COURS DU GOLF 2017

Quelles associations avec l'immunothérapie ?

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Head of the EORTC Lung Cancer Group

Disclosures

- No personal financial disclosures
- Institutional grants for clinical and translational research
  - AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis, GSK, Servier, EOS, Onxeo, OncoMed, Inivata, OSE Pharma

Summary

- **Immunotherapy impact on cancer outcomes**
  - Example of tail
  - Opportunities to expand population benefit
- **Rational combination strategies**
  - IO-IO
  - IO-Chemo
  - IO-Targeted therapies
  - IO-Radiation
- **The future**

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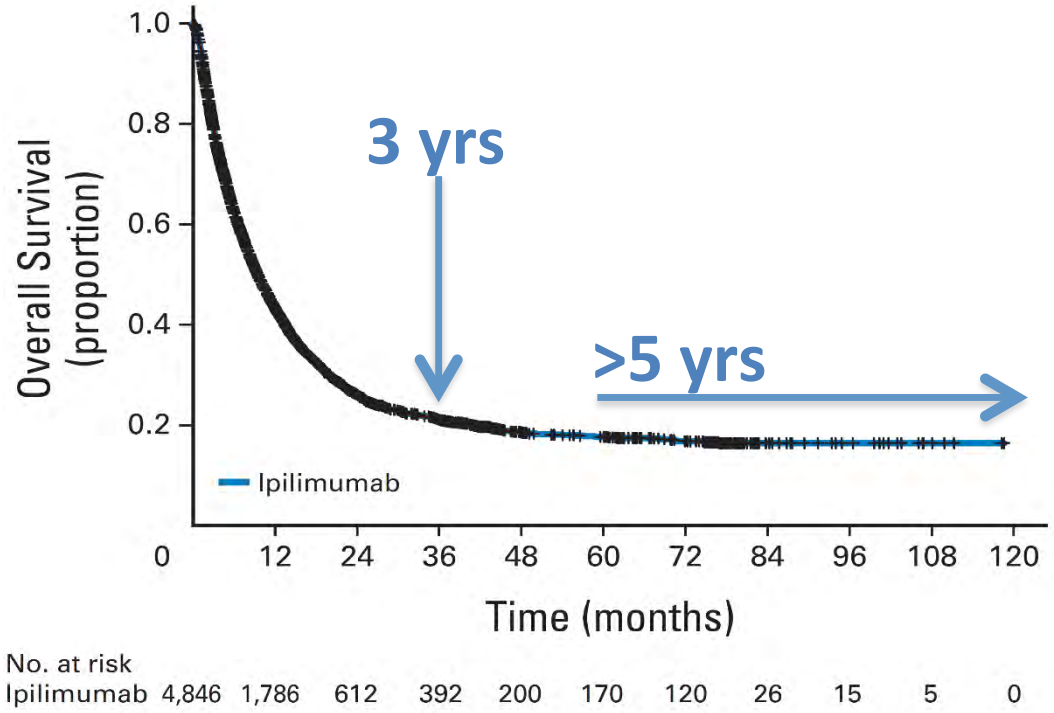
About the Tail – Example of Melanoma



EAP ipilimumab

n = 4846

3-year OS = 21% (95% CI, 20% to 22%)

- The tail starts at 3 years
- Long responders may experience CR/PR but also SD or PD
- Right definition for pt with OS >5 years?

Cured?

al. *J Clin Oncol.* 2015.

IO: EMA Approval Status

DICATION	MELANOMA	LUNG (NSCLC)	GU (BLADDER)	H&N
DJUVANT erapy	-	-	-	-
st line	IPILIMUMAB NIVOLUMAB PEMBROLIZUMAB	PEMBROLIZUMAB only PD-L1+ ≥50%	- PEMBROLIZUMAB ATEZOLIZUMAB	-
cond line	IPILIMUMAB NIVOLUMAB PEMBROLIZUMAB	NIVOLUMAB PEMBROLIZUMAB only PD-L1+ ≥1% ATEZOLIZUMAB	NIVOLUMAB	NIVOLUMAB PEMBROLIZUMAB

s: Nivolumab approved (June 2); Atezolizumab (July 21), and pembrolizumab (July 21) CHMP recommended.

IO: EMA/FDA Approval Status

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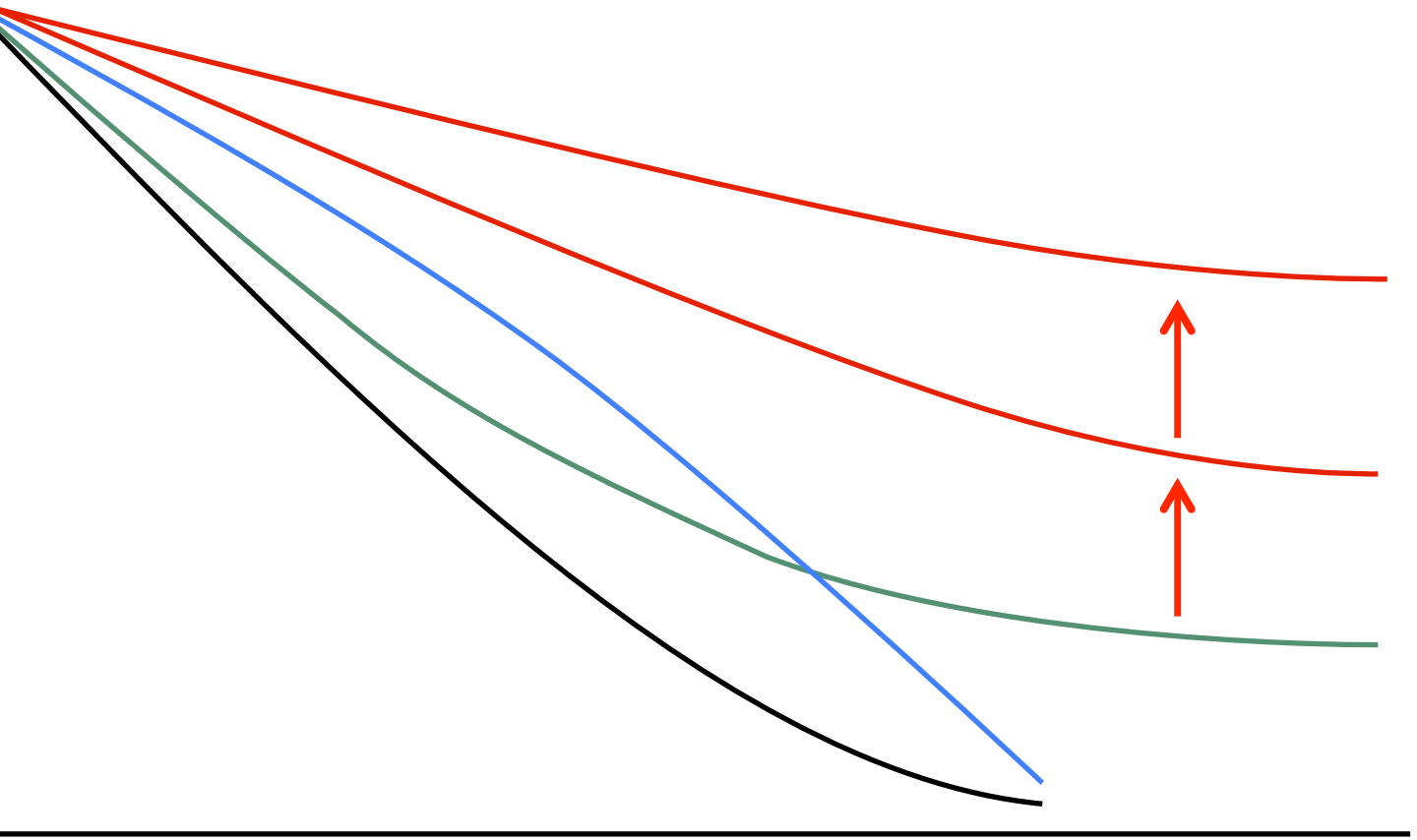
Immunotherapies in Combination May Enable Better Long-Term Survival



Control

Targeted therapies or chemotherapies

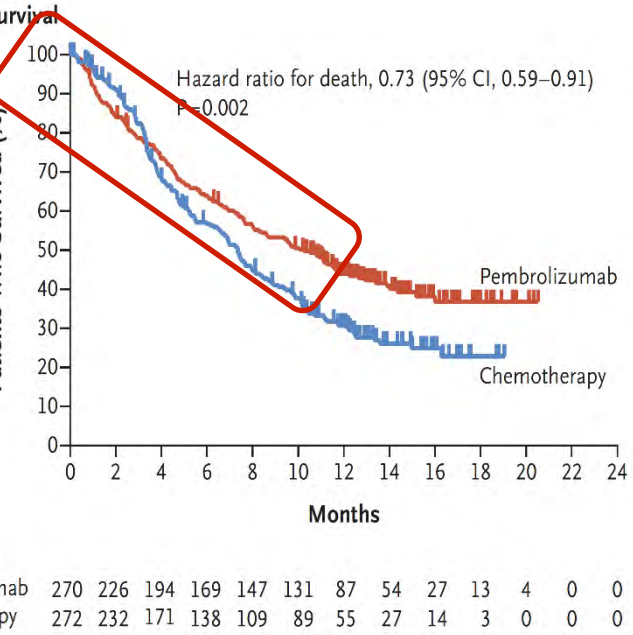
Immunotherapy

Immunotherapy +

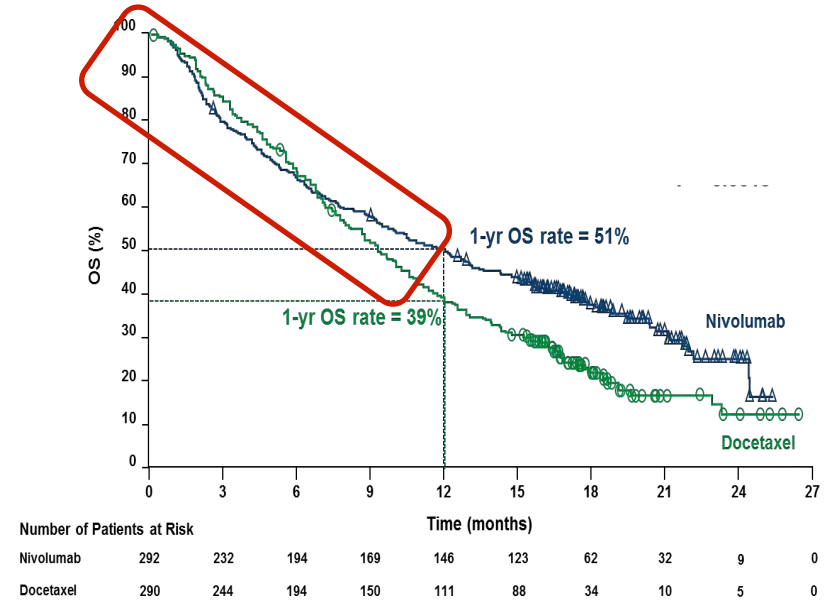
- Chemotherapy,
- Targeted therapy, and/o
- Other Immunotherapies

Common Pattern?

