Checking the Immune System in Cancer

What the General Internist Should know

Michael B. Dabrow, DO, FACOI
Medical Director, Paoli Hospital Cancer Center

Disclosure Information

ACOI Annual convention 2016

-
- I have no financial relationships to disclose.

-.

-I will discuss the following off label use and/or investigational use in my presentation: nivolumab

75 YEARS OF DEDICATION TO OUR MEMBERS

Michael B. Dabrow, DO
dabrowm@mlhs.org

S-Venn Diagram

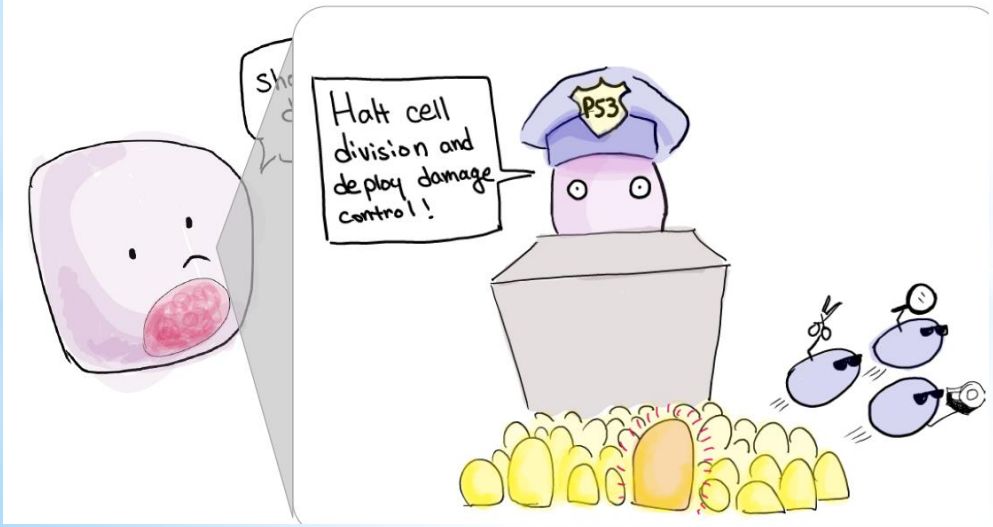
What's so great about immunotherapy?

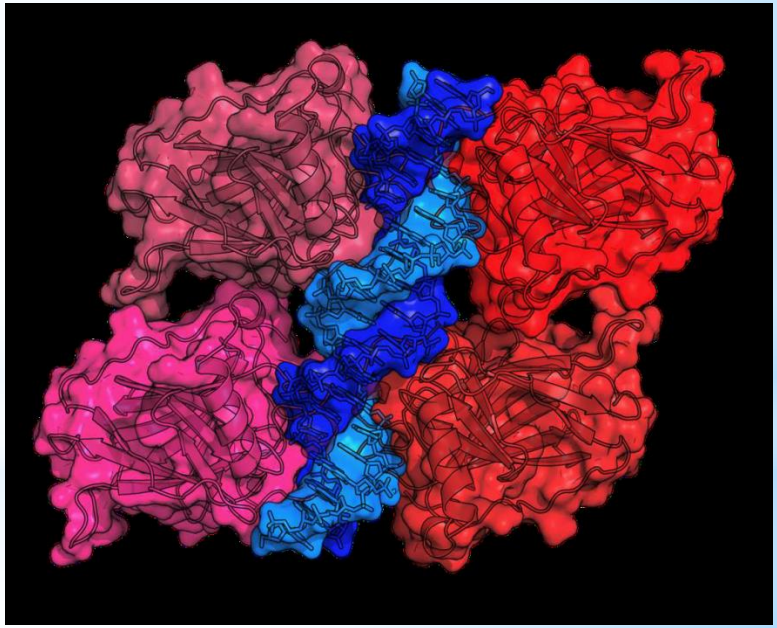
- **2011**: The first immune checkpoint inhibitor, ipilimumab, was approved by the FDA
- **2014**: Two new checkpoint inhibitors, pembrolizumab and nivolumab, were approved
- There are currently more than **150 clinical trials** for using **immune checkpoint inhibitors** to treat lung, skin, kidney, ovarian, and bladder cancers

Mutations are especially bad if they occur in **tumor suppressors**

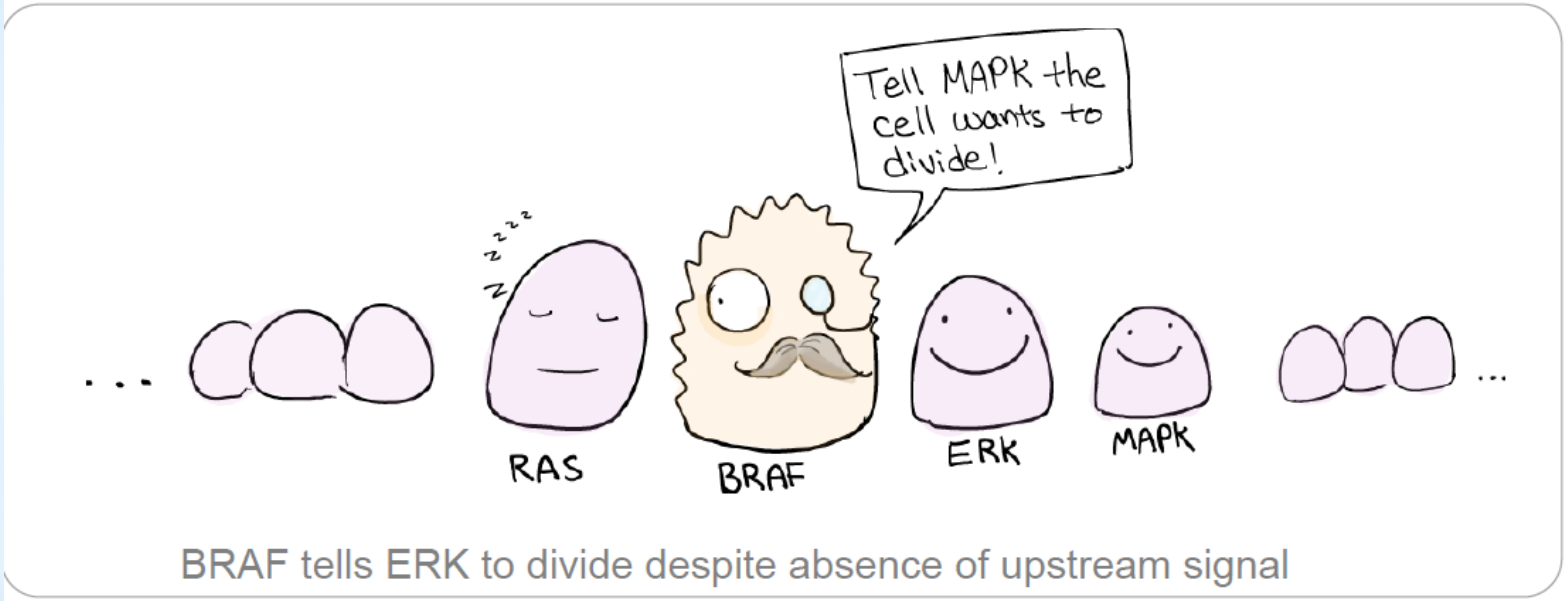
Tumor suppressors tell cells to stop dividing when DNA damage is detected, or tell cells when to die when damage is too severe

When DNA damage is found, p53 stops cell division and activates repair pathways





Mutated BRAF is an **oncogene** frequently found in cancer

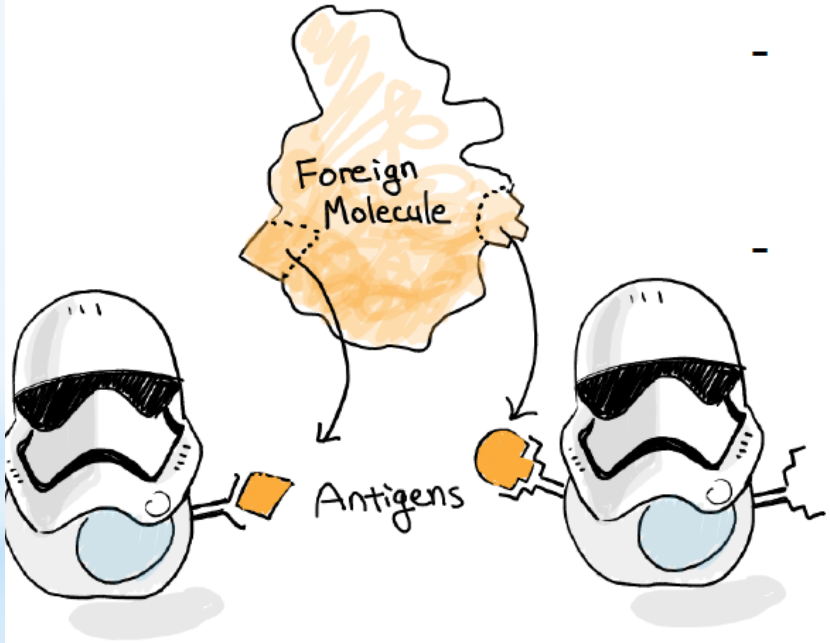


BRAF tells ERK to divide despite absence of upstream signal

BRAF mutation V600E

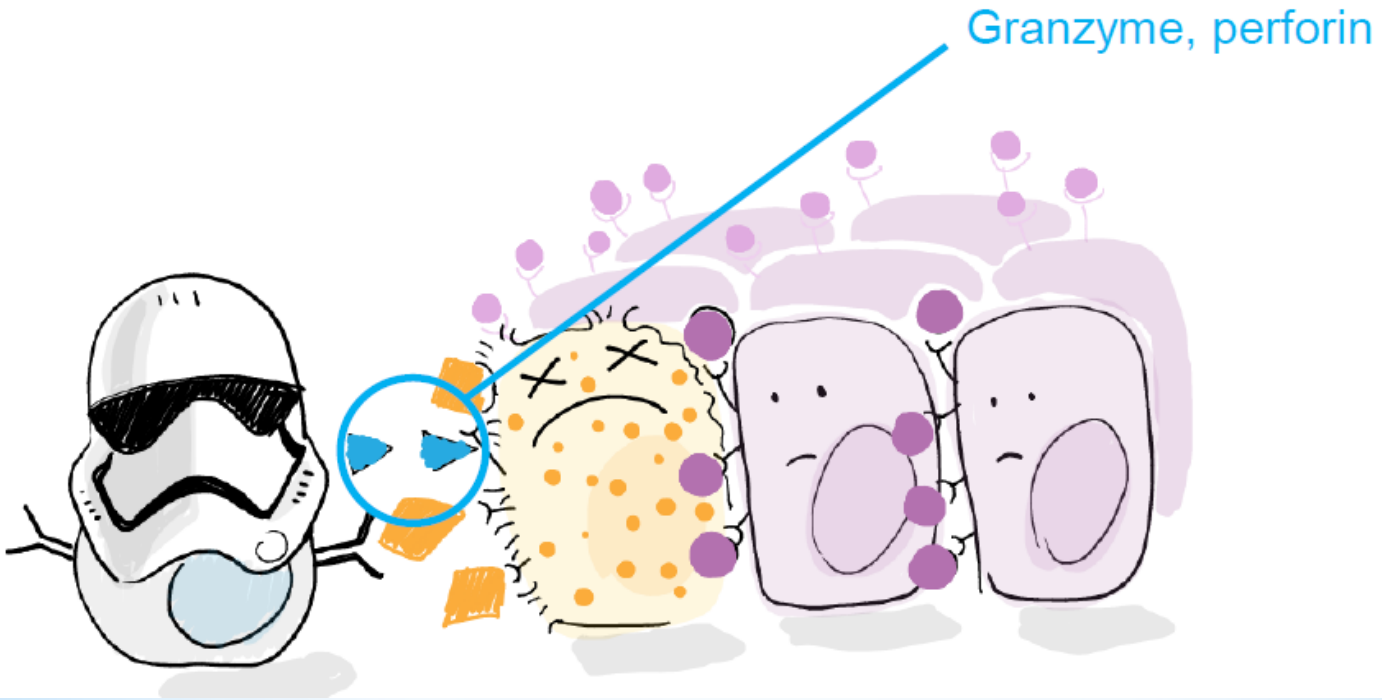
The immune system determines what does belongs doesn't belong in the body

