Immunotherapy in advanced NSCLC patients
Changing the course of the disease

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Outline

1. Introduction
2. Immunotherapy in 2nd Line treatment
3. Immunotherapy in 1st Line treatment
4. Who (not) to give immunotherapy?
5. Toxicity
6. Conclusions

Outline

New revolution in cancer treatment

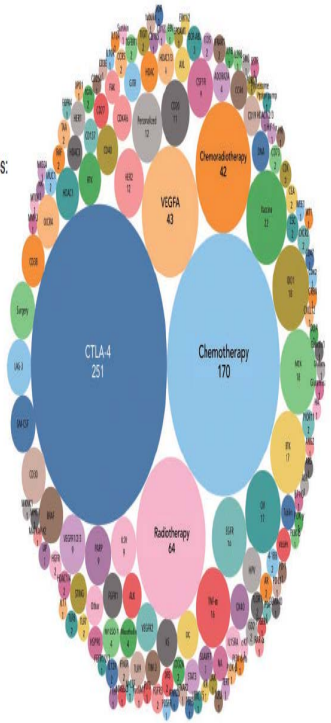
2013

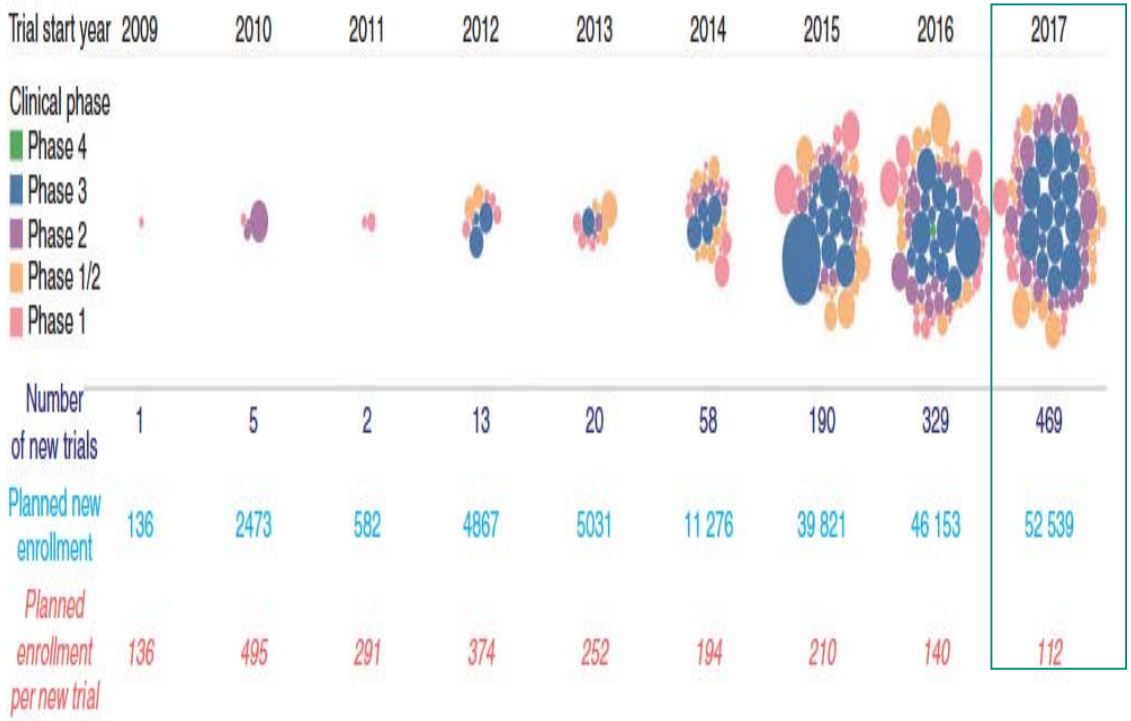
2015

Comprehensive analysis of the IO landscape

Numbers of trials using common combo strategies:

1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42



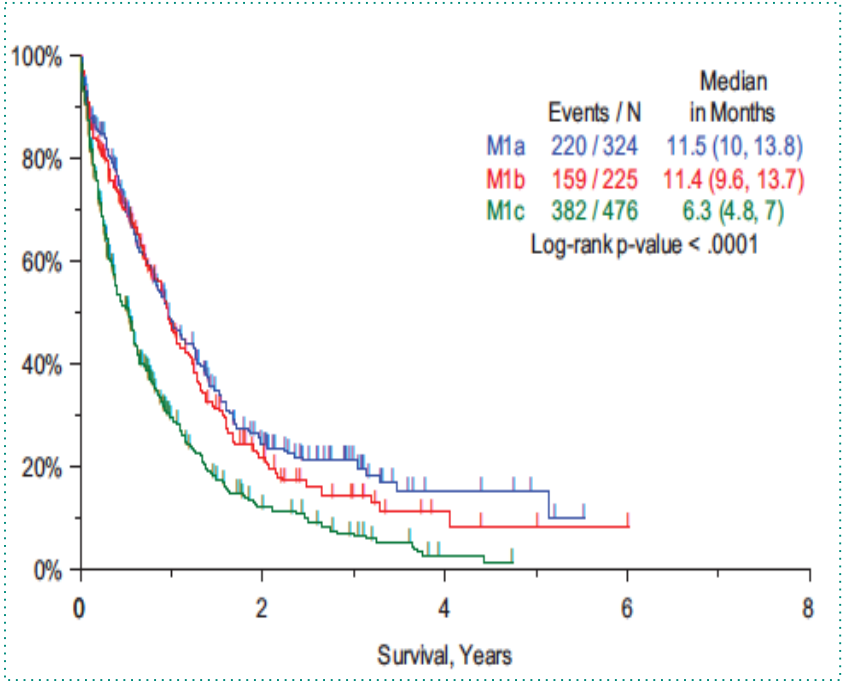


Trial start year	2009	2010	2011	2012	2013	2014	2015	2016	2017
Number of new trials	1	5	2	13	20	58	190	329	469
Planned new enrollment	136	2473	582	4867	5031	11 276	39 821	46 153	52 539
Planned enrollment per new trial	*136*	*495*	*291*	*374*	*252*	*194*	*210*	*140*	*112*

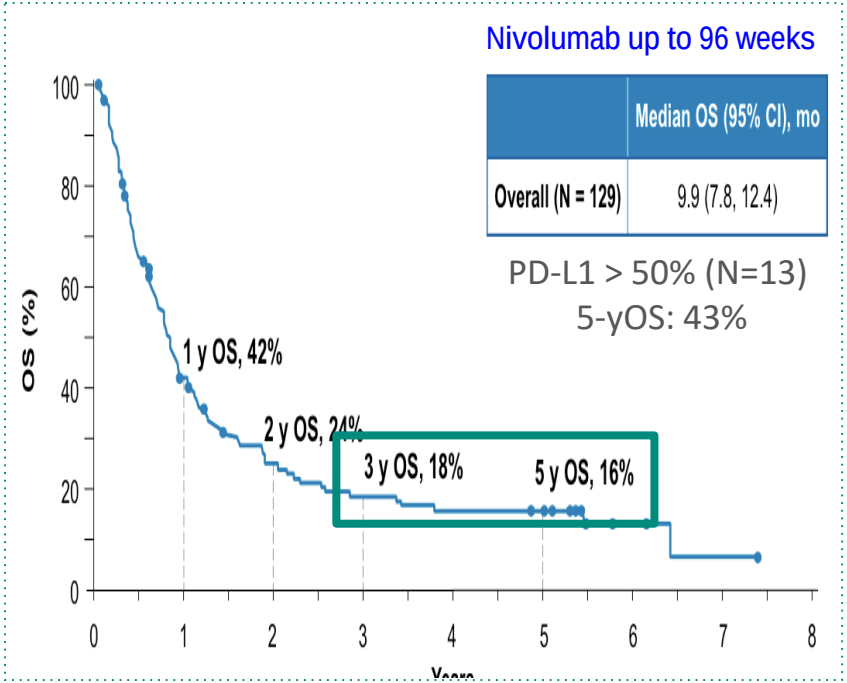
Tang – Ann Oncol 2018 * Schmidt – Nature 2017

The tail effect with immunotherapy

5y OS IN 8TH TNM for M1c: 0%



5y OS with Nivolumab in phase I trial

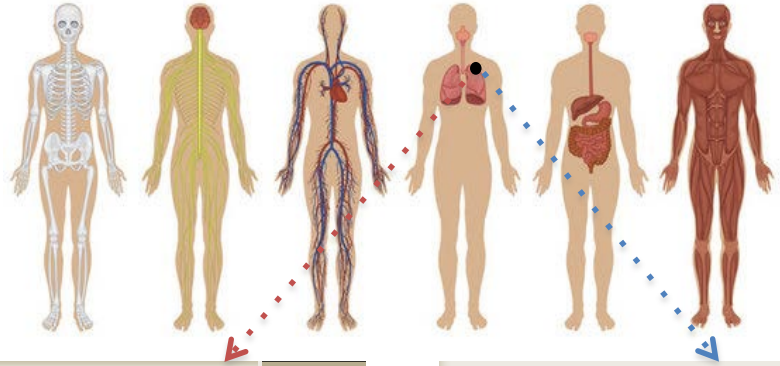


Gettinger – JCO 2018 * Vokes – Ann Oncol 2018 * Eberhardt – J Thorac Oncol 2015

New treatment perspective

TRADITIONAL ONCOLOGY VIEW

A CANCER THAT GROWS

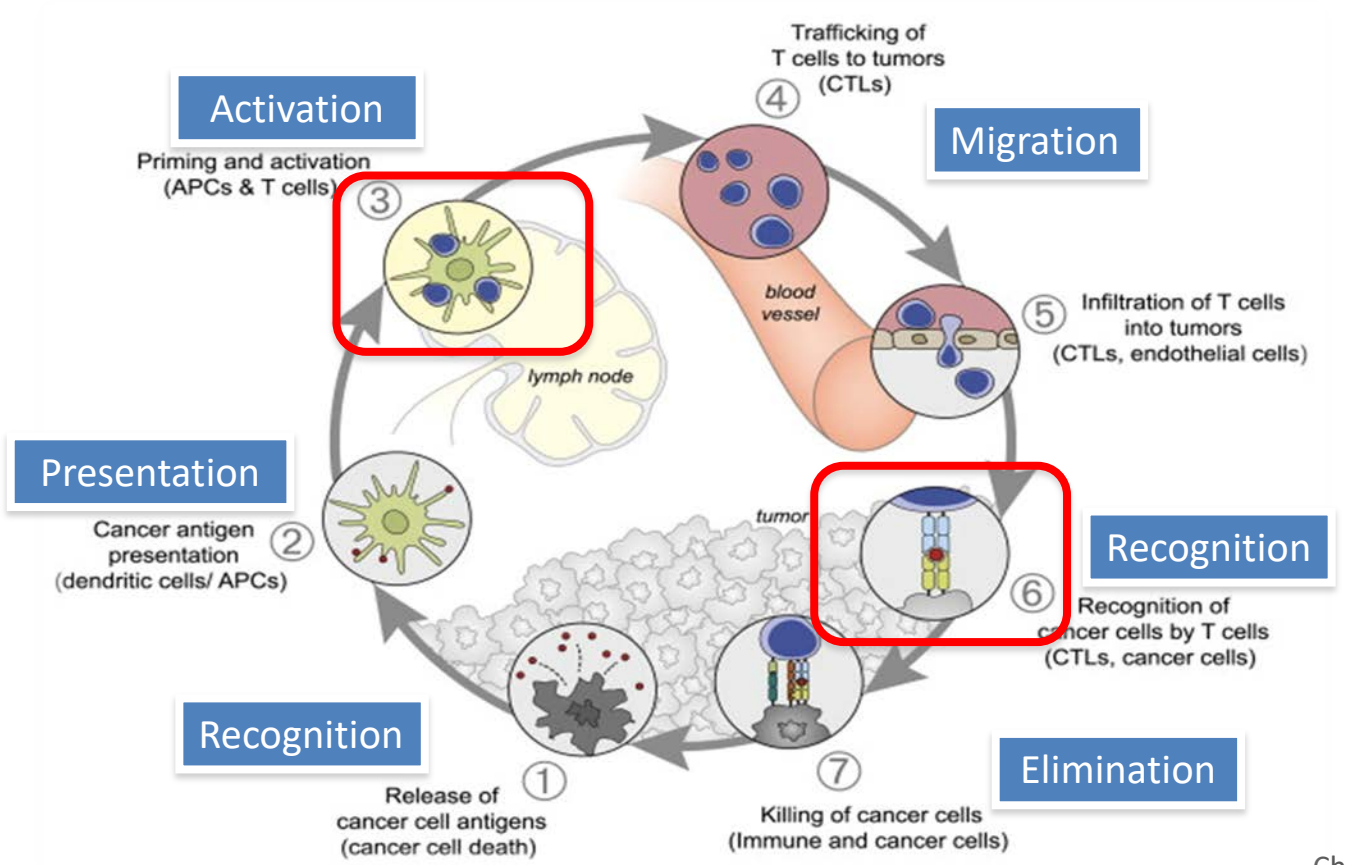


IMMUNO-ONCOLOGY VIEW

A BODY THAT LETS A CANCER GROW

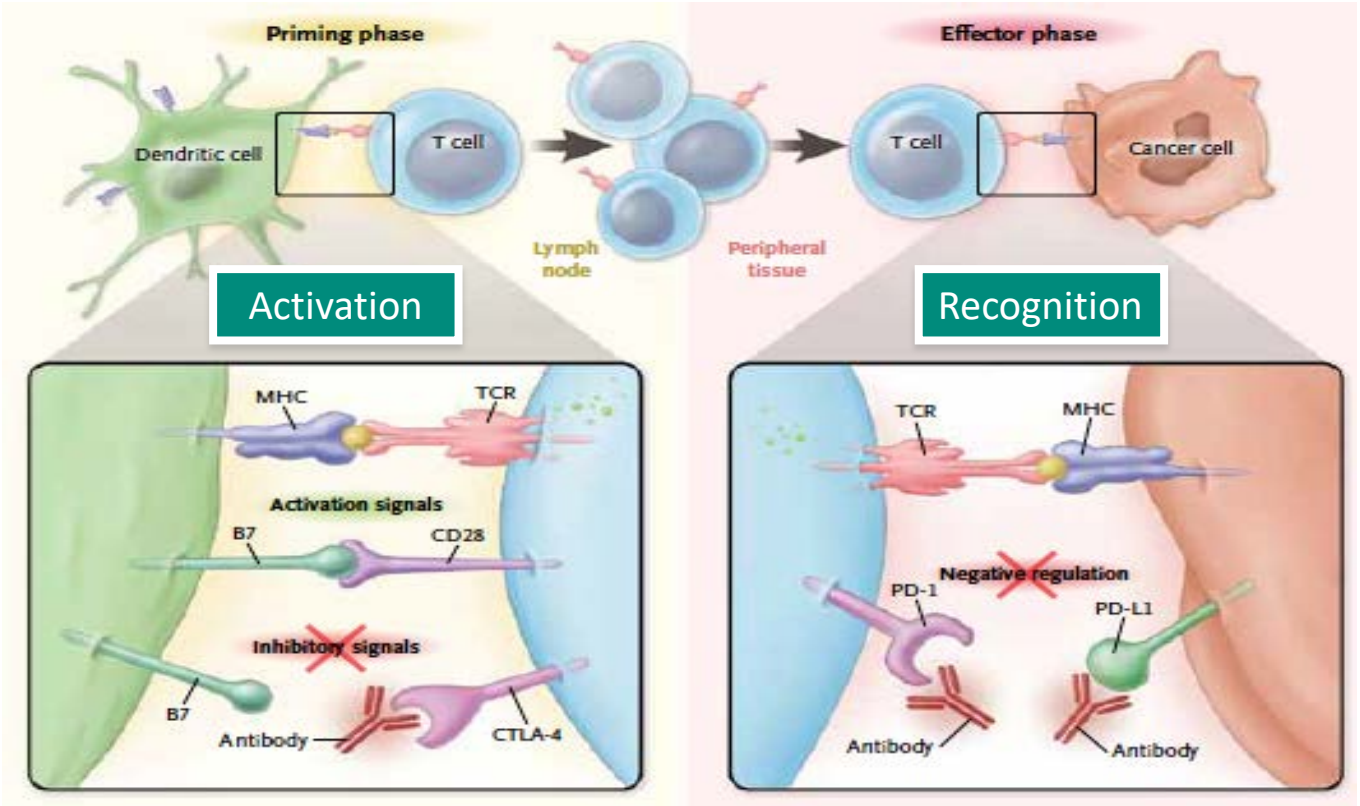
Courtesy of Pr Besse

How does cancer induce immunosurveillance?



