Immunotherapies in Cancer: Promise and Burden

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Faculty Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Daiichi	x	x						
Eli-Lilly	x	x						
Novartis	x	x	x					
Pfizer	x	x						
Roche	x	x	x					

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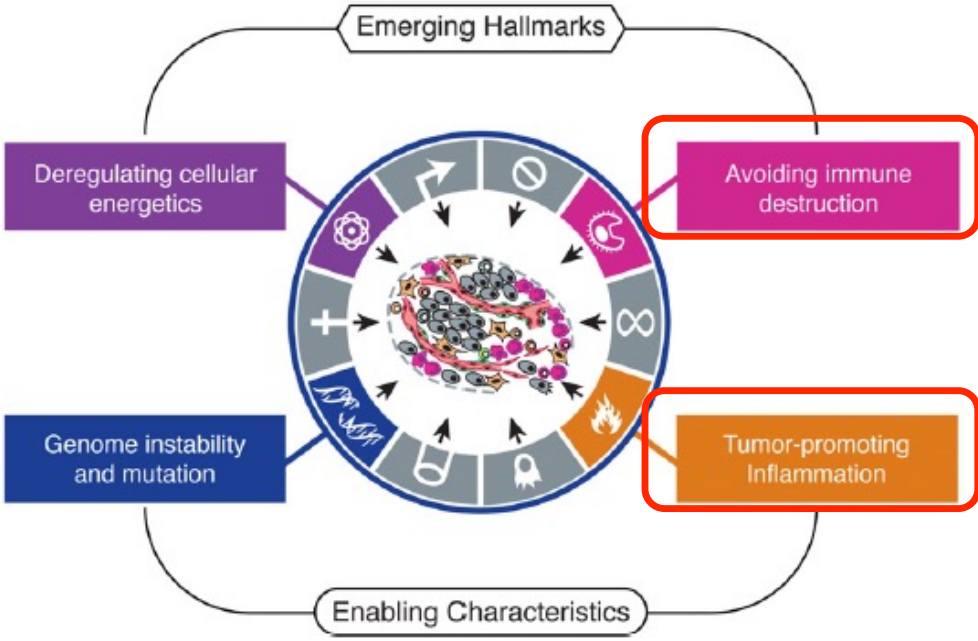
Hallmarks of Cancer [1,2]

- Tradintional hallmarks of cancer

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

- Adding new hallmarks



Leading Edge Review

Hallmarks of Cancer: The Next Generation

1 Hanahan D and Weinberg RA. Cell 2000;100:57-70.
2 Hanahan D and Weinberg RA. Cell 2011;144:646-674.

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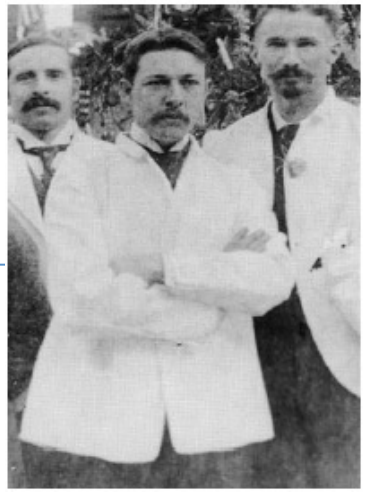

Immunotherapy in Oncology

- A modern concept?
- William B. Coley usually regaerded as the father of immunotherapy [1,2]
- 1891: patient with recurrent and inoperable sarcoma
  injected locally with *Erysipelas*, response after one month, OS 8 years [2]
- Idea of bacterial infection as treatment of sarcoma based on an earlier case report (1885) : Infection of a surgeical wound with *Streptococcus pyogenes* resulted in a durable remission of seven years in a patient with inoperable round-cell sarkoma [3]

1 Levine DB. HSS J 2008;4:1-9.
2 Burdick CG. Ann Surg 1937;105:152-155.
3 Levine DB. HSS J 2005;1:3-8.
4 Levine DB. HSS J 2006;2:1-6.

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Immunotherapy in Oncology

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

This fluid which is known to medical men as "mixed toxins of erysipelas and bacillus prodigiosus," has saved many lives all over the world, medical men say. It has in recent years come to be used in almost every country where the medical profession is in an advanced state of progress. A peculiarity of its effect is that it gives the patient a mild form of erysipelas, and the system in struggling against the new disease, throws off the other and more serious disease. There

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

1 The New York Timer, July 29th, 1908.
Avaiable at http://query.nytimes.com/mem/archive-free/pdf?res=9805E4DC123EE233A2575AC2A9619C946997D6CF
Last acsessed March 9th 2017

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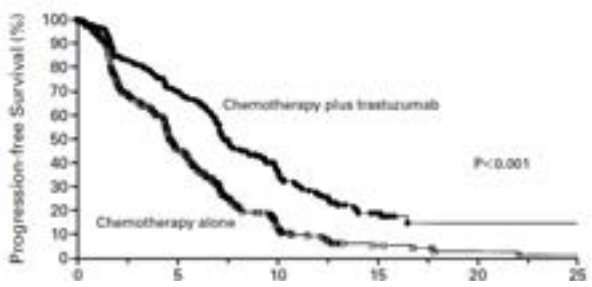
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

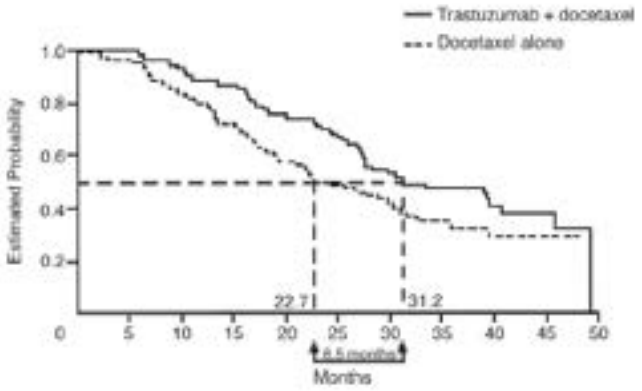
DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

HER2: A Unique Story of Success

- Phase III trial, 469 pts., MBC, HER2-pos., first-line
  AC +/- trastuzumab or paclitaxel +/- trastuzumab
  PFS: 7.4 *versus* 4.6 months; $p<0.001$
  OS: 25.1 *versus* 20.3 months; $p=0.046$ [1]



- Phase II trial, 186 pts., MBC, first-line
  Docetaxel +/- trastuzumab
  PFS: 11.7 *versus* 6.1 months; $p=0.0001$
  OS: 31.2 *versus* 22.7 months; $p=0.0325$ [2]



- HER2 as therapeutic target

1 Slamon D et al. N Engl J Med 2001; 344:783-792.
2 Marty M et al. J Clin Oncol 2005; 23:4265-4274.

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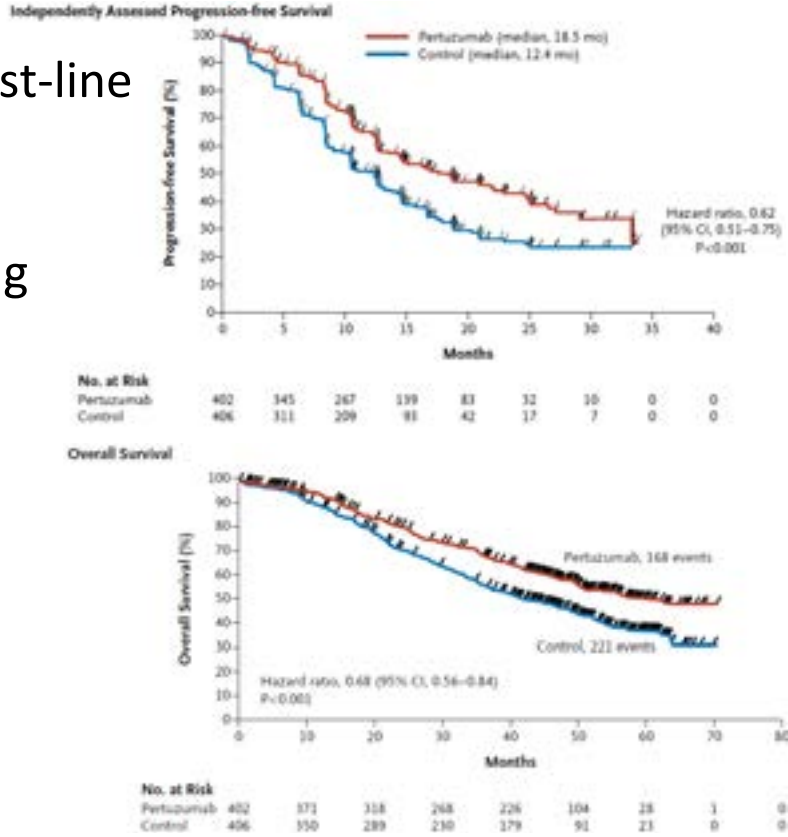
HER2: A Unique Story of Success