Immune cells recognize **antigens** based on "shape" with immune receptors

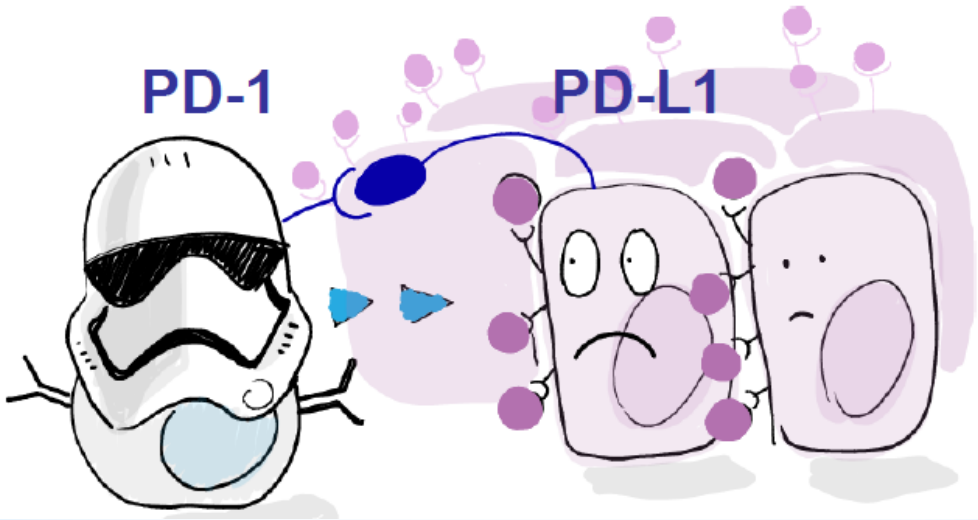


- An **antigen** is any molecule capable of inducing an immune response
- Antigens are frequently derived from pieces of bacteria and viruses

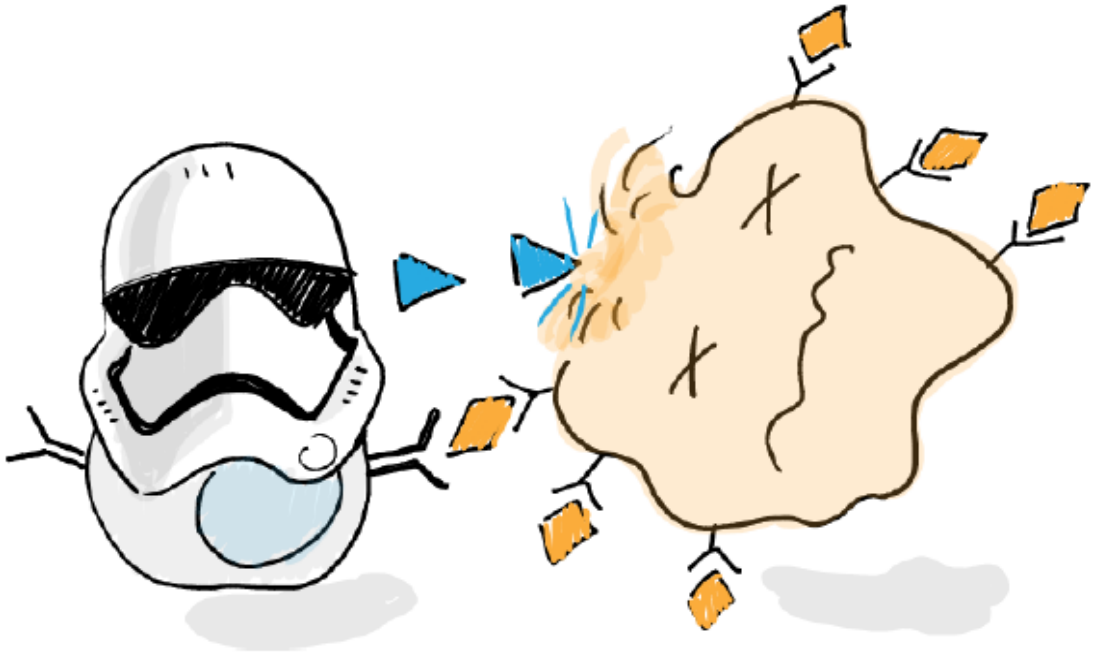
The T cell secrete special proteins that kill the infected cell, thereby stopping the spread of infection



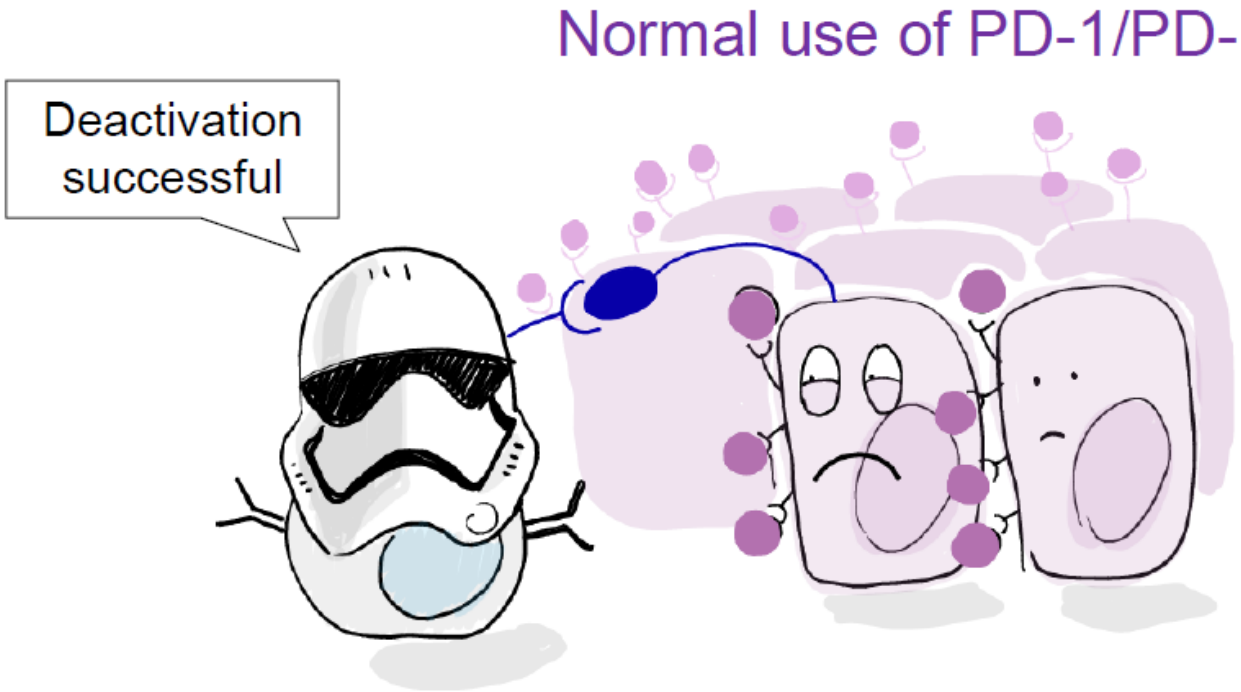
To limit collateral damage, normal cells deactivate T cells using a protein called **PD-L1** (programmed death ligand 1), which bind to a receptor called **PD-1** on the T cell



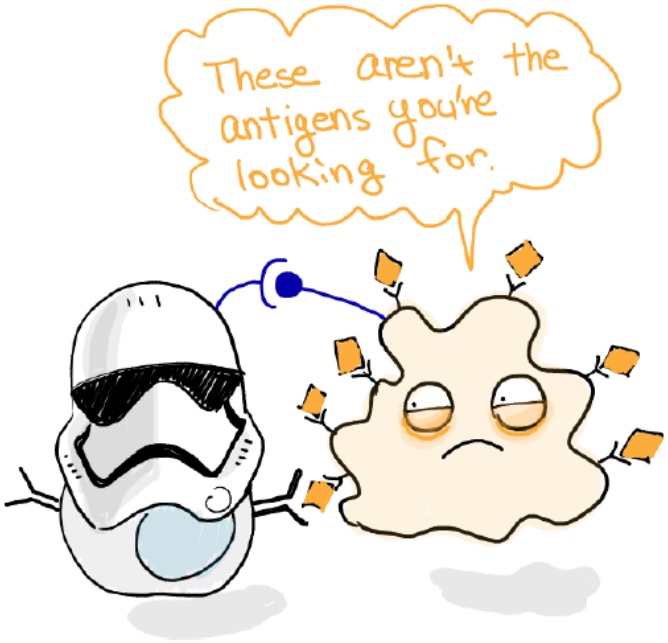
T cells with receptors that recognize **neoantigens** can kill cancer cells



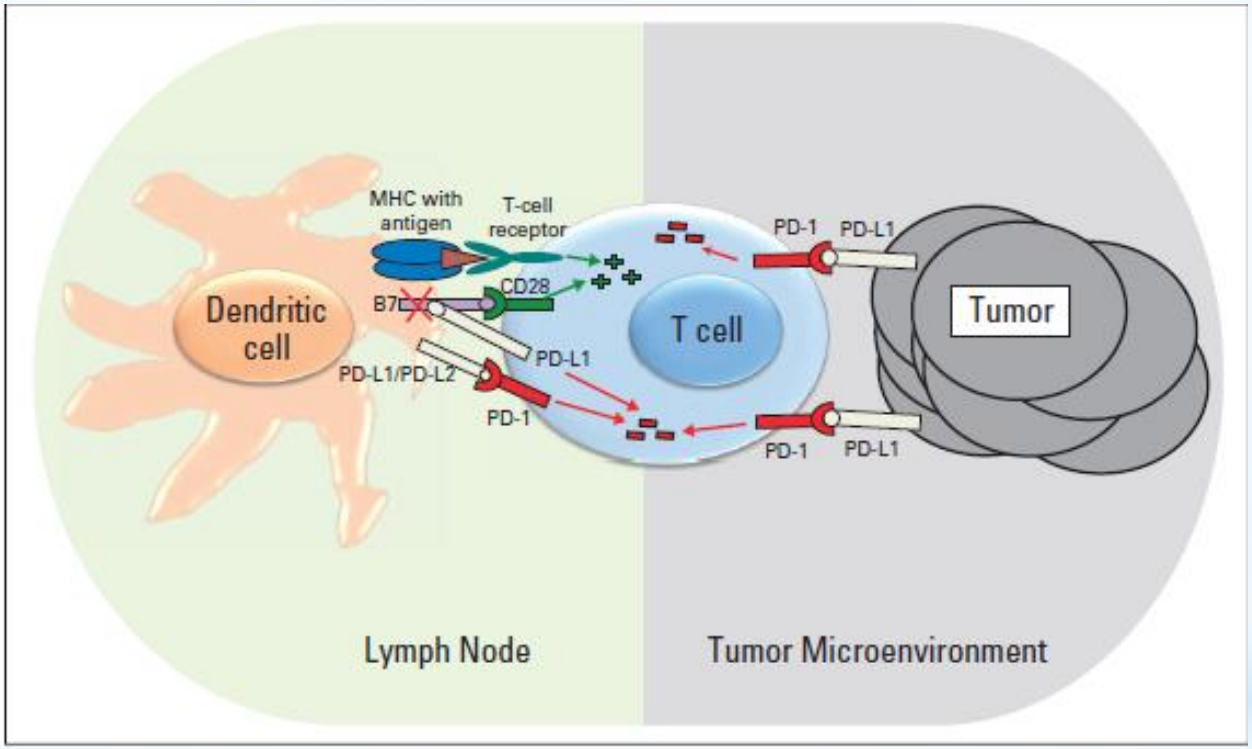
However, cancer cells can also use **PD-L1** to escape killing by T cells



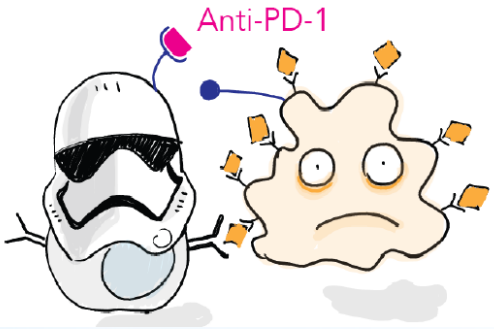
However, cancer cells can also use **PD-L1** to escape killing by T cells

