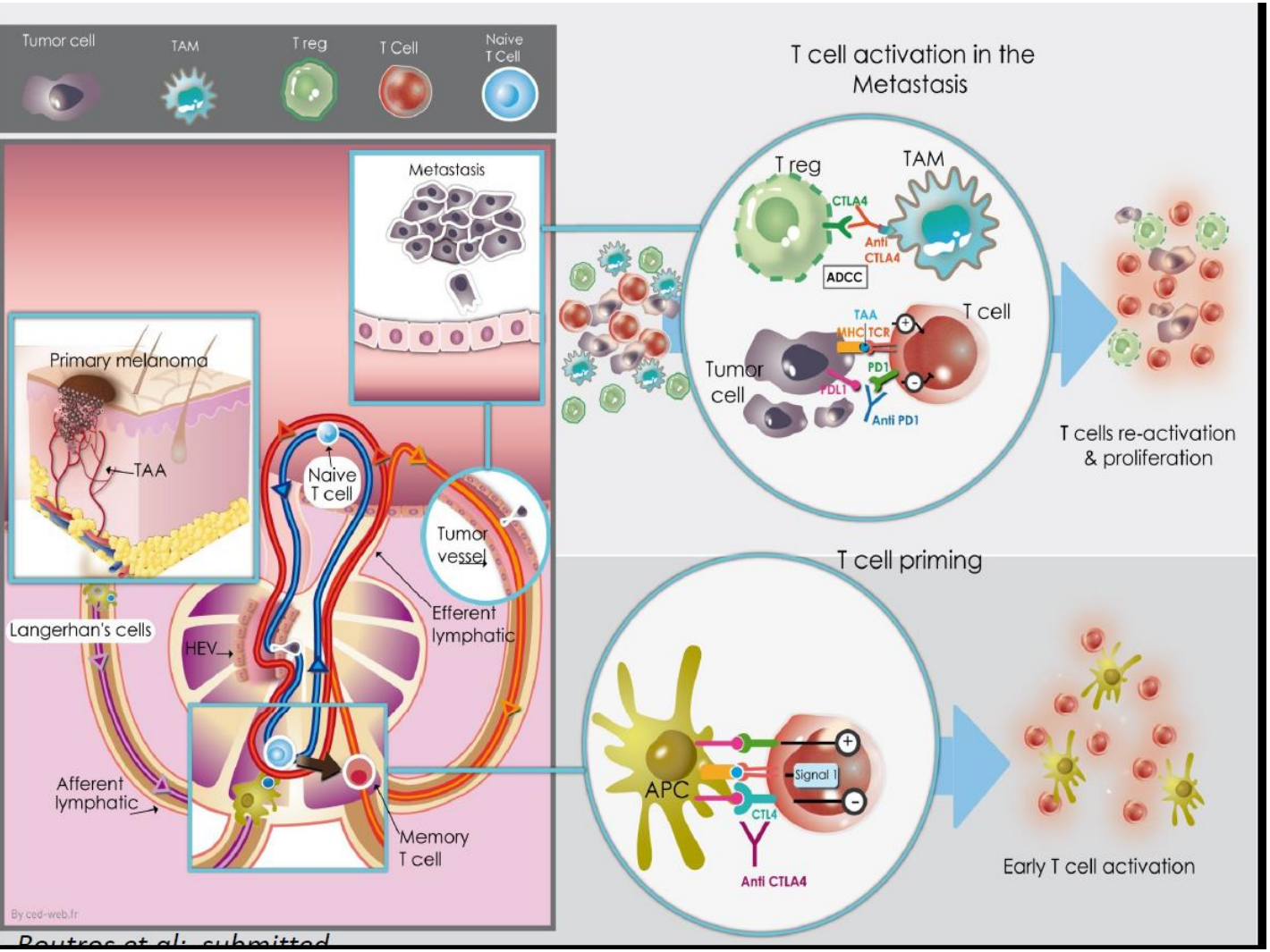
Immunotherapies Challenges

At all steps of drug development (melanoma, NSCLC)

- **Conceptual challenge**
  - tumour immuno-microenvironment
- **PD-L1 expression**
- **Choice of dose(s)**
  - no clear relationship with anti-tumour activity and toxicity
- **Study design**
  - Unselected or enriched?
- **Assessment of response to treatment**
  - Pseudo-progression (tumour infiltration by T cells)
  - Cross-over
  - Absence of OS data for very recent comparators