- Phase III trial, 808 pat., MBC, HER2-pos., first-line
  Docetaxel + trastuzumab +/- pertuzumab

- Pertuzumab: Anti-HER2 antibody preventing
  HER2 / HER3 heterodimerization

- OS 37.6 months *vs*. not reached
  HR=0.66; 95% CI 0.52–0.84; *p*=0.0008

- 50 months median follow-up:
  D+TP 56.5 *vs*. D+T 40.8 months
  HR 0.68; 95% CI 0.56–0.84; *p*=0.0002



1 Baselga J et al. N Engl J Med 2012;366:109-119.
2 Swain SM et al. Lancet Oncol 2013;14:461-471.
3 Swain S et al. N Engl J Med 2015;372:724-734

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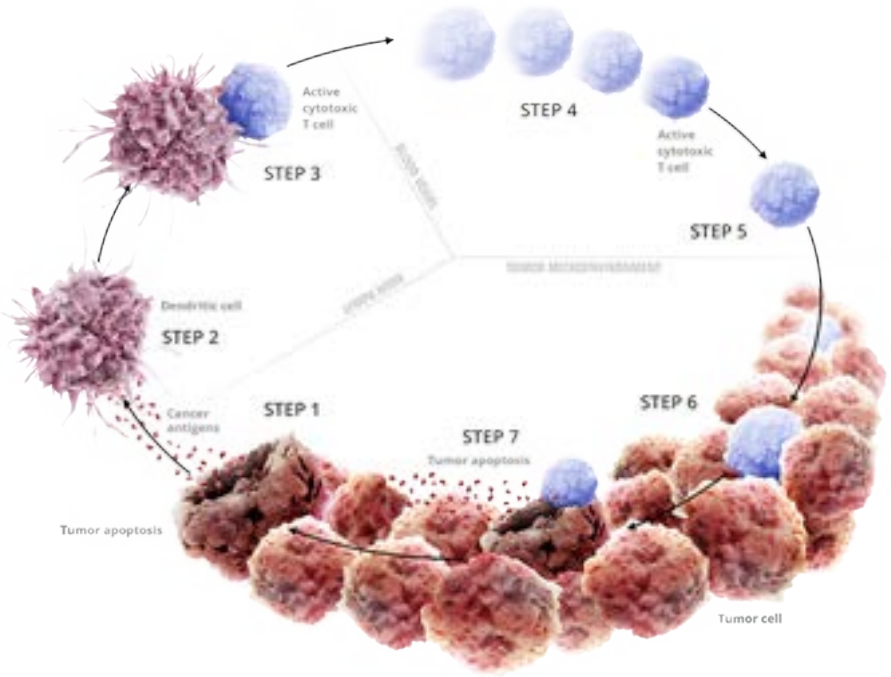
Immune-Cycle in Malignancies[1]

- T-cells as novel approach after unspecific immunotherapy and antibodies



Steps 1-3
New antigenes evolve during oncogenesis, neoantigens are presented to T-cells by dendritic cells (DCs), resulting in the actviation of cyctotoxic T-cells

Steps 4-5
Activated T-cells infiltrate the tumor microenvirenment

Steps 6-7
Activated T-cells recognize and destroy cancer cells, resultig in the liberation of further antigens

1 Avaiable at http://www.researchcancerimmunotherapy.com/overview/cancer-immunity-cycle. Last acsessed March 10th 2017.

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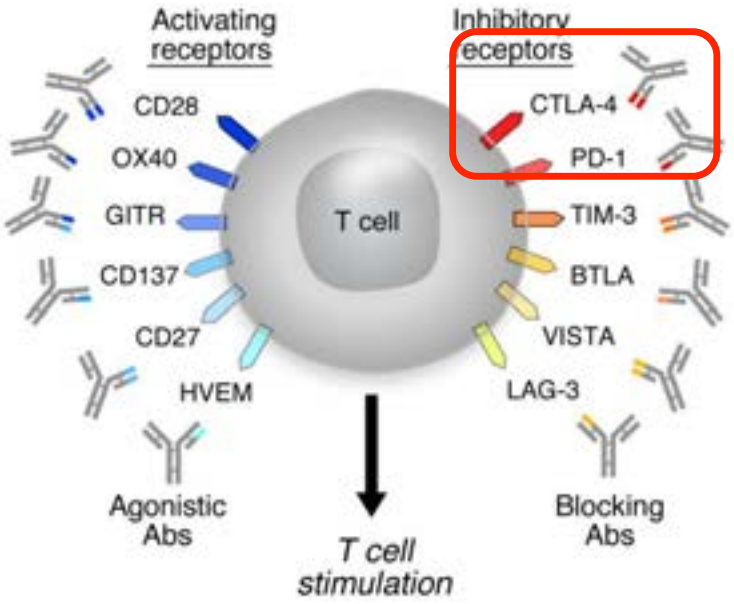
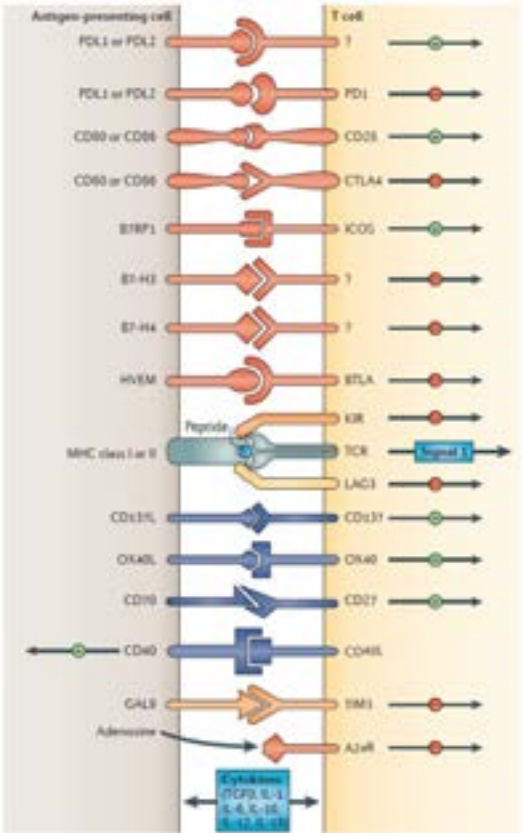
A Central Role for T-Cells[1,2]

- Multiple receptor moleculs interact in the regulation of T-cell activation or the inhibiton of T-cell activation





1 Mellmann I et al. Nature 2011;480:480-489.
2 Pardoll DM et al. Nat Rev Cancer 2012;12:252-564.

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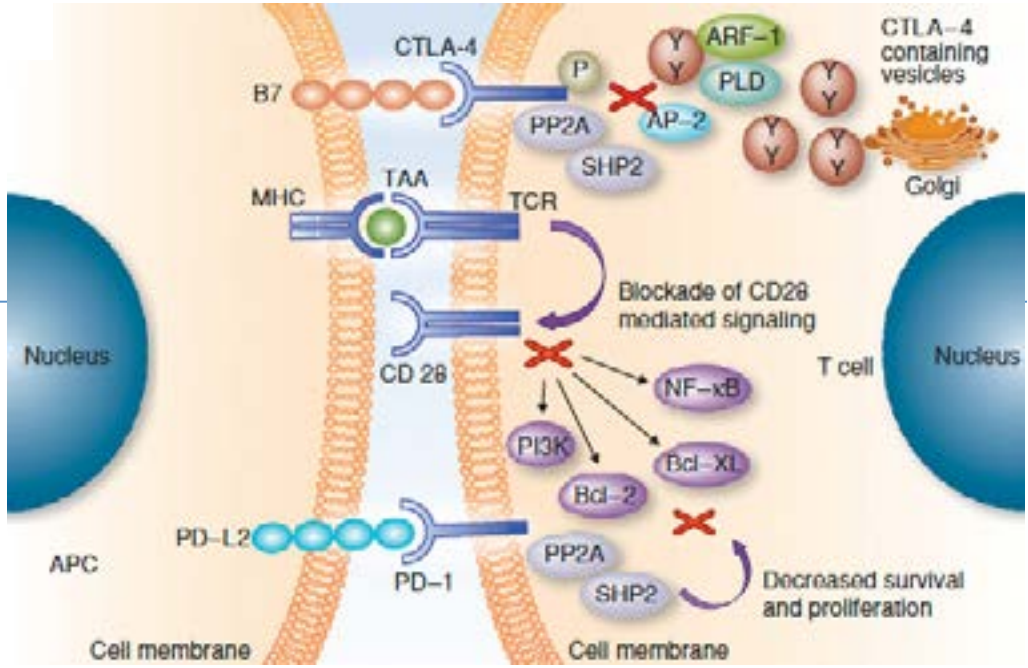
T-Cell Activation[1]