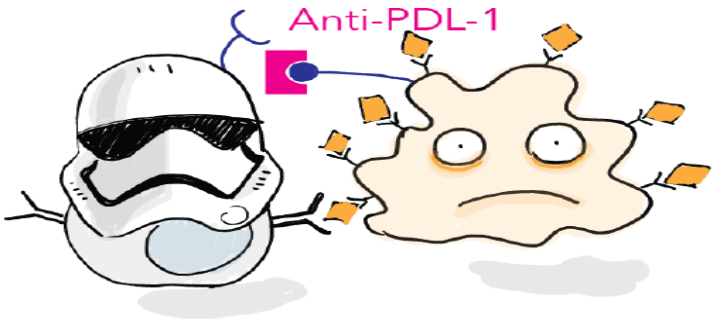


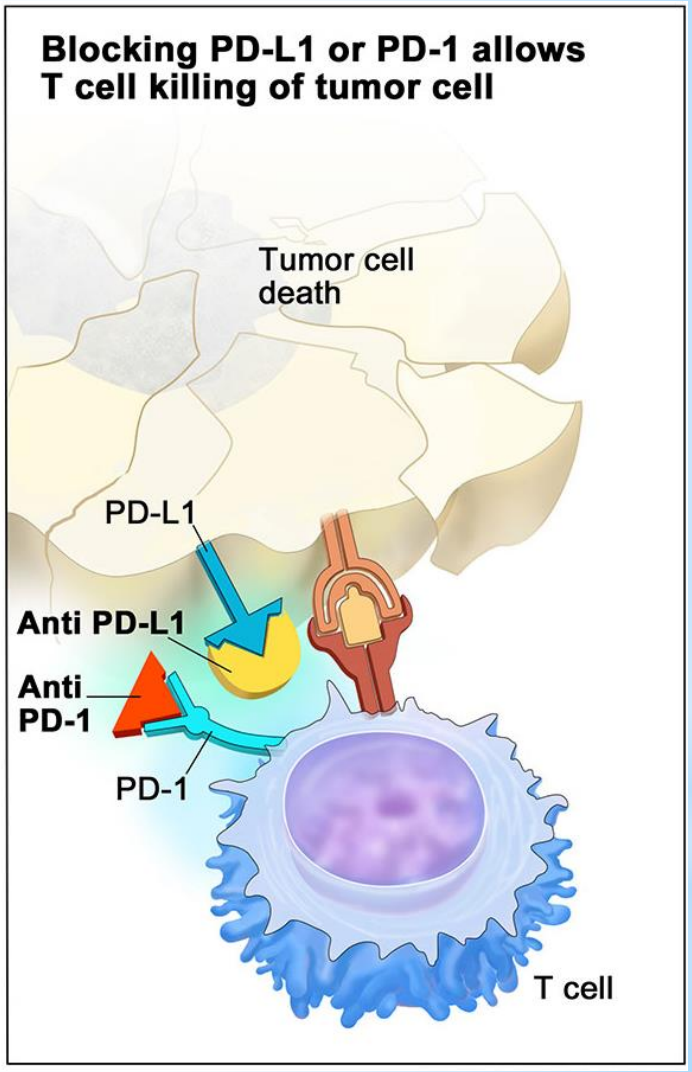
Tumor cells expressing PDL-1 to escape immune response



Immune checkpoint inhibitors target proteins like PD-1 and PD-L1 to prevent cancer from "escaping" the immune system

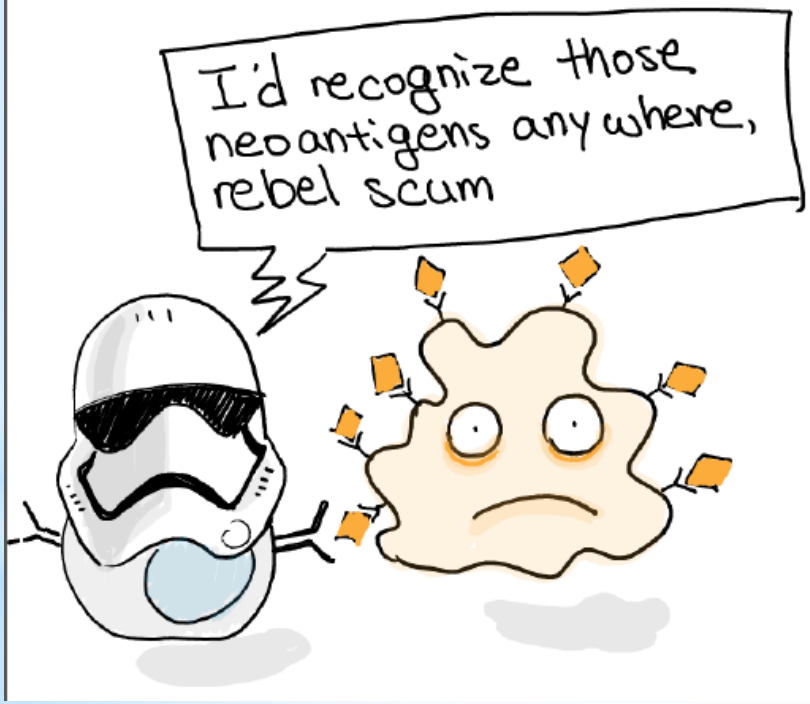




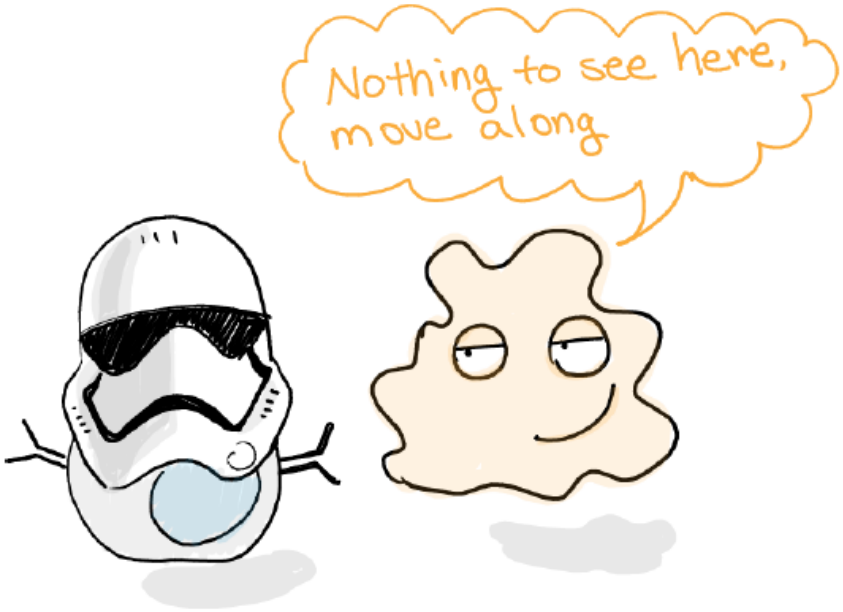


Many relapses are caused by mutations that disable MHC-I presentation

Response



Relapse



Cytotoxic T lymphocyte - Associated Antigen-4

upregulated on T-cells after T-cell activation

downregulates T-cells via CD28 interaction and B7 ligand

CTLA-4 Knockout mice model

lymphoproliferative disease

melanocytic differentiation proteins have been shown to be targets for cytotoxic T lymphocytes

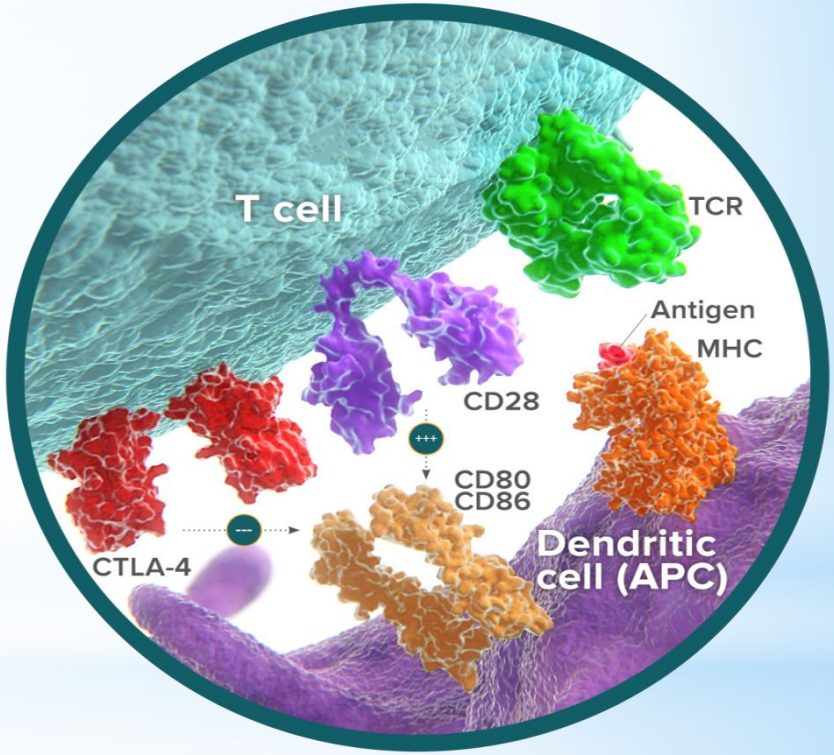
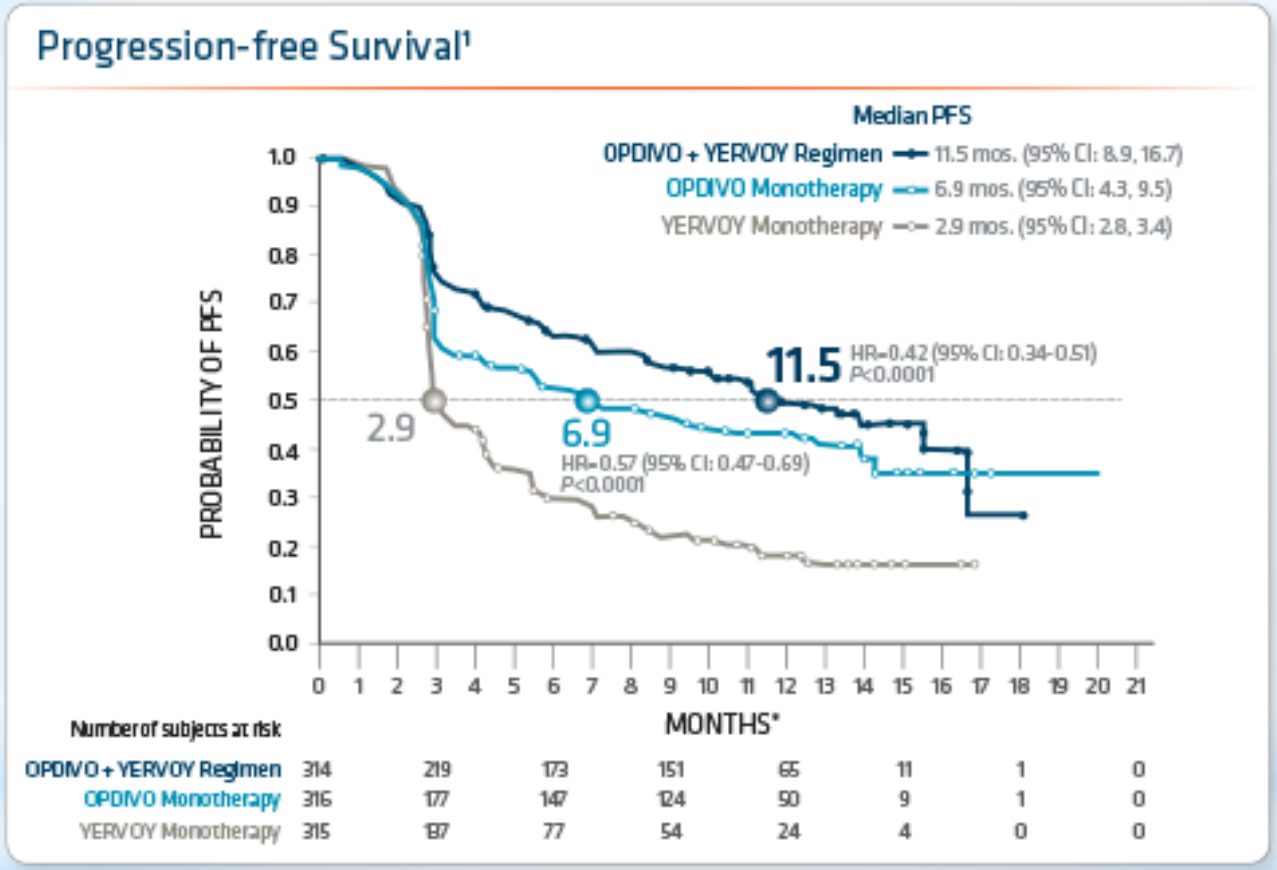


Table 1. Checkpoint Inhibitors Under Development in NSCLC With Second-Line Clinical Trial Outcomes

