Klinische Stand van Zaken CTLA4/PD1-PD-L1

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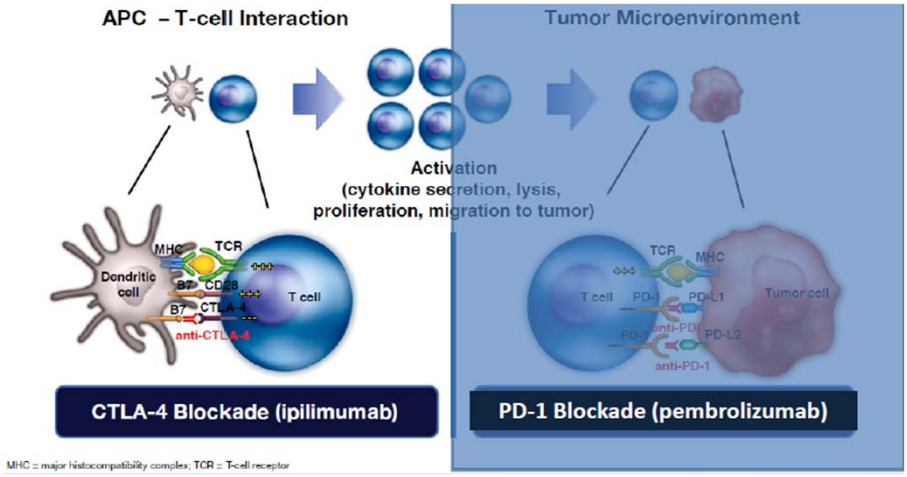
11 Jan 2017

Advanced Immune therapy approaches

- Checkpoints inhibitors
- Adoptive cells therapy approaches (TILs, TCR, CAR)
- Intratumoral: Oncolytic viruses (e.g., T-VEC,..)
- IDO inhibitors

Priming phase → Effector phase



Callahan M et al. ASCO 2014

Immune checkpoints approved or reaching clinical practice

- Melanoma : Nivolumab +/- ipilimumab, pembrolizumab (1st line)
- NSCLC: Pembrolizumab (1st line PD-L1 ≥ 50%)
- NSCLC (sq and non-sq) : Nivolumab, Pembrolizumab (2d line) & Atezolizumab (2L/3L)
- RCC : Nivolumab (Prior TKIs)

- Bladder : Atezolizumab
- Head & Neck : Pembrolizumab
- Merkel : Pembrolizumab, Avelumab

Efficacy of checkpoint inhibitors in different solid tumors: An overview of ESMO/ASCO 2016

Tumor	ORR (%)	Disease control rate (%)
MSI-high	27-53	72-89
Hepatocellular	16	68
Cervix	13	25
Merkel	30	41
Anal	27	70
H&N/Nasopharyngeal	11-18/26	15-36
Gastric / GEJ	9-26	29-38

Efficacy of checkpoint inhibitors in different solid tumors: An overview of ESMO/ASCO 2016

Tumor	ORR (%)	Disease control rate (%)
Urothelial	15-38	NA
Prostate	13	NA
Ovarian	11-15	NA
TNBC	9-19	31-46
ER+ BC	3-12	28

Efficacy of checkpoint inhibitors in rare solid tumors: An overview of ESMO/ASCO 2016

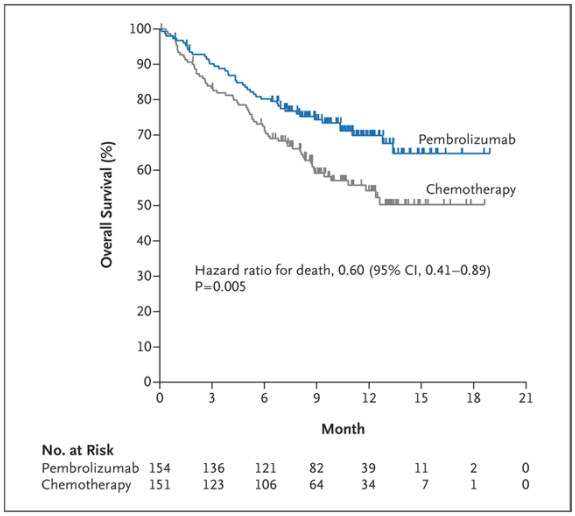
Tumor	ORR (%)	Disease control rate (%)
Glioblastoma	NA	40
Salivary gland	12	76
Sarcoma	15	50
Endometrial	13	26
Adrenocortical	11	37
Uterus leiomyosarcoma	0	0

Predictive biomarkers of checkpoint inhibitors

- **PD-L1 expression (in tumor cells or tumor-infiltrating immune cells)**

  Overall, there is a correlation but not perfect and variable between drugs, tumor types and settings

- **«Mutanome»**
- **INFγ signature ?**
- **TILS/CD8+T ?**
- **Other non-validated biomarkers**



Reck M et al. N Engl J Med 2016;375:1823-1833.