- Complex interaction with co-activators and co-repressors in the acitivation and inhibiton of T-cells

- CTLA4 – regulates the amplitude of early activation of naive and memory T-cells following TCR engagement

- CTLA4-deficient mice exhibit dramatic lymphoproliferative and auto-immune disorders

1 Zitvogel L and Kroemer G. Oncoimmunology 2012;1:1223-1225.

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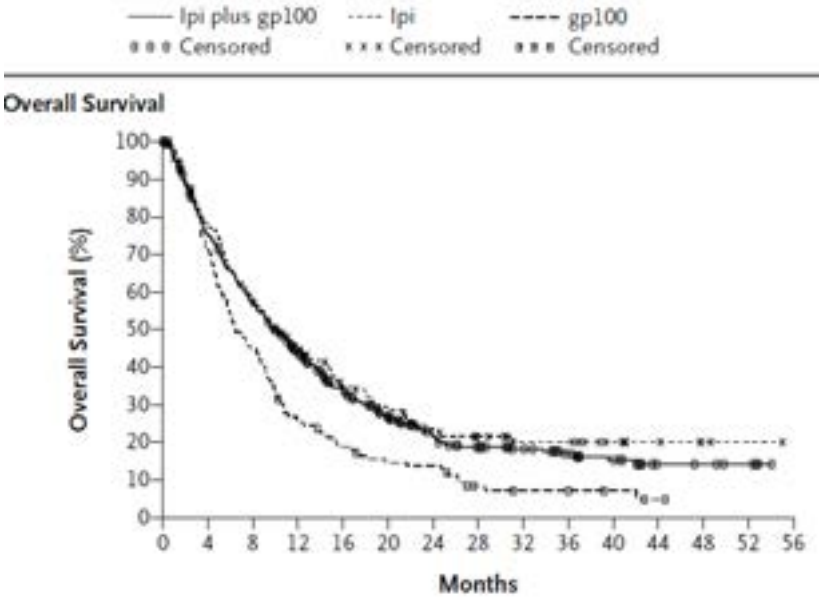
CTLA4-Inhibition in Melanoma[1]

- Prospective randomized phase III trial
- Ipilimumab (fully human mab targeting CTLA4) +/- gp100 *versus* gp100
- 676 pretreated pts.,
stage III (inoperabel) and IV



- Grade 3/4 toxicity ipilumumab ~15% (mostly immune-related adverse events; irAEs)

1 Hodi FS et al. N Engl J Med 2010;363:711-723.

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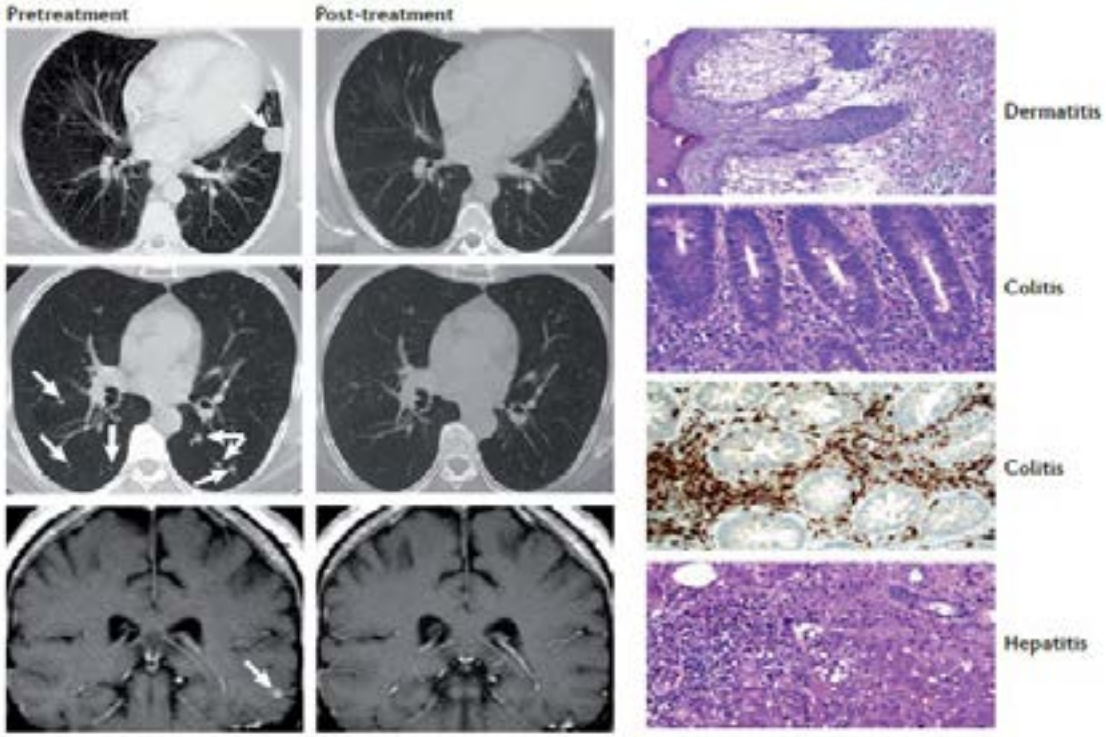
CTLA4-Inhibition in Melanoma[1]

- Treatment effect and toxicity



1 Pardoll DM et al. Nat Rev Cancer 2012;12:252-564.

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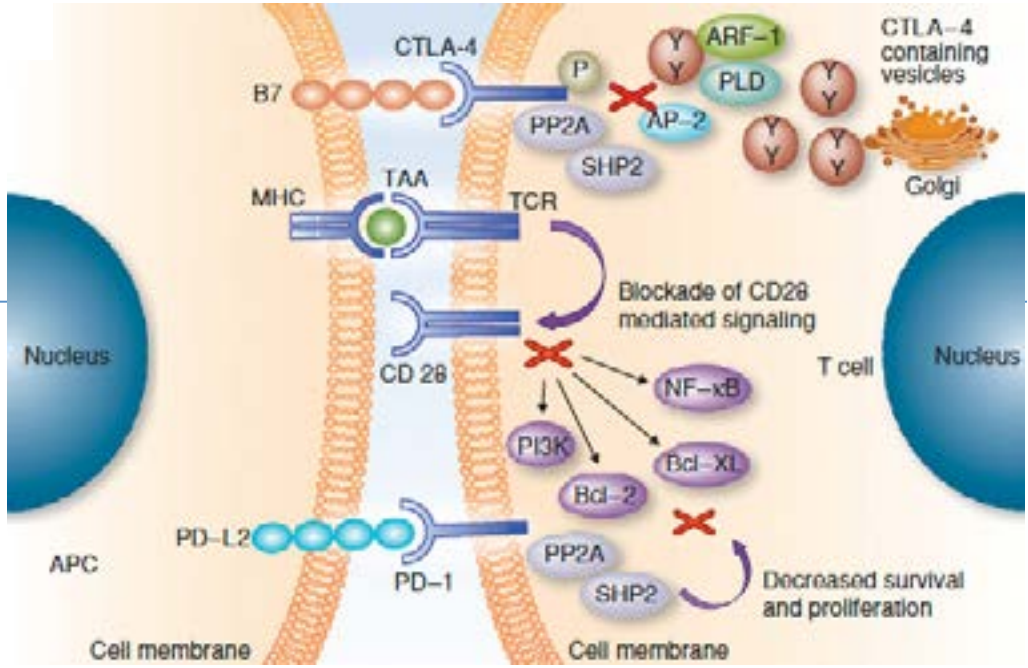
T-Cell Activation[1]



- PD-1/PD-L1 interaction blocks proliferation, survival and function (zytotoxicity, zytokine release) of T-cells