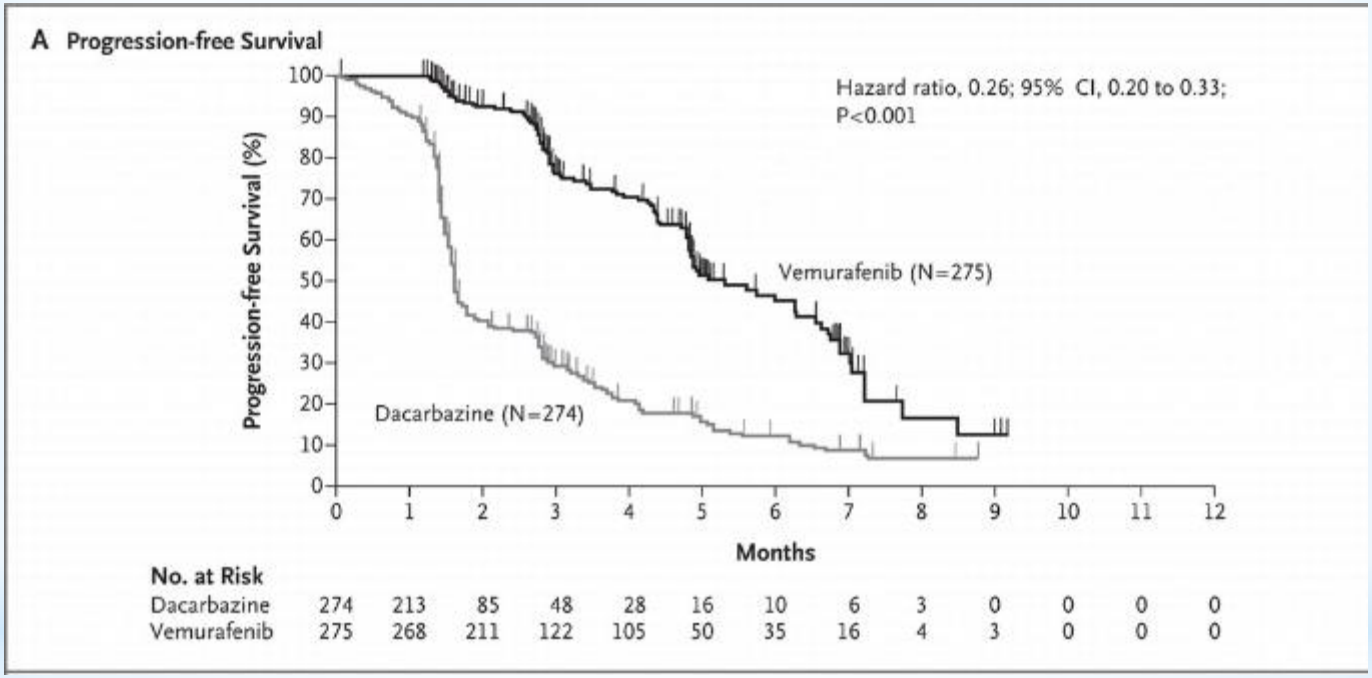
Generic Name	Alternate Names	Manufacturer	Stage of Clinical Development
CTLA-4 inhibitors			
Ipilimumab	MDX-010, MDX-101	Bristol-Myers Squibb	TWR: Rd phase II OCT: Phase III
Tremelimumab	Ticilimumab, CP-675206	AstraZeneca, Pfizer	TWR: Rd phase II OCT: Phase III
PD-1 inhibitors			
Nivolumab	ONO-4538, BMS-936558, MDX1106	Bristol-Myers Squibb	TWR: Phase III OCT: Phase III Approved (accelerated)
Pembrolizumab	Lambrolizumab, MK-3475	Merck	TWR: Rd phase I/II (NSCLC dose finding) OCT: Phase III Approved (accelerated)
PD-L1 inhibitors			
BMS-936559		Bristol-Myers Squibb	TWR: Phase I (NSCLC expansion)
Atezolizumab	MPDL3280A	Roche	TWR: Rd phase II OCT: Phase III
Durvalumab	MEDI4736	AstraZeneca	TWR: Phase I/II OCT: Phase III
Avelumab	MSB0010718C	Merck KGaA, EMD Serono, Pfizer	TWR: Phase Ib (NSCLC expansion) OCT: Phase III

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; NSCLC, non–small-cell lung cancer; OCT, ongoing clinical trial (without results); PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; Rd, randomized; TWR, trial with results.

Metastatic Melanoma



Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation



OPDIVO™ (nivolumab)

INJECTION FOR INTRAVENOUS USE 10 mg/mL

1-855-OPDIVO-1

OPDIVO in other Indications >

For U.S. Healthcare Professionals >

Questions to Ask Your Doctor PDF

SIGN UP

This site is intended for U.S. residents 18 years of age or older.

MENU

- What Is OPDIVO?
- Is OPDIVO Right for You?
- Getting an OPDIVO Infusion
- Paying for OPDIVO
- Patient Resources

PDF U.S. Full Prescribing Information | PDF Medication Guide | Full Indication

SIGN UP FOR OPDIVO RESOURCES & SUPPORT

If you have a type of advanced-stage lung cancer,

THIS IS BIG.

Watch the TV commercial

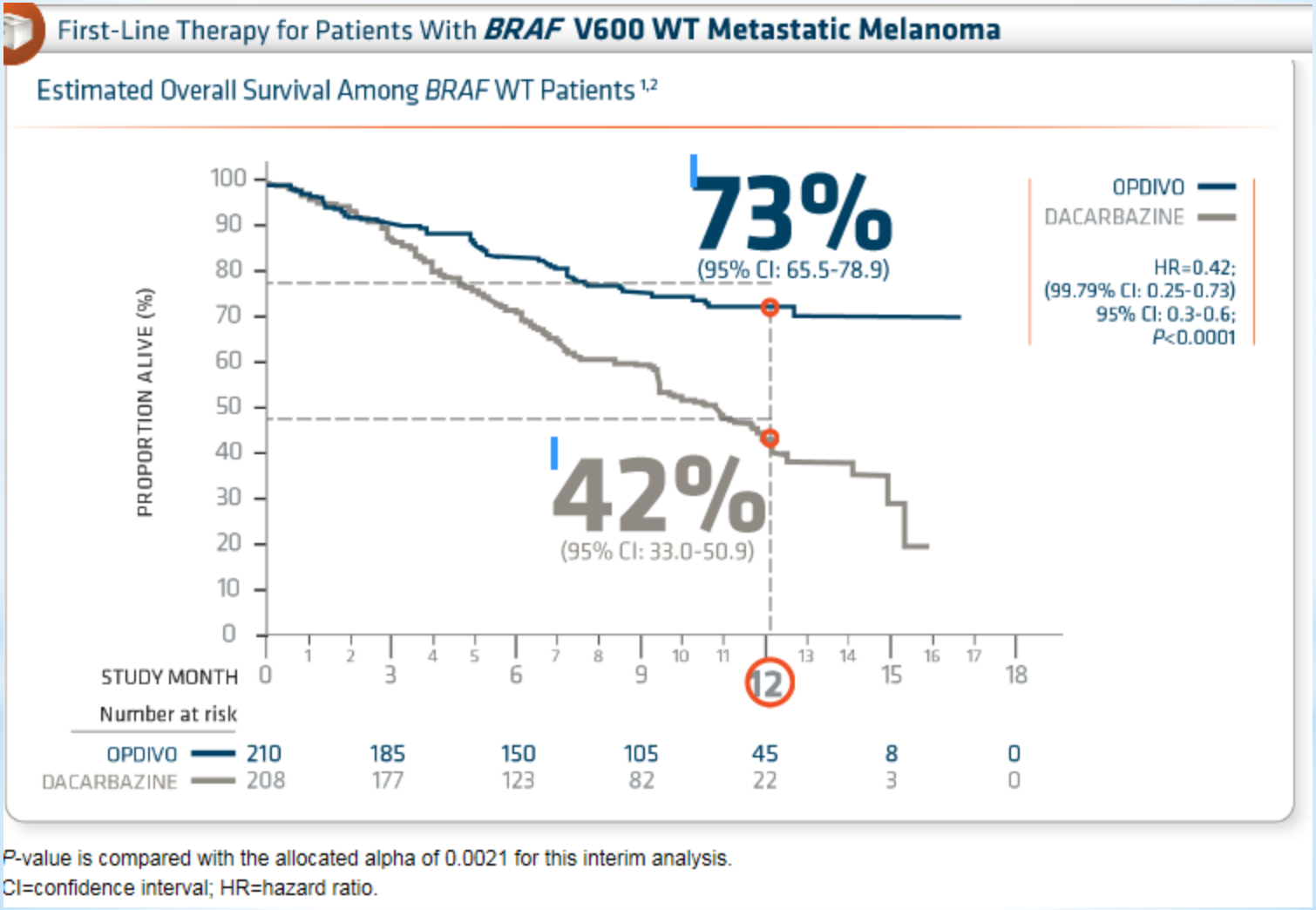
Advanced Non-Squamous NSCLC Trial

In a clinical trial of 582 patients whose advanced non-squamous NSCLC had spread or grown after treatment with platinum-based chemotherapy, 292 were treated with OPDIVO, 290 were treated with chemotherapy (docetaxel). OPDIVO was shown to reduce the risk of dying by 27% compared to chemotherapy (docetaxel). Half of the patients on OPDIVO were still alive at 12.2 months, compared to 9.4 months with chemotherapy (docetaxel). Please see additional study information here.

Advanced Squamous NSCLC Trial

In a clinical trial of 272 patients whose advanced squamous NSCLC had spread or grown after treatment with platinum-based chemotherapy, 135 were treated with OPDIVO, 137 were treated with chemotherapy (docetaxel). OPDIVO was shown to reduce the risk of dying by 41% compared to chemotherapy (docetaxel). Half of the patients on OPDIVO were still alive at 9.2 months, compared to 6 months with chemotherapy (docetaxel). OPDIVO will not work for everyone. Individual results may vary.

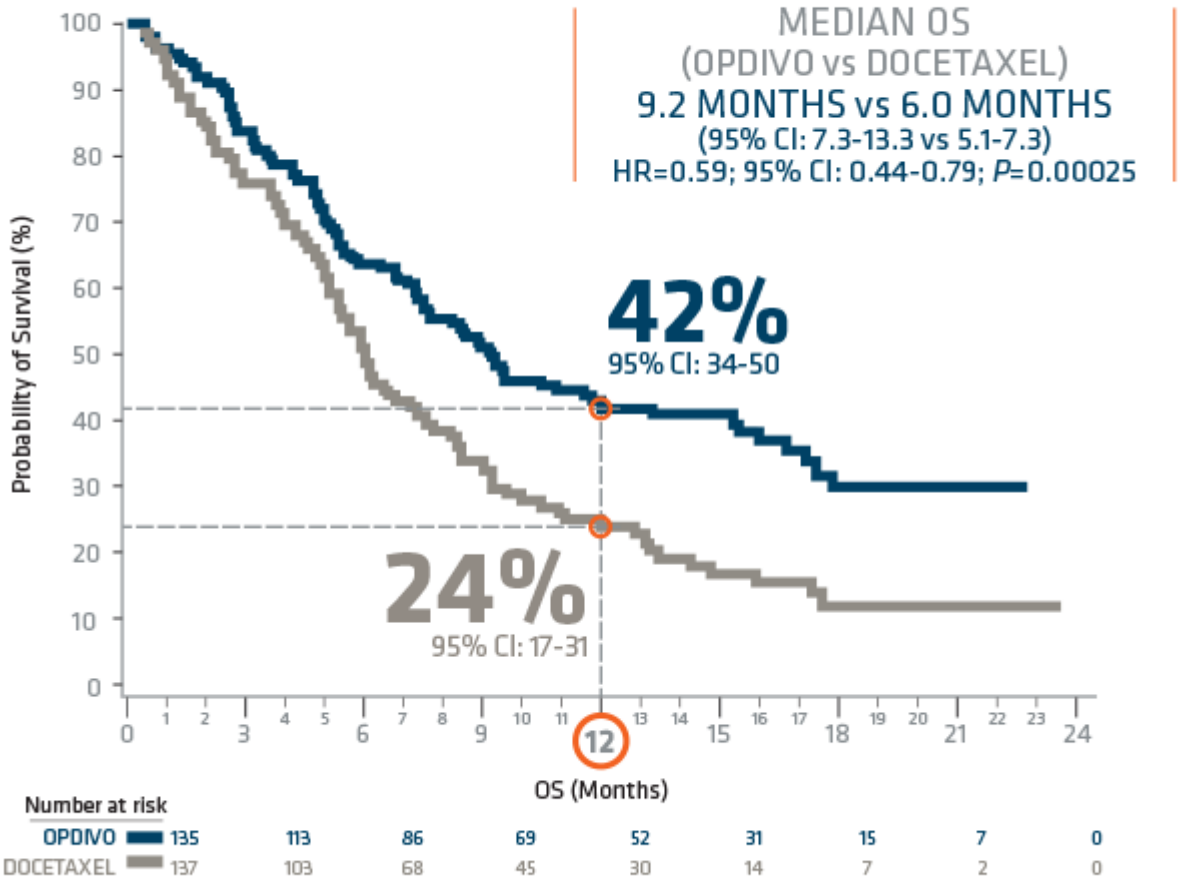
Nivolumab in BRAF negative Metastatic Melanoma