Why are checkpoints inhibitors efficacious in a group of PD-L1 negative tumors?

- False negativity of PD-L1 (technical problem)
- PD-L1 expression is a dynamic process (and not static)
- PD-L2 expression instead of PD-L1

Checkpoints inhibitors: Management of significant side effects

- Interrupt/discontinue therapy
- Autoimmune disorders
  - Steroids
  - TNF blockade (e.g., Colitis)

Checkpoints inhibitors: Tumor response patterns

- How to image / follow tumors – Role of PET/CT?
- Tumor response «profile» (e.g., tumor progression before shrinkage)
- Time to response (e.g., shorter for PD-1 inhibitors and longer for Ipilimumab)
- Treatment effect beyond tumor progression
- Duration of response/therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

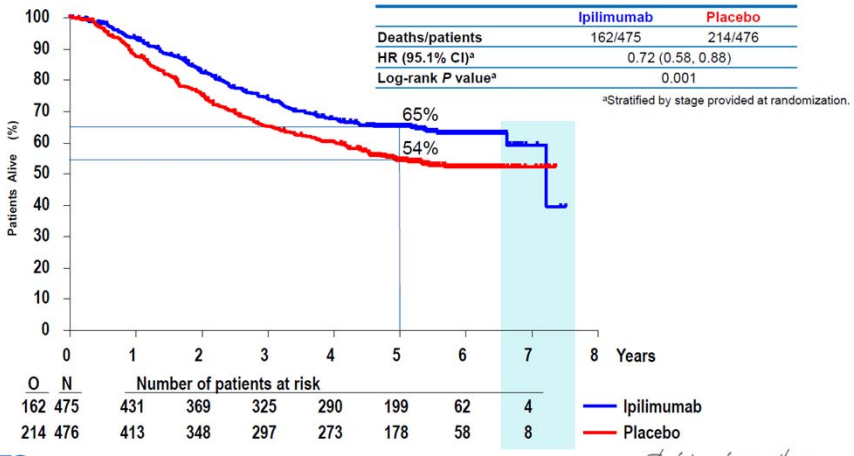
EORTC

The future of cancer therapy 2

OS

	Ipilimumab	Placebo
Deaths/patients	162/475	214/476
HR (95.1% CI)[a]	0.72 (0.58, 0.88)	
Log-rank *P* value[a]	0.001	

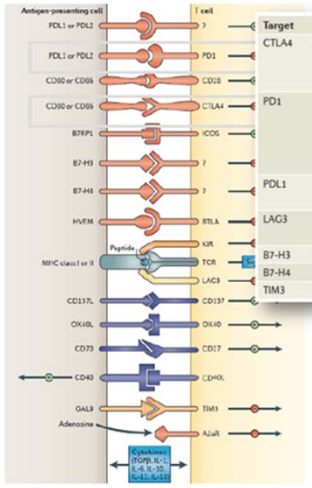
[a]Stratified by stage provided at randomization.