- PD-1/PD-L1 interaction induces apoptosis of tumor-specific T-cells and the differentiation of CD4+ cells into Foxp3+ regulatory T-cells

- PD-1 deficiency results in less autoimmune disorders as compared to CTLA-4 deficiency

1 Zitvogel L and Kroemer G. Oncoimmunology 2012;1:1223-1225.

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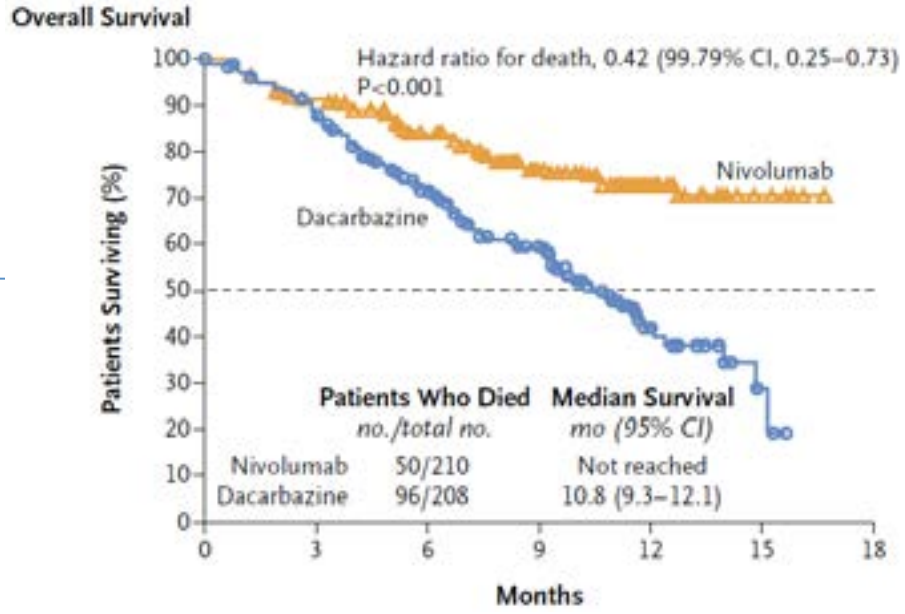
PD-1/PD-L1 Inhibition in Melanoma[1]



- Prospective randomized phase III trial
- Nivolumab (fully human mab targeting PD-1) *versus* dacarbazin
- 418 treatment-*naive* pts., stage IV melanoma, *BRAF*wt
- One year OS 72.9% *versus* 42.1% (HR 0.42; 0.25-0.73; *p*<0.001)
- Median PFS 5.1 *versus* 2.2 months
- RR 40% *versus* 13.9%
- Grade 3/4 toxicity 11.7% nivolumab, 17.6% dacarbazine

1 Robert C et al. N Engl J Med 2015;372:320-330.

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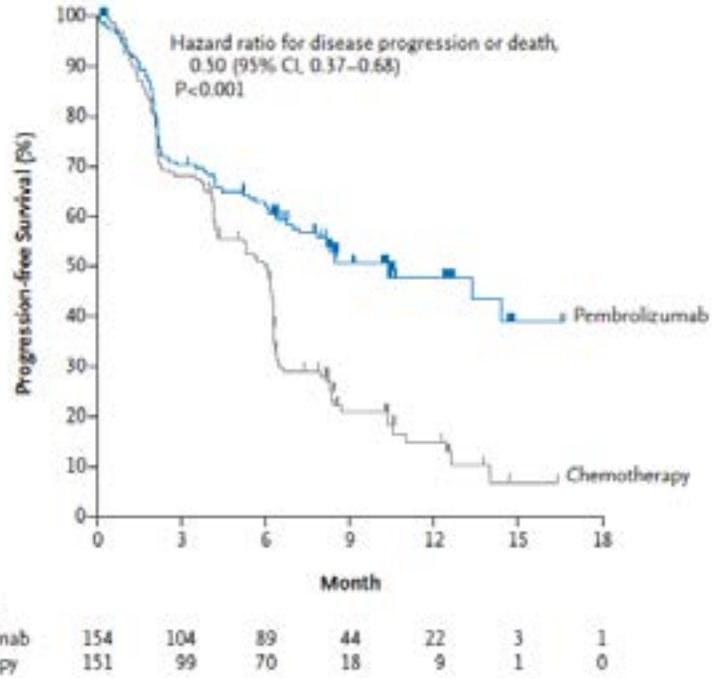
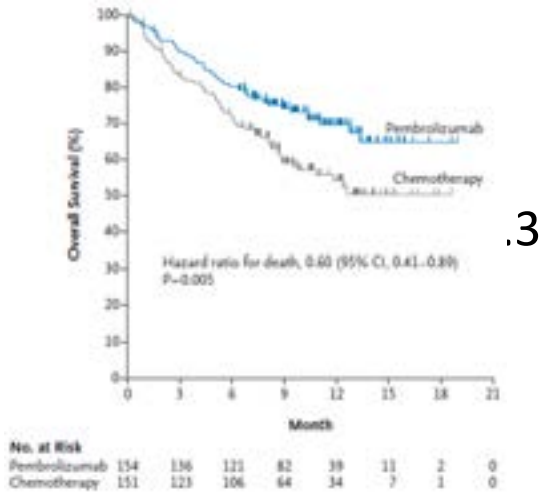
PD-1/PD-L1 Inhibition in Lung Cancer[1]



- Prospective randomized phase III trial
- Pembrolizumab (humanized mab targeting PD-1) *versus* cisplatin-containing chemotherapy of investigators choice
- 305 treatment-*naive* pat., advanced NSCLC (>80% non-SQ), PD-L1 expression ≥50% (EGFRmut, *ALK*-pos. pts excluded)
- PFS (median) 10.3 vs. 6.0 months
  95% CI 0.37-0.68; $p<0.001$)
- RR 44.8% *vs*. 27.8%; duration of response: .3 months
- Grade 3-5 toxicity 26.6% *vs*. 53.3%



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

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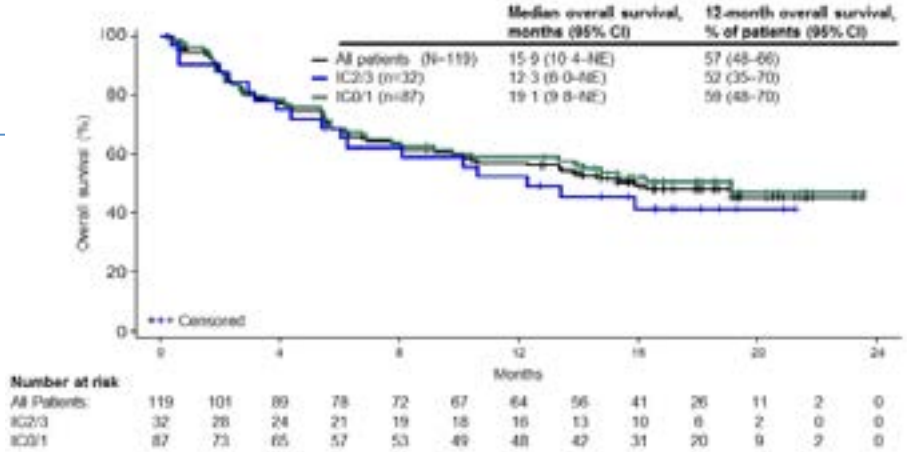
PD-1/PD-L1 Inhibition in Urothelial Cancer[1]



- Prospective single-arm phase II trial
- Atezolizumab (humanized mab targeting PD-L1)
- 119 treatment-*naive* pts., locally advanced or metastatic urothelial cancer, cisplatin ineligible
- RR 23% (95% CI 16–31); CR 9%; median response duration was not reached (17.2 months median follow-up)
- Median PFS 2.7 months; median OS 15.9 months
- Mutational load was associated with response
- AEs (≥10% of pts.): fatigue, diarrhoea, pruritus

1 Balar AY et al. Lancet 2017;389(:67-76.

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Toxicity

- Ipilimumab: irAEs in 60%-85% of patients [1]
- 10%-27% grade 3/4 [1,2]
- 2.1% toxic deaths due to irAEs [1]
- Adjuvant setting (10 mg/kg), grade 3/4 irAEs 41.6% [3]
- Most common side effects [3]:
  - Diarrhoe 41.2% (grade 3/4 9.8%)
  - Rash 34.2% (1.1%)
  - Increased liver enzymes 17.6% (4.3%)
  - Hypophysitis 16.3% (4.4%)
  - Colitis 15.5% (7.6%)