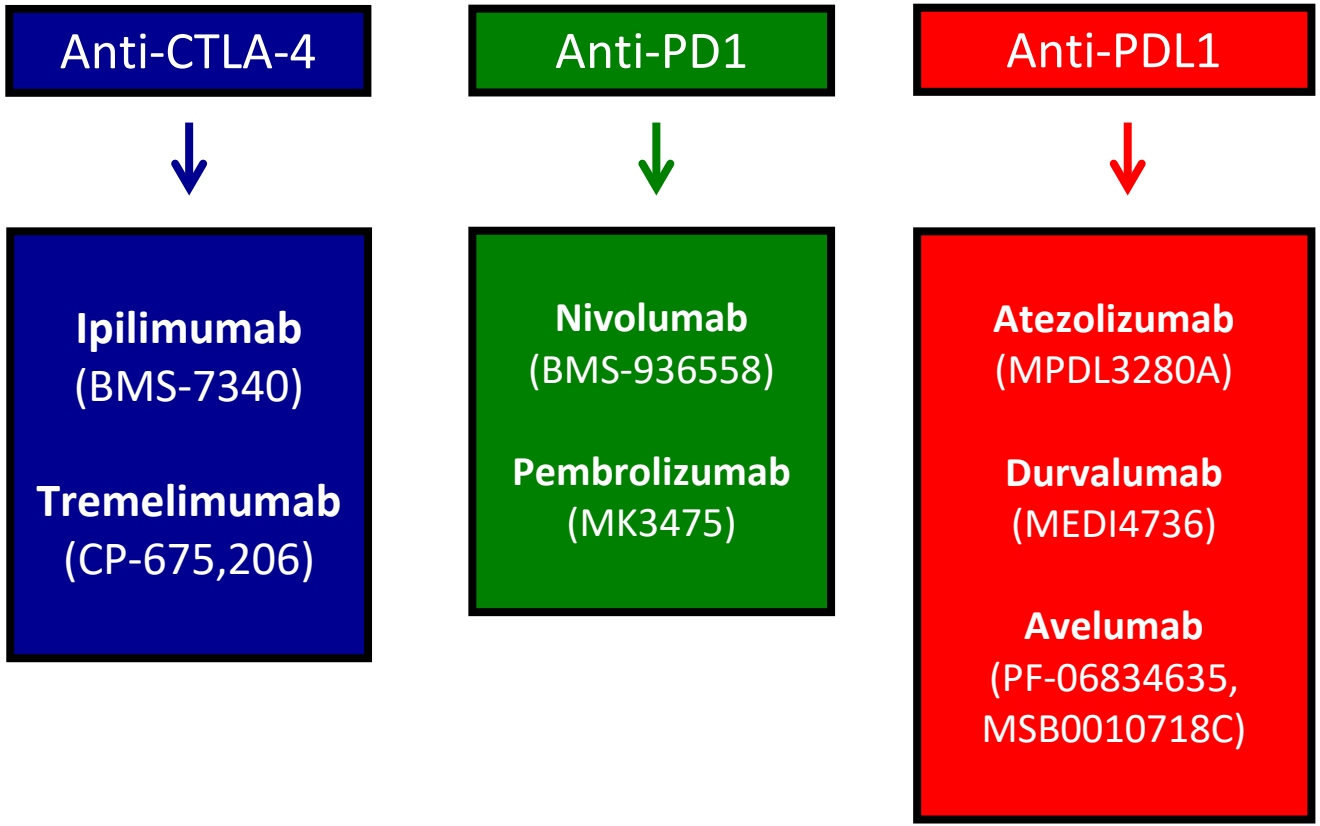
Chen Immunity 2013

How does cancer induce immunosurveillance?



Ribas - NEJM 2012

Immune checkpoint inhibitors



Outline

2 Immunotherapy in 2nd Line treatment

Past, present, future treatment approaches

PAST

FIRST-LINE TREATMENT

Chemotherapy

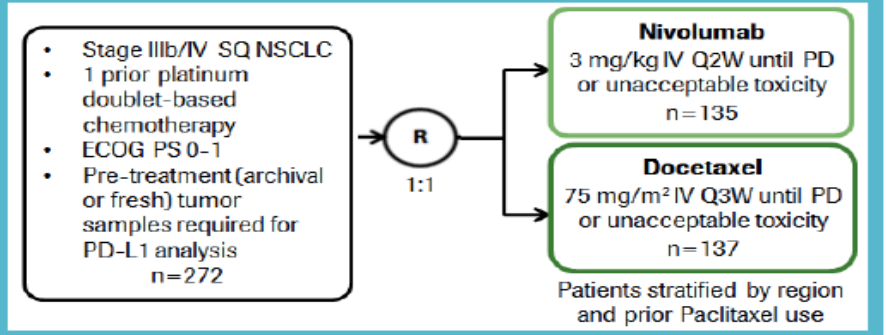
SECOND-LINE TREATMENT

Chemotherapy Immunotherapy

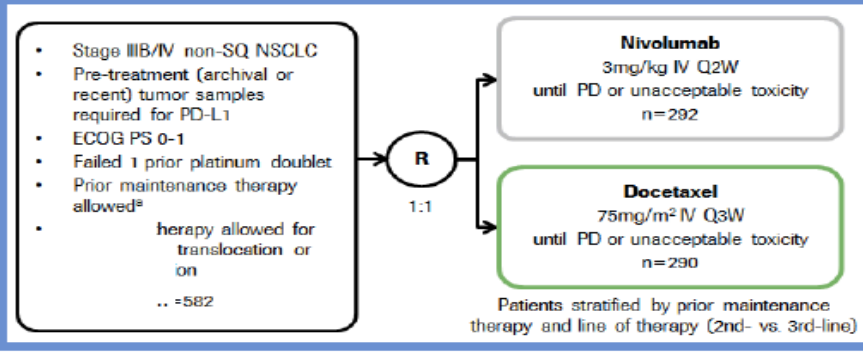
Courtesy Prof. Soria
(modified)

2nd line treatment with ICI in NSCLC patients

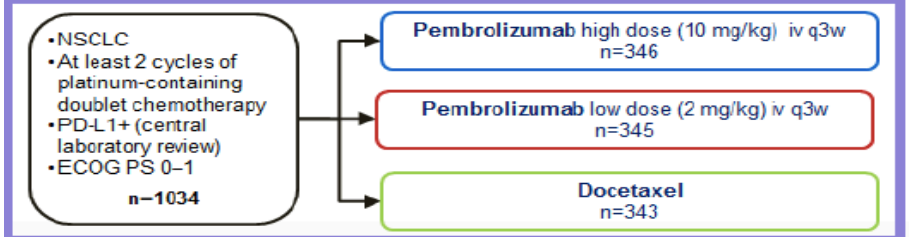
Nivolumab – CheckMate 017 (PIII)
2nd Line, squamous, PD-L1 All-Comer



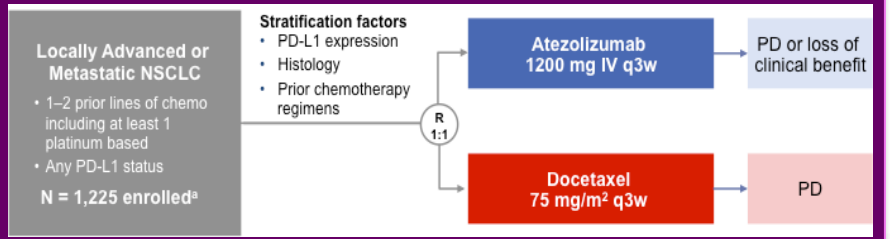
Nivolumab – CheckMate 057 (PIII)
2nd Line, non-squamous, PD-L1 All-Comer



Pembrolizumab - Keynote 010 (PII/III)
2nd+ Line, PD-L1 TPS ≥1%

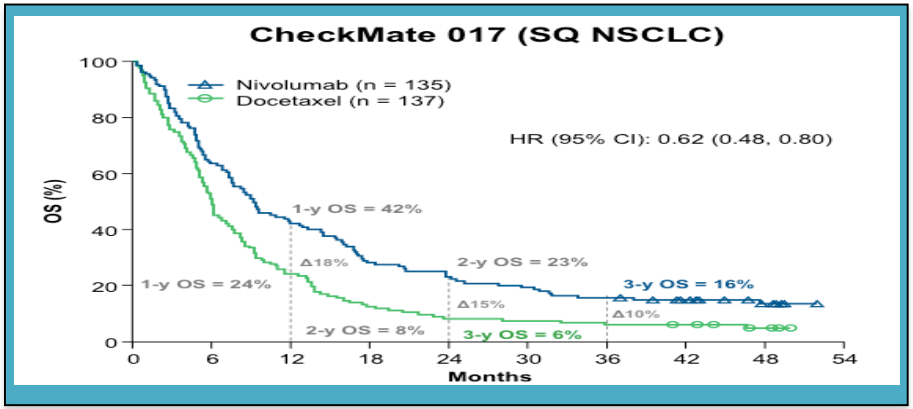


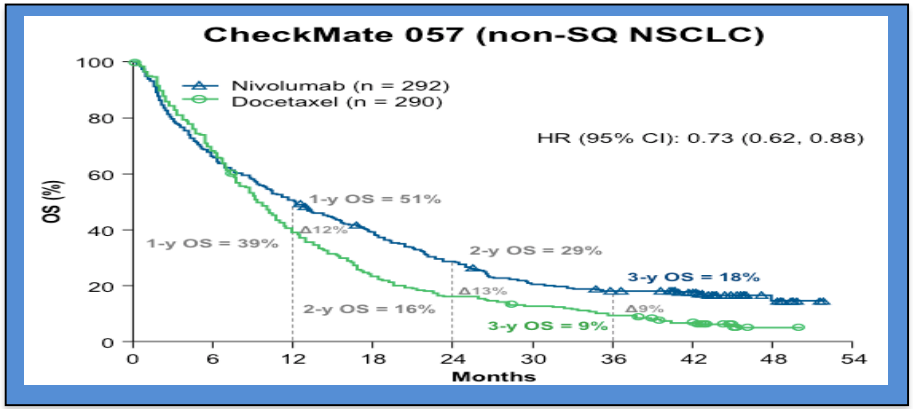
Atezolizumab – OAK (P III)
2nd Line, PD-L1 All-comer

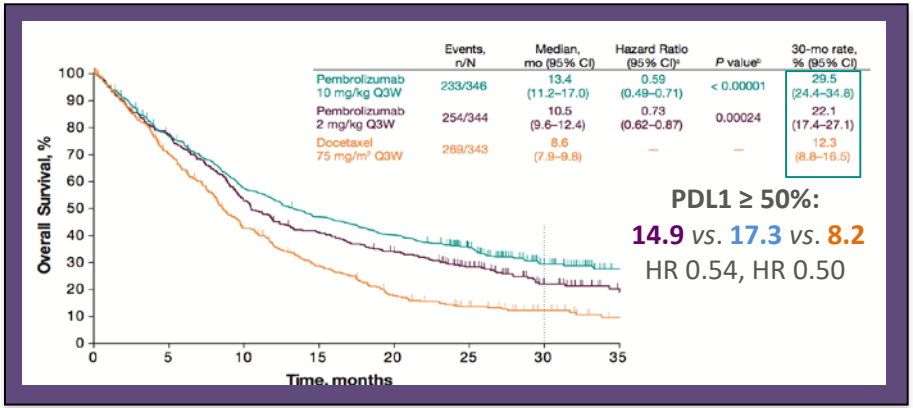


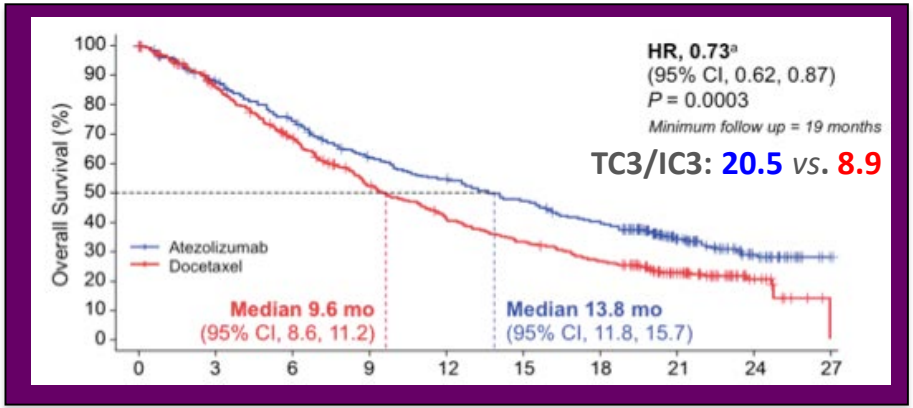
Brahmer –NEJM 2015 * Borghaei – NEJM 2015 * Vokes – Ann Oncol 2018 * Herbst – Lancet Oncol 2016 * Rittmeyer – Lancet 2017

2nd line treatment with ICI in NSCLC patients: OS









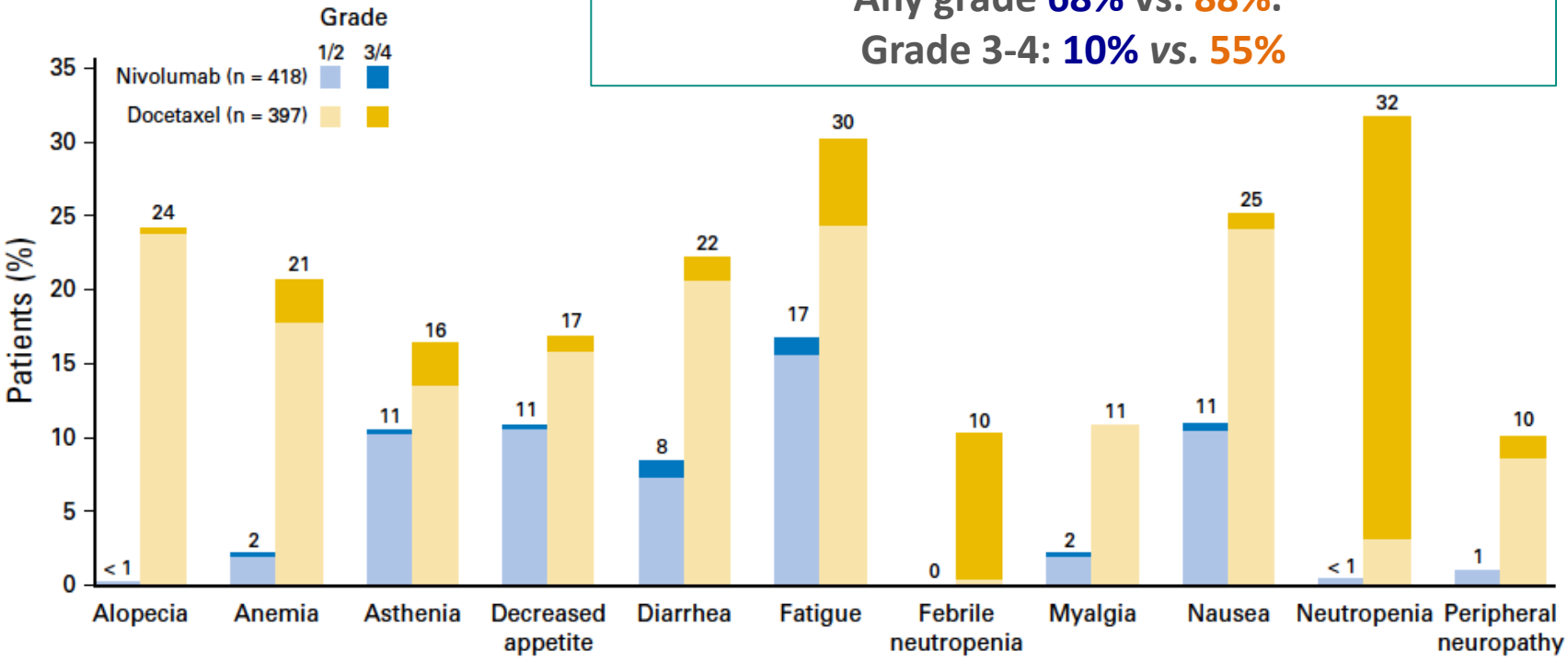
Brahmer –NEJM 2015 * Borghaei – NEJM 2015 * Vokes – Ann Oncol 2018 * Herbst – Lancet Oncol 2016 * Herbst – ESMO 2016 * Herbst – ASCO 2017 * Rittmeyer – Lancet 2017

2nd line treatment with ICI in NSCLC patients

Updated CheckMate017 & 057 (2-years follow-up)

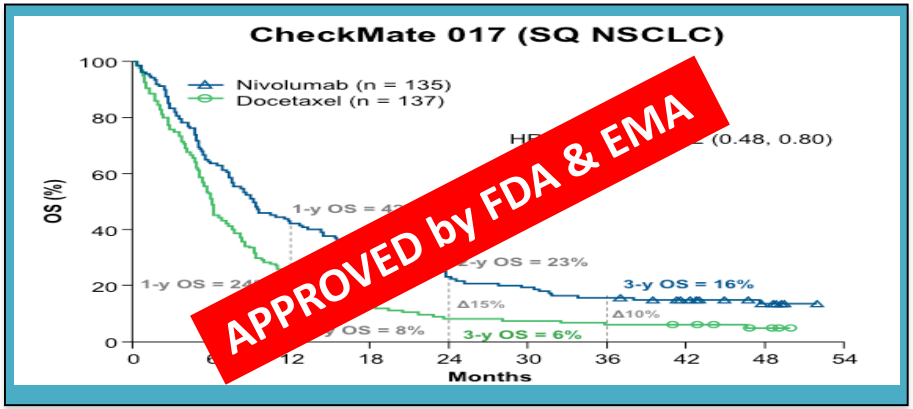
Any grade **68%** vs. **88%**.