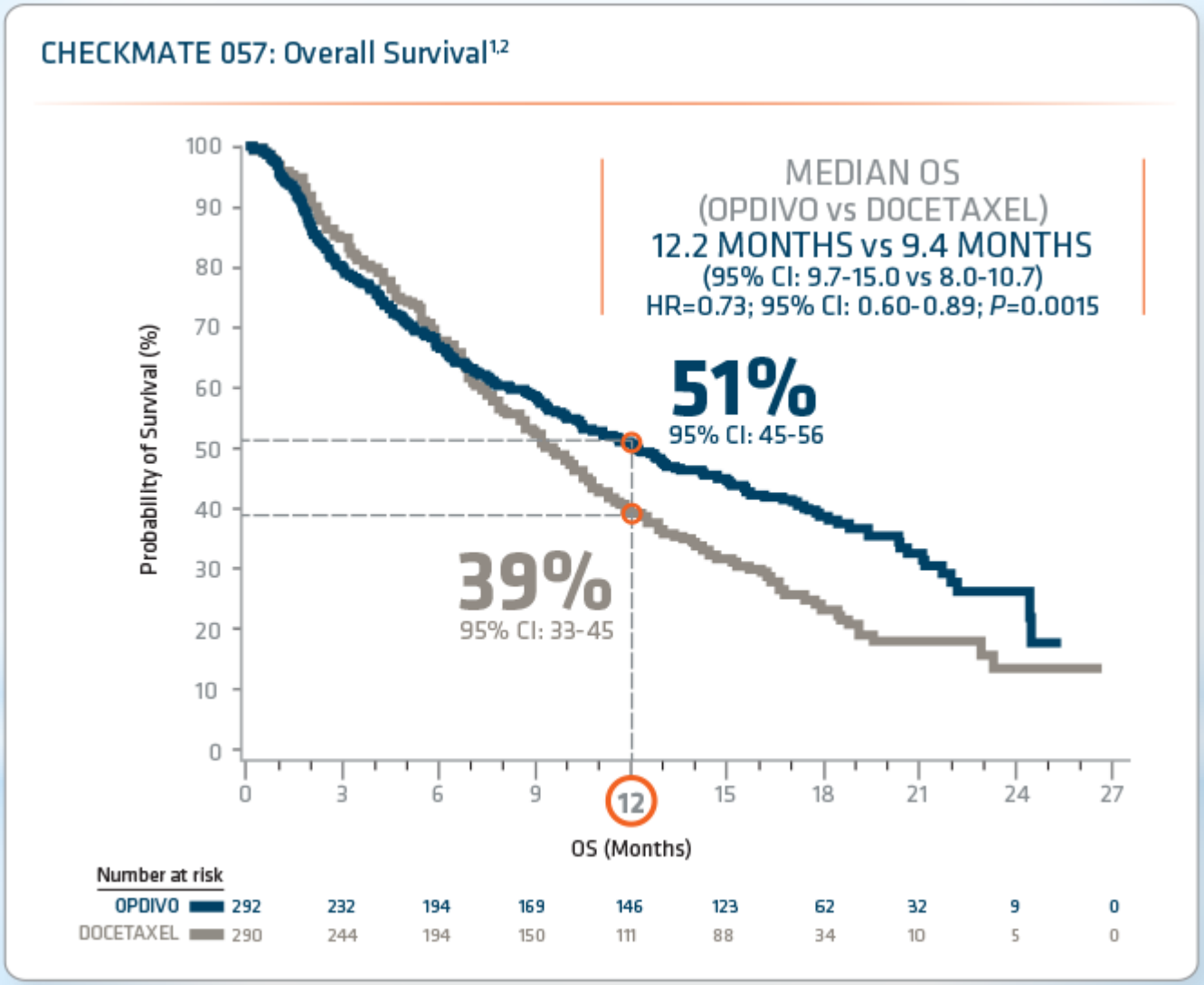
P-value is compared with the allocated alpha of 0.0021 for this interim analysis.
CI=confidence interval; HR=hazard ratio.

Metastatic Squamous Cell Lung Cancer – previously treated

CHECKMATE 017: Overall Survival[1,3]



Metastatic Non-Squamous Cell Lung Cancer – previously treated



How do we use these new therapies?

Metastatic Melanoma

KEYNOTE -6: pembrolizumab v ipilimumab

33%	12%	RR
70%	58%	1 yr OS

much less toxicity with pembrolizumab

CHECKMATE: ipilimumab v ipilimumab/nivolumab

61%	11%	RR
4.4 mo	not yet	PFS
54%	24%	grade 3-5

What do we do in B-raf mutants?

Can we combine treatment on other tumor types?

Doctor, what are the possible side effects of this drug?

Anything that ends in an -itis.

Selected side effects in the YERVOY pivotal phase 3 study

SYSTEM ORGAN CLASS/ PREFERRED TERM	PERCENTAGE (%) OF PATIENTS[a]					
	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg + gp100 n=380		gp100 n=132	
	Any grade	Grade 3-5	Any grade	Grade 3-5	Any grade	Grade 3-5
Gastrointestinal disorders						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Skin and subcutaneous tissue disorders						
Pruritus	31	0	21	<1	11	0
Rash	29	2	25	2	8	0
General disorders and administration site conditions						
Fatigue	41	7	34	5	31	3

[a] Incidences presented in this table are based on reports of side effects regardless of casualty.

Severe to fatal immune-mediated side effects in the YERVOY pivotal phase 3 study

n=511	PERCENTAGE (%) OF PATIENTS	
	YERVOY 3 mg/kg n=131	YERVOY 3 mg/kg + gp100 n=380
Any immune-mediated side effect	15	12
Enterocolitis[a,b]	7	7
Hepatotoxicity[a]	1	2
Dermatitis[a]	2	3
Neuropathy[a]	1	<1
Endocrinopathy	4	1
Hypopituitarism	4	1
Adrenal insufficiency	0	1
Other		
Pneumonitis	0	<1
Meningitis	0	<1
Nephritis	1	0
Eosinophilia[c]	1	0
Pericarditis[a,c]	0	<1

[a]Including fatal outcome; [b]Including intestinal perforation; [c]Underlying etiology not established.

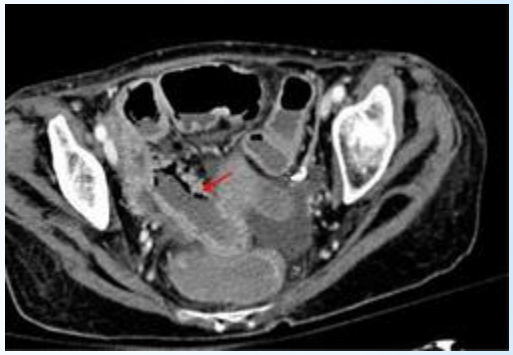
Immune Mediated Entercolitis

Typically after 6 weeks of treatment – 10% incidence with ipilimumab

2% incidence with PD-1 agents

DIARRHEA

Severe: Diarrhea ≥7 stools above baseline, fever, ileus, peritoneal signs consistent with bowel perforation; Grade 3–5

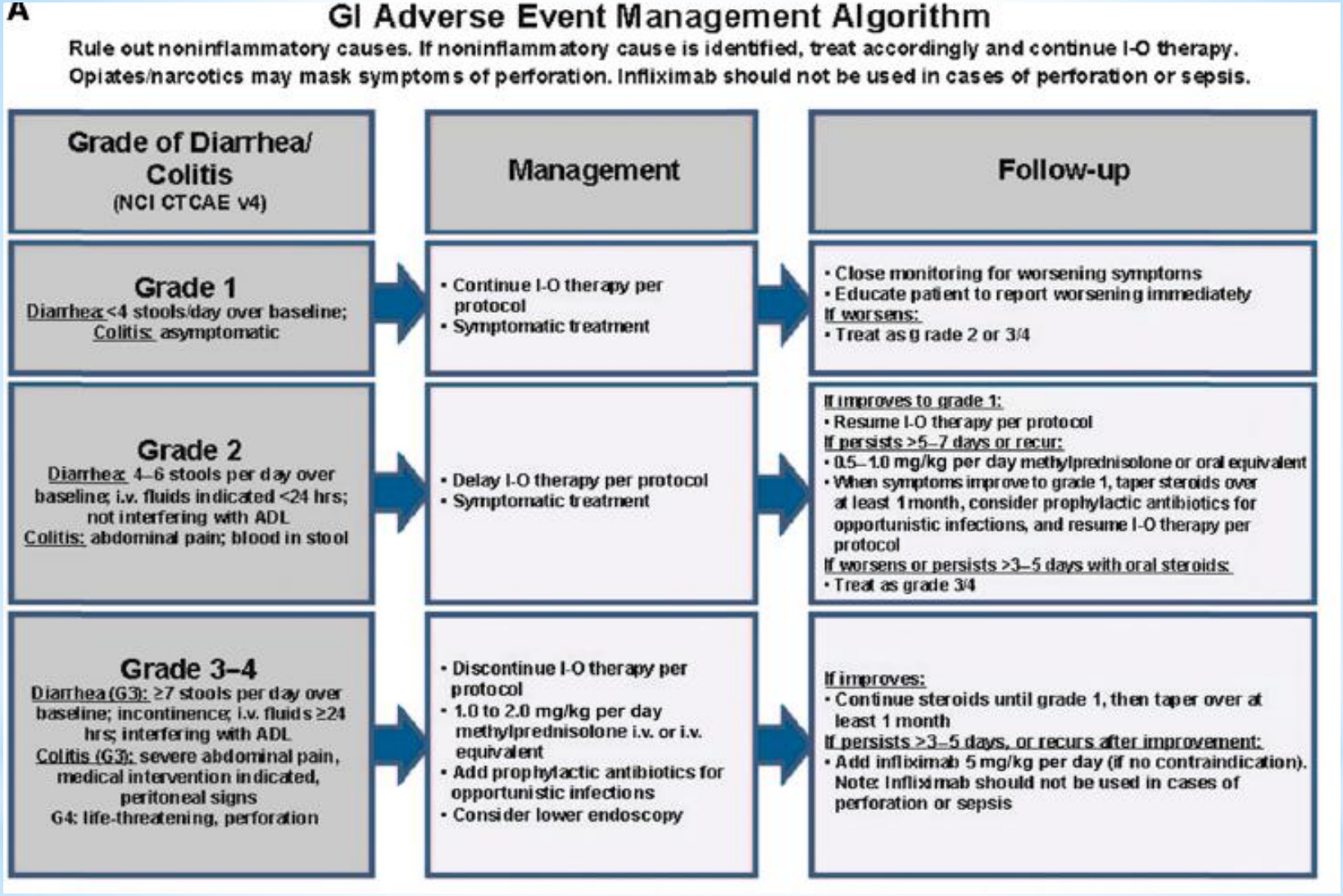


Management

STOP ipilimumab

oral steroids (.5 mg/kg/day to 2 mg/kg/day prednisone) taper over 4 weeks

Infliximab 5 mg/kg q o week



May need to start with IV steroids

Immune-mediated Hepatits

usually asymptomtic, more common with CTLA-4 inhibitors (10% v 1-2%)

511 patient study: grade 3-5 toxicity = 1.6% with 3 deaths

Severe: AST or ALT elevations >5 × ULN and/or total bilirubin elevations >3 × ULN;Grade 3–5