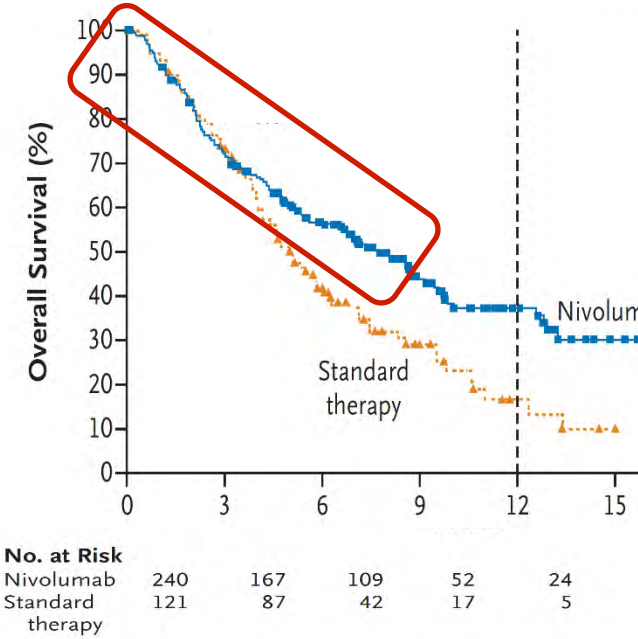
UROTHELIAL
KEYNOTE-045



LUNG
CHECKMATE-057



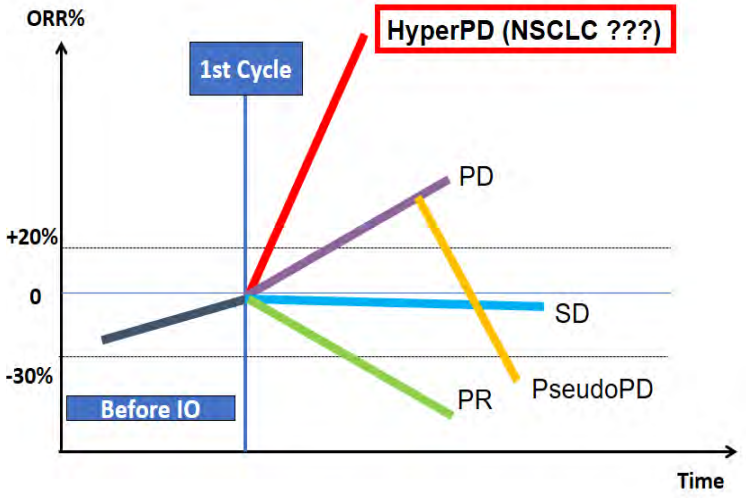
H&N
CHECKMATE-141

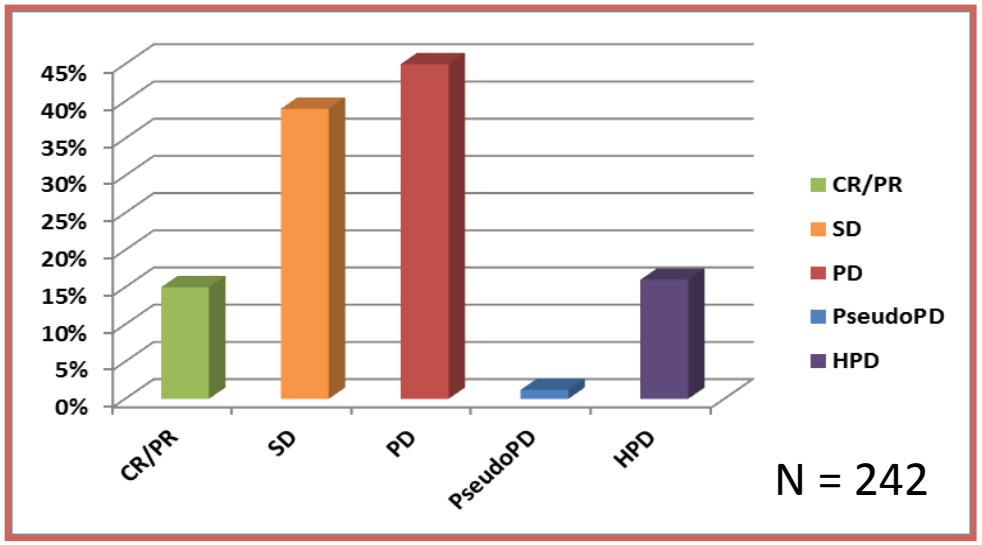


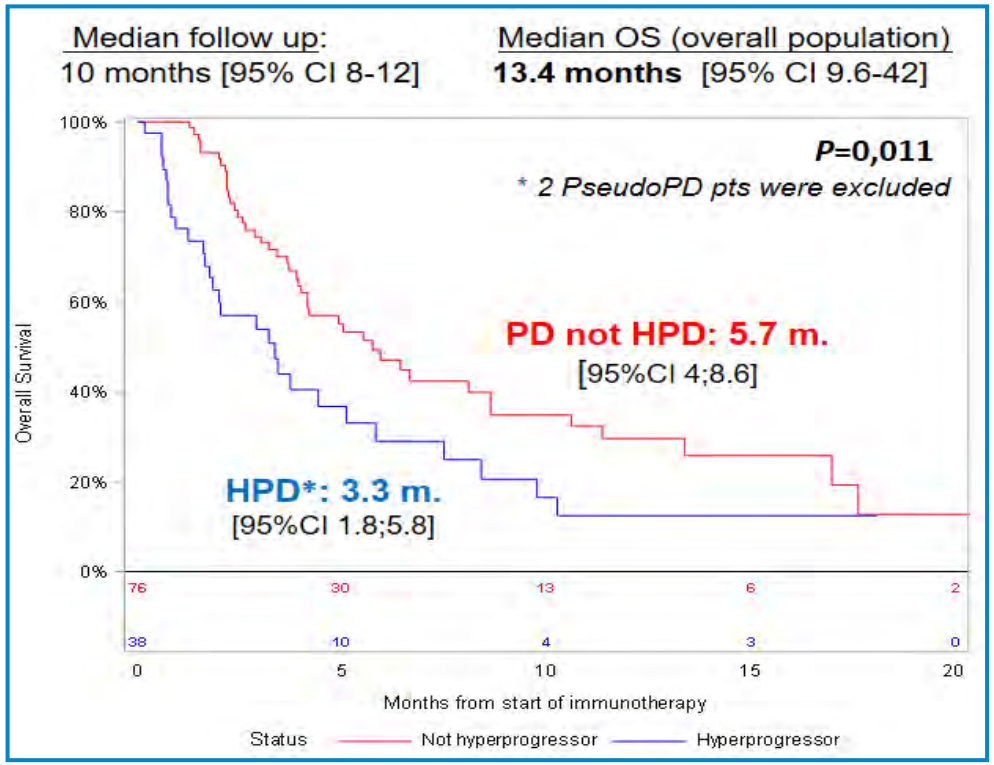
Curves cross, suggesting a deleterious effect in a subgroup of patients

et al. *N Engl J Med.* 2017;376(11):1015-1026; Ferris R, Gillison ML. *N Engl J Med.* 2017;376(6):596; Borghaei H, et al. *N Engl J Med.* 2015;373(17):1627-1639.

Hyperprogressive Disease in Lung Cancer







HPD:
16% of NSCLC
26% of H&N
25% of bladder

t al. ESMO 2017. Abstract 1306PD; Saâda-Bouzid E, et al. *Ann Oncol.* 2017;28(7):1605-1611; Champiat S, et al. *Clin Cancer Res.* 2017;23(8):1920-1928.

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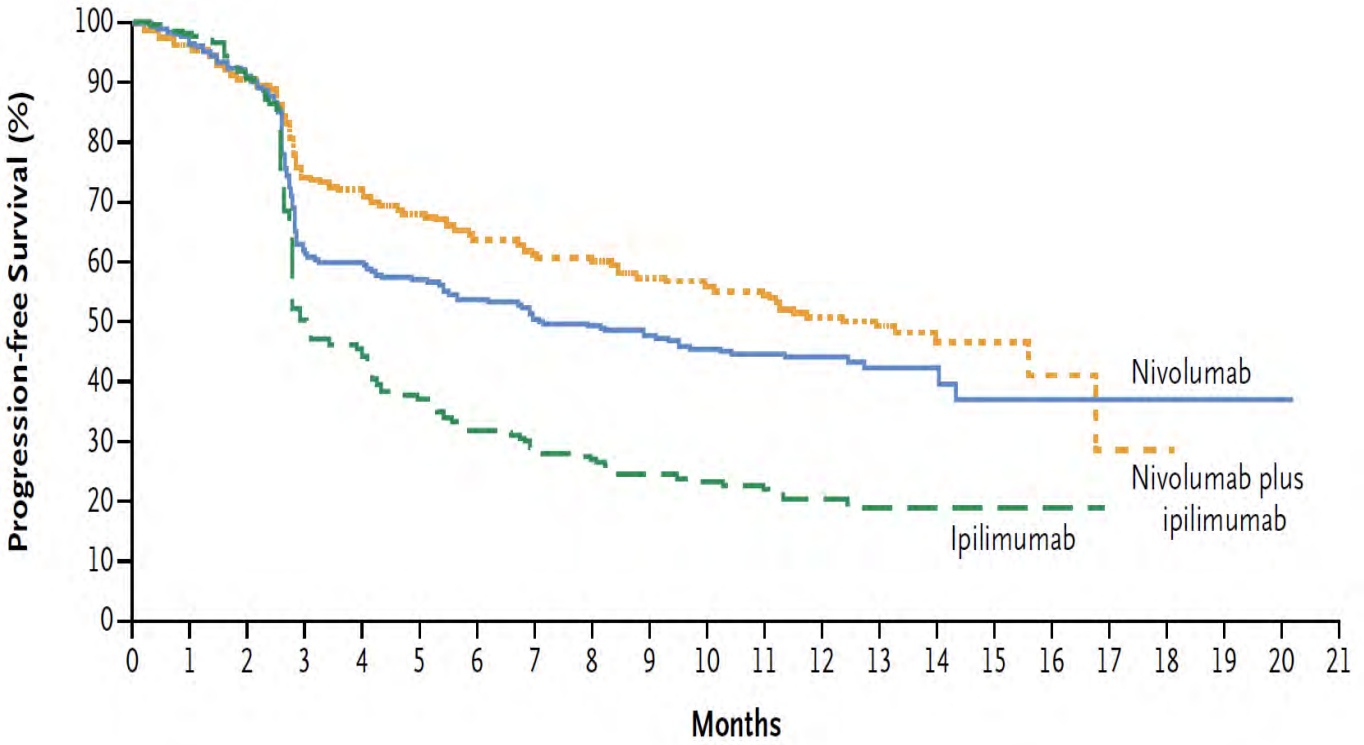
Iconic Combo in Melanoma



	316	292	271	177	170	160	147	136	132	124	106	86	50	38	14	9	6	2	1	1	1	0
b	314	293	275	219	208	191	173	164	163	151	137	116	65	54	18	11	7	2	1	0	0	0
	315	285	265	137	118	95	77	68	63	54	47	42	24	17	7	4	3	0	0	0	0	0

- Ipilimumab + nivolumab each single agent
- Restricted to PD-L1–?