EORTC

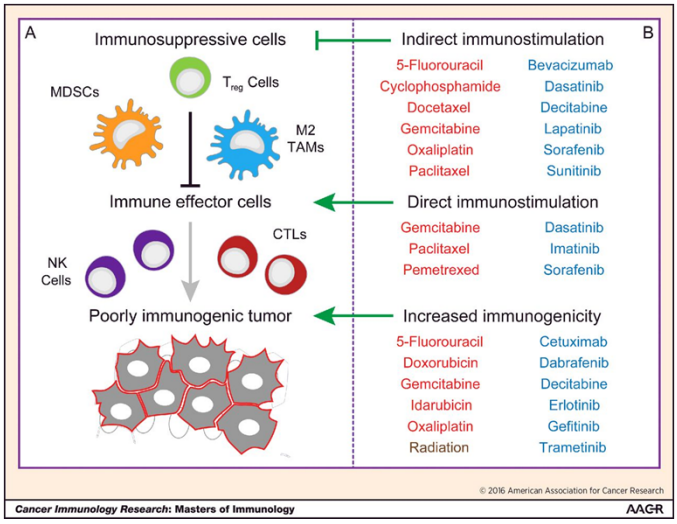
The future of cancer therapy 11

Druggable immune check-points: Intense clinical research



Target	Biological function	Antibody or Ig fusion protein	State of clinical development*
CTLA4	Inhibitory receptor	Ipilimumab	FDA approved for melanoma, Phase II and Phase III trials ongoing for multiple cancers
		Tremelimumab	Previously tested in a Phase III trial of patients with melanoma; not currently active
PD1	Inhibitory receptor	MDX-1106 (also known as BMS-936558)	Phase I/II trials in patients with melanoma and renal and lung cancers
		MK3475	Phase I trial in multiple cancers
		CT-011[a]	Phase I trial in multiple cancers
		AMP-224[b]	Phase I trial in multiple cancers
PDL1	Ligand for PD1	MDX-1105	Phase I trial in multiple cancers
		Multiple mAbs	Phase I trials planned for 2012
LAG3	Inhibitory receptor	IMP321[a]	Phase III trial in breast cancer
		Multiple mAbs	Preclinical development
B7-H3	Inhibitory ligand	MGA271	Phase I trial in multiple cancers
B7-H4	Inhibitory ligand		Preclinical development
TIM3	Inhibitory receptor		Preclinical development

Immunological effects of anticancer therapy.



Lorenzo Galluzzi et al. Cancer Immunol Res 2016;4:895-902

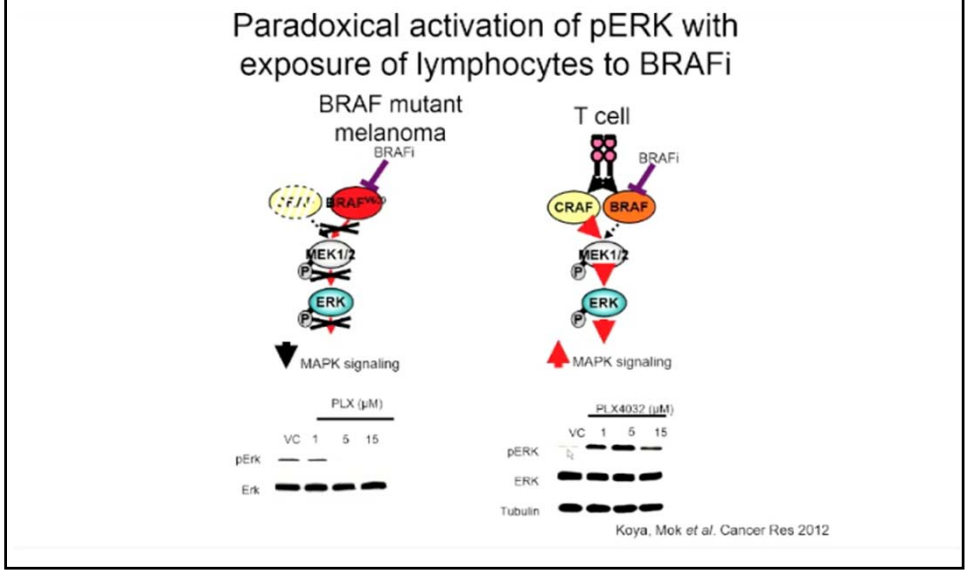
Cancer Immunology Research
AACR

Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.*

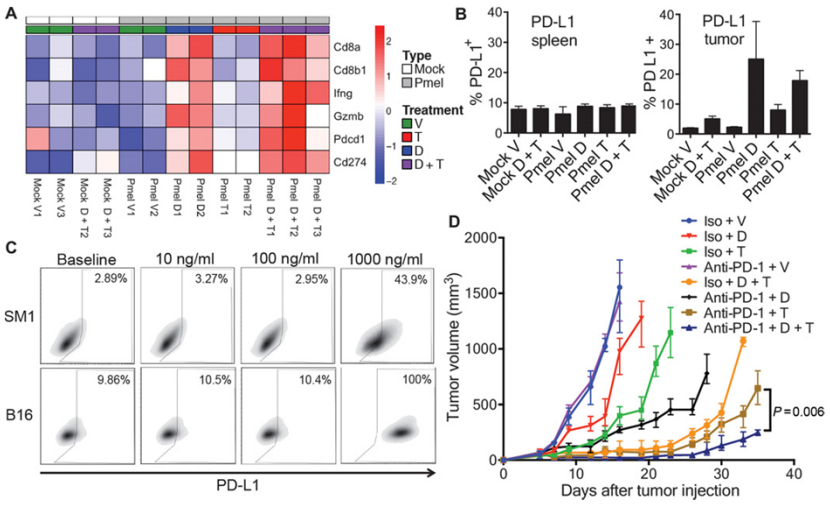
Study Cohort and Patient No.	No. of Doses of Ipilimumab before ALT–AST Elevation	Time to Onset of ALT–AST Elevation after First Dose of Ipilimumab	Treatment	Time to Resolution of ALT–AST Elevation	Toxicity Relapse with Repeated Ipilimumab
First cohort					
4	1	21 days	Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab permanently discontinued	4 days	NA
5	2	36 days	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)	6 days	No
6†	1	21 days	Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab continued (1 dose)	6 days	No
8	1	19 days	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (1 dose)	12 days	Yes
Second cohort					
10	1	15 days	Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued	10 days	NA
16‡	1	13 days	Vemurafenib and ipilimumab permanently discontinued	20 days	NA