Immunotherapies: challenges

Tumour immuno-microenvironment

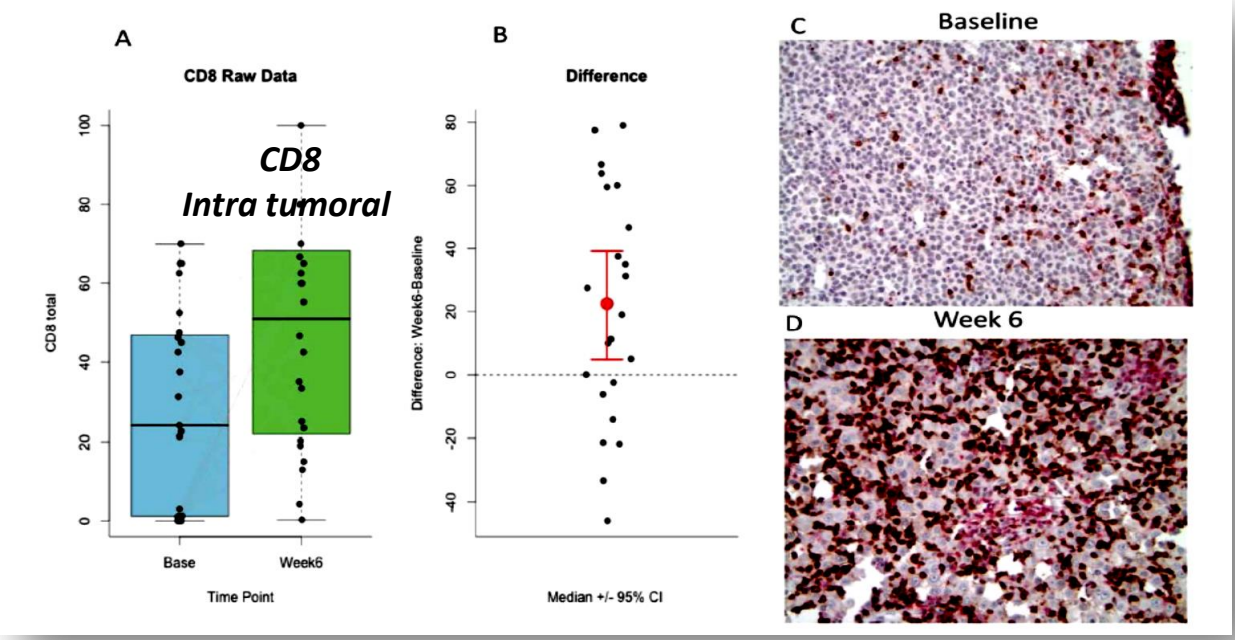


Routres et al; submitted

- Not fully understood
- Differs within and between tumour lesions
- Dynamic interactions between APC, tumour cells, T cells, and other co-stimulatory and co-inhibitory molecules
- Additional variables (e.g. intra-tumour CD8+ T cells)

Immunotherapies: challenges

Tumour immuno-microenvironment



Ipilimumab: *Cancer Immunol Immunother* ***2014:*** *DOI 10.1007/s00262-014-1545-8*

See also:

The Distribution of Cutaneous Metastases Correlates With Local Immunologic Milieu

(JAAD, January 9, 2016 Epub Ahead of Print): low proportion of CD8+ T cells and high density of regulatory T cells in metastases as compared to normal skin

Immunotherapies: challenges
PD-L1

- PD-L1 expression
  - Staining performed in variety of biopsy samples before and during treatment
  - Various levels of expression in different tumour sites (same patient) and at different time points
  - No validated assay
  - Different IHC expression cut off levels used: positive if 1, 5, 10, 50% cells stain
    - **1%** cells express PD-L1 by IHC (pembro – MM, NSCLC),
    - **5%** cells express PD-L1 by IHC (nivo – NSCLC)
    - **50%** cells express PD-L1 by IHC (pembro-NSCLC, ongoing trials)

- No clear correlation with response to treatment in melanoma
- NSCLC: two drugs, two different developments
    - nivolumab – overall population
    - pembrolizumab: PD-L1 positive patients (50% cut off)
- It would be interesting to review efficacy/effectiveness data by using different (relevant?) cut-offs for PD-1 expression

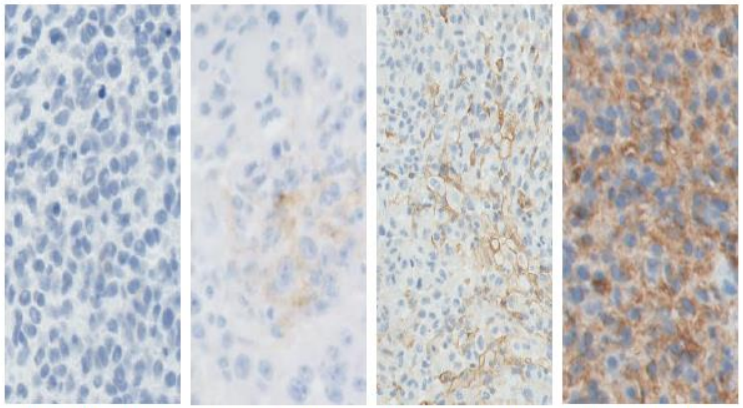
Immunotherapies: challenges

What is relevant cut-off ?