Event	Ipilimumab (N=471)			
	Any Grade	Grade 3	Grade 4	Grade 5
Any immune-related adverse event	426 (90.4)	169 (35.9)	27 (5.7)	5 (1.1)
Any dermatologic event	298 (63.3)	20 (4.2)	0	0
Rash	161 (34.2)	5 (1.1)	0	0
Any gastrointestinal event†	217 (46.1)	70 (14.9)	6 (1.3)	3 (0.6)
Diarrhea	194 (41.2)	46 (9.8)	0	0
Colitis	73 (15.5)	32 (6.8)	4 (0.8)	3 (0.6)
Any endocrine-system event	178 (37.8)	34 (7.2)	3 (0.6)	0
Hypophysitis	77 (16.3)	20 (4.2)	1 (0.2)	0
Any hepatic event	115 (24.4)	38 (8.1)	13 (2.8)	0
Increase in liver-enzyme levels	83 (17.6)	14 (3.0)	6 (1.3)	0
Any neurologic event	21 (4.5)	5 (1.1)	4 (0.8)	0
Other‡	111 (23.6)	34 (7.2)	2 (0.4)	2 (0.4)

1 Hodi FS et al. N Engl J Med 2010;363:711–723.
2 Larkin J et al. N Engl J Med 2015;373:23–34.
3 Eggermont AM. N Engl J Med 2016;375:1845–1855.

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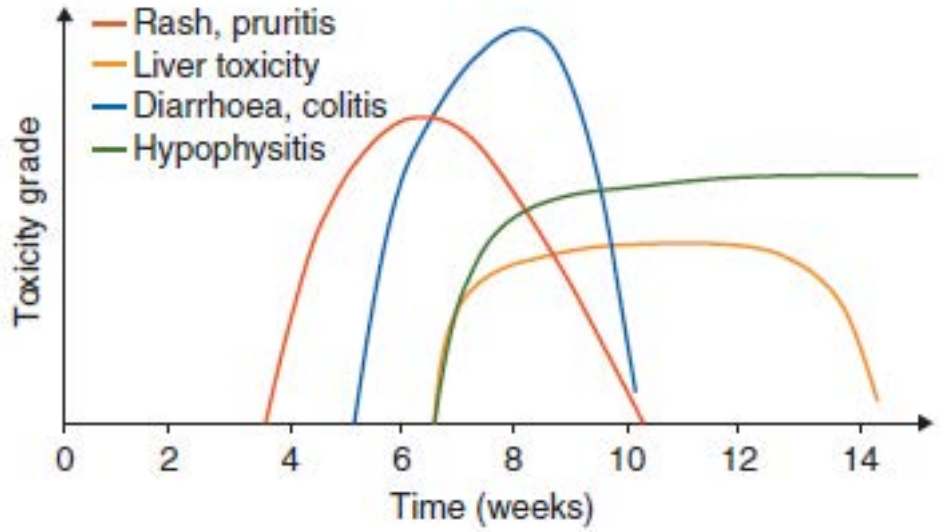
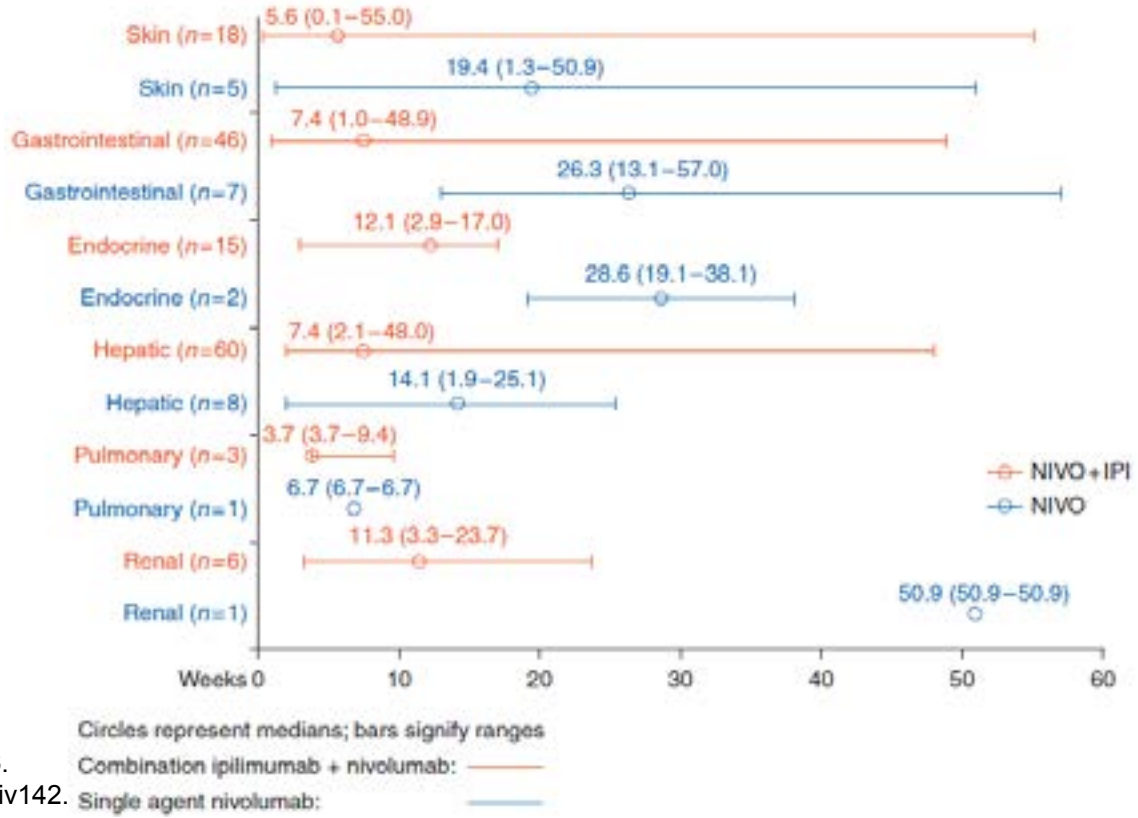
Toxicity



- Timing of irAEs in pts. receiving ipilimumab [1]
- Time to onset of irAEs depends upon treatment intensity – e.g. nivolumab *versus* nivolumab plus ipilimumab [2]
- Onset up to one year after discontinuation possible [3]



1 Weber JS et al. J Clin Oncol 2012;30:2691-2697.
2 Larkin J et al. Eur J Cancer 2015;51(Suppl3);S664-S66.
3 Haanen JBAG et al. Ann Oncol 2017;28(Suupl4):iv119-iv142.

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Toxicity

- PD-1/PD-L1 inhibitors: irAEs less common compared with ipilimumab [1]
- Superior side-effect profile compared with chemotherapy [2]:
- AEs (any grade) 73.4% *vs*. 90.0%; AEs (grade 3 to 5) 26.6% *vs*. 53.3%
- irAEs 29.2%; grade 3/4 irAEs 9.7%
- irAEs occurring in >5% of pts.:
  - Hypothyroidism
  - Hyperthyroidism
  - Pneumonitis
  - Severe skin reactions

Adverse Event	Pembrolizumab Group (N=154)	
	Any Grade	Grade 3, 4, or 5
Immune-mediated§		
Any	45 (29.2)	15 (9.7)
Hypothyroidism	14 (9.1)	0
Hyperthyroidism	12 (7.8)	0
Pneumonitis	9 (5.8)	4 (2.6)
Infusion reaction	7 (4.5)	0
Severe skin reaction	6 (3.9)	6 (3.9)
Thyroiditis	4 (2.6)	0
Colitis	3 (1.9)	2 (1.3)
Myositis	3 (1.9)	0
Hypophysitis	1 (0.6)	1 (0.6)
Nephritis	1 (0.6)	1 (0.6)
Pancreatitis	1 (0.6)	1 (0.6)
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)

1 Haanen JBAG et al. Ann Oncol 2017;28(Suupl4):iv119-iv142.
2 Reck M et al. N Engl J Med 2016;375:1823-1833.

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Toxicity Management: General Considerations [1]

- Predisposing factors:
  - Prexisting autoimmune-disorders
  - irAEs on prior treatment
- Early diagnosis crucial
- General Managament (ESMO [1]):
  - Withhold immunotherapy in case of grade ≥2, initiate immunospressive therapy – e.g. prednislon 0.5-4 mg/kg body weight
  - Consider escalation of immunospressive therapy if required (TNFα-inhibiots, mycophenolate, tacrolimus)
  - Low threshold for treatment interruption in case of neurological side-effects
  - Less strict in case of skin toxicity or arthralgia
  - No clear data indicating that outcome is compromised by immunosuppressive treatment [2,3]

1 Haanen JBAG et al. Ann Oncol 2017;28(Suupl4):iv119-iv142.
2 Weber JS et al. J Clin Oncol 2012;30:2691-2697.
3 Horvat TZ et al. J Clin Oncol 2015;33:3193–3198.