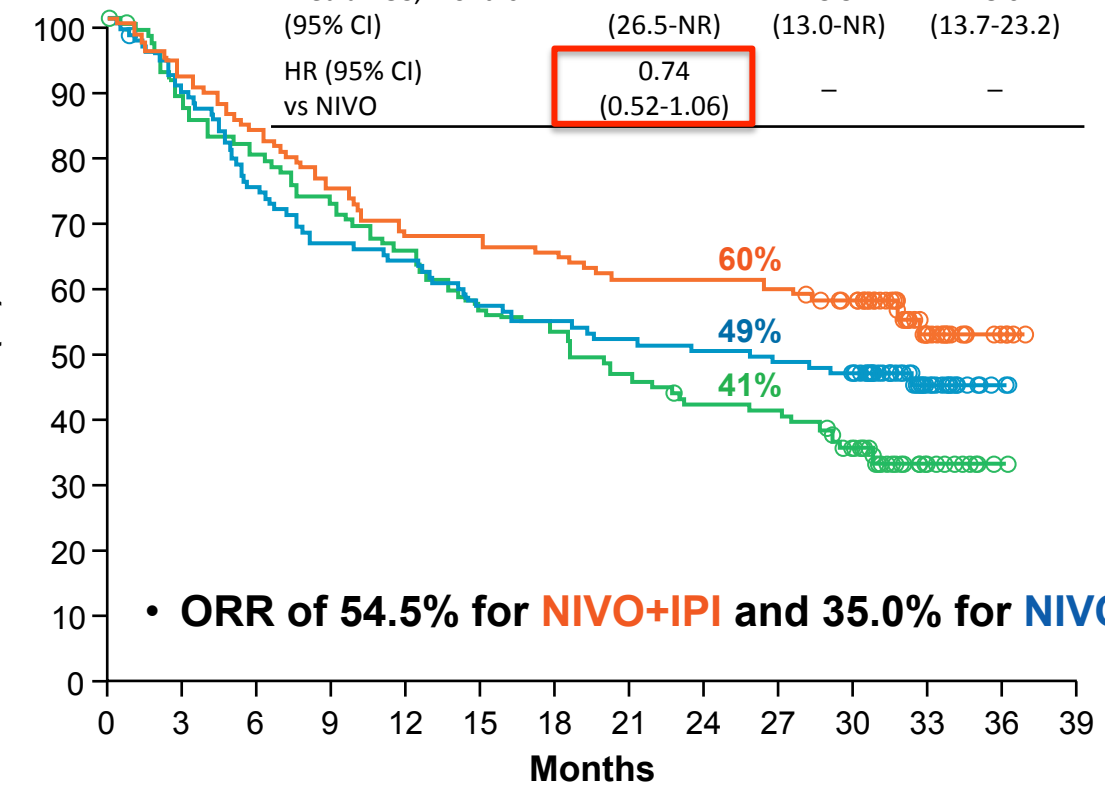
	G3/4 Toxicity
Nivolumab	16.3%
Ipilimumab	27.3%
Combo	55%

al. *N Engl J Med.* 2015;373(1):23-34.

Iconic Combo in Melanoma

PD-L1 Expression Level <1%

<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, months (95% CI)	NR (26.5-NR)	23.5 (13.0-NR)	18.6 (13.7-23.2)
HR (95% CI) vs NIVO	0.74 (0.52-1.06)	–	–



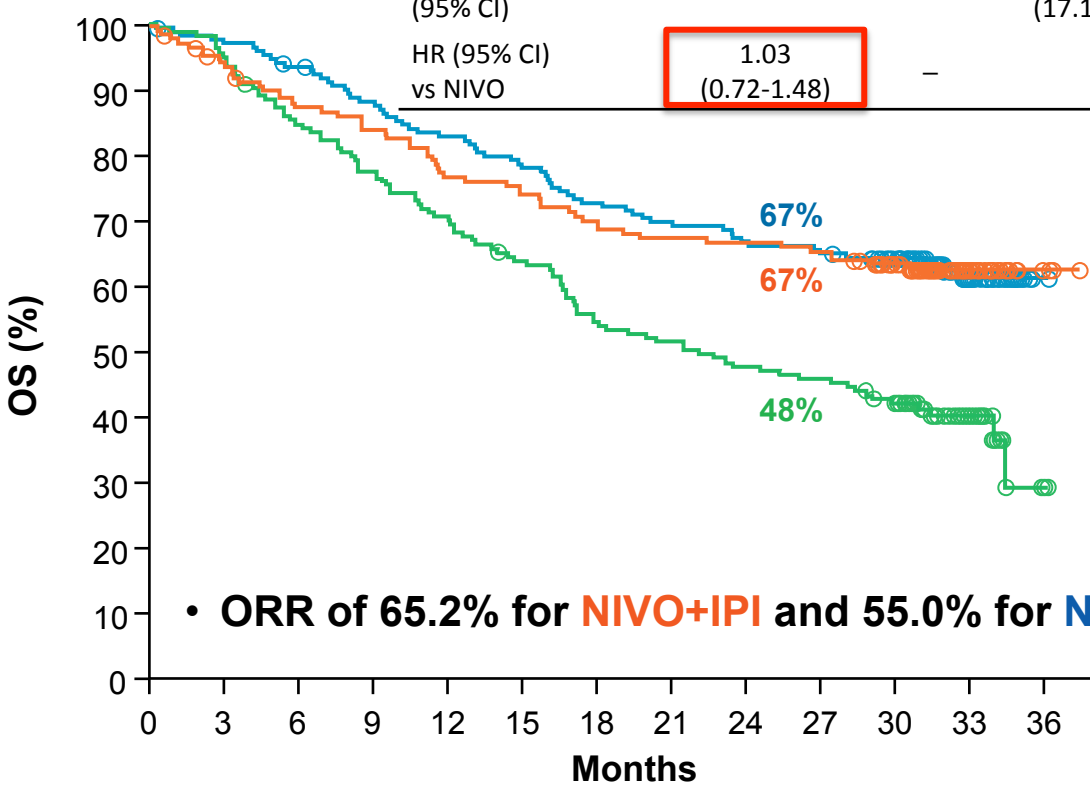
- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

Patients at risk:

NIVO+IPI	123	113	102	91	82	82	79	74	74	72	66	18	4	0
NIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
IPI	113	96	87	79	71	61	57	50	44	43	32	10	1	0

PD-L1 Expression Level ≥1%

≥1% PD-L1	NIVO+IPI	NIVO	I
Median OS, months (95% CI)	NR	NR	2 (17.1
HR (95% CI) vs NIVO	1.03 (0.72-1.48)	–	



- ORR of 65.2% for NIVO+IPI and 55.0% for N

Patients at risk:

NIVO+IPI	155	144	132	127	116	112	105	102	101	99	85	27	3	
NIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	
IPI	164	155	138	126	115	102	89	83	77	74	64	21	2	

arkin J, et al. Presented at: 2017 American Association for Cancer Research Annual Meeting; April 1-5, 2017; Washington, DC. Abstract CT075.

Nivolumab Plus Ipilimumab in First-line NSCLC:

Checkmate 012

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
onfirmed ORR, % (95% CI)	**47** (31, 64)	**39** (23, 55)	**23** (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)
est overall response, %			
Complete response	0	0	8
Partial response	47	39	15
Stable disease	32	18	27
Progressive disease	13	28	38
Unable to determine	8	15	12
Median PFS, mo (95% CI)	8.1 (5.6, 13.6)	3.9 (2.6, 13.2)	3.6 (2.3, 6.6)
-year OS rate, % (95% CI)	NC	69 (52, 81)	73 (59, 83)

calculated (when >25% of patients are censored); NR = not reached

tion data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

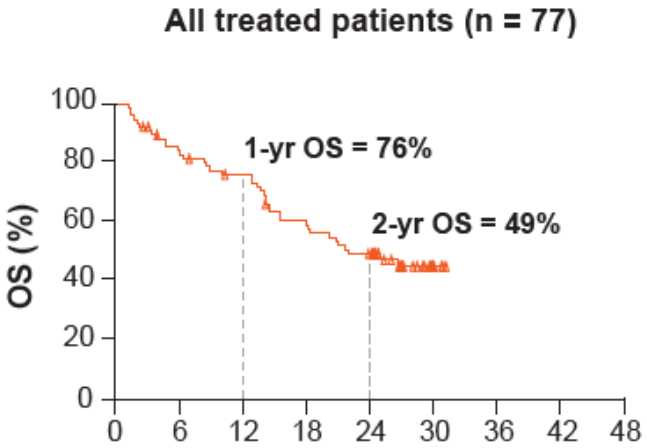
Hellman, ASCO 2016

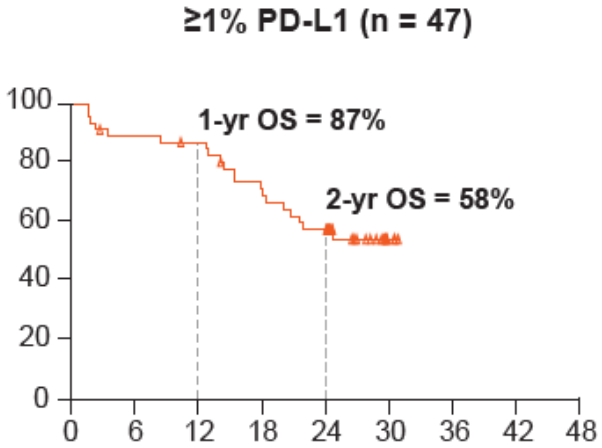
Nivolumab Plus Ipilimumab in First-line NSCLC:

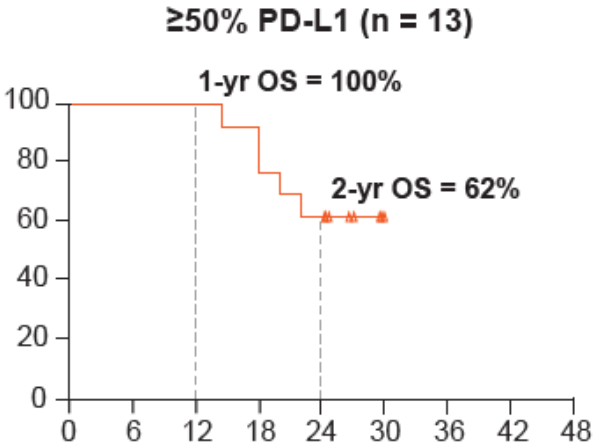
Checkmate 012

Combo catches the PDL1- NSCLC patient?

o 3 Q2W +
1 Q12W/Q6W[a]