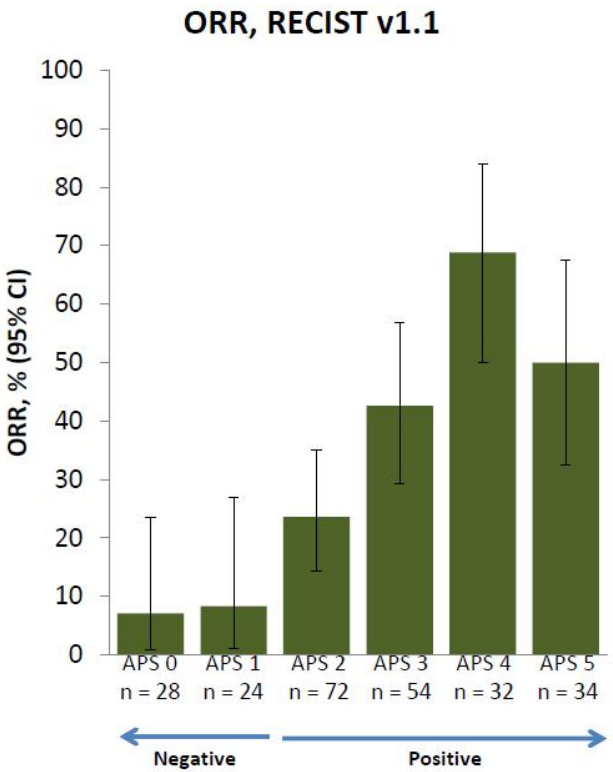
1%? <10%? 10-33%? 33-66%? >66%?

PD-L1 Expression and Relationship With Response

- Among first 411 patients enrolled, 67% evaluable for PD-L1 status
- Correlation between PD-L1 expression and ORR ($P < 0.0001$)



PD-L1 Negative 0% Staining APS = 0 | PD-L1 Positive 1-10% Staining APS = 2 | PD-L1 Positive 10-33% Staining APS = 3 | PD-L1 Positive 66-100% Staining APS = 5



APS, Allred proportion score.
Analysis cut-off date: October 18, 2014.

Daud et al ASCO 2015

Immunotherapies: challenges
Choice of dose

Pembrolizumab:

- No MTD (maximum tolerated dose)
- No clear correlation between dose, efficacy and toxicities
- Switch from traditional dose escalation design (N=30-50 patients) to parallel cohorts design (multiple dosage at the same time)(Keynote 0001)
- Large phase I trials with long term follow up (expansion cohorts design (N=655)
  - enables to explore both dosage and activity