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Toxicity Management: Specific Considerations

- ESMO [1]:
  - CTLA4 mabs: TSH screening every cycle, after cycle 4 every 4-6 weeks
  - PD-1/PD-L1 mabs: TSH screening every cycle for the first three cycles, every seond cycle thereafter
  - Liver function parameters every cycle
  - Renal toxicity: Serum sodium, potassium, creatinine and urea should be measured before every treatment cycle
  - Pneumonitis: typical late-onset irAE, usually observed several months after treatment initiation
  - Neurological irAEs: Consider phlasmapheresis and i.v. immunoglobulin - Guillain-Barré like syndrome may be steroid-sensitive! [2]

1 Haanen JBAG et al. Ann Oncol 2017;28(Suupl4):iv119-iv142.
2 Cuzzubbo S et al. Eur J Cancer 2017;73:1-8.

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Toxicity Management: General Considerations

- ASCO/NCCN [1]:
  - ICPis should be continued with close monitoring for grade 1 toxicities – lower threshold for interruption in patients with neurologic, hematologic, and cardiac irAEs
  - Treatment interruption in pts. with grade 2 irAEs generally recommended
  - Administration of corticosteroids should be considered, treatment may be resumed when symptoms revert to grade 1
  - Grade 3 irAEs: Treatment interruptions and high-dose corticosteroids (e.g. prednisone 1-2 mg/kg/d; methylprednisolone 1-2 mg/kg/d)
  - Corticosteroids should be tapered over the course of at least 4 to 6 weeks
  - Consider infliximab or other immunosuppressants in case of refractory irAEs
  - In case of grade 4 irAEs, ICPis should be permanently discontinued with the exception of endocrinopathies and adequate hormone-replacement

1 Brahmer JR et al. J Clin Oncol 2018;36:1714-1768.

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Toxicity Management: Specific Considerations

- ASCO/NCCN [1]:
  - Colitis can predict a corticosteroid-refractory course, which may require early infliximab
  - Calprotectin may be used for monitoring disease activity
  - AST, ALT and bilirubin should be tested every cycle; in case of grade 1 liver function test elevation weekly tests should be conducted
  - No routine monitoring of amylase and lipase
  - TSH and fT4 monitoring every 4 to 6 weeks
  - Kidney: Kreatinine levels prior to every cycle; routine urinalysis is not necessary other than to rule out urinary tract infections, etc. If no potential alternative cause of acute kidney injury (AKI) is identified, forego biopsy and proceed directly with immunosuppressive therapy.
  - Quick initiation of immunosuppressive therapy is important.

1 Brahmer JR et al. J Clin Oncol 2018;36:1714-1768.

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Spectrum of Immune-Related Adverse Events[1]

Endocrine
Hyper or hypothyroidism
Hypohysitis
Adrenal insufficiency
Diabetes

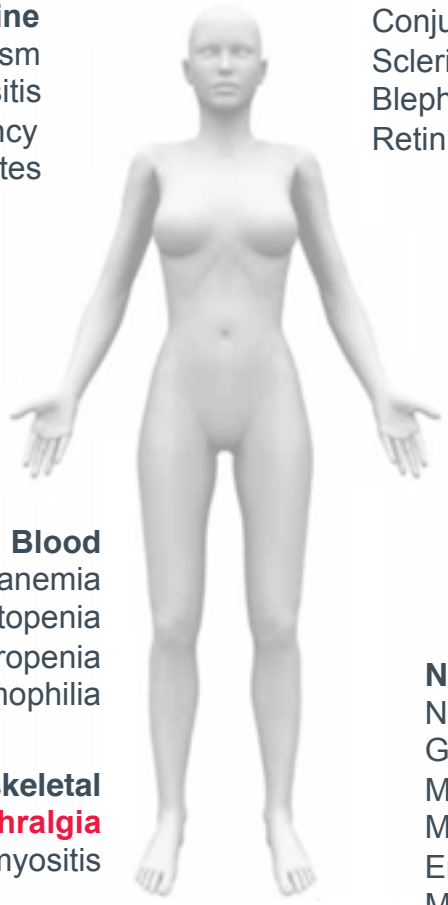
Eye
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis

Respiratory
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis

Liver
Hepatitis

Cardiac vascular
Myocarditis
Pericarditis
Vasculitis

Skin
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson



Renal
Nephritis

Gastro-intestinal
Colitis
Nausea
Ileitis
Pancreatitis
Gastritis

Blood
Hemolytic anemia
Thombocytopenia
Neutropenia
Hemophilia

Neurological
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia

Musculo skeletal
Arthritis / **Athralgia**
Dermatomyositis

1 Champiat S et al.
Ann Oncol 2016;27:559-574.

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Detection of Immune-Related Adverse Events[1]

- Physician and patient education required

- Three typical etiologies of AEs/ clinical symptoms:
  - Disease progression
  - Fortuitous event (without treamtment-related cause; e.g. coincidential viral infection)
  - Treatment-related dysimmune toxicity

- Most frequently symptoms are related to disease progression – but immune-related AEs should always be considered

1 Champiat S et al. Ann Oncol 2016;27:559-574.

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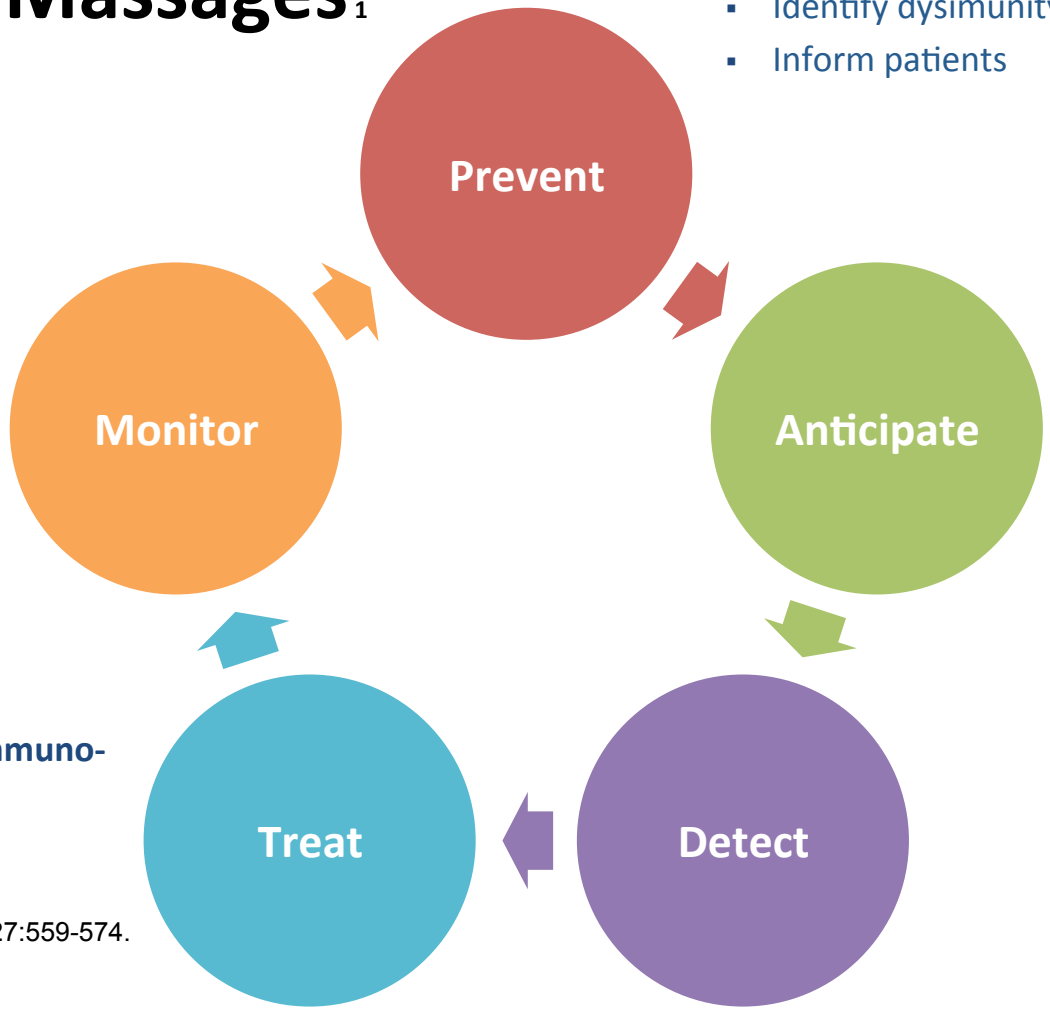
Take-Home Massages[1]

- **Know the immune-toxicity spectrum**
- Identify dysimunity risk factors
- Inform patients



- Therapy **suspension**?
- Refer to organ specialist?
- Corticosteroids or other **immuno-suppressive drugs**?