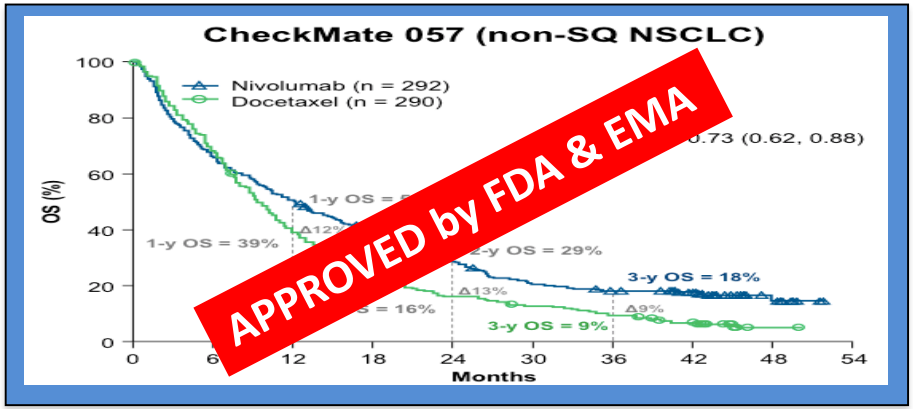
Grade 3-4: **10%** *vs*. **55%**

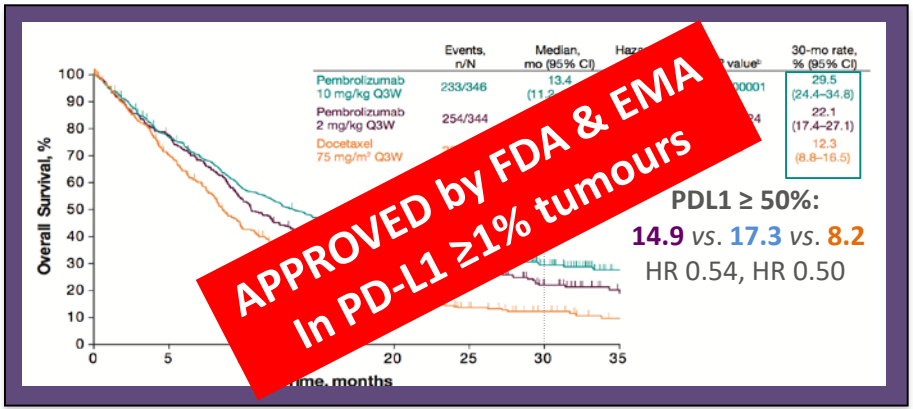


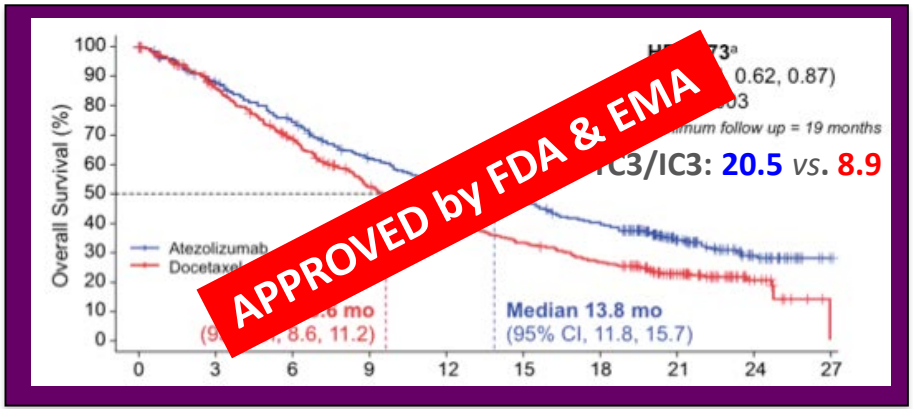
Horn – JCO 2017

2nd line treatment with ICI in NSCLC patients: OS









Brahmer –NEJM 2015 * Borghaei – NEJM 2015 * Vokes – Ann Oncol 2018 * Herbst – Lancet Oncol 2016 * Herbst – ESMO 2016 * Herbst – ASCO 2017 * Rittmeyer – Lancet 2017

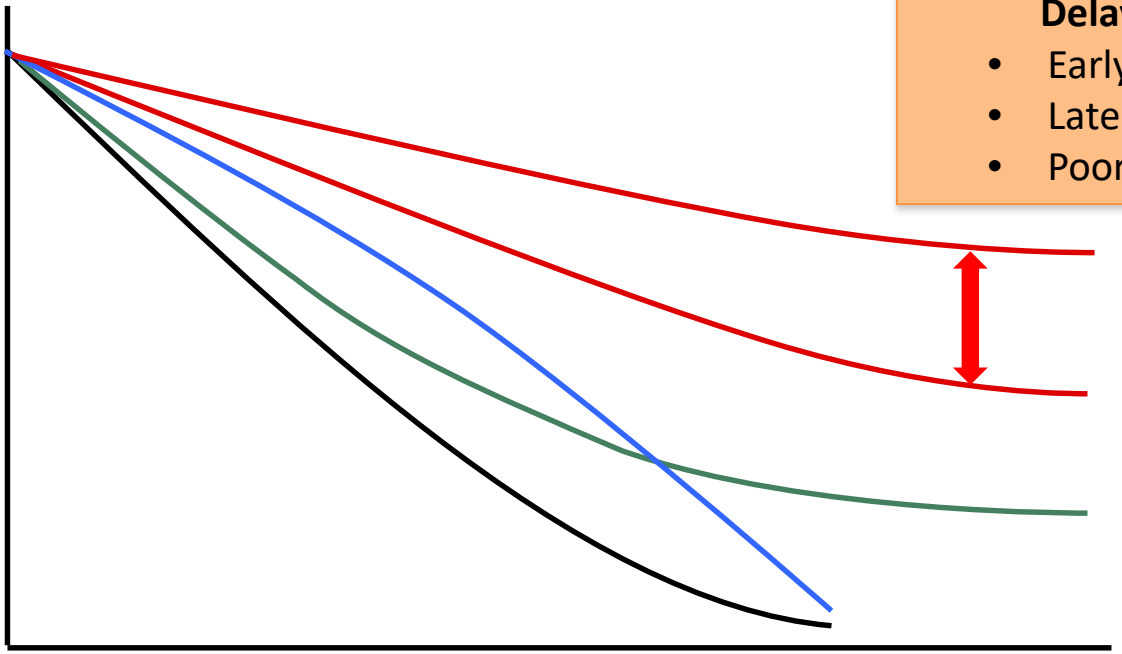
Past, present, future treatment approaches

	FIRST-LINE TREATMENT	SECOND-LINE TREATMENT
PAST	 Chemotherapy	 Chemotherapy
PRESENT AND FUTURE		 PD(L)-1 Antibody

Outline

3 Immunotherapy in 1st Line treatment

Benefit of monotherapy with ICI is limited



Delayed separation of curves

- Early progressors?
- Later time to response?
- Poorly immunogenic tumor?

Control

Targeted therapies or Chemotherapies

Immunotherapy

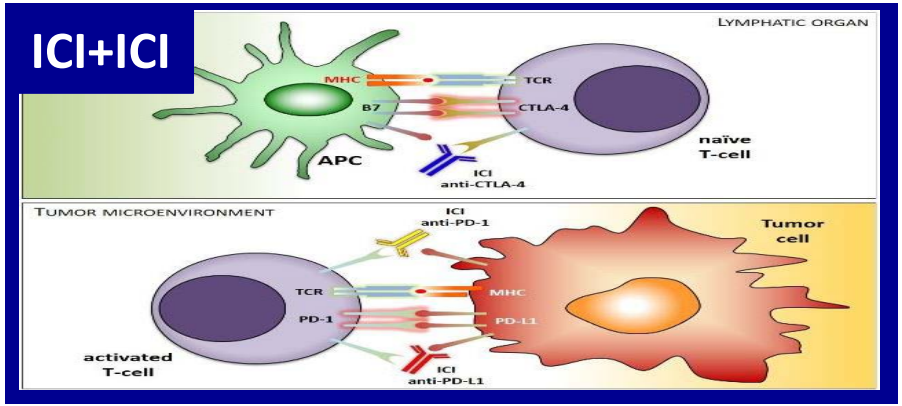
Immunotherapy +

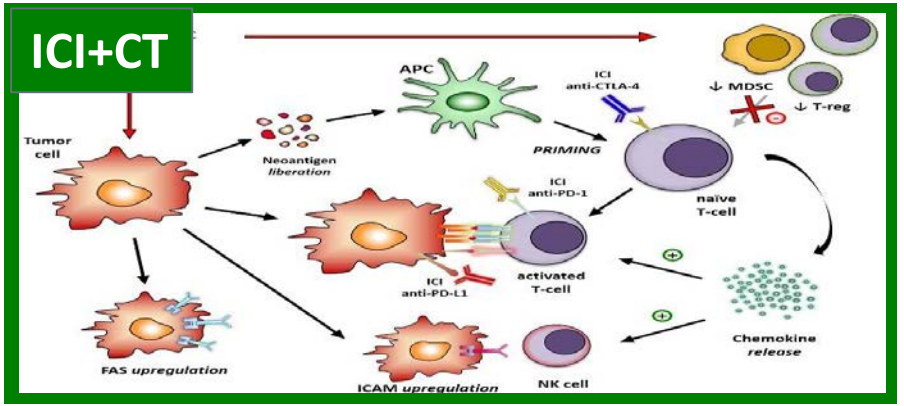
- **Chemotherapy,**
- **Targeted Therapy, and/or**
- **Other Immunotherapies**

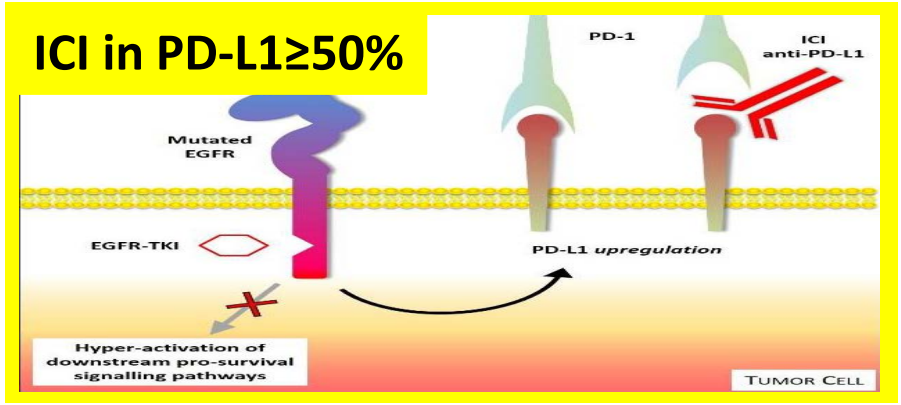
Important to improve number of patients who may get benefit and duration of benefit

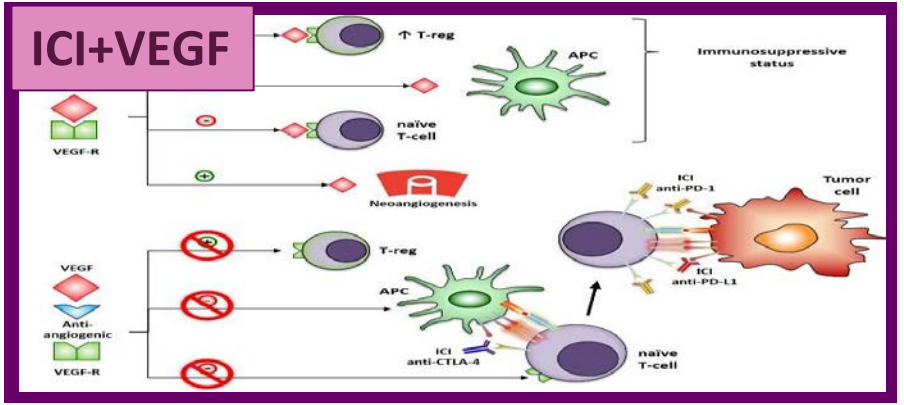
Courtesy of Prof. Soria (modified)

Different strategies to improve outcome





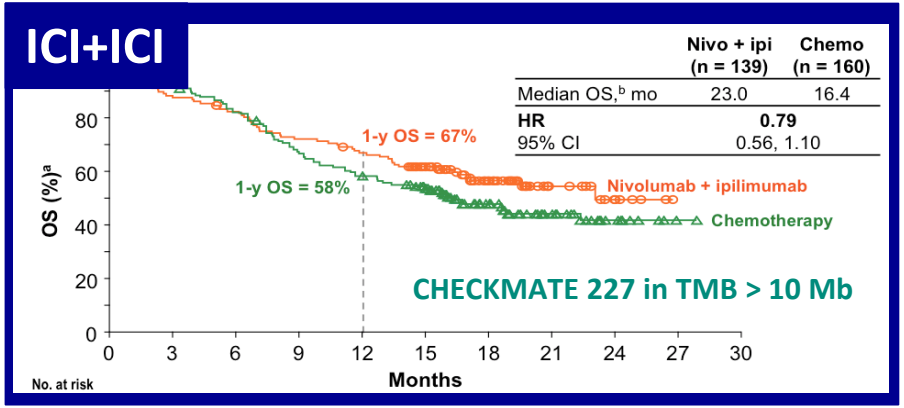




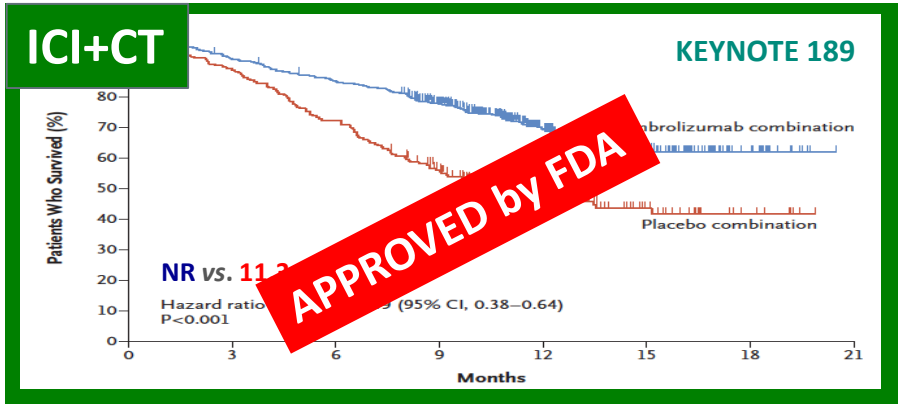
Attili – Critical Rev in Oncol Hematol 2017 (modified)