- Dose uncertainty remains
  - Regulatory challenge

Immunotherapies: challenges

Assessment of response to treatment

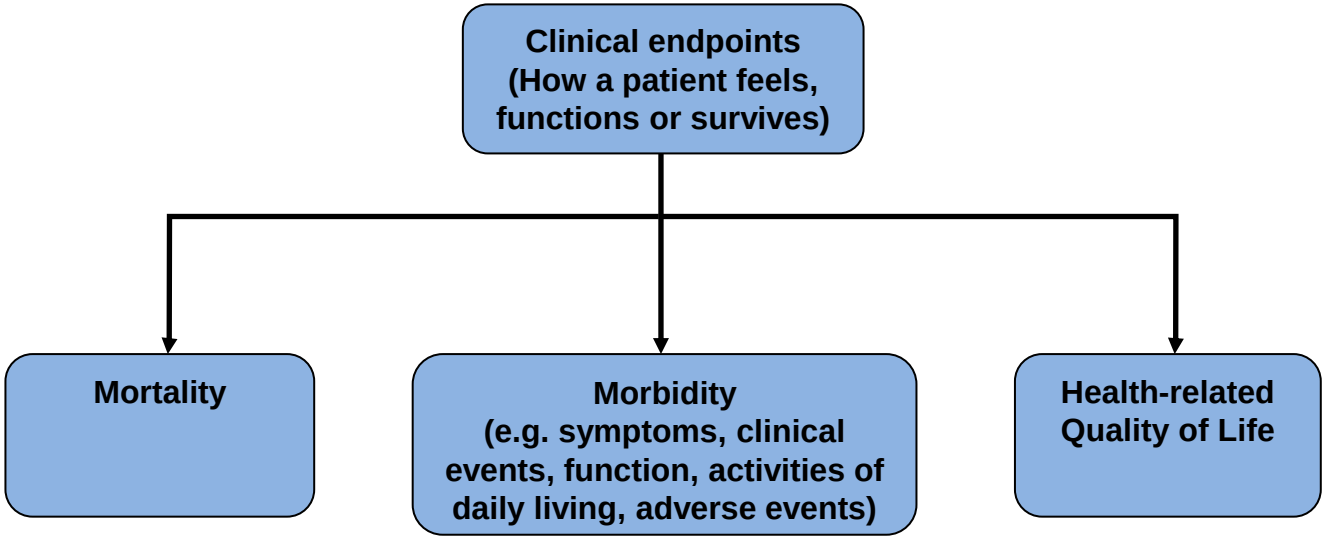
- Pseudo-progression
  - tumour infiltration by T cells
- Wait up to 6 months to assess patient's true response
  - Adapt RECIST rules?
- When does patient really progress?
  - When to allow for cross-over?
  - In clinical practice, physicians wait to be sure that patient progresses to change treatment
- Absence of OS data for recent comparators

REA- Assessment of added benefit

- Added clinical benefit of a new drug is assessed:
  - **in adequate patient population** (population granted MA or more restricted)
  - **in comparison to an adequate comparator** (defined by HTA bodies)
  - **on relevant clinical endpoints:**
    - Primary endpoint (final patient-relevant endpoint or acceptable surrogate)
    - Other endpoints considered relevant for the disease and aim of treatment

REA- Patient relevant endpoints Conceptual framework

- **Clinical endpoints relevant to patients**: death, pain (symptoms), disability, effects of the disease or its treatments on activities of daily living and quality of life



Immunotherapies
REA – data requirements

- **OS data requested to support added benefit**
  - PFS not considered adequate
  - Lower added benefit of only PFS data
  - Data on other patient-relevant endpoints and HRQoL recommended
- **OS is not the only relevant endpoint**
  - speed of action, response rate, duration of response, duration of treatment, side effects profile, effectiveness in relevant subpopulations
  - REA should support clinical practice guidelines:
    - data to support potential place of the product in the treatment strategy within the same line of treatment needed:
      - slowly progressing vs fast progressing patients, comparison of different treatment strategies, sequential regimens?

Immunotherapies
REA – data requirements ctd

- **Interim analysis not recommended**
  - especially on PFS
  - also on OS whenever possible (mature OS data requested)
- **Comparison with relevant comparators (defined by HTA bodies)**
  - Choice of comparator depends on pre-treatment (if any) and tumour mutation(s)
  - No added benefit if inadequate comparator (exceptions)

Targeted therapies – REA Added benefit (HAS)

Product	disease	OS gain (m)	ASMR (HAS)
Kadcyla	Breast K	5,8	2
Zelboraf	Melanoma	1,5 – 3,6	3
Tafinlar/Mekinist	Melanoma	NR (1y), 7 (2y)	3
Opdivo	Melanoma	NR (1y)	3
Keytruda	Melanoma		
Yervoy	Melanoma	3,6	4*
Tafinlar	Melanoma	NS	5

Adequate study design, comparators, endpoints

*Inadequate comparator

IQWIG:

OPDIVO: considerable benefit (M) and minor benefit (W) in naive patients

KEYTRUDA: considerable benefit in pretreated patients and minor benefit in naïve BRAF neg patients

Tafinlar/Mekinist: major benefit in women, non-quantifiable benefit in men BRAF+

Cancer immunotherapeutic drugs
Challenges in evaluating relative effectiveness
CONCLUSION

Challenges:

- more academic and regulatory then HTA

HTA challenges to assess added clinical benefit:

- **Adequate patient population**
  - Difficult - multiple markers
  - In practice, no further restriction based on PD-1 expression
- **Approved dosage**
  - Use of non-authorised dosage increases uncertainty
- **Adequate comparator**
- **Relevant clinical endpoints:**
  - OS of course
  - Other relevant information
    - Place of the product in the therapeutic strategy
    - Treatment after progression
    - Possibility/success of subsequent therapies
- **Cost-effectiveness** (combination therapies)

THANK YOU

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