<u>Management</u>

Grade 2: WITHHOLD ipilimumab/PD-1

Grade 3-4: STOP ipilimumab/PD-1

Prednisone 1-2 mg/kg/day

taper over 4 weeks when LTFs return to normal

DO NOT USE INFLIXIMAB

Immune-mediated dermal lesions

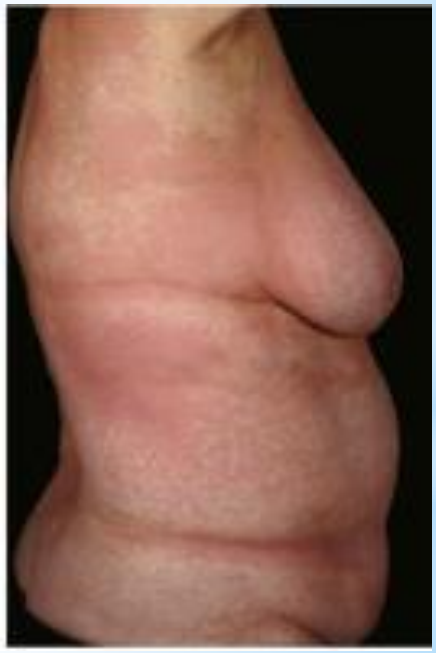
Most common irAE: occurs early

reticular, maculopapular rash on trunk or extremities

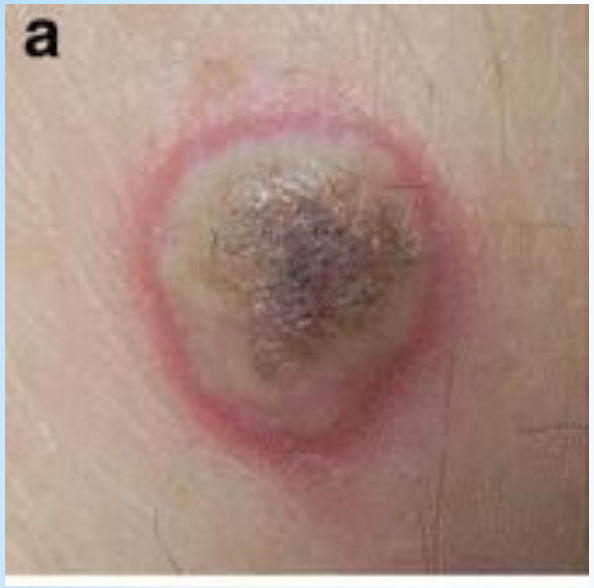
Grade 2 = 10%

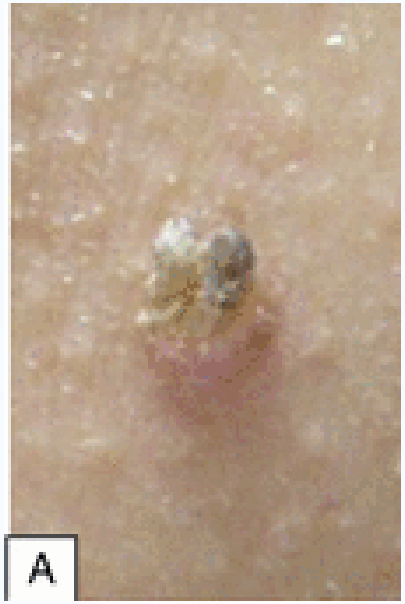
Grade 3-5 = 2.5% (1 death TEN in 511 patients)

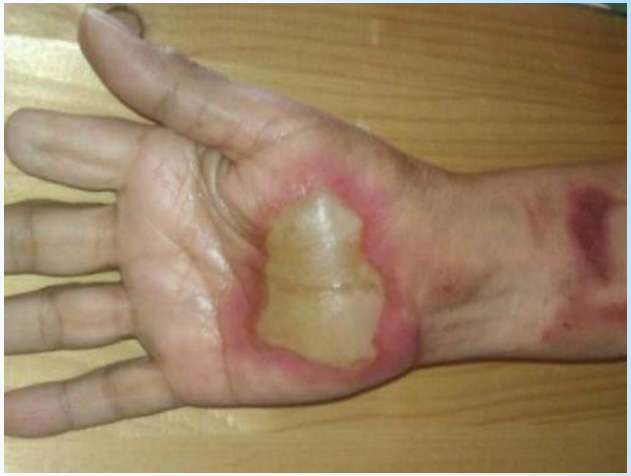
Severe: Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full-thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5

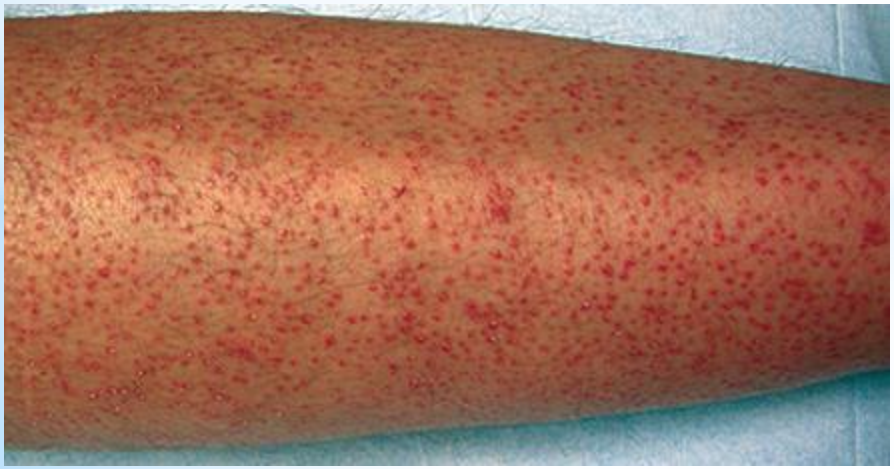


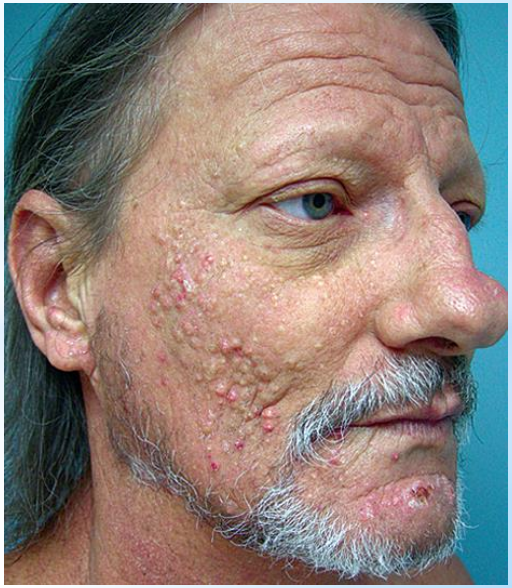
Squamous Cell Skin Cancer - Vemurafenib











Immune-mediated dermal lesions

Management

Moderate: WITHHOLD Ipilimumab/PD-1 drug

Severe: STOP Ipilimumab/PD-1 drug

Prednisone 1-2 mg/kg/day. Wean over 4 weeks

Unique to PD-1 drugs: oral mucositis, dry mouth

Immune-mediated Neuropathy

peripheral sensory neuropathy – grade 3-4 = .4%

peripheral motor neuropathy - grade 3-4 = .4%

1 case fatal Guillain-Barre

Management

Moderate neuropathy: WITHHOLD Ipilimumab/PD-1 drug

Severe neuropathy: STOP Ipilimumab/PD-1 drug

consider Prednisone 1-2 mg/kg/day

Immune-mediated Endocrinopathies

	grade 3-4
hypopituitarism	2.1%
adrenal insufficiency	.3%
hypothyroidism	.1%

Enlargement of pituitary, gonadal dysfunction

Management

WITHHOLD ipilimumab/PD-1 drug

Prednisone 1-2 mg/kg/day

Appropriate hormone therapy

Assorted immune-mediated Adverse Reactions

Nephritis

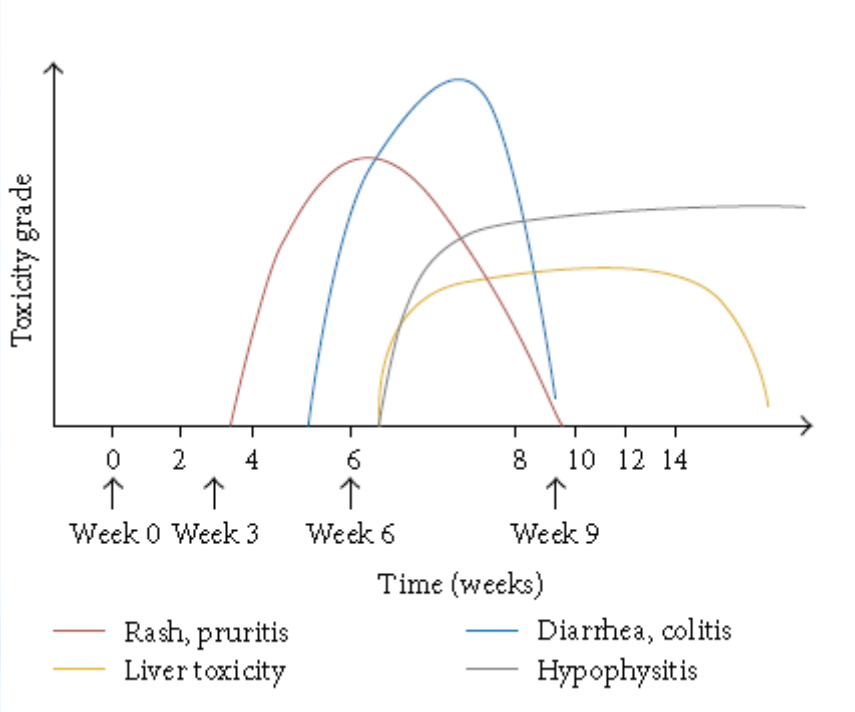
Pneumonitis

Myocarditis

Myositis

COST	Ipilimumab	$30,000.00 per infusion/	$120,000.00 per course
	Nivolumab	$15,172.00/month	
	Vemurafenib	$10,770.00/month	

Timeline for Immune Related Adverse Events



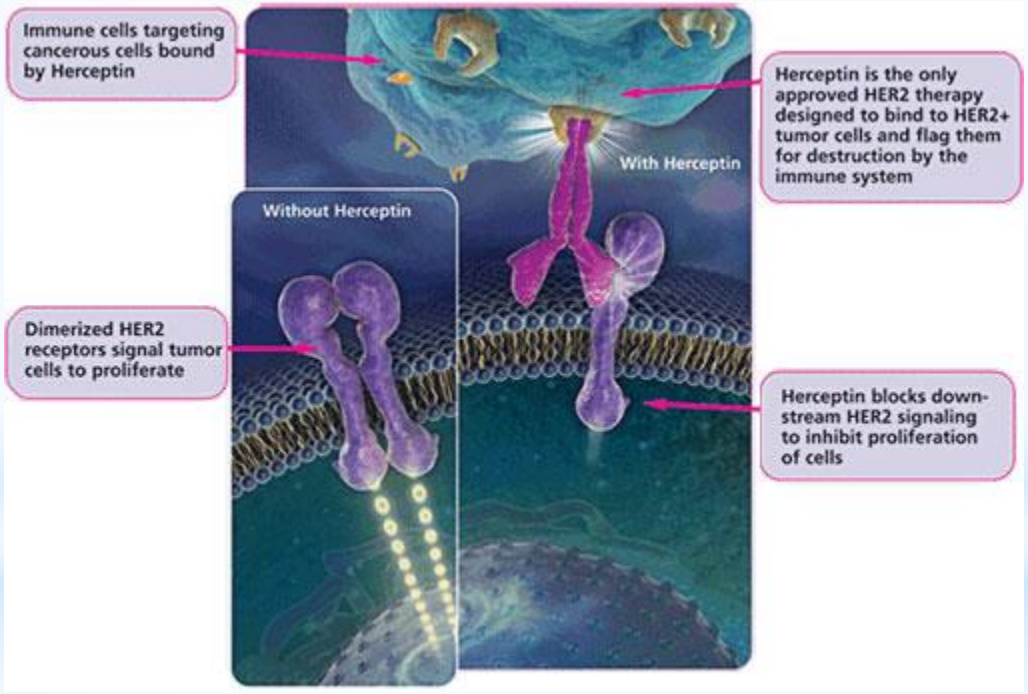
Toxicity of Toxicity Treatment

Aspergillus pneumonia

High blood sugars

Immunotherapy in Breast Cancer

Trastuzumab (Herceptin)



Immunotherapy in Breast Cancer – Metastatic Disease

Table 2. Randomized Trials Comparing Chemotherapy Alone with Chemotherapy plus Trastuzumab for Metastatic Disease.