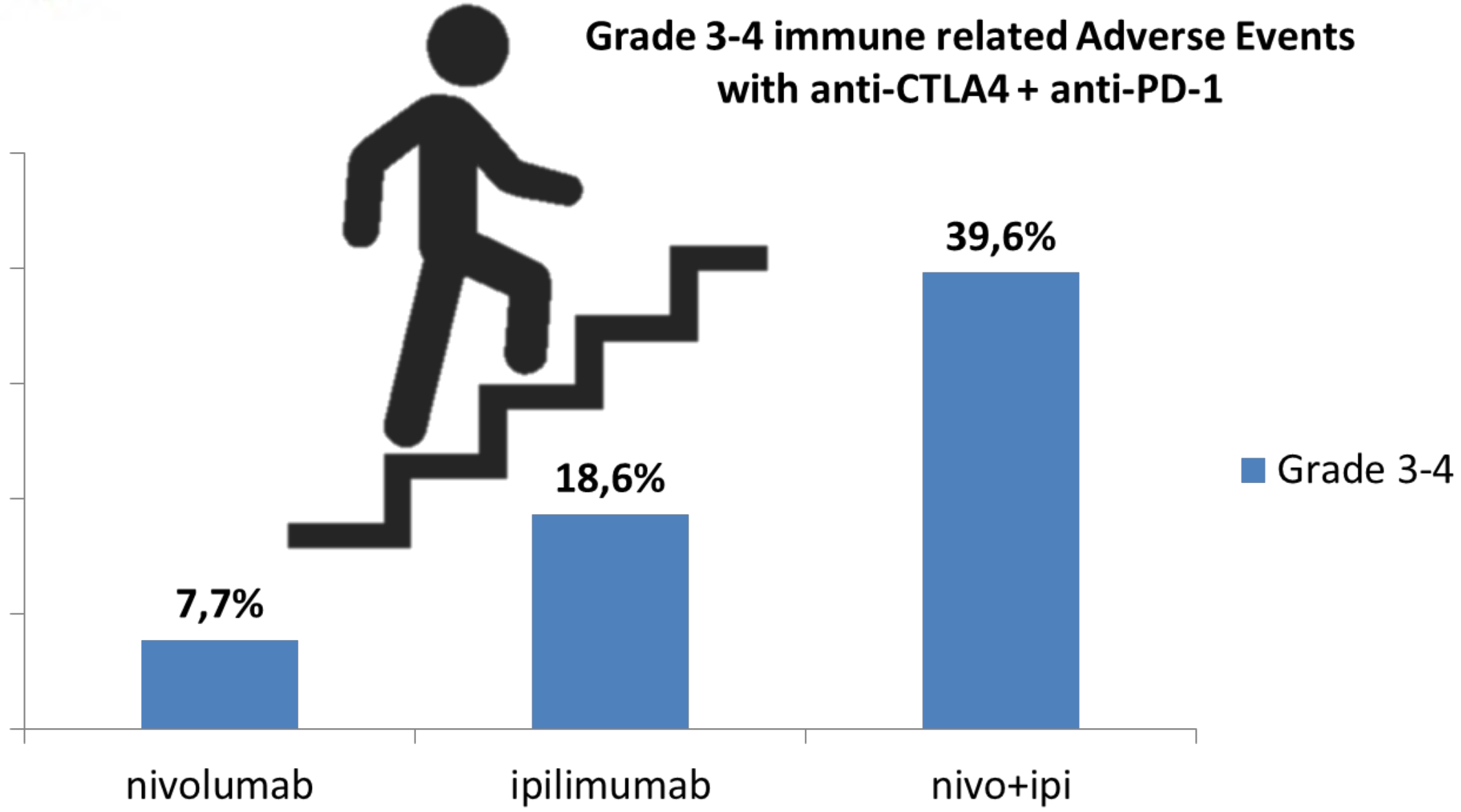
All treated patients (n = 52)

≥1% PD-L1 (n = 32)

≥50% PD-L1 (n = 12)

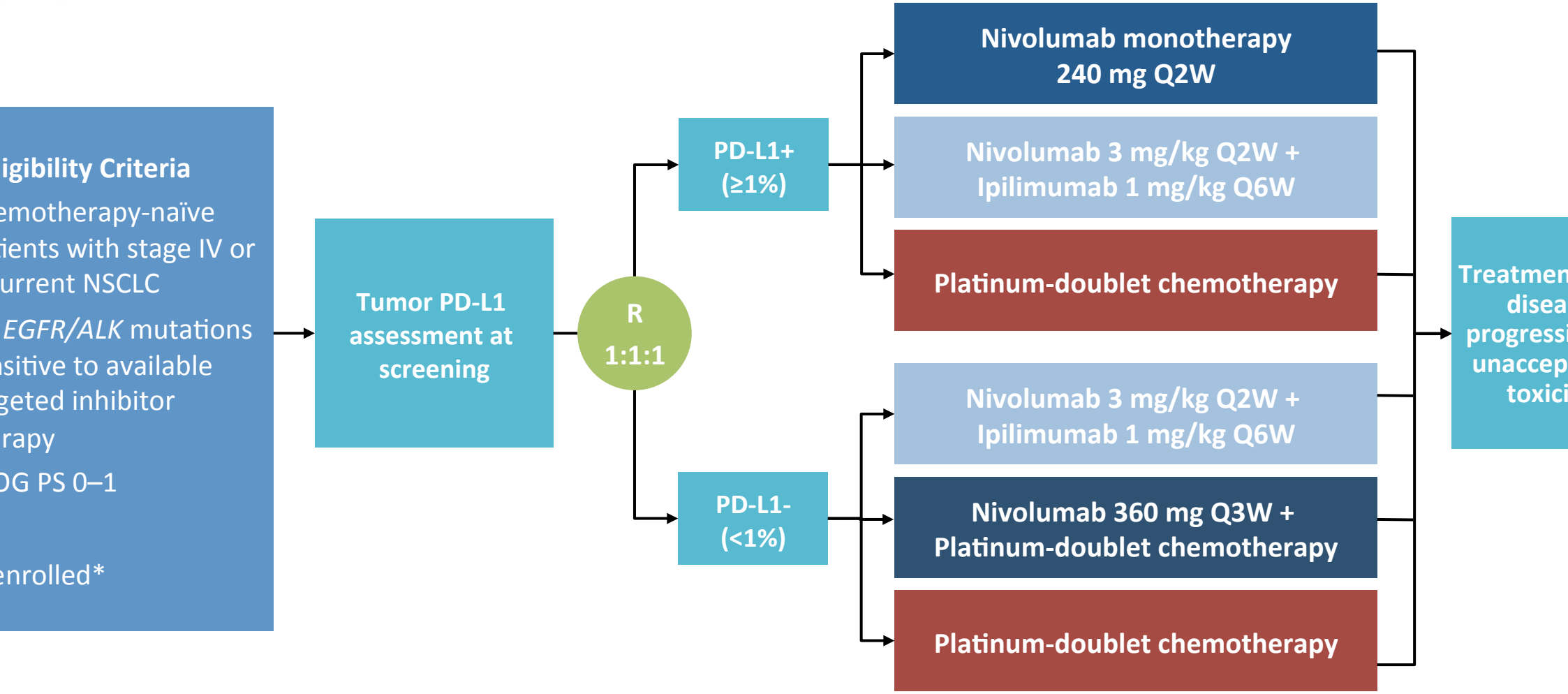
Goldman, ASCO 2017

irAEs are NOT so rare when used in combination



Larkin et al, N Engl J Med 2015

CHECKMATE 227

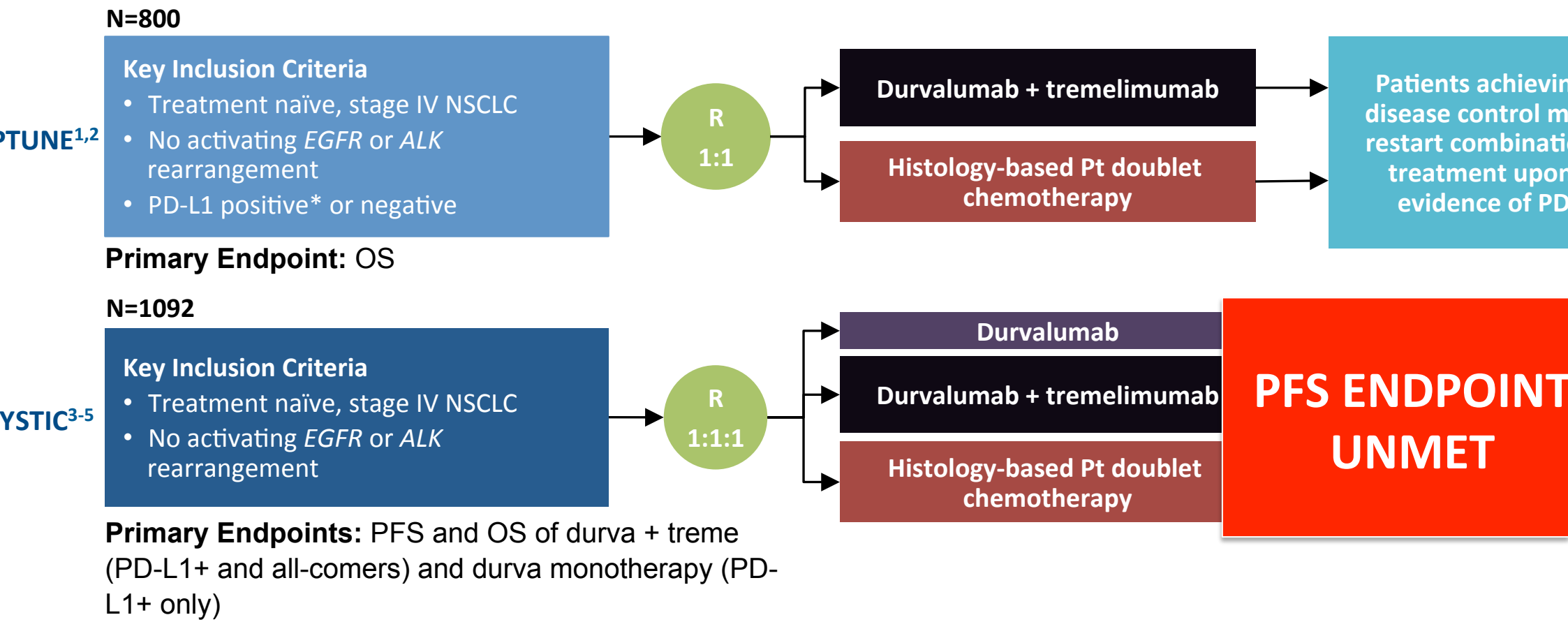


*Stratification factor at randomization: histology (squamous versus non-squamous).
ALK=anaplastic lymphoma kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *EGFR*=epidermal growth factor receptor; I-O=immuno-oncology; NSCLC=non-small cancer; PD-L1=programmed death ligand 1; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; R=randomized.

1. Clinicaltrials.gov. NCT02477826 (CheckMate 227). Accessed April 12, 2017. 2. Data on file. Checkmate 227. Princeton, NJ: Bristol-Myers Squibb Company; 2017.

Neptune and mystic:

Phase 3, open-label trials of anti–PD-L1 ± anti–CTLA-4 vs Pt-based doublet chemotherapy for first-line treatment of stage IV NSCLC



*PD-L1 positivity defined as ≥25% of tumor cells with membrane staining as determined by the Ventana PD-L1 IHC assay.