* The first cohort started with a run-in period of 1 month of single-agent vemurafenib (960 mg orally twice daily), followed by four infusions of ipilimumab (3 mg per kilogram of body weight every 3 weeks) and concurrent twice-daily doses of vemurafenib. The second cohort received a lower dose of vemurafenib (720 mg twice daily) together with the full dose of ipilimumab. NA denotes not available.
† This patient also had a grade 2 increase in the total bilirubin level.
‡ This patient also had a grade 3 increase in the total bilirubin level.

Ribas A et al. N Engl J Med 2013;368:1365-1366.

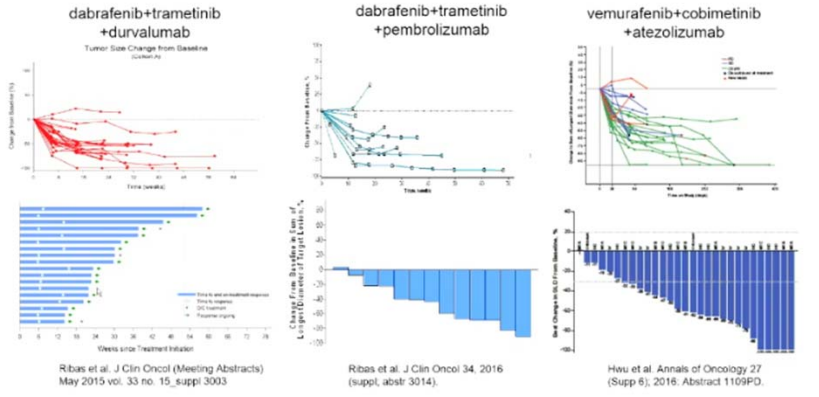


Up-regulation of PD-L1 and triple combination of dabrafenib, trametinib, and PD1 blockade is superior in antitumor effect.



Siwen Hu-Lieskovan et al., Sci Transl Med 2015;7:279ra41

Clinical trials combining BRAFi+MEKi+anti-PD-1/L1



Ribas et al. J Clin Oncol (Meeting Abstracts) May 2015 vol. 33 no. 15_suppl 3003

Ribas et al. J Clin Oncol 34, 2016 (suppl; abstr 3014).

Hwu et al. Annals of Oncology 27 (Supp 6); 2016. Abstract 1109PD.

PD-1/PD-L1 inhibitors in solid cancers in 2016

1. Are standard of care in NSCLC, melanoma, RCC, Urothelial and head & neck cancers
2. Overall, one fifth to one third of the patients objectively responded to these agents in different solid cancers. DCR is much higher
3. No convincing efficacy seen so far in sarcomas or glioblastoma. Hint of activity in prostate and rare tumors and no data on pancreatic cancer

PD-1/PD-L1 inhibitors in solid cancers in 2016

4. PD-L1 expression in tumor/immune cells correlated with a better objective response but PD-L1 negative tumors showed also some efficacy
5. It is « preferable » to develop predictive biomarkers of resistance to avoid in our patients the side effects and for the society the cost burden
6. As single agents administration, the side effects are overall manageable

Modern Immunotherapy has broken many dogmas in oncology…

Not true that:

1. **Immunotherapy did not work in bulky tumors**
2. **Immunotherapy works only in what were considered « immunologic tumors » such as melanoma and RCC**
3. **Significant survival rate (cure?) is difficult to obtain in metastatic disease**

Modern Immunotherapy has broken many dogmas in oncology…

Not true that:

1. **Progressive disease should always trigger stopping the therapy (So what about pseudo progression and late responses?)**
2. **Immunotherapy should not be combined with chemotherapy and/or radiotherapy**

Immune checkpoints inhibitors : Major research questions

- Fully define spectrum of clinical activity (single agent; combinations)
- Optimal dose / schedule / sequence and duration of therapy
- Mechanisms of de novo / acquired resistance (and how to overcome)
- Predictive biomarkers (mainly of resistance) and how to convert non-immunogenic tumors to immunogenic ones

Immune checkpoints inhibitors : Major research questions

- How to manage optimaly the side effects ?
- Benefit in virus-induced tumors?
- Benefit / risk in elderly patients
- Benefit / risk in patients with autoimmune diseases
- Efficacy in brain metastases
- Role in (neo)adjuvant therapy