1st Line treatment with ICI in NSCLC: OS

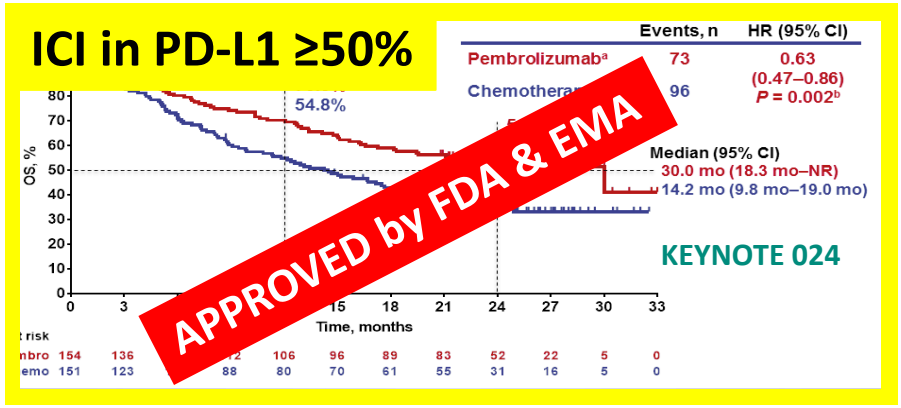
ICI+ICI



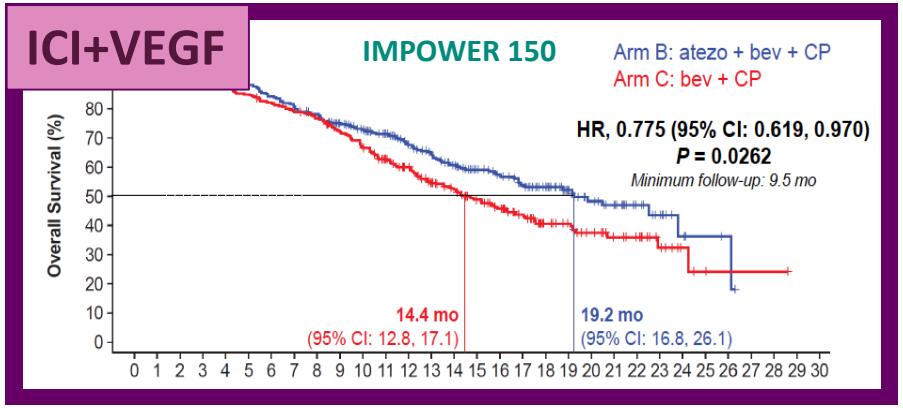
ICI+CT



ICI in PD-L1 ≥50%



ICI+VEGF



Hellman – NEJM 2015 * Ghandi – NEJM 2018 * Reck - NEJM 2016 * Reck – ESMO IO 2016

Past, present, future treatment approaches

FIRST-LINE TREATMENT

SECOND-LINE TREATMENT

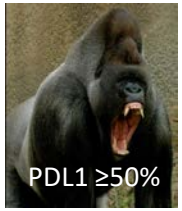
PAST

Chemotherapy

Chemotherapy

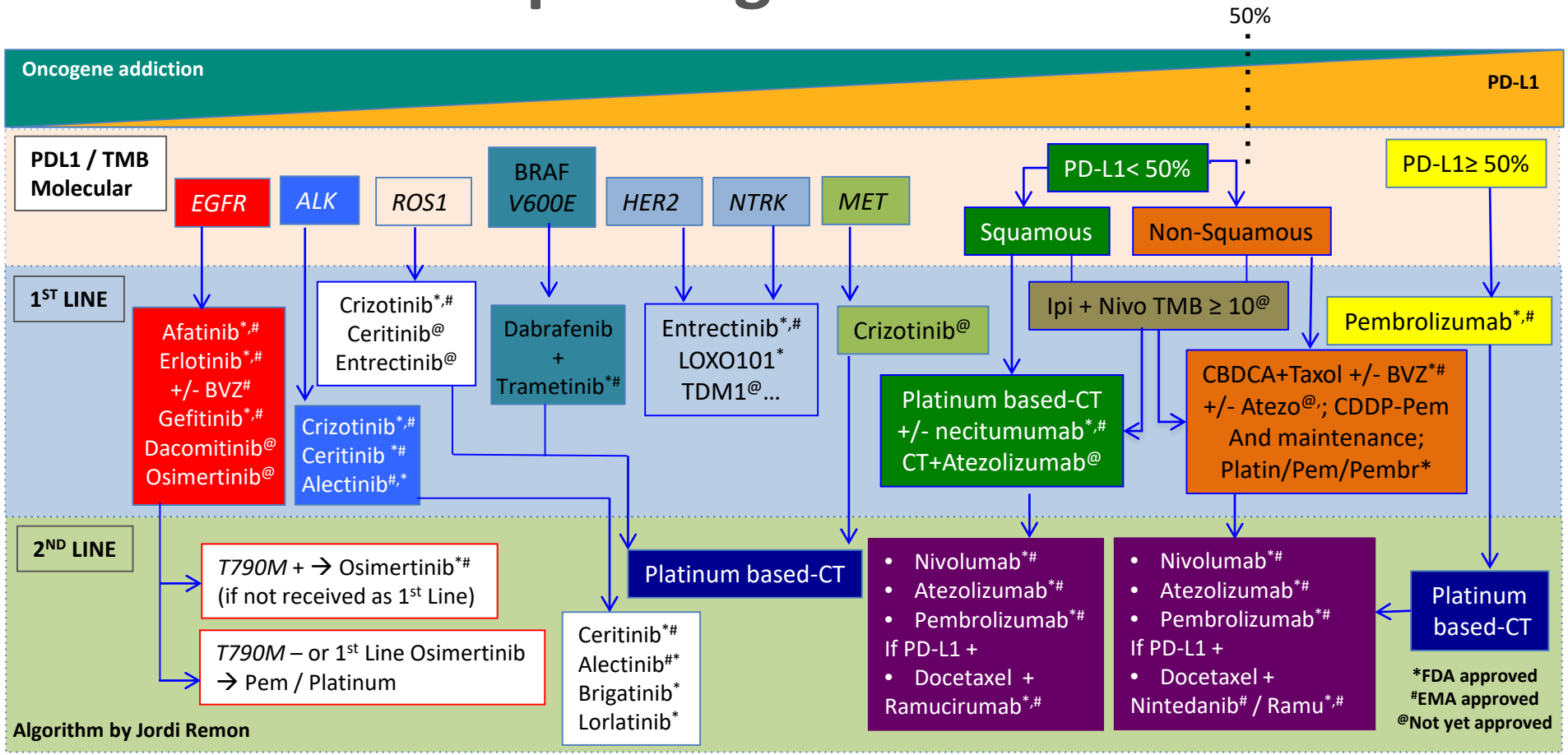
PRESENT AND FUTURE

PD(L)-1 Antibody

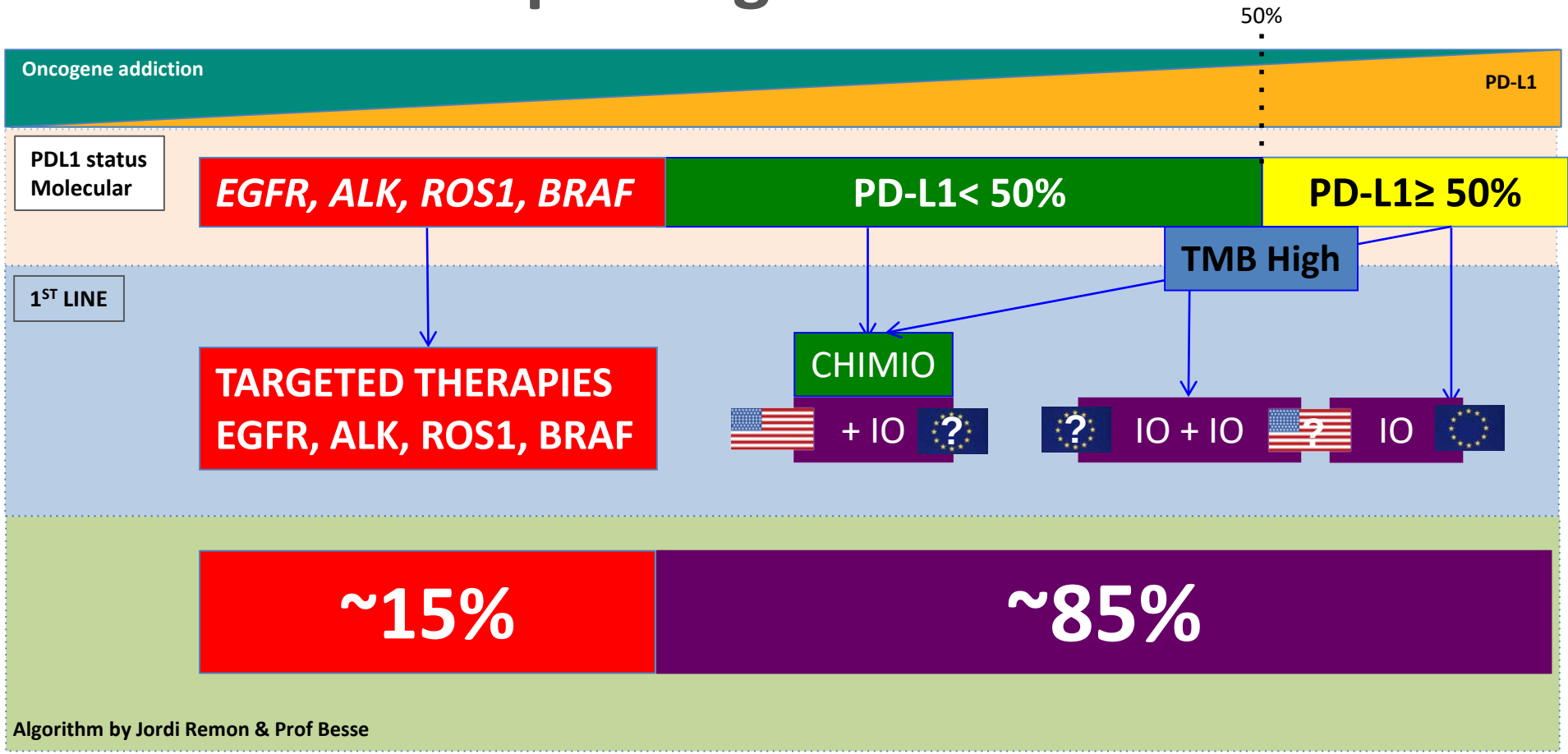


Courtesy Prof. Soria (modified)

New treatment paradigm in NSCLC



New treatment paradigm in NSCLC

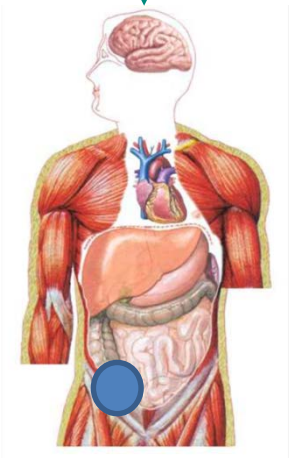


Outline

4 Who (not) to give immunotherapy?

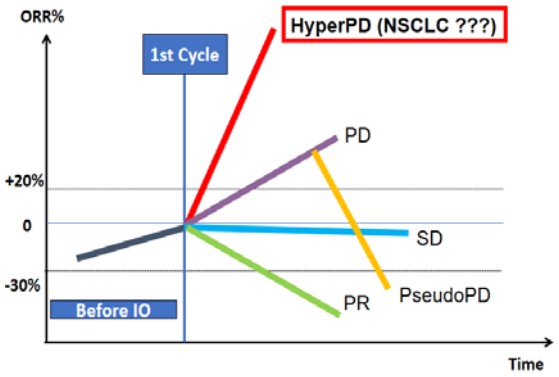
Who (not) to give?

SELECT THE RIGHT PATIENT FOR EFFICACY

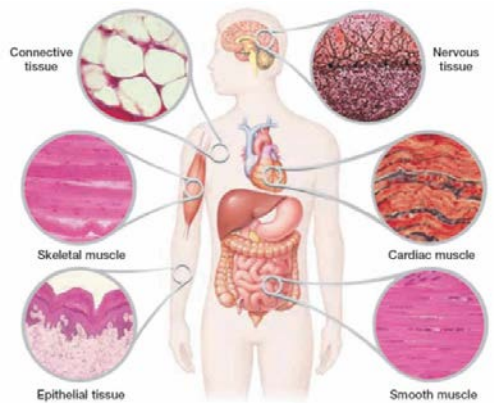


Courtesy of Prof Besse

AVOID A DETREMENTAL EFFECT



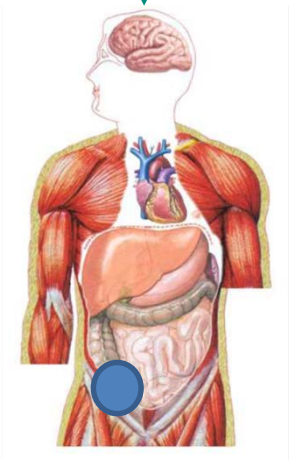
AVOID TOXICITIES IN NON-RESPONDERS



Ferrara R, et al. WCLC 2017. Saâda-Bouzid E, et al. Ann Oncol. 2017; Champiat S, et al. Clin Cancer Res. 2017;

Who (not) to give?

SELECT THE RIGHT PATIENT FOR EFFICACY



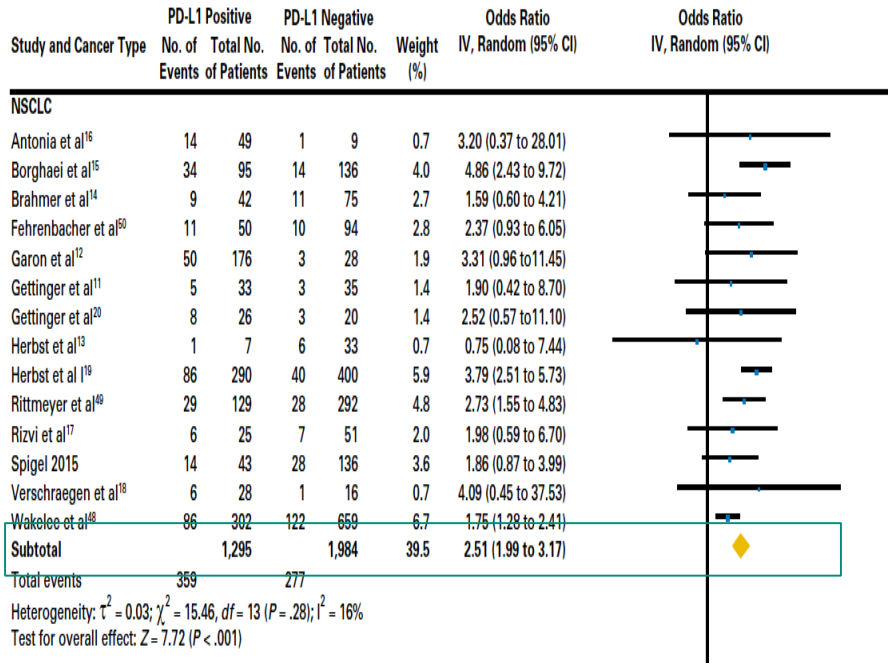
PD-L1 expression

Tumor Mutational Burden (TMB)

measurement of the overall number of genomic alterations seen in a cancer

Who to give?: PD-L1 expression

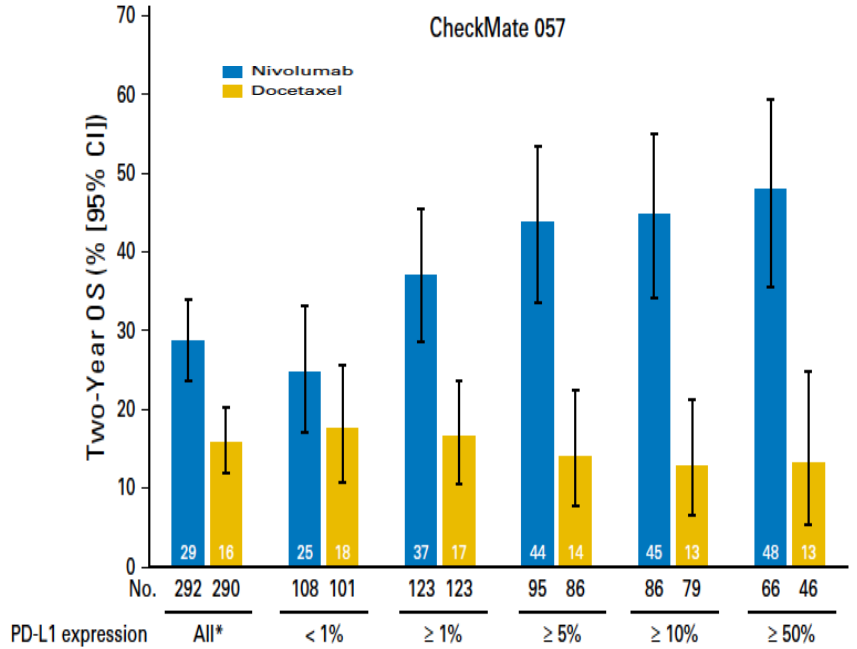
In NSCLC, PD-L1 expression correlates with RR and OS