Trial and End Result	Chemotherapy	Chemotherapy plus Trastuzumab	P Value
Slamon et al.[46]			
No. of patients	234 (doxorubicin and cyclophosphamide or paclitaxel)	235 (doxorubicin and cyclophosphamide or paclitaxel)	
Time to disease progression (mo)	4.6	7.4	<0.001
Response rate (%)	32	50	<0.001
Median overall survival (mo)	20	25	0.046
Marty et al.[47]			
No. of patients	94 (docetaxel)	92 (docetaxel)	
Time to disease progression (mo)	6.1	10.7	0.001
Response rate (%)	34	61	0.001
Median overall survival (mo)	23	31	0.032

Immunotherapy in Breast Cancer – Adjuvant Therapy

Table 4. Trials of Adjuvant Trastuzumab in HER2-Positive Early-Stage Breast Cancer.*

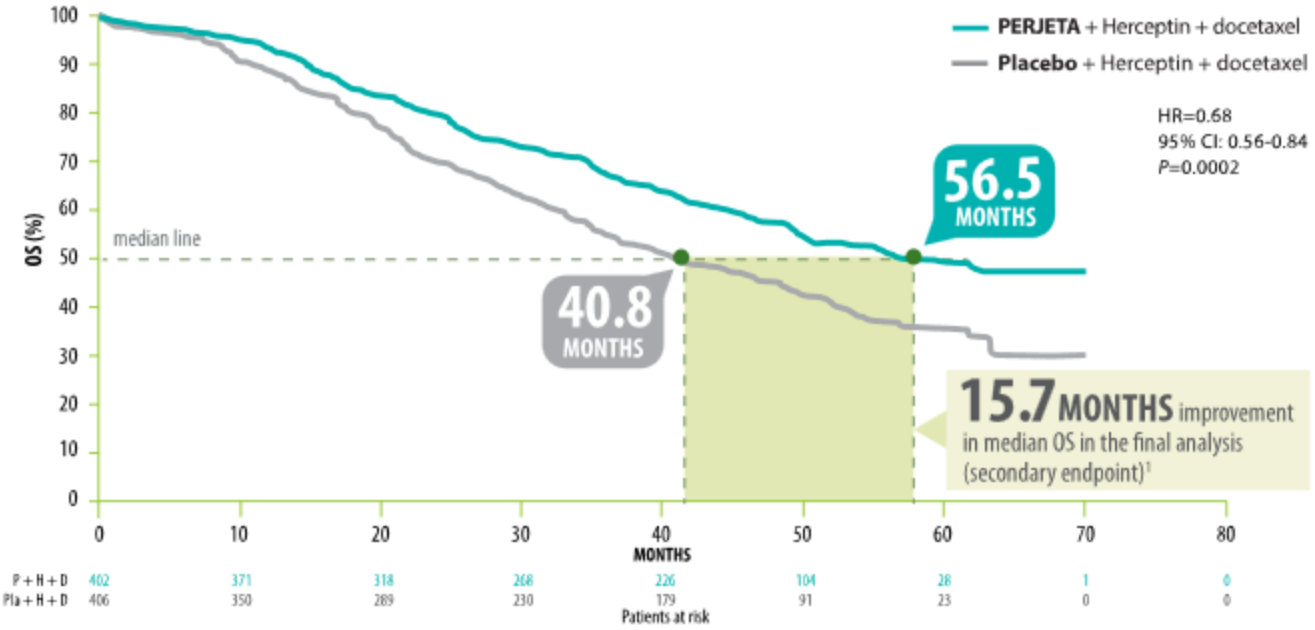
Trial	Study Regimen	No. of Patients	Disease-free Survival	Hazard Ratio	P Value	Overall Survival	Hazard Ratio	P Value
			%			%		
NSABP B-31 and NCCTG N-9831[79]	Doxorubicin and cyclophosphamide, then paclitaxel	1679	67			87		
	Doxorubicin and cyclophosphamide, then paclitaxel plus trastuzumab, then trastuzumab	1672	85	0.48	<0.001	91	0.67	0.02
NCCTG N-9831[80]	Doxorubicin and cyclophosphamide, then paclitaxel	979						
	Doxorubicin and cyclophosphamide, then paclitaxel, then trastuzumab	985		0.87	0.29†		0.85	0.48†
	Doxorubicin and cyclophosphamide, then paclitaxel plus trastuzumab, then trastuzumab	840		0.64 0.48	0.01† <0.01†		0.74	0.27‡
HERA[81]‡	Observation	1698	74			90		
	Trastuzumab for 1 year	1703	81	0.64	<0.001	92	0.66	0.011
BCIRG 006[82]	Doxorubicin and cyclophosphamide, then docetaxel	1073	73			86		
	Doxorubicin and cyclophosphamide, then docetaxel plus trastuzumab, then trastuzumab	1074	84	0.49	0.001†	92	0.59	0.004
	Docetaxel, carboplatin, and trastuzumab	1075	80	0.61	<0.01†	91	0.66	0.02
FinHer[83]	Chemotherapy	116	78			90		
	Chemotherapy plus trastuzumab	116	89	0.42	0.01	96	0.41	0.07

* Trial-registration numbers are as follows: NSABP, ClinicalTrials.gov number, NCT00004067; NCCTG, NCT00005970; HERA, NCT00045032; BCIRG, NCT00021255; and Finland Herceptin Study (FinHer),Current Controlled Trials number, ISRCTN76560285).
† The P value is for the comparison with the control group.
‡ Data were not available for the third group of the study.

Immunotherapy in Breast Cancer

pertuzumab – a second HER-2 antibody: metastatic disease

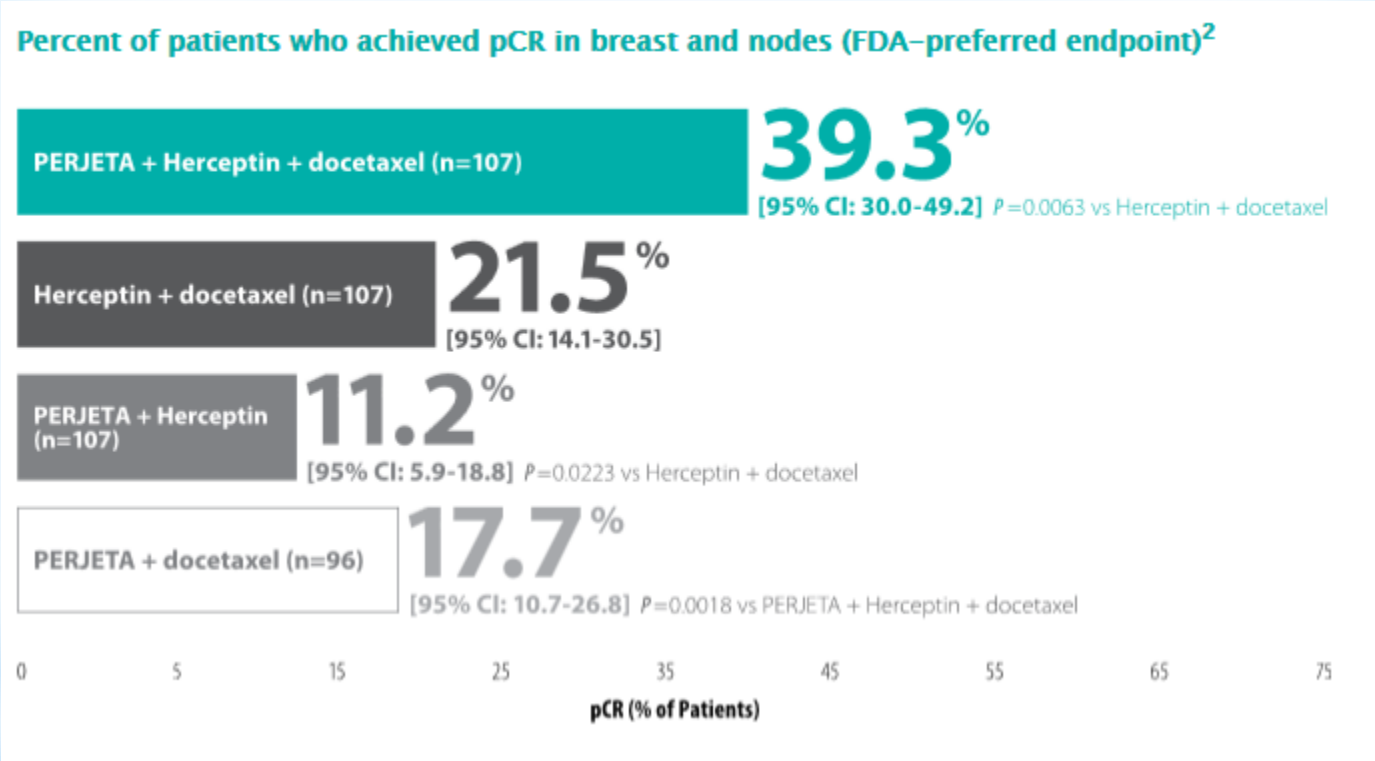
PERJETA demonstrated an OS (overall survival) improvement when combined with Herceptin + docetaxel at the final analysis[1]



- The final OS analysis was performed when 221 patient deaths occurred in the placebo-treated group and 168 occurred in the PERJETA-treated group.[1]