1 Champiat S et al. Ann Oncol 2016;27:559-574.

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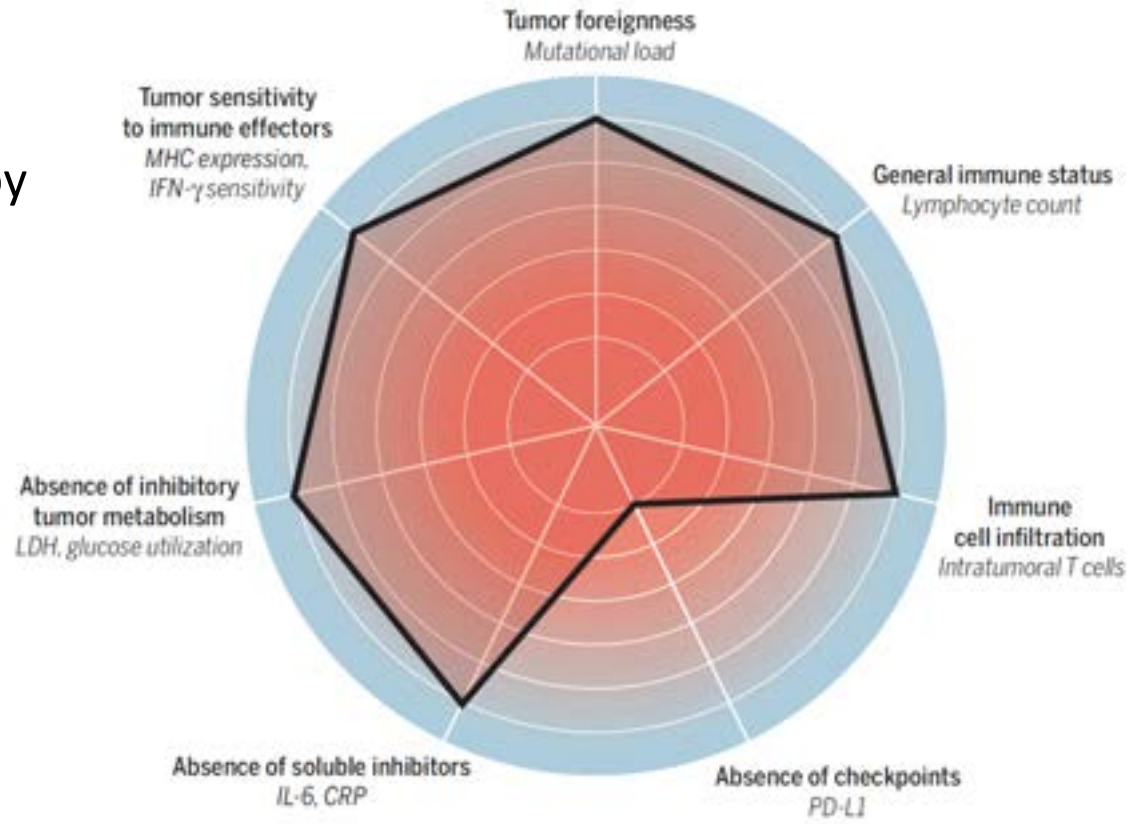
Predictive Biomarkers

- Multiple factors beyond PD-L1 may influence activity of immunotherapy in cancer patients [1]



1 Blank CU et al. Science 2016;352:658-660.

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Backup

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Summary

- Immunotherapy with ICPis has changed the treatment paradigm in multiple malignancies
- Greatest impact in meloanoma dn lung cancer
- irAEs as clinically relevant burden
- More pronounced (and earlier onset) with more intense treatment but irAEsmay also occur
- Early detection and treatment of irAEs recommended
- High costs of ICPis increase disparity in cancer care
- Identification of predictive makers to identify patients who may truly benefit from treatment and eleviate the financial burden

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Prevention of Immune-Related Adverse Events[1]

- Knowledge of the immune-toxicity spectrum
- Inform patients and their family doctors
- History of autoimmune diseases (personal and familiar)
- Risk for opportunistic pathogens (HIV, PCP, tuberculosis, hepatitis virus)
- Potential symptoms and complications of pseudoprogressions

1 Champiat S et al. Ann Oncol 2016;27:559-574.

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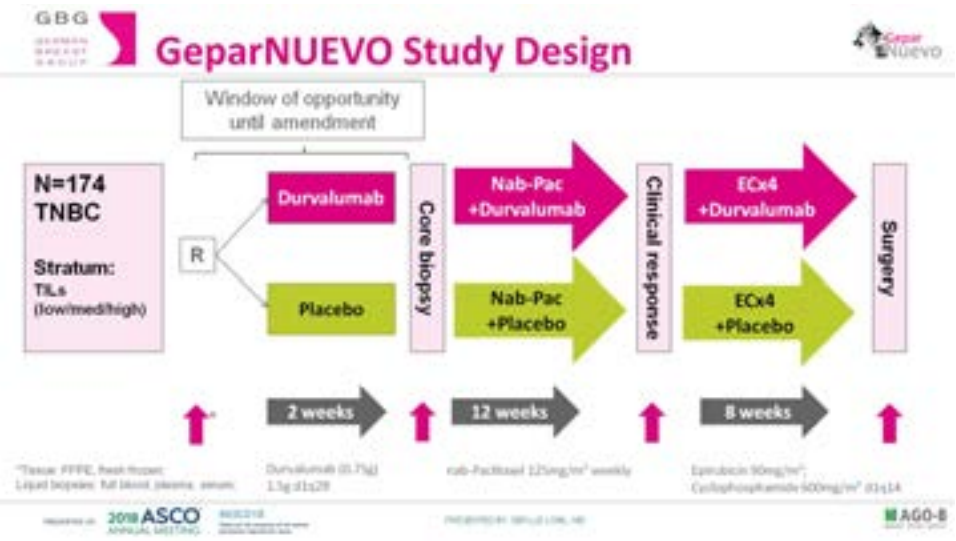
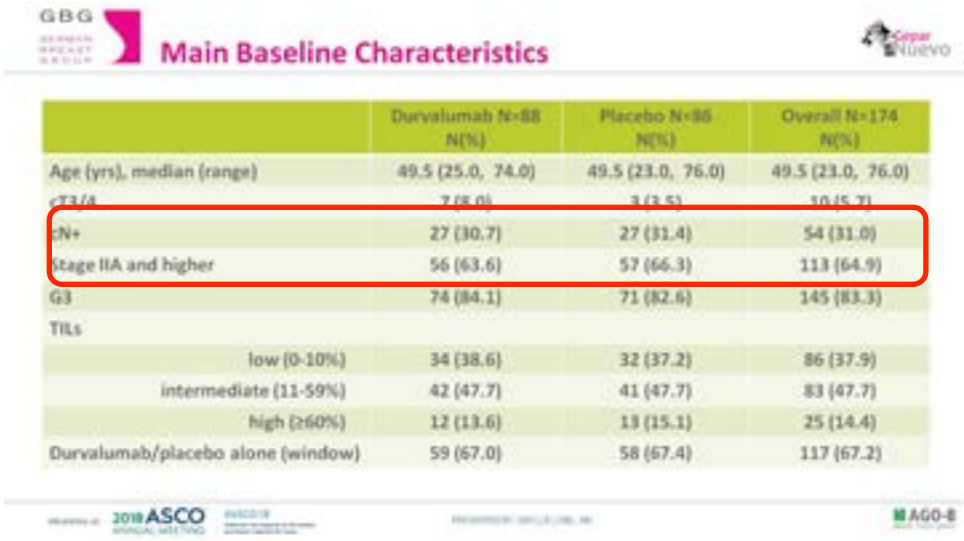
GeparNuevo[1]