Study and Cancer Type	PD-L1 Positive No. of Events	PD-L1 Positive Total No. of Patients	PD-L1 Negative No. of Events	PD-L1 Negative Total No. of Patients	Weight (%)	Odds Ratio IV, Random (95% CI)
NSCLC						
Antonia et al[16]	14	49	1	9	0.7	3.20 (0.37 to 28.01)
Borghaei et al[15]	34	95	14	136	4.0	4.86 (2.43 to 9.72)
Brahmer et al[14]	9	42	11	75	2.7	1.59 (0.60 to 4.21)
Fehrenbacher et al[50]	11	50	10	94	2.8	2.37 (0.93 to 6.05)
Garon et al[12]	50	176	3	28	1.9	3.31 (0.96 to11.45)
Gettinger et al[11]	5	33	3	35	1.4	1.90 (0.42 to 8.70)
Gettinger et al[20]	8	26	3	20	1.4	2.52 (0.57 to11.10)
Herbst et al[13]	1	7	6	33	0.7	0.75 (0.08 to 7.44)
Herbst et al I[19]	86	290	40	400	5.9	3.79 (2.51 to 5.73)
Rittmeyer et al[49]	29	129	28	292	4.8	2.73 (1.55 to 4.83)
Rizvi et al[17]	6	25	7	51	2.0	1.98 (0.59 to 6.70)
Spigel 2015	14	43	28	136	3.6	1.86 (0.87 to 3.99)
Verschraegen et al[18]	6	28	1	16	0.7	4.09 (0.45 to 37.53)
Wakelee et al[48]	86	302	122	659	6.7	1.75 (1.28 to 2.41)
Subtotal		**1,295**		**1,984**	**39.5**	**2.51 (1.99 to 3.17)**
Total events	359		277			

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 15.46$, $df = 13$ ($P = .28$); $I^2 = 16\%$

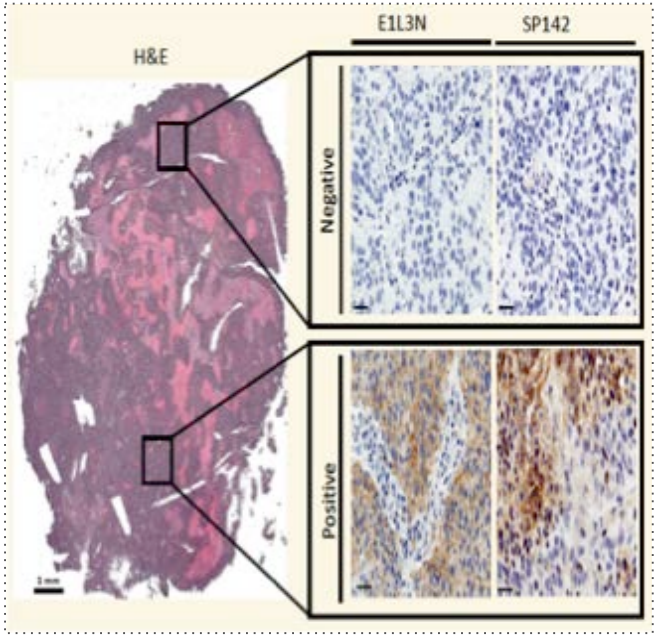
Test for overall effect: $Z = 7.72$ ($P < .001$)



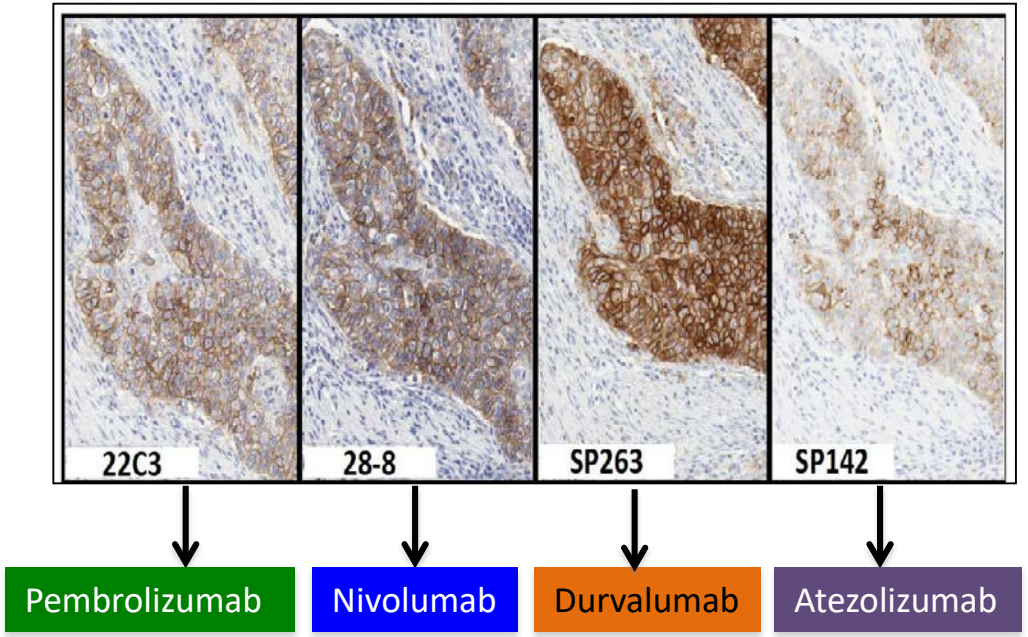
Khunger – JCO Precision Oncology 2017 * Horn – J Clin Oncol 2017

Who to give?: PD-L1 expression

PD-L1 expression is heterogeneous



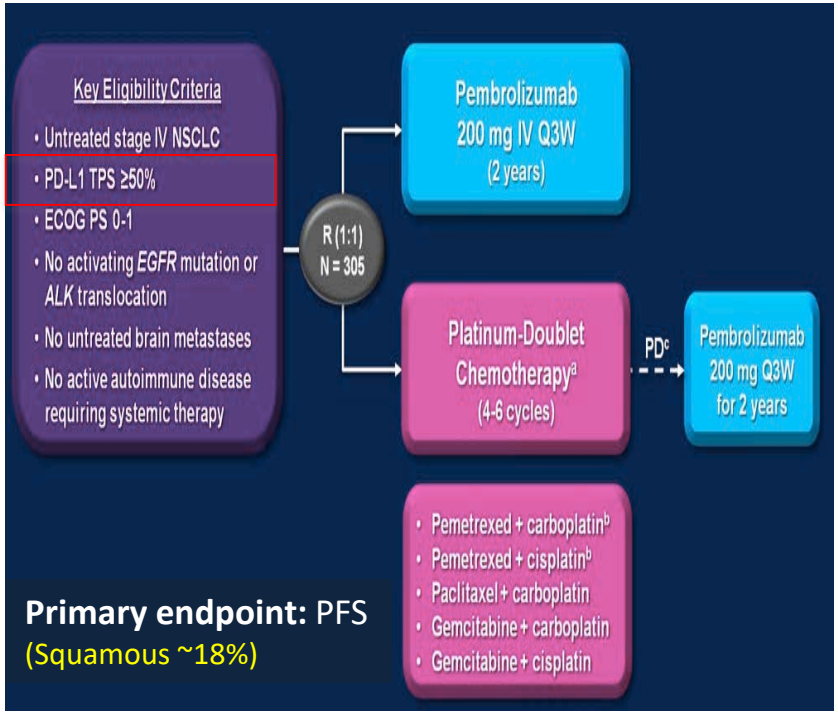
Blueprint PD-L1 IHC Diagnostic Assays

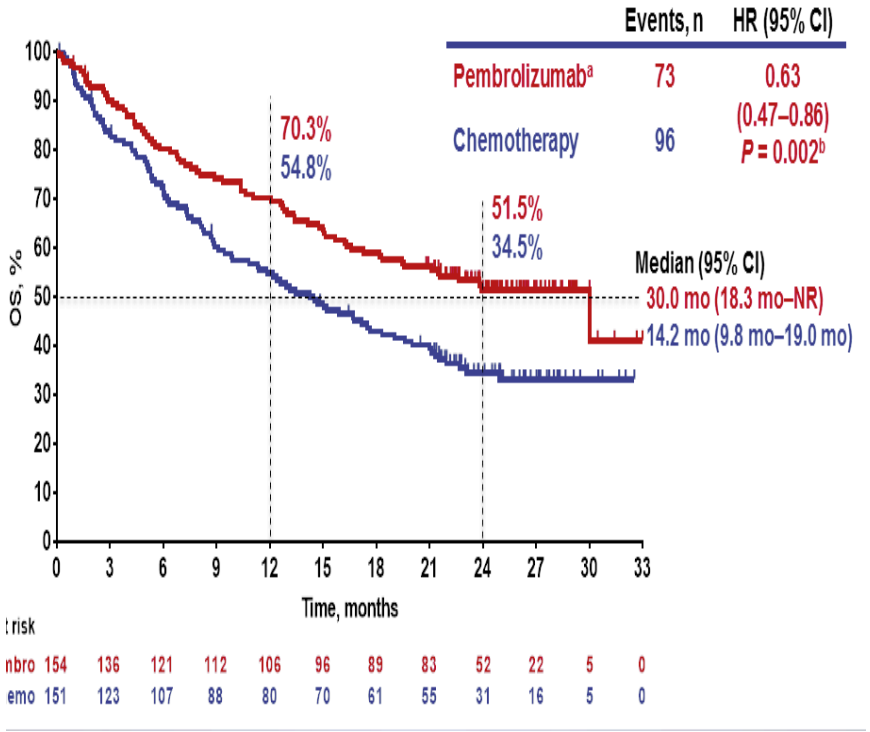


McLaughlin – JAMA Oncology 2016 * Ilie – Ann Oncol 2016 * Hirsch – JTO 2017 * Adam – Ann Oncol 2018

PD-L1 is a reality in daily clinical practice

KEYNOTE 024 in PD-L1 ≥ 50% by 22C3

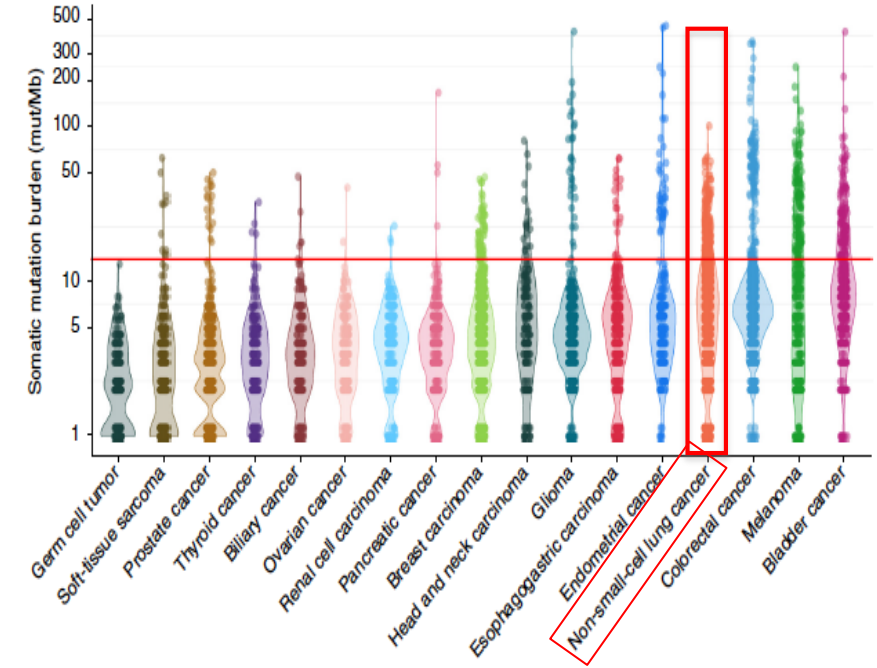




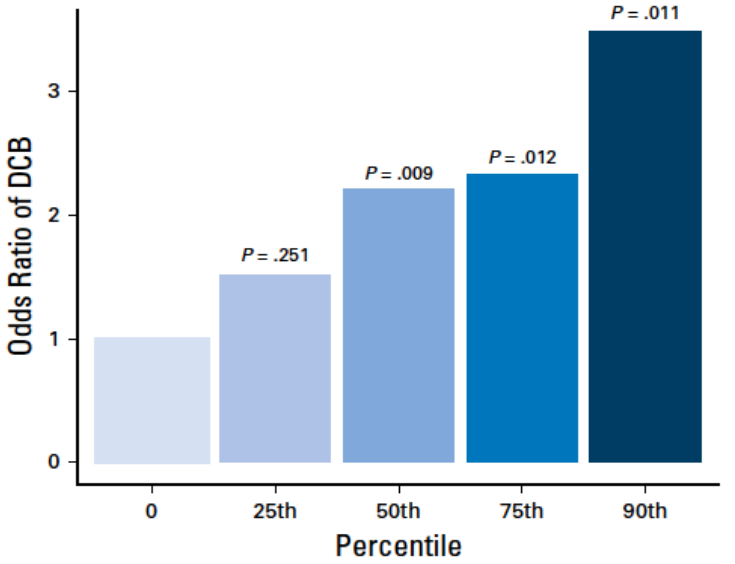
Reck – NEJM 2016 * Brahmer – WCLC 2017

Who to give?: High TMB

NSCLC are cancers with highest TMB

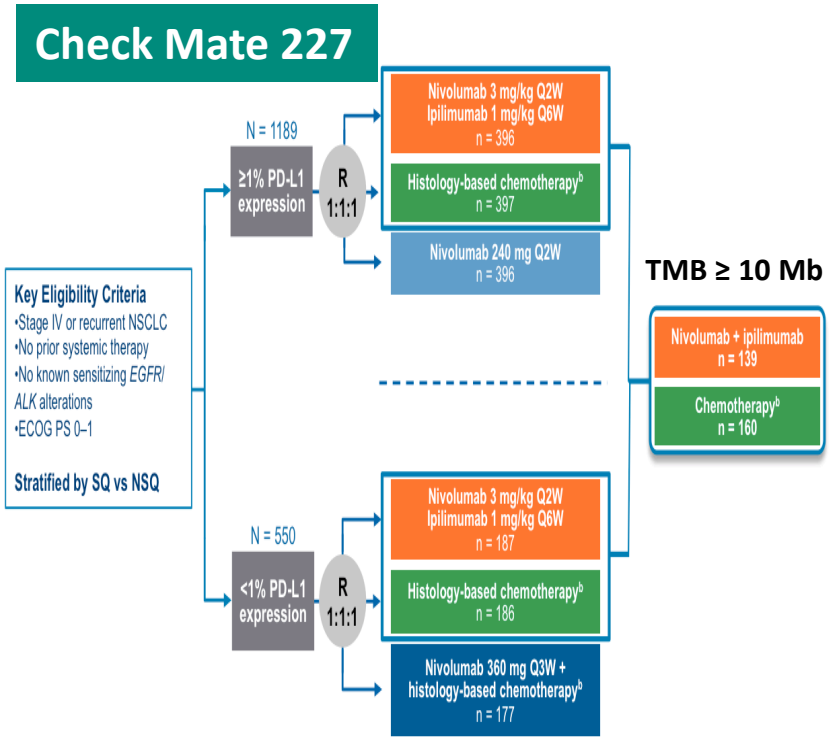


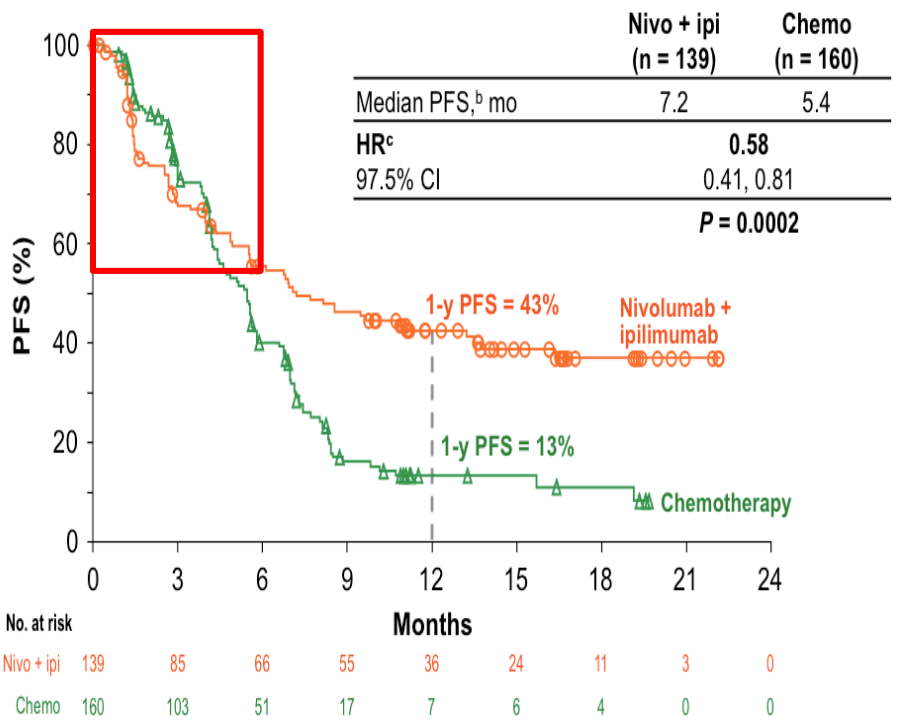
Correlation between TMB and RR (p<0.001)



Zheir – Nature Medicine 2017 * Yarchoan – NEJM 2017 * Rizvi – Science 2015 * Rizvi – J Clin Oncol 2018

Who to give?: High TMB



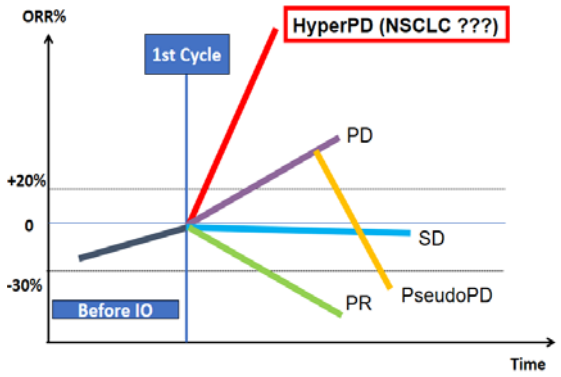


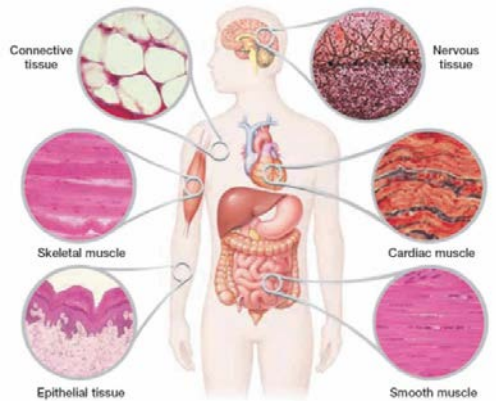
Hellmann - NEJM 2018

Who (not) to give?