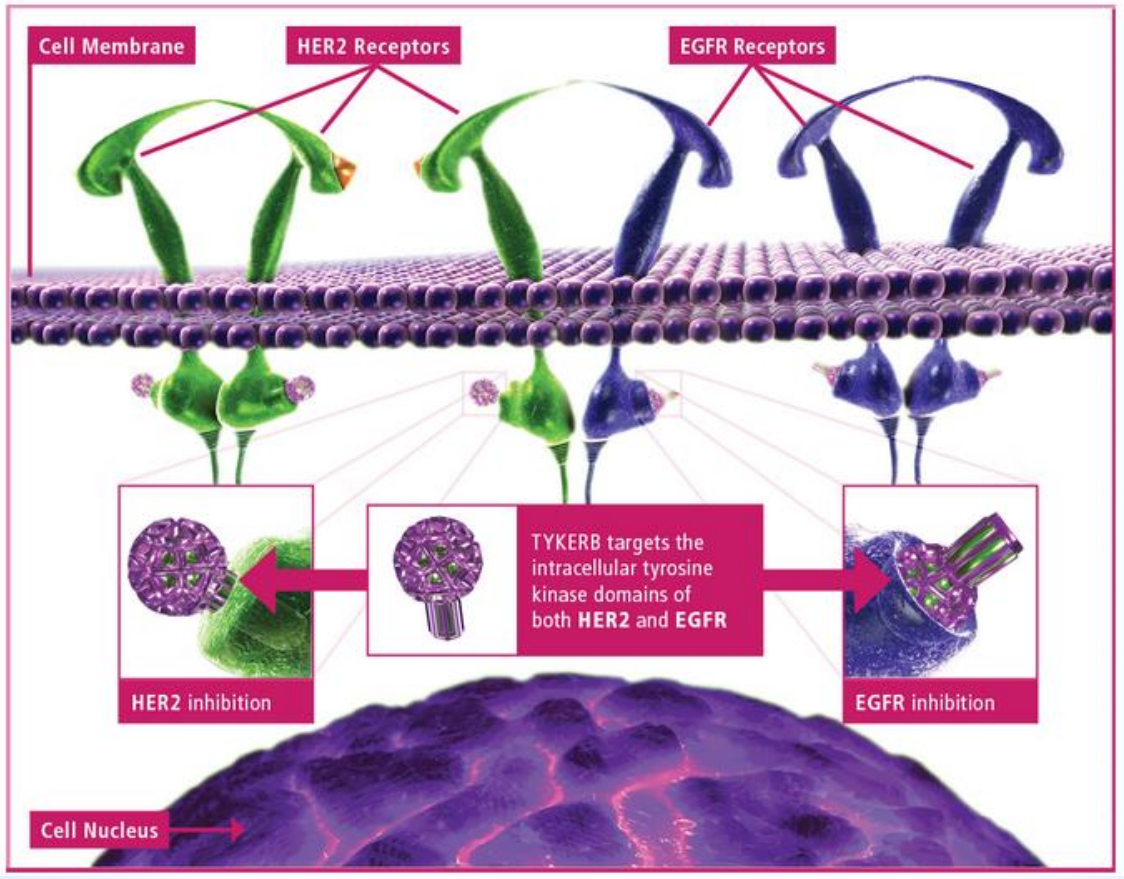
Immunotherapy in Breast Cancer

pertuzumab – a second HER-2 antibody: neo-adjuvant treatment



Immunotherapy in Breast Cancer

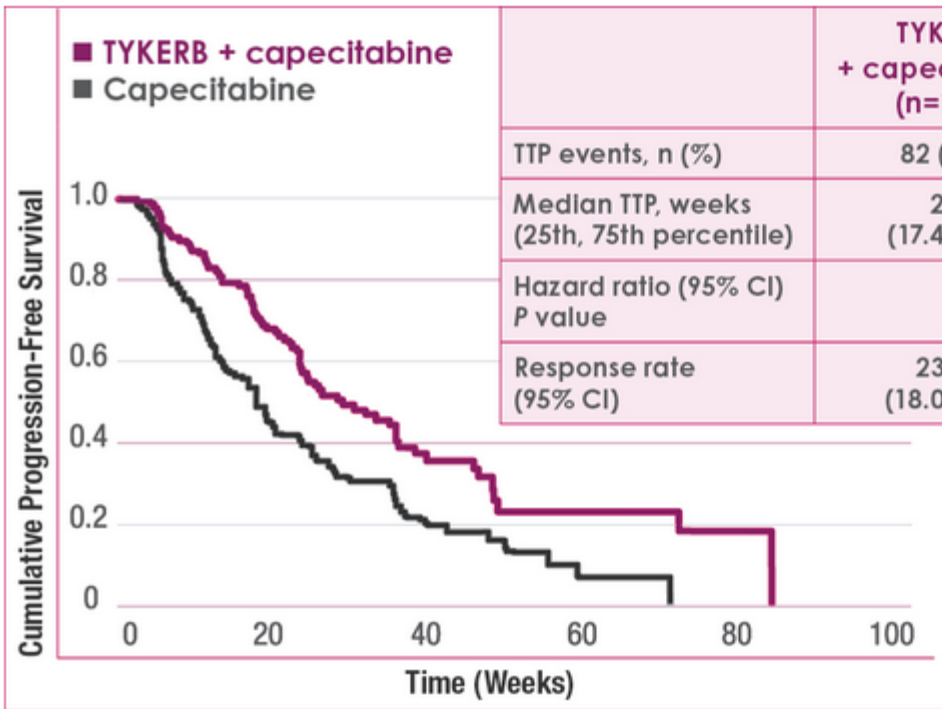
Lapatinib



Immunotherapy in Breast Cancer

lapatinib: metastatic disease after anthracycline, taxane, trastuzumab

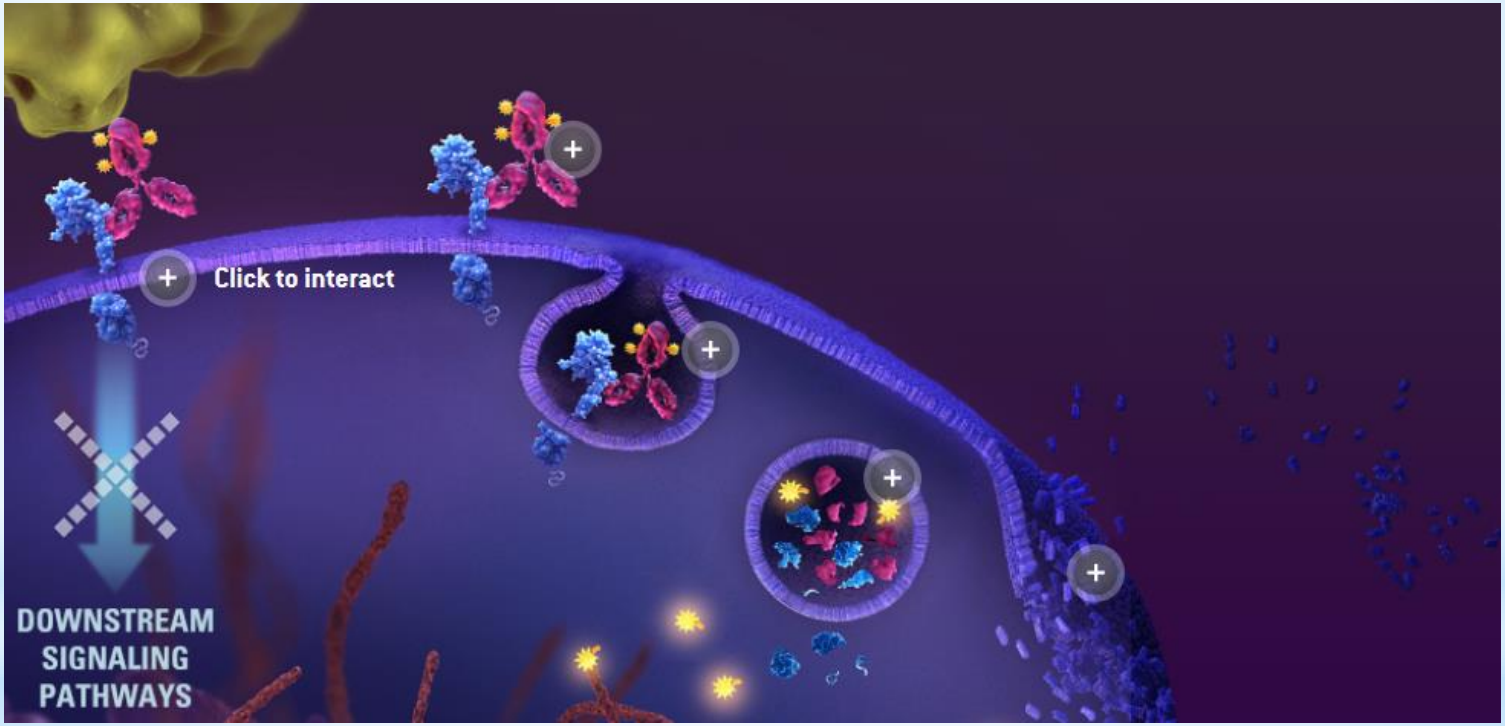
Time to Progression[a] (Independent Assessment)[b] in the Intent-to-Treat Population[1]



	TYKERB + capecitabine (n=198)	Capecitabine (n=201)
TTP events, n (%)	82 (41%)	102 (51%)
Median TTP, weeks (25th, 75th percentile)	27.1 (17.4, 49.4)	18.6 (9.1, 36.9)
Hazard ratio (95% CI) *P* value	0.57 (0.43, 0.77) 0.00013	
Response rate (95% CI)	23.7% (18.0, 30.3)	13.9% (9.5, 19.5)

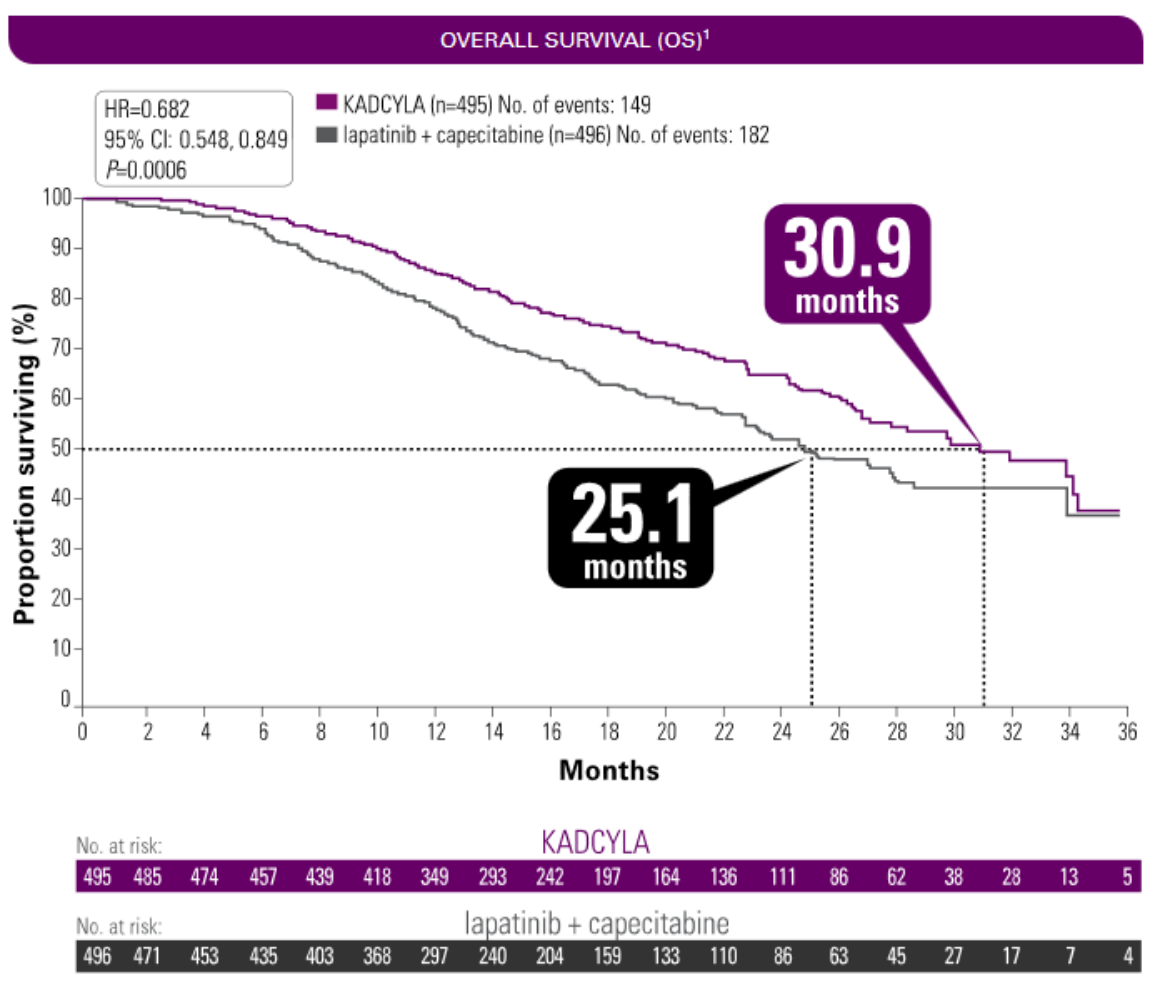
Immunotherapy in Breast Cancer

antibody conjugates – ado-trastuzumab emtansine



Immunotherapy in Breast Cancer

immunoconjugate



Immunotherapy in Breast Cancer

Toxicities of HER-2 blockade

Cardiac

	Cardiac Toxicity
Slamon: Adriamycin/Cytoxan/Trastuzumab	27%
Taxol/Trastuzumab	13%
Trastuzumab	3-7%
Lapatinib	1.6%
Ado-Trastuzumab Emtansine	1.7%
Pertuzumab v Control	6.6% v 8.6%

Vaccines for Breast Cancer

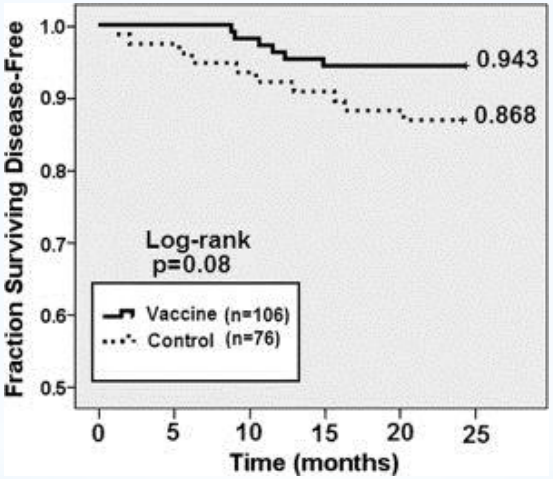
NeuVax (nelipepimut-S, E75) plus GM-CSF: PRESENT Study

secondary prevention in patients with low/intermediate HER-2

limited to HLA-A2 or A3

accrual completed – expect first analysis April 2018

Phase II trial of E75 vaccine to prevent recurrence in high risk breast cancer patients



Cancer
Volume 118, Issue 10, pages 2594-2602, 11 OCT 2011 DOI: 10.1002/cncr.26574
http://onlinelibrary.wiley.com/doi/10.1002/cncr.26574/full#fig2

References

Treating cancer by targeting the Immune system. Hwu, P., NEJM 2010, 363:779-781.

Releasing the brakes on cancer immunotherapy. Ribas, A., NEJM 2015, 373:1490-1492.

Immune checkpoint blockade in cancer therapy. Postow, MA, Callahan, MK, Wolchok, JD. Journal of Clinical Oncology 33:1974-1982.

Management of adverse events following treatment with anti-programmed death-1 agents. Weber, JS, Postow, M, Lao, CD, Schadendorf, D. Oncologist 2016, 21:1230.1240.