- Prospective randomized phase II, 174 pts., TNBC, addition of durvalumab (PD-L1 mab) to standard neoadjuvant chemotherapy
- Statistical hypothesis: increase in pCR rates from 48% to 66%





	Durvalumab N=88 N(%)	Placebo N=86 N(%)	Overall N=174 N(%)
Age (yrs), median (range)	49.5 (25.0, 74.0)	49.5 (23.0, 76.0)	49.5 (23.0, 76.0)
cT3/4	7 (8.0)	3 (3.5)	10 (5.7)
cN+	27 (30.7)	27 (31.4)	54 (31.0)
Stage IIA and higher	56 (63.6)	57 (66.3)	113 (64.9)
G3	74 (84.1)	71 (82.6)	145 (83.3)
TILs			
low (0-10%)	34 (38.6)	32 (37.2)	86 (37.9)
intermediate (11-59%)	42 (47.7)	41 (47.7)	83 (47.7)
high (≥60%)	12 (13.6)	13 (15.1)	25 (14.4)
Durvalumab/placebo alone (window)	59 (67.0)	58 (67.4)	117 (67.2)

1 Loibl S et al. Abst. 104; presented at the 2018 ASCO Annual Meeting, June 2018, Chicago, Illinois, USA.

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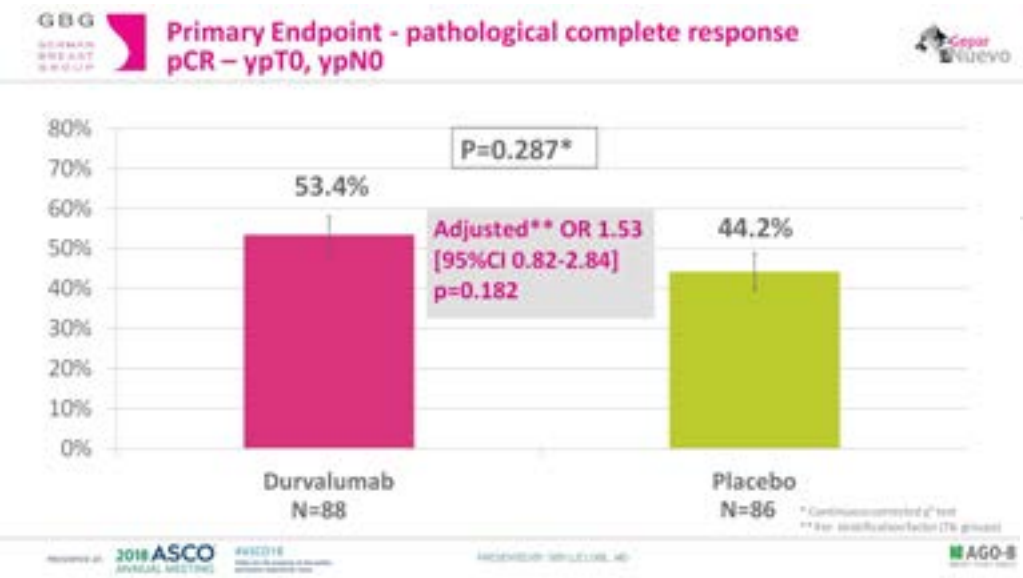
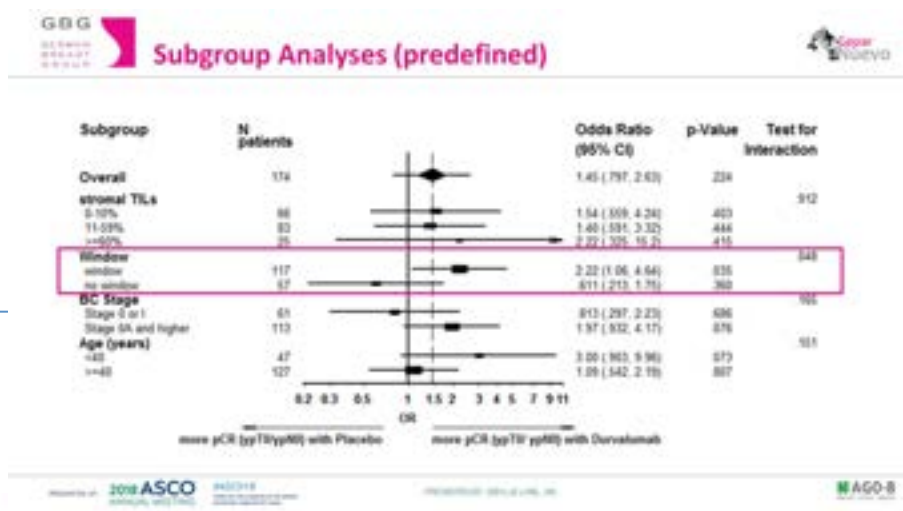
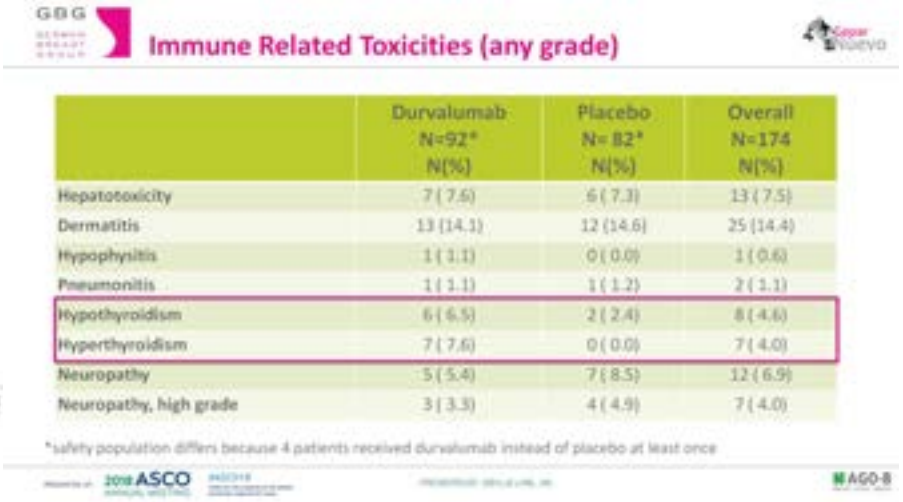
GeparNuevo[1]







- GeparNuevo formally negative but a potentially relevant was observed in subroups – further evaluation in prospective phase III trials warranted

1 Loibl S et al. Abst. 104; presented at the 2018 ASCO Annual Meeting, June 2018, Chicago, Illinois, USA.

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Neoadjuvant Immunotherapy[1,2]

- Dual HER2-inhibition with trastuzumab and pertuzumab in the neoadjuvant setting

- NEOSPHERE: Randomized, four-arm, phase II, chemo-backbone docetaxel x4

- pCR: (breast)

D+T:	29%	(95% CI 20.6-38.5)
D+P:	24%	(95% CI 15.8-33.7)
D+T+P:	45,8%	(95% CI 36.1-55.7)
T+P:	16,8%	(95% CI 10.3-25.3)

	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
Pathological complete response in ITT population	31 (29·0%, 20·6–38·5)	49 (45·8%, 36·1–55·7)*	18 (16·8%, 10·3–25·3)†	23 (24·0%, 15·8–33·7)‡
Pathological complete response and N– at surgery	23 (21·5%, 14·1–30·5)	42 (39·3%, 30·0–49·2)	12 (11·2%, 5·9–18·8)	17 (17·7%, 10·7–26·8)
Pathological complete response and N+ at surgery	8 (7·5%, 3·3–14·2)	7 (6·5%, 2·7–13·0)	6 (5·6%, 2·1–11·8)	6 (6·3%, 2·3–13·1)
Pathological complete response in ER positive or PR positive, or both, women	10/50 (20·0%, 10·0–33·7)	13/50 (26·0%, 14·6–40·3)	3/51 (5·9%, 1·2–16·2)	8/46 (17·4%, 7·8–31·4)
Pathological complete response in ER negative and PR negative women	21/57 (36·8%, 24·4–50·7)	36/57 (63·2%, 49·3–75·6)	15/55 (27·3%, 16·1–41·0)	15/50 (30·0%, 17·9–44·6)

1 Gianni L et al. Lancet Oncol 2012;13:25-32.
2 Gianni L et al. Lancet Oncol 2016;17:791-800.