AVOID A DETREMENTAL EFFECT

AVOID TOXICITIES IN NON-RESPONDERS





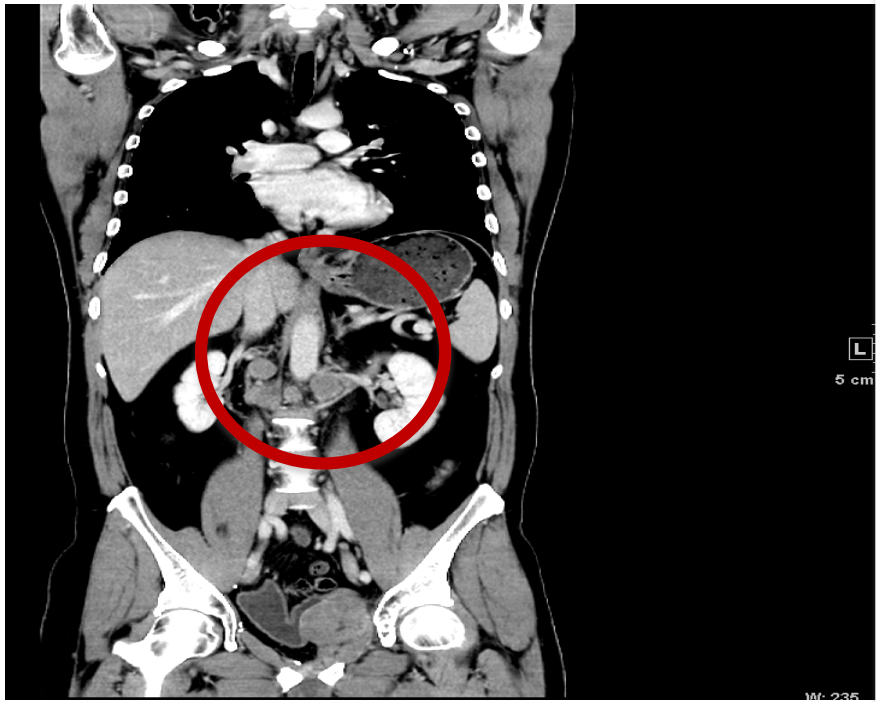
Courtesy of Prof Besse

Ferrara R, et al. WCLC 2017. Saâda-Bouzid E, et al. Ann Oncol. 2017; Champiat S, et al. Clin Cancer Res. 2017;

Hyperprogressive disease under IO

Urothelial carcinoma 49 yo male
COMBO anti-PDL1 + other immunotherapy
C1J1 18/10/2016

Baseline 06/10/2016



Hyperprogressive disease under IO

Urothelial carcinoma 49 yo male
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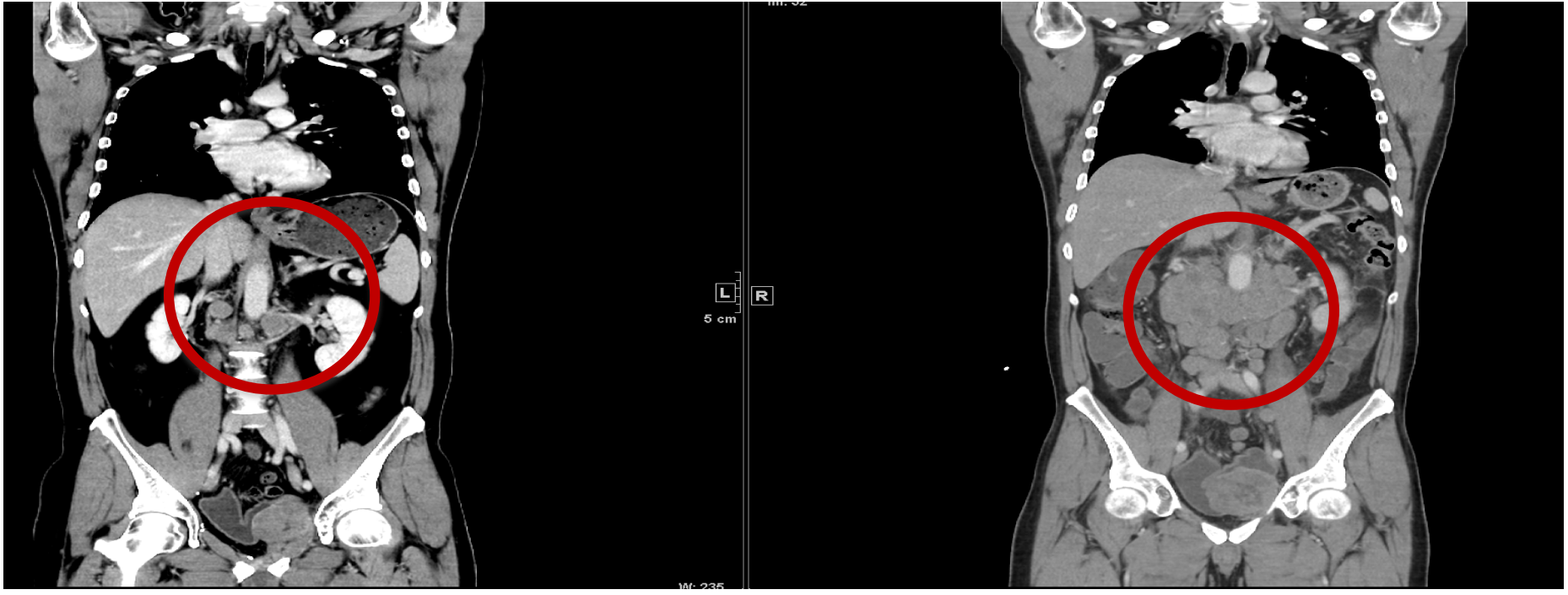
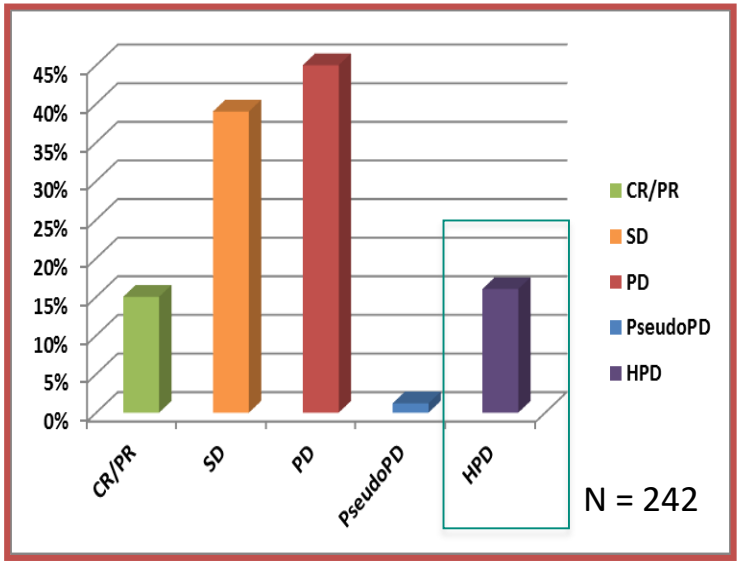
C1J1 18/10/2016

Baseline 06/10/2016

@3 wks - 09/11/2016

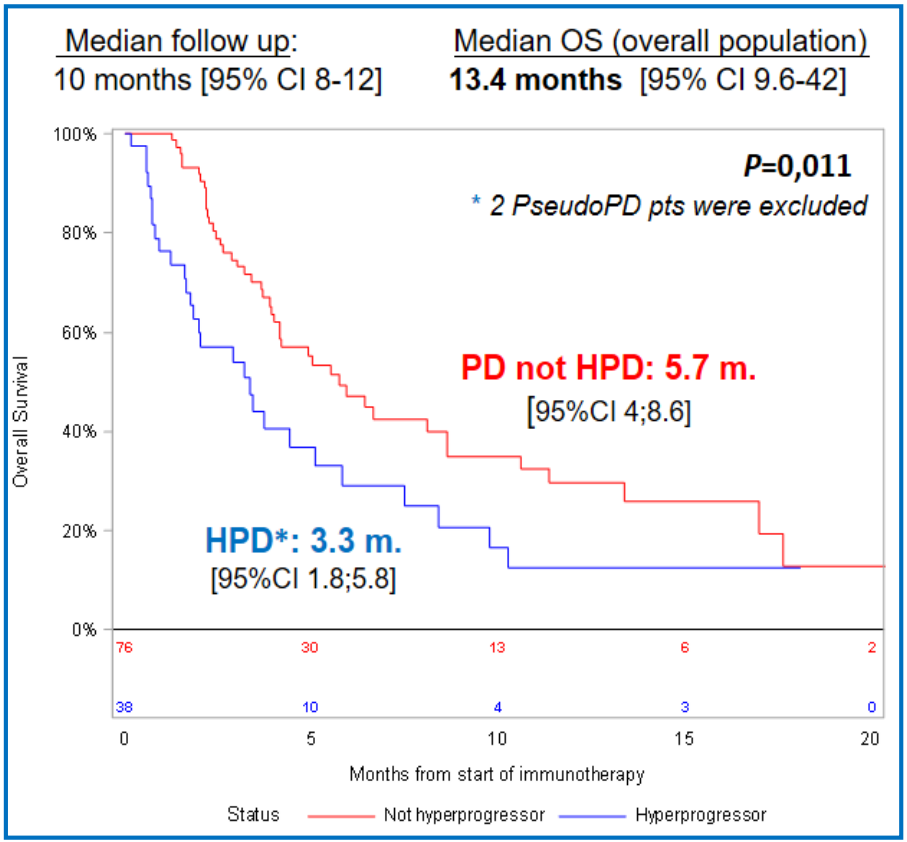


Hyperprogressive disease



14% HPD with IO *vs.* 5% with CT

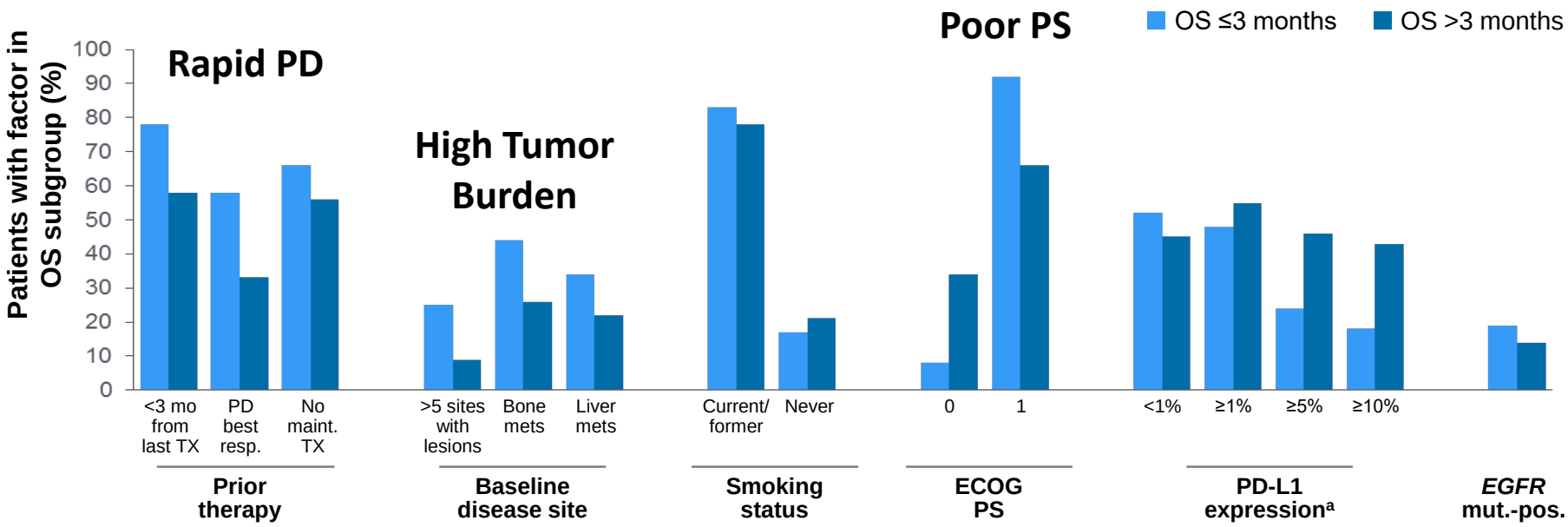
Ferrara – WCLC 2017



Early deaths (<3 mo.): characteristics

Single Baseline Characteristics by OS With Nivolumab

CheckMate 057: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

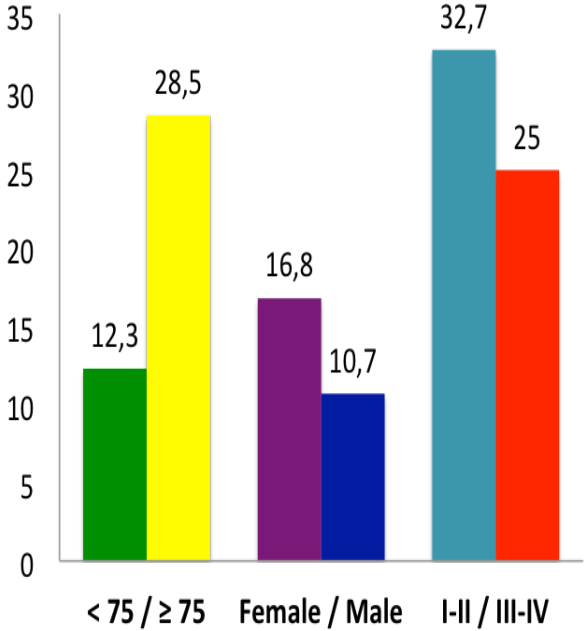


Peters – WCLC 2016

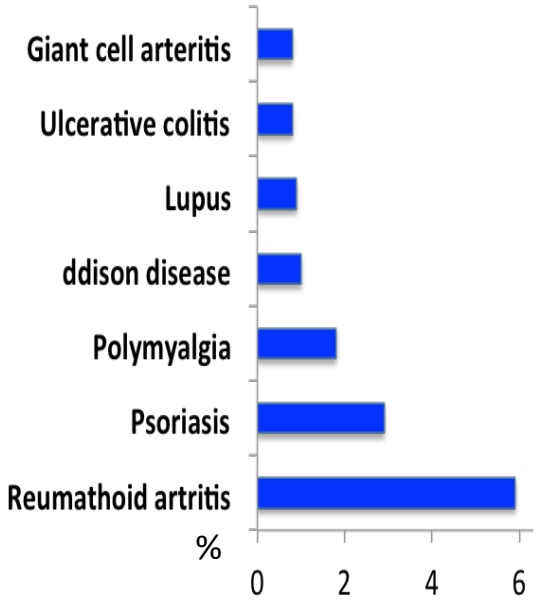
Baseline autoimmune disorders in NSCLC

In a SEER database, from 14% to 25% of NSCLC patients have ≥ 1 autoimmune diseases