1. Clinicaltrials.gov. NCT02542293. Accessed April 28, 2017. 2. Mok T et al. Poster presentation at ESMO Asia 2015. 480TiP. 3. Clinicaltrials.gov. NCT02453282. Accessed April 28, 2017. 4. Peters S et al. Poster presentation at ELCC 2016. 191TiP. 5. AstraZeneca [press release]. January 17, 2017.

Immune Checkpoint Blockade for Therapeutic Action Against Multiple Cancer Clones

αPD-1

αPD-L1

αCTLA4

αOX40

α4-1BB

αCD47

αKIR

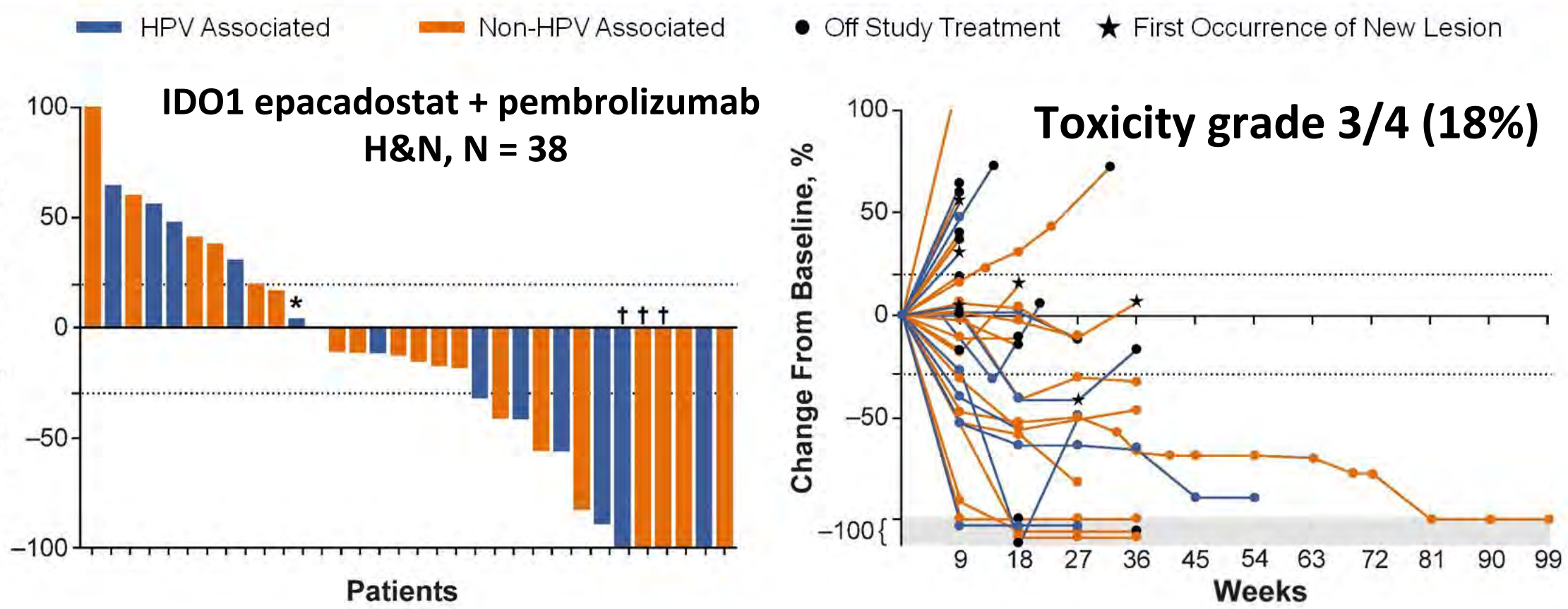
αCD40

αLAG-3

αTIM-3

αGITR

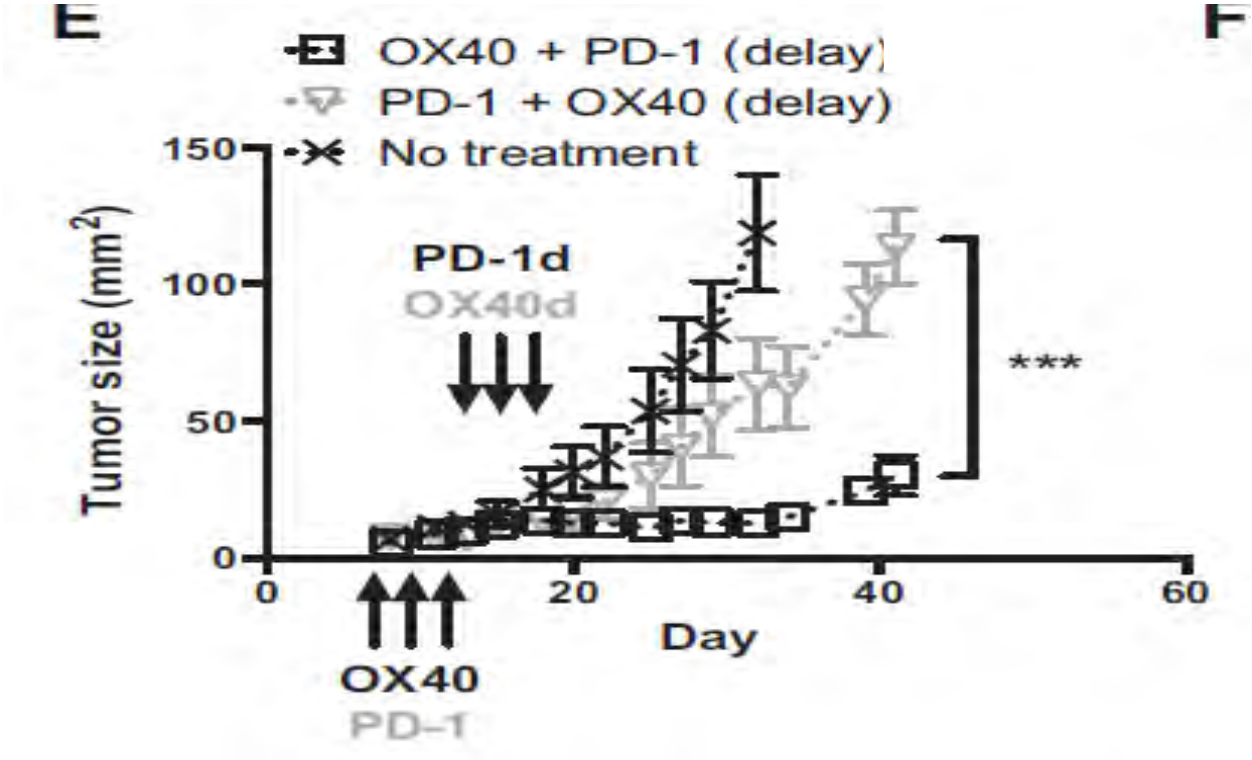
Rising Stars . . . or Not



complete response; HPV, human papillomavirus; PD, progressive disease; PR, partial response; SD, stable disease.
8 efficacy-evaluable patients, data are shown for the 32 with ≥1 postbaseline scan that included assessment of target lesions. Six patients are not included in this figure: 2 patients were PD per
ons (target lesions were not assessed); 2 patients had clinical progression and discontinued treatment prior to the first postbaseline scan; and 2 patients died before the first postbaseline scan.
verall response is PD (SD per target lesions, PD per new lesions). † Overall response is PR (CR per target lesions, non-CR/non-PD per nontarget lesions).

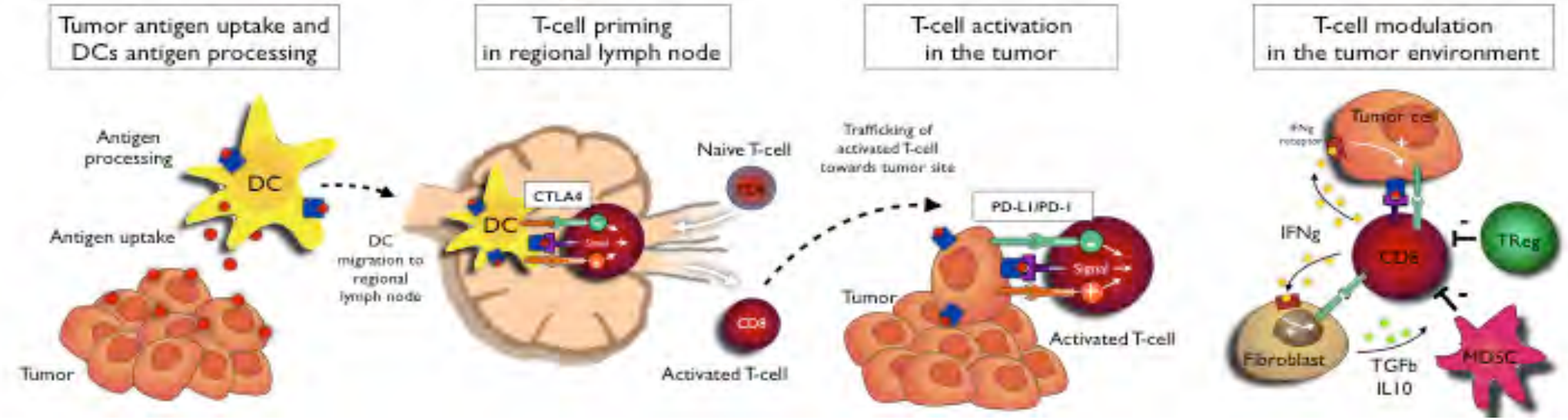
al. ASCO 2017. Abstract 6010; Messenheimer DJ, et al. *Clin Cancer Res.* 2017 Aug 28. Epub ahead of print.

Rising Stars . . . or Not



ner DJ, et al. *Clin Cancer Res.* 2017 Aug 28. Epub ahead of print.

IO-CT



Immunogenic cell death
CT, RT

Up-regulation of MHCI
Paclitaxel, gemcitabine, erlotinib

DC maturation
Paclitaxel, docetaxel, bevacizumab

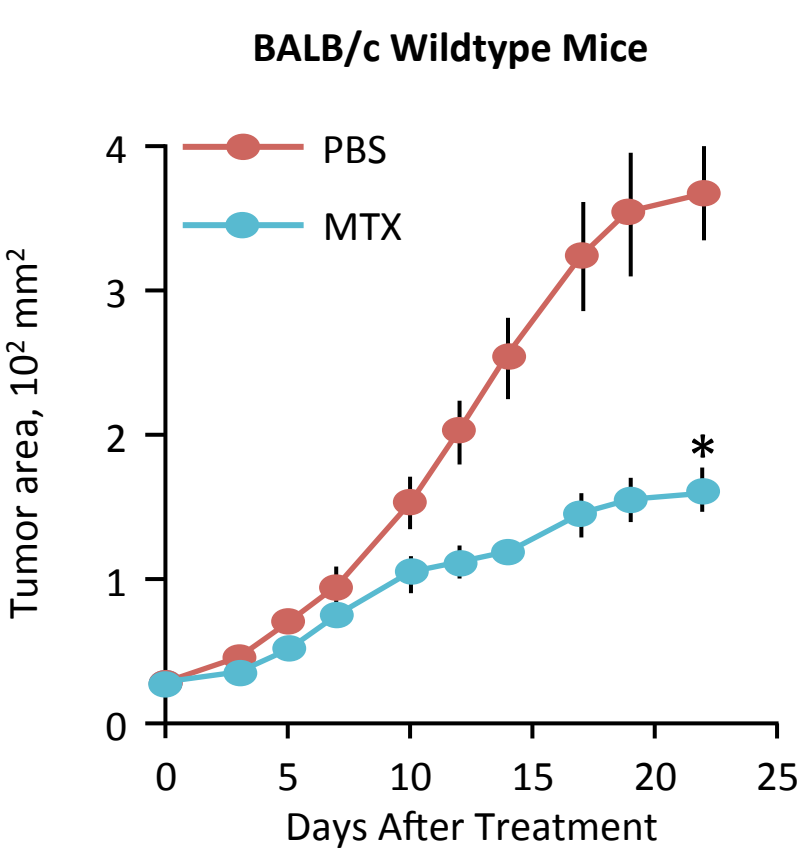
Up-regulation of PD-L1
Paclitaxel, etoposide

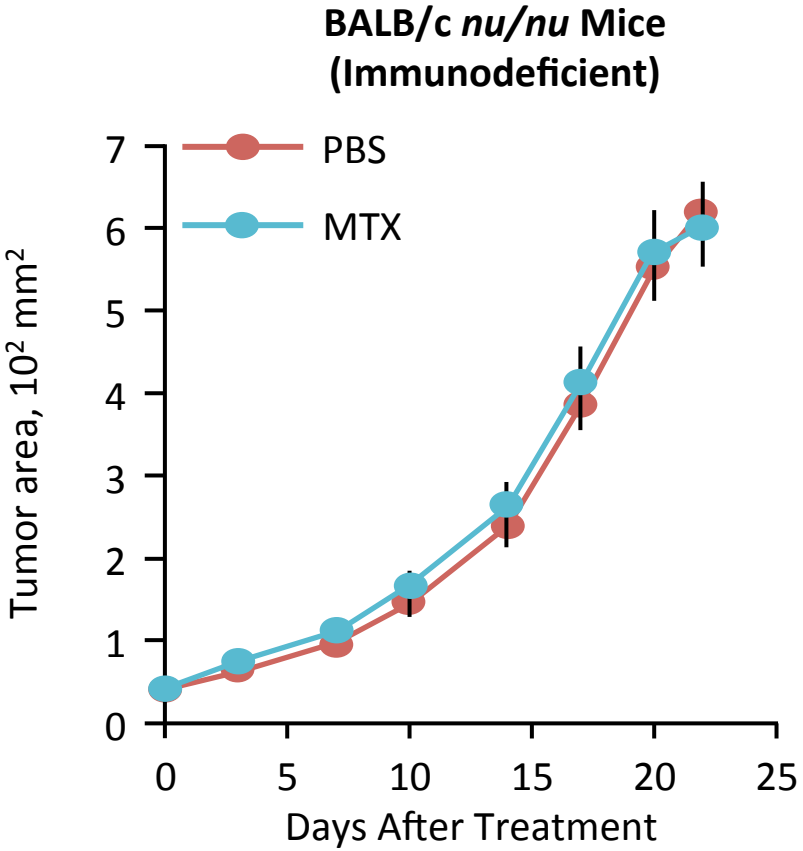
T-Reg inhibition
Cisplatin, paclitaxel, bevacizumab

Down-regulation of PD-L1
Pi3K? MEKi? crizotininb

T, chemotherapy; DC, dendritic cell; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; RT, radiotherapy; TReg, T regulatory cells
hampiat S, et al. *J Thorac Oncol.* 2014;9(2):144-153. Galluzzi L, et al. *Cancer Cell.* 2015;28(6):690-714.

Chemotherapy Efficacy & the Immune System



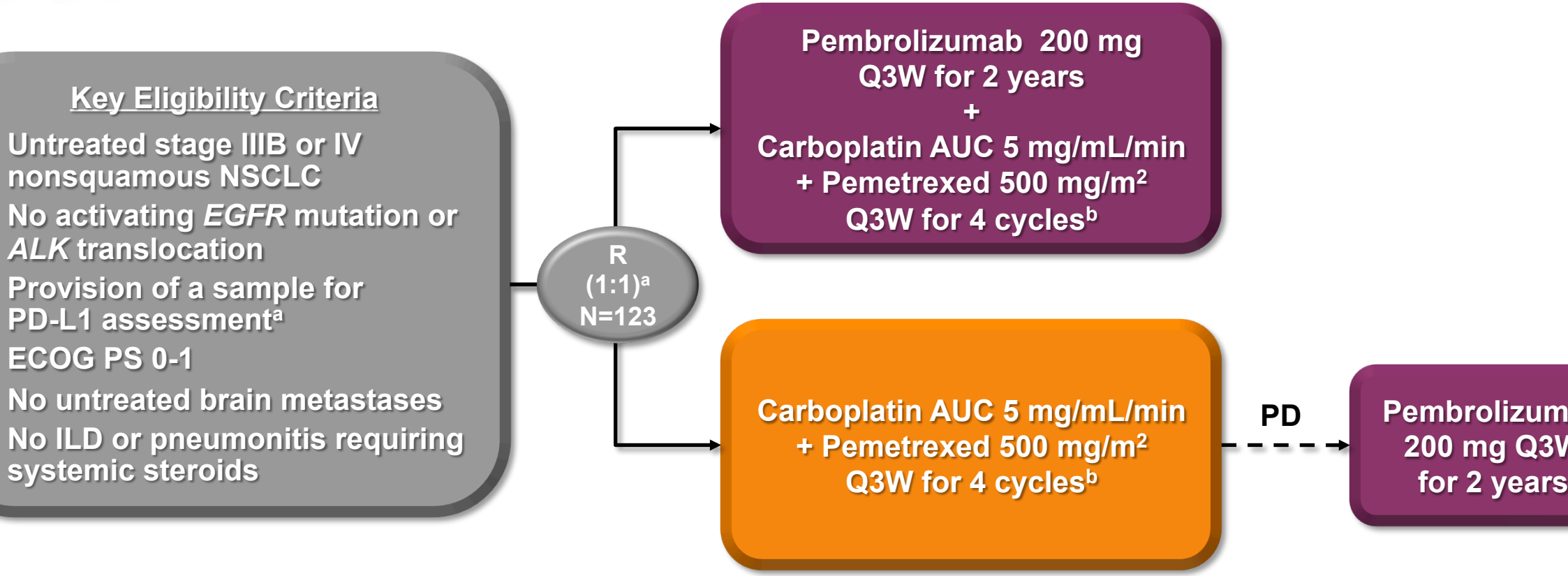


*P<.05; n = 10 mice per group; means ± SEM are s

TX, mitoxantrone; PBS, phosphate-buffered saline (control)

lichaud M, et al. *Science.* 2011;334(6062):1573-1577.

KEYNOTE-021 Cohort G



nd Points

rimary: ORR (RECIST v1.1 per blinded, independent central review)

ey secondary: PFS

ther secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

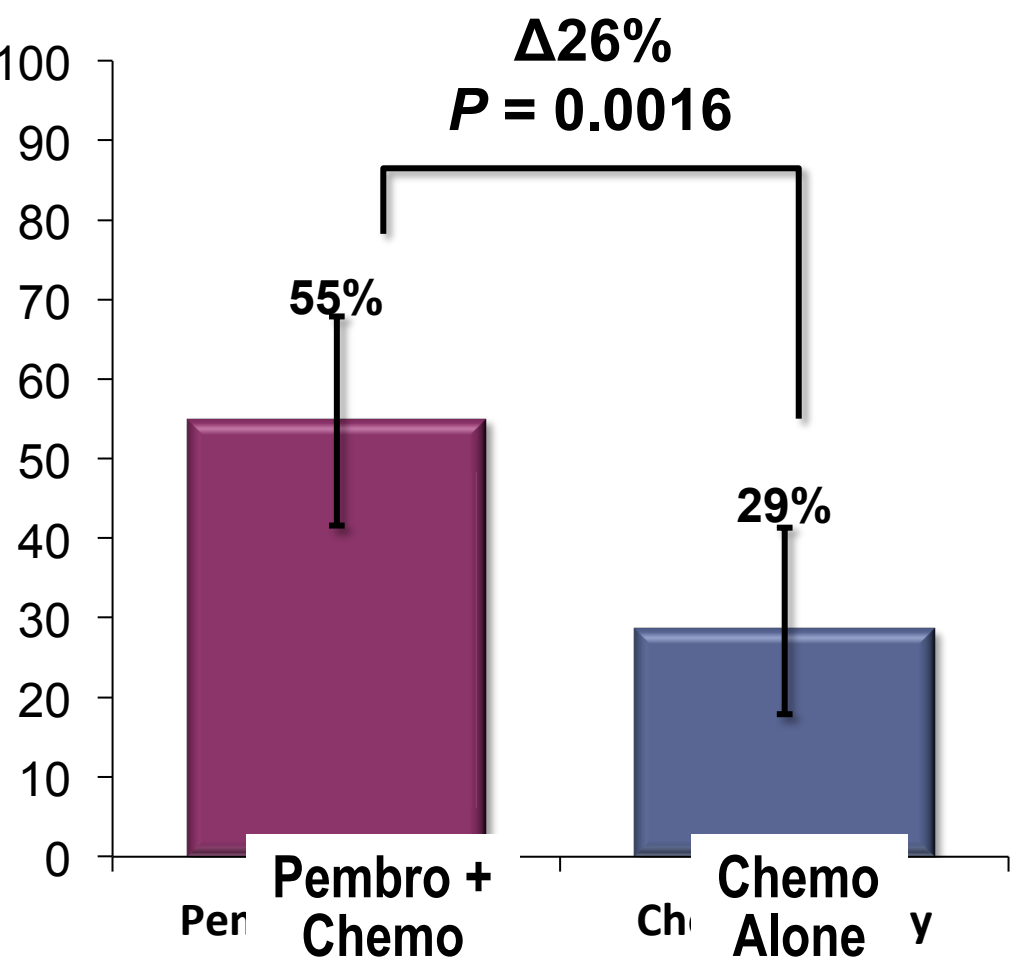
ization was stratified by PD-L1 TPS <1% vs ≥1%.
e maintenance therapy with pemetrexed 500 mg/m² Q3W permitted.

Baseline Characteristics

	Pembro + Chemo N = 60	Chemo Alone N = 63
Median age (range), y	62.5 (40-77)	66.0 (37-80)
Women, n (%)	38 (63)	37 (59)
ECOG PS 1, n (%)	35 (58)	34 (54)
Adenocarcinoma histology, n (%)	58 (97)	55 (87)
Stage IV disease, n (%)	59 (98)	60 (95)
Smoking status, n (%)		
Current or former	45 (75)	54 (86)
Never	15 (25)	9 (14)
Stable brain metastases, n (%)	9 (15)	6 (10)
PD-L1 TPS, n (%)		
<1%	21 (35)	23 (37)
1%-49%	19 (32)	23 (37)
≥50%	20 (33)	17 (27)

off: August 8, 2016.

Objective Response

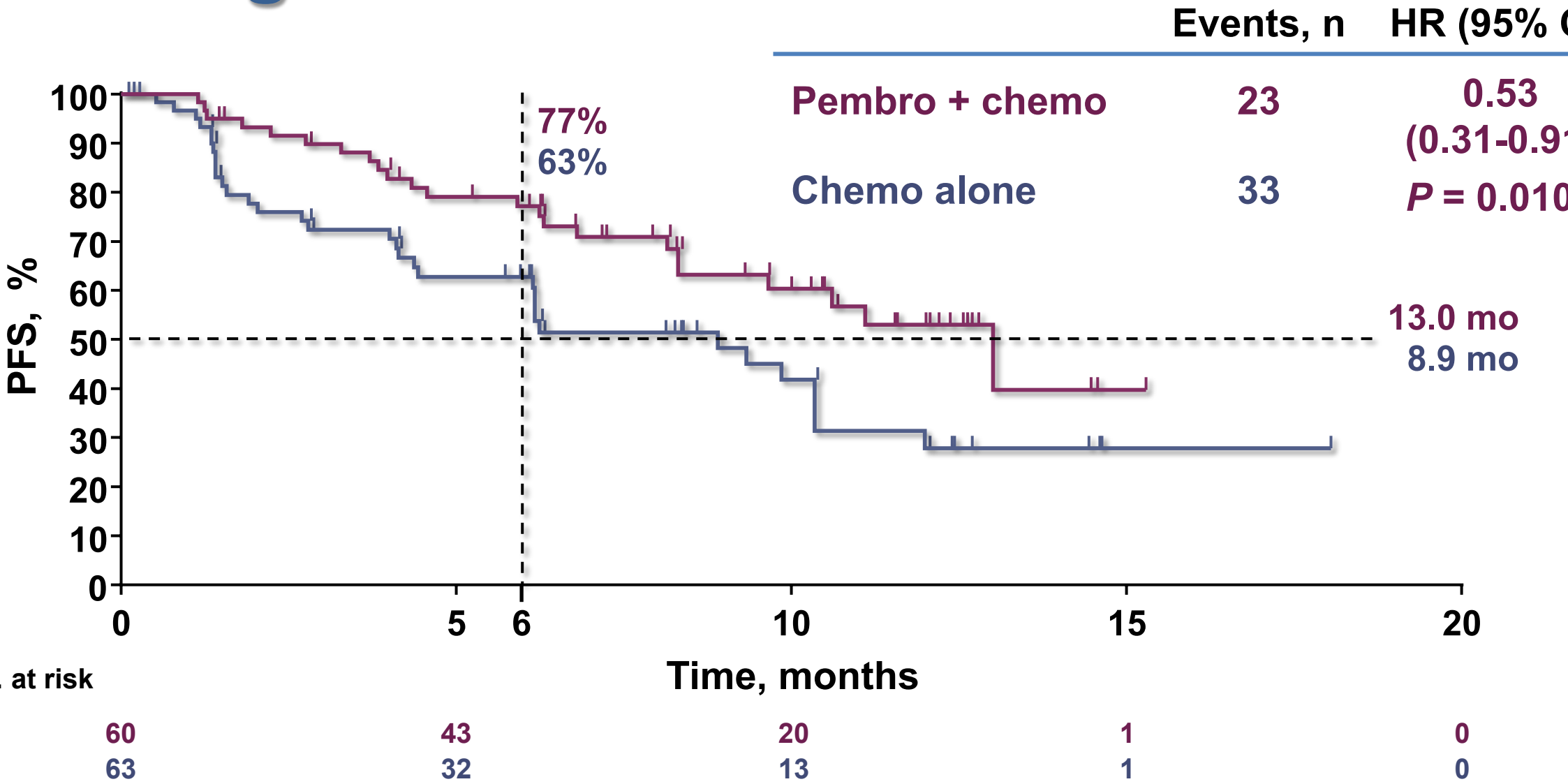


	Pembro + Chemo Responders n = 33	Chemo Alo Responde n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2
Ongoing response,[a] n (%)	29 (88)	14 (78)

per RECIST v1.1 by blinded, independent central review.
off: August 8, 2016.

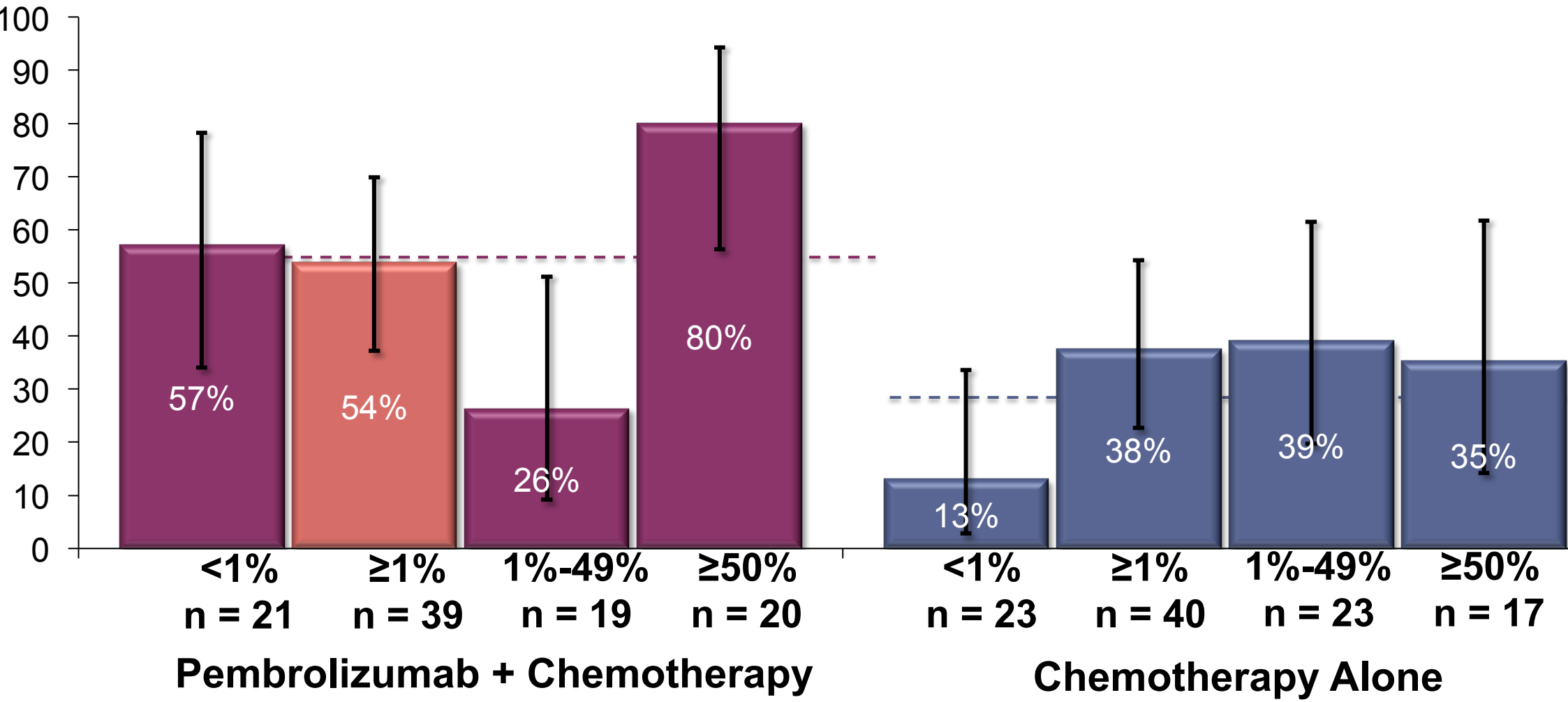
DOR = duration of response; TTR = time to response.
[a]Alive without subsequent disease progression.

Progression-Free Survival



per RECIST v1.1 by blinded, independent central review.
off: August 8, 2016.

Objective Response by PD-L1 TPS



l dotted lines represent the ORR in the total population.
per RECIST v1.1 by blinded, independent central review.
off: August 8, 2016.

KEYNOTE-021 Cohort G

y eligibility
teria

Untreated stage
V NSCLC

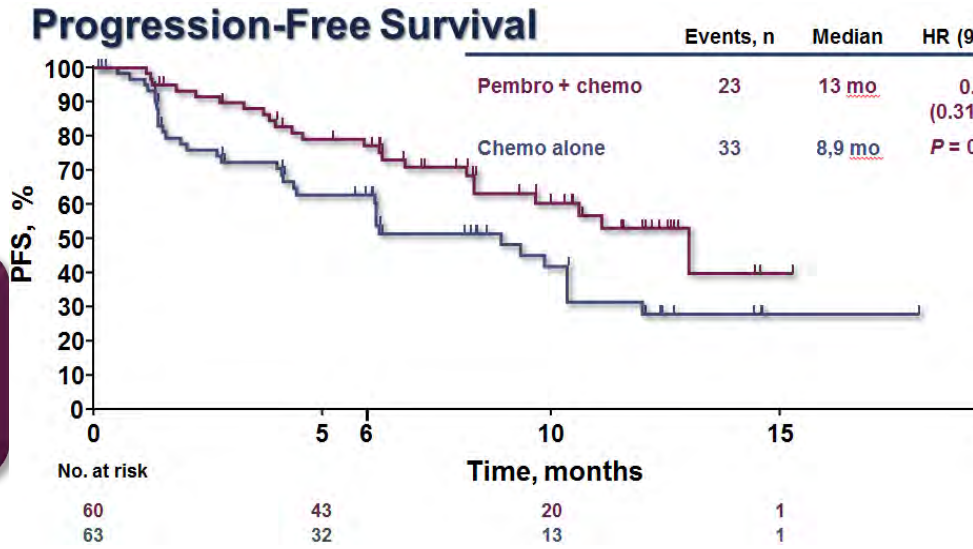
NY PD-L1

Pembrolizumab Q3W for 2 years + Carboplatin + Pemetrexed Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for 2 years

Carboplatin + Pemetrexed Q3W for 4 cycles

Primary endpoint: ORR

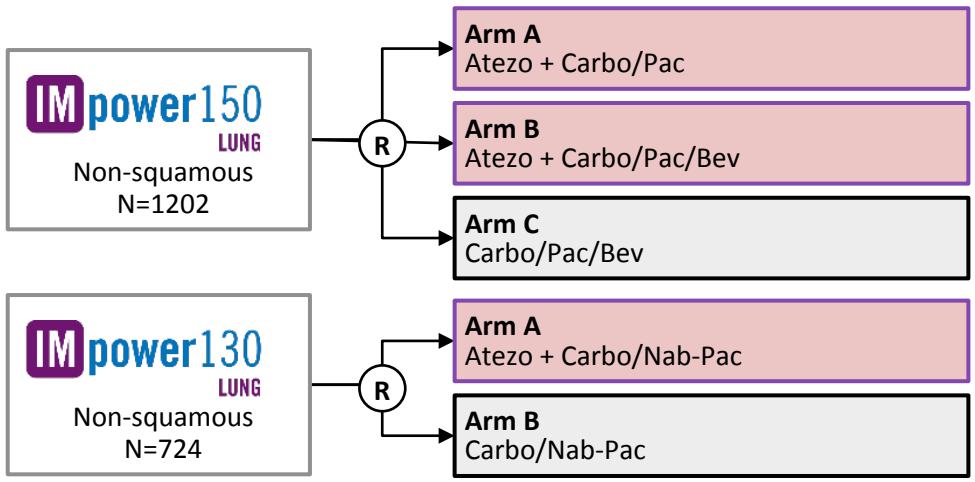


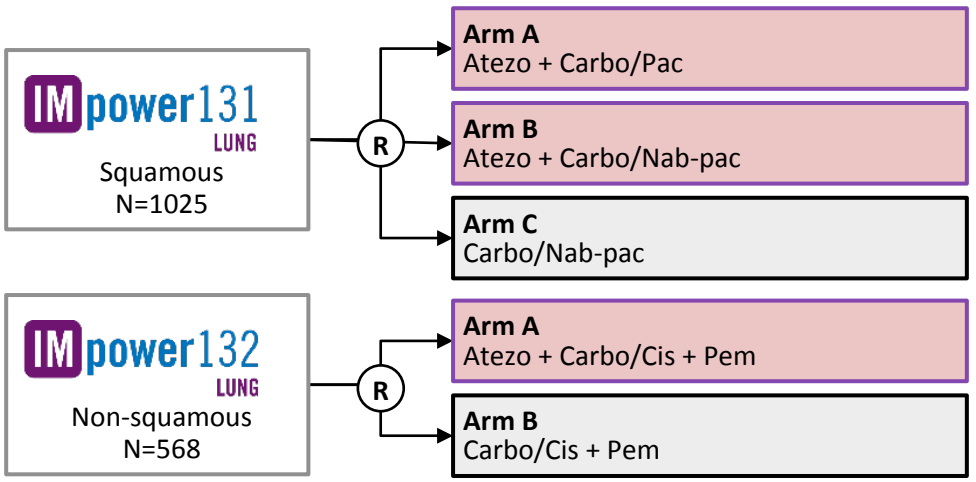
FDA approved

- For PD-L1+ >50% (~30%)
- Pembro alone might be enough
- Risk: overtreatment

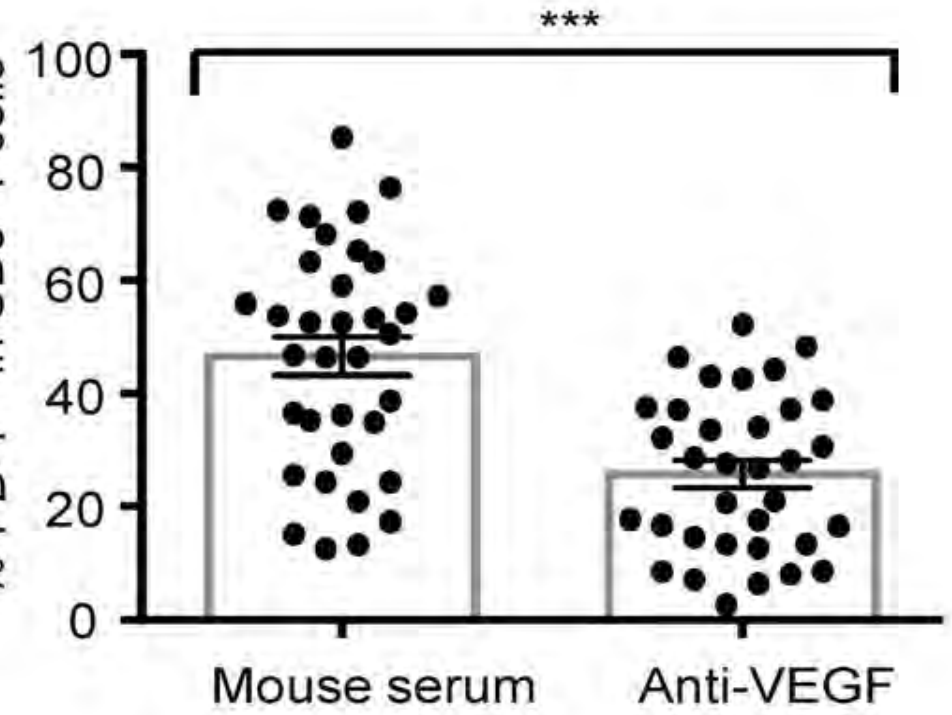
al. *Lancet Oncol.* 2016;17(11):1497-1508.

Atezolizumab clinical development programme in first-line NSCLC



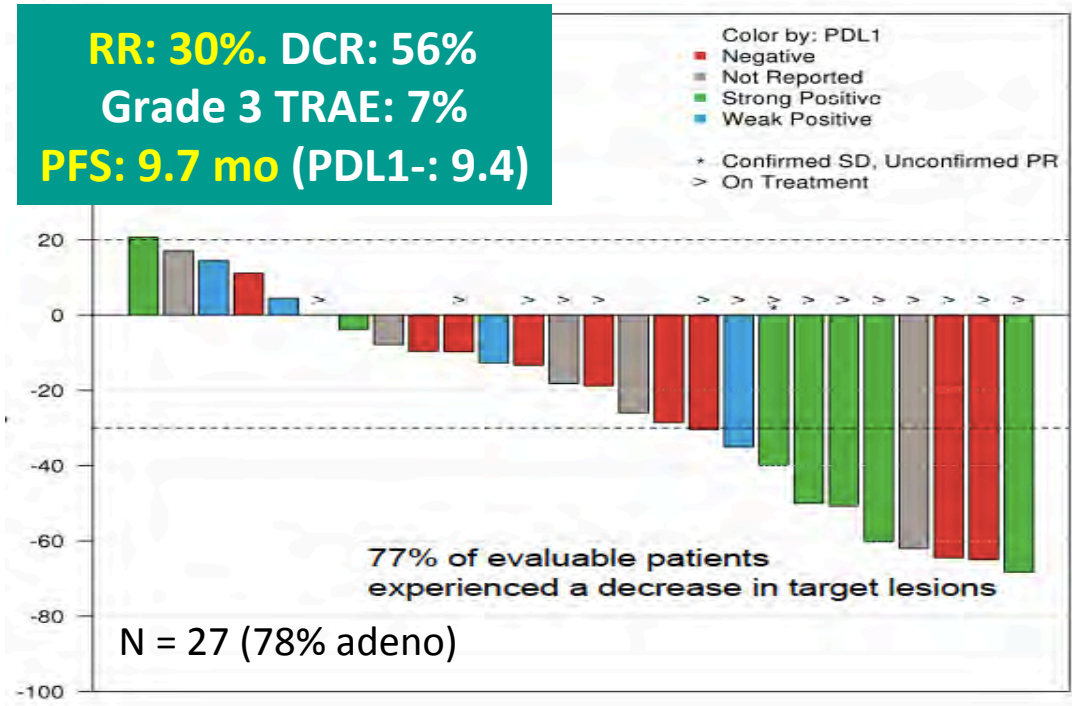


IO + Antiangiogenic



Phase I: Pembrolizumab + ramucirumab
41% PD-L1 (≥50%: 26%)

RR: 30%. DCR: 56%
Grade 3 TRAE: 7%
PFS: 9.7 mo (PDL1-: 9.4)

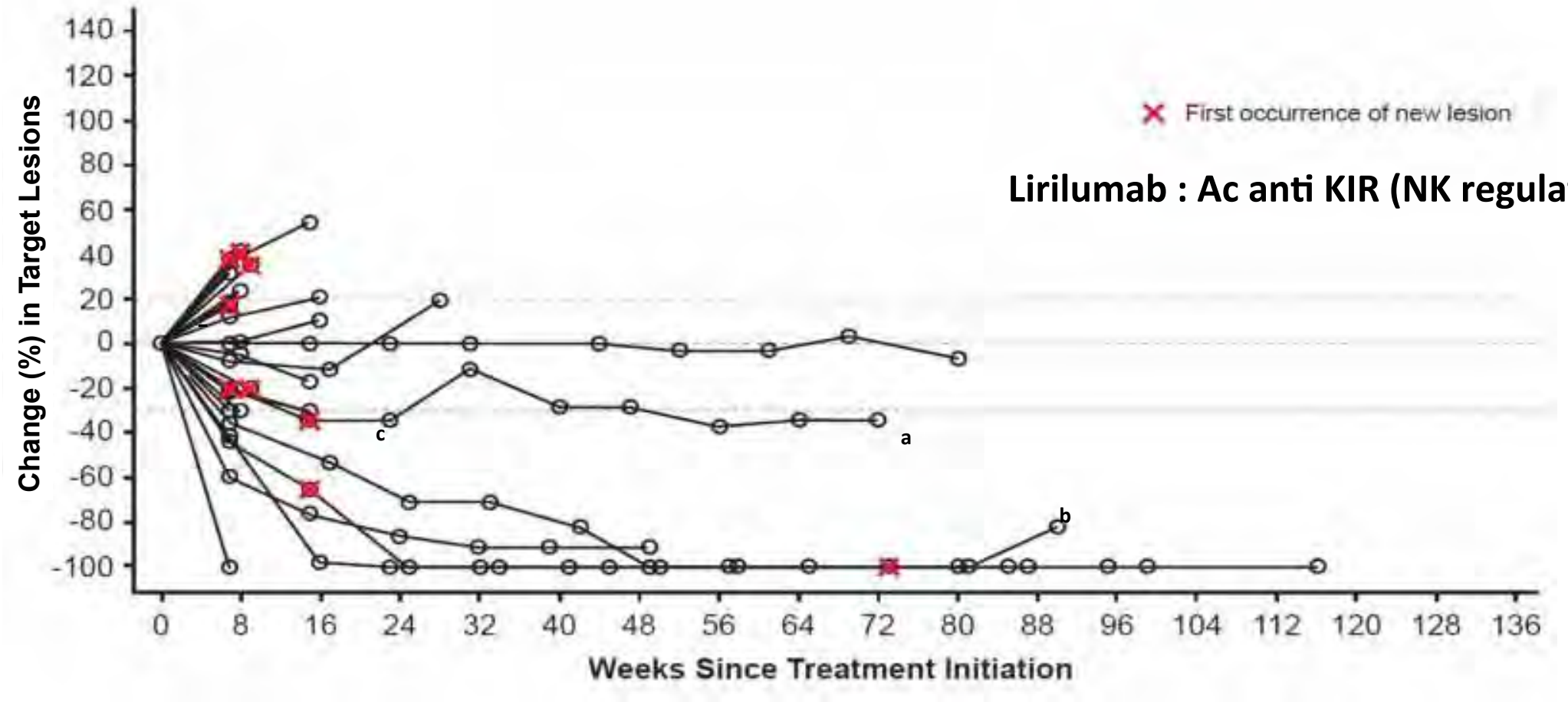


NCT02856425: Phase I trial of pembro + ninted

NCT03074513: Phase II trial of atezolizumab + **BVZ**

t al. ELCC 2017. Abstract 89PD; Voron T, et al. J Exp Med. 