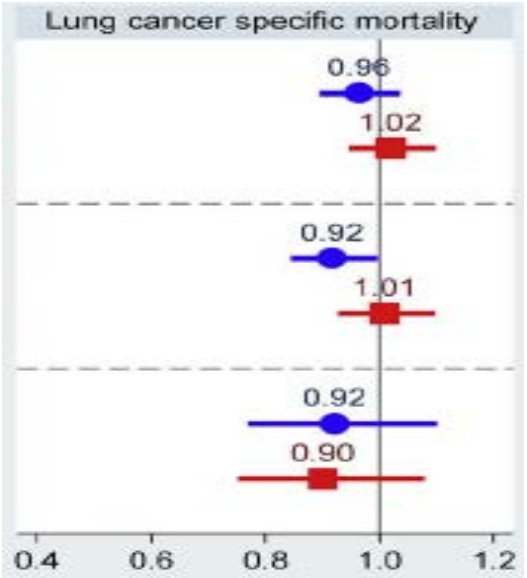
Patients' Characteristics with autoimmune disease



Most common Autoimmune diseases



In lung cancer patients, AD not associated higher mortality



Khan – JAMA Oncol 2016 * Khan – Lung Cancer 2018

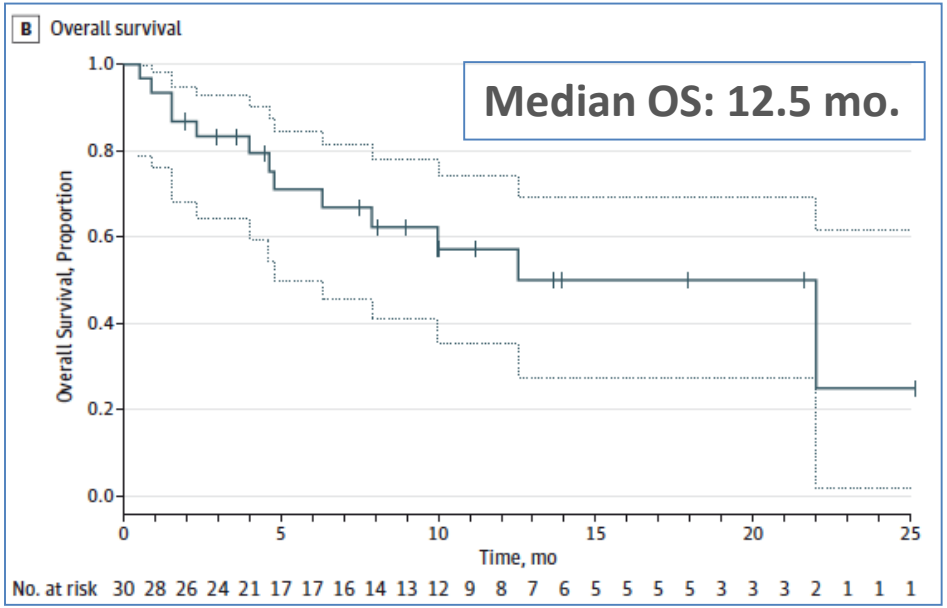
ICI in patients with baseline autoimmune diseases

41% had disease exacerbation during ICIs therapy,
No difference in onset of AE's in patients with active *vs*. inactive baseline AD.

Melanoma and Ipilimumab

- In phase II&III, mOS: 11.4 mo

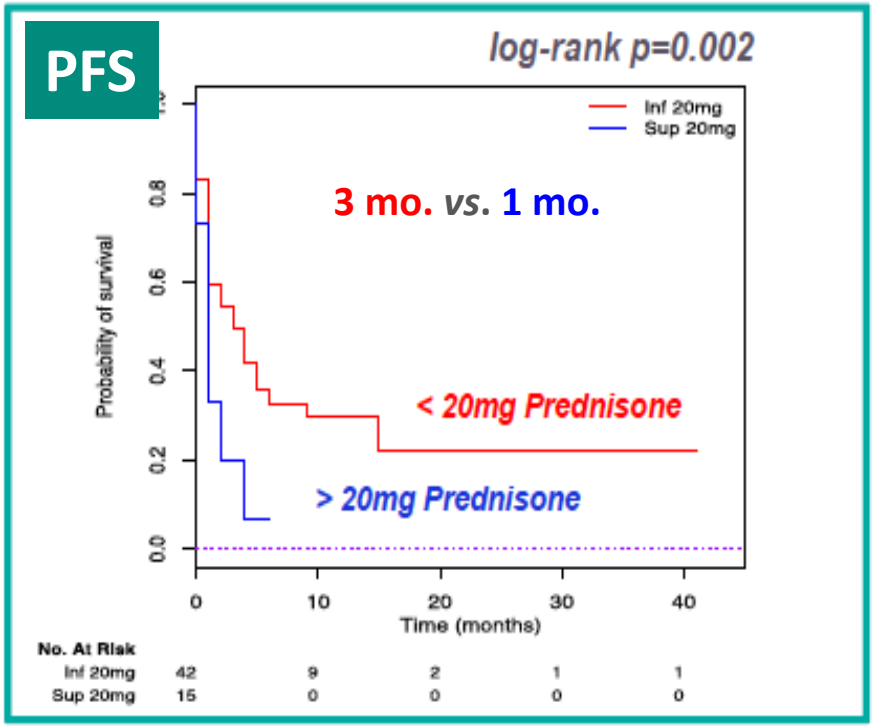
- 30 melanoma with baseline AD:
  - 43% receiving IS therapy
  - 27% had exacerbations
  - 33% of grade 3-5 ir-AE's
  - Response Rate 20%

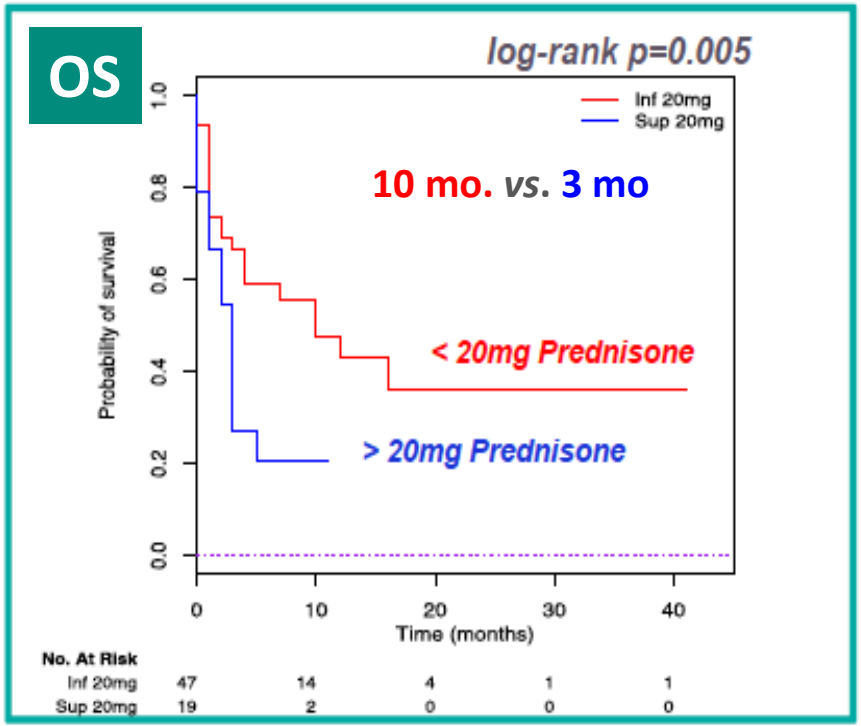


Abdel-Wahab – Ann Intern Med 2018 * Johanson – JAMA Oncol 2016 * Shadendorf – JCO 2015 * Danlos – Eur J Cancer 2018

Baseline steroids and ICI

66 out of 244 patients (27%) received steroids at baseline



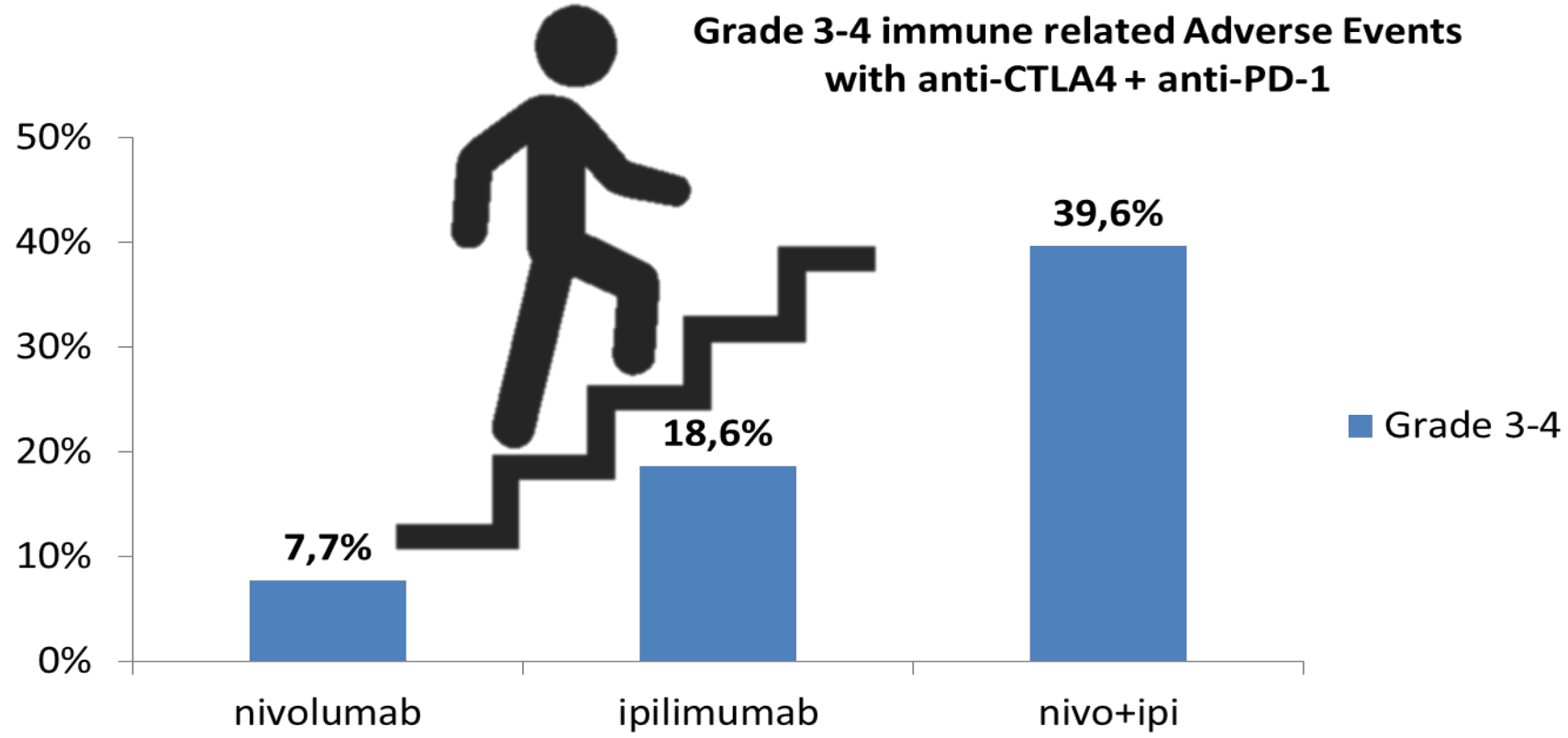


Martinez – ESMO 2017

Outline

5 Toxicity

Ir-AE's are NOT so rare when used in combination

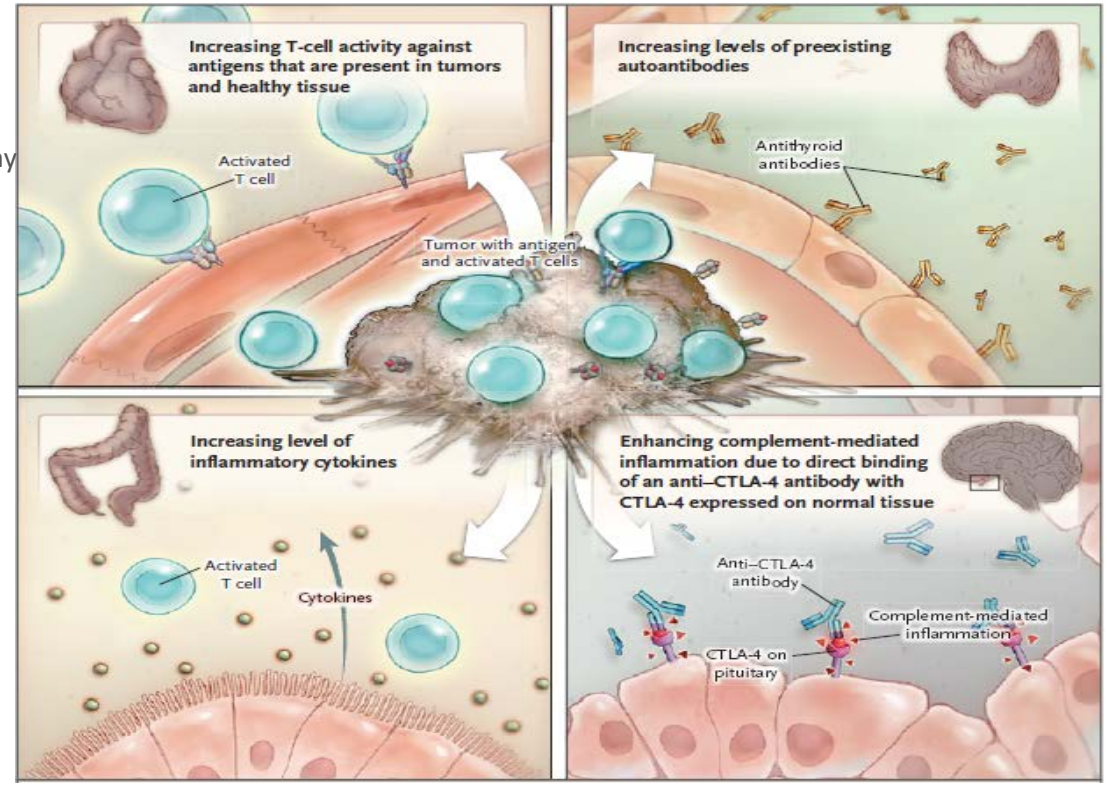


Courtesy of Dr. Champiat

Larkin et al, N Engl J Med 2015.

Aetiology

Increasing T-cell activity against antigens that are present in tumors and healthy tissue



Increasing levels of preexisting autoantibodies

Increase in the level of inflammatory cytokines

Enhanced complement-mediated inflammation due to direct binding of a CTLA-4 with CTLA-4 expressed on normal tissue, such as the pituitary gland

Postow - NEJM 2018

It’s not about the frequency…**it’ s about diversity !**

Courtesy of Dr. Champiat

It’s not about the frequency…**it’ s about diversity !**

Pneumonitis

Encephalitis

Retinitis

Adrenal insufficiency

Myocarditis

Nephritis

Pancreatitis

DRESS

Guillain Barré

Thrombopenia

Gastritis

Hemolytic anemia

Myasthenia

Myositis

REPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis

EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis

ENDOCRINE
Hyper or hypothyroidism
Hypophysitis
Adrenal insufficiency
Diabetes

CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis

- New
- Diverse
- Uncommon

GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis

RENAL
Nephritis

LIVER
Hepatitis

NEUROLOGIC
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia

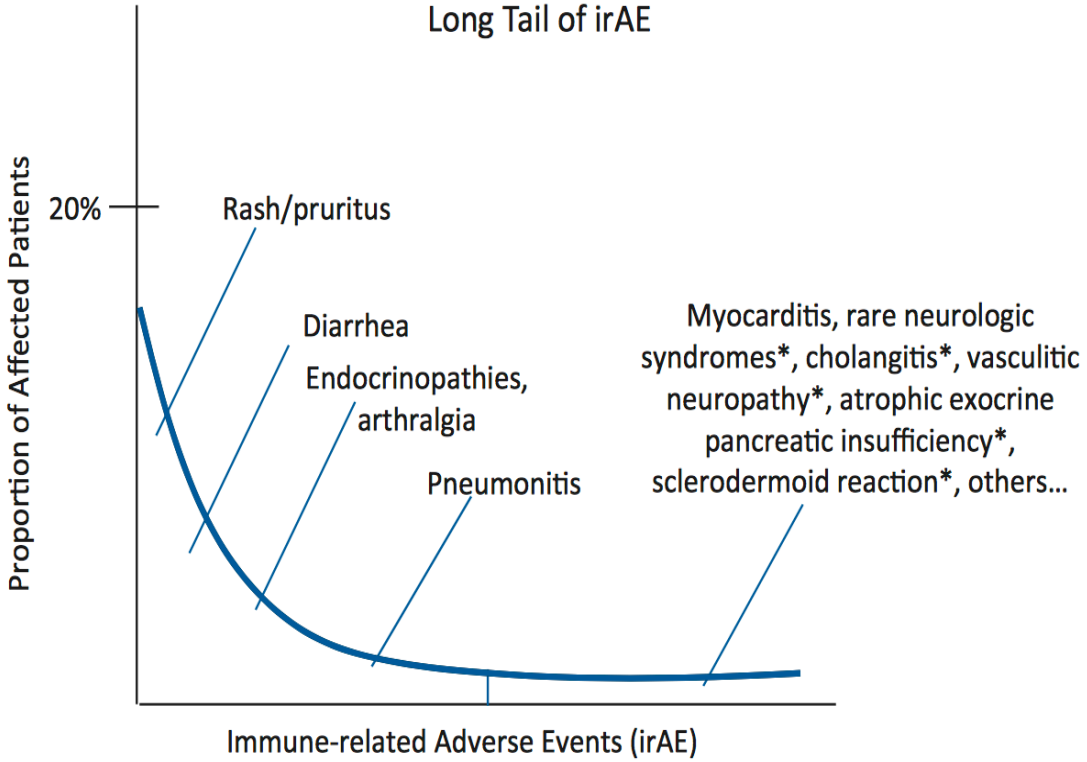
SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson

BLOOD
Hemolytic anemia
Thrombocytopenia
Neutropenia
Hemophilia

MUSCULO SKELETAL
Arthritis
Dermatomyositis

Champiat – Ann Oncol 2015

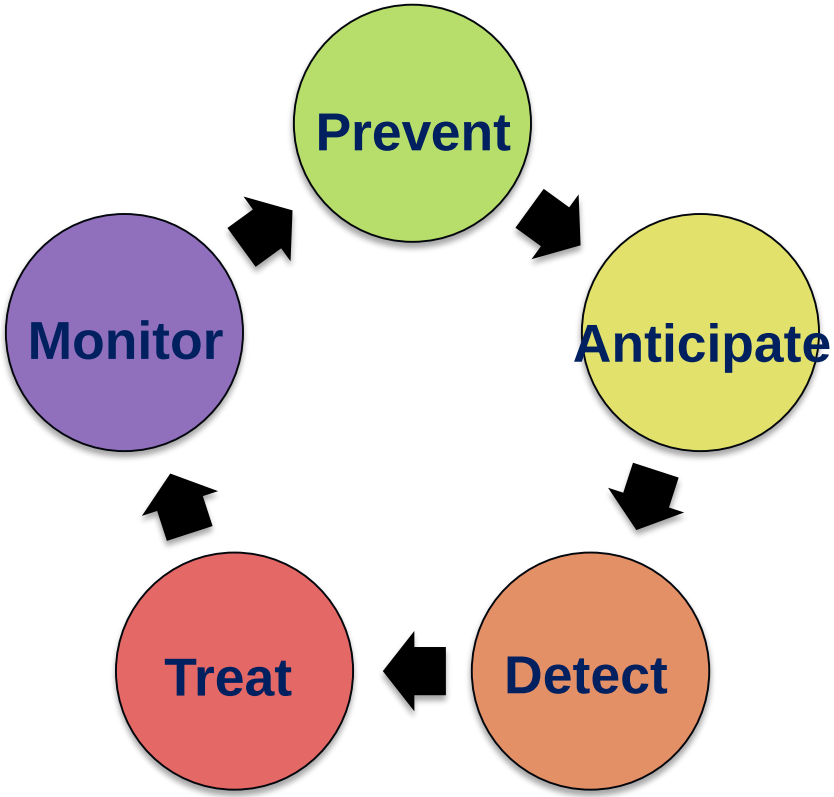
Atypical autoinmune side effects



@iTOXreport

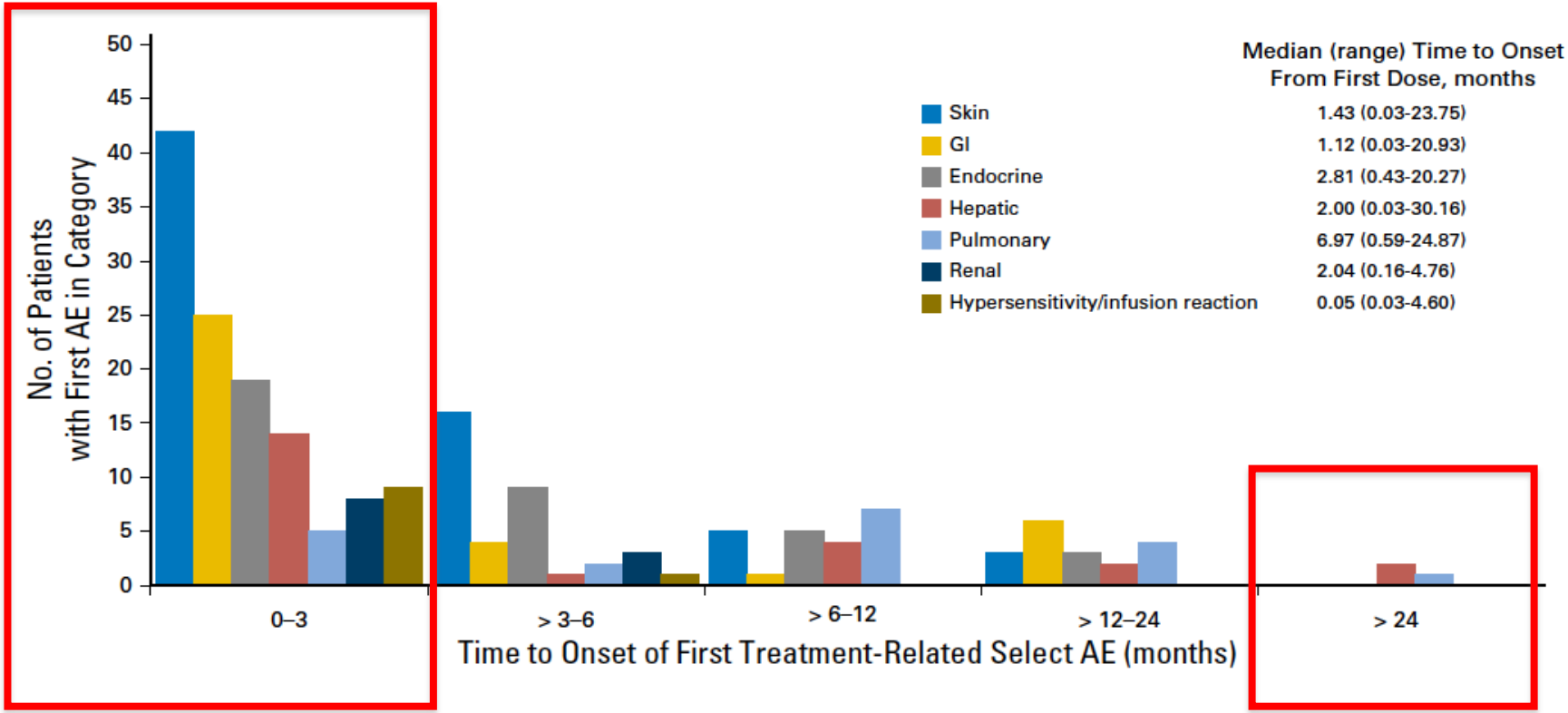
Friedman - Ann Oncol 2017

Immunotherapy toxicity management



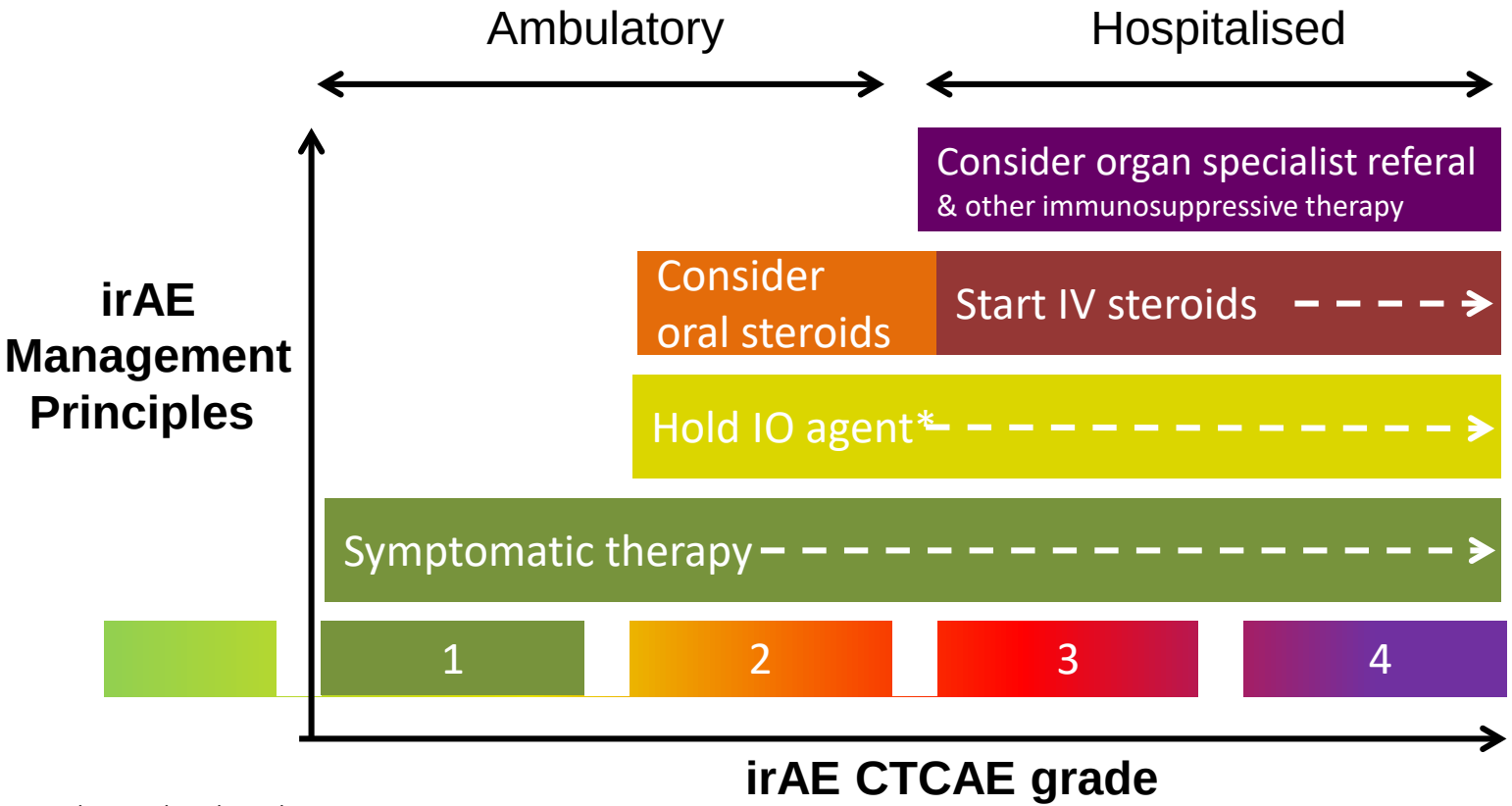
Champiat et al. , Annals of Oncology, 2015

Onset of irAE's in NSCLC patients



Horn – J Clin Oncol 2017

General management strategies for irAEs



- outside skin or endocrine disorders where immunotherapy can be maintained

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

POSITION ARTICLE AND GUIDELINES | Open Access

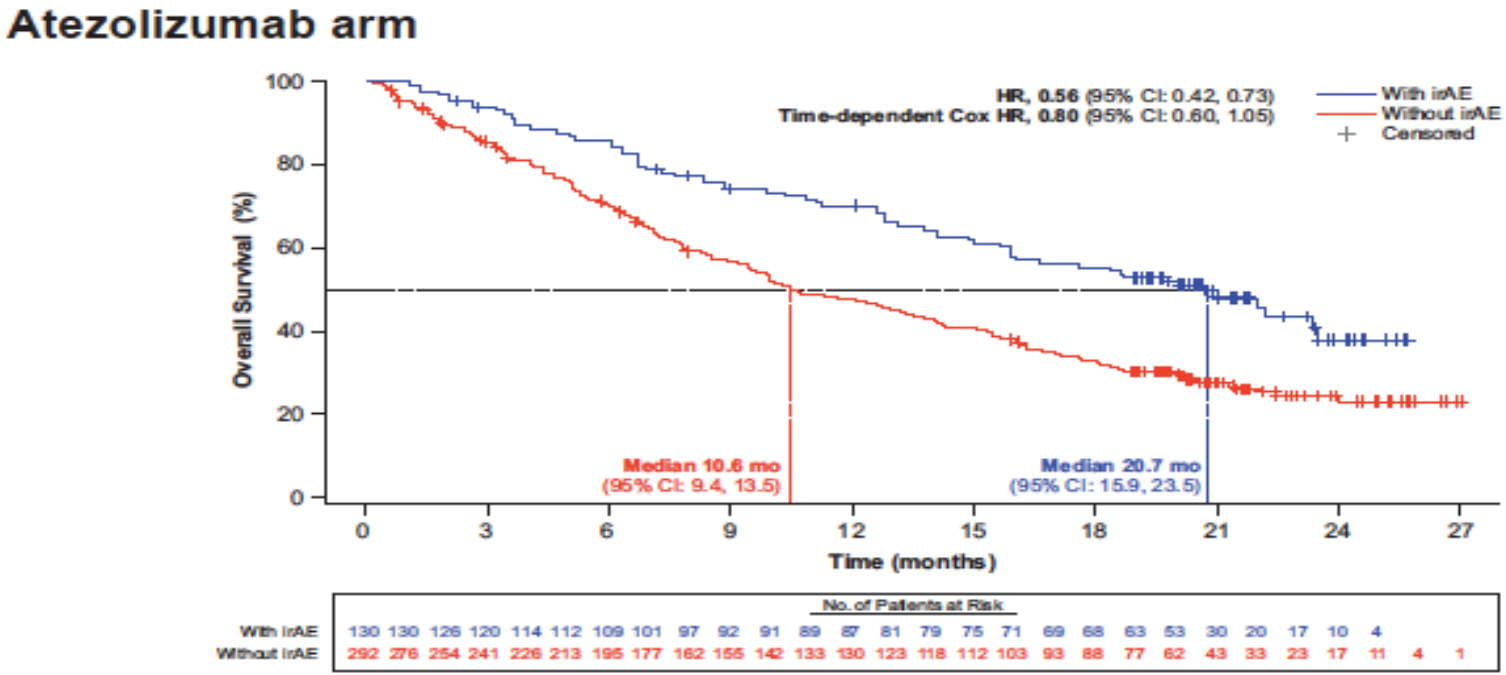
CrossMark

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[1†], A. Diab[2†], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[12†], M. S. Ernstoff[1*†] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

Onset of ir-AE's and survival in NSCLC

OAK trial: OS was in favor of atezo arm pts with irAEs vs those without irAEs (10.6 vs. 29.7 months, HR 0.56 in atezolizuamb arm without vs. with-irAE's (Von-Pawel. ESMO 2017).



Conclusions

1	Introduction	ICI are treatment options in almost all cancers
2	1st Line	Almost all patients will receive ICI alone +/ combos
3	2nd Line	We need new treatment options in PD to 1st Line IO
4	Biomarkers	PD-L1 remains gold-standard. TMB next one?
5	Toxicity	Why not a multidisciplinary board about ICI toxicity?

PAST TIME IN NSCLC TREATMET

PRESENT TIME IN NSCLC TREATMET. WHAT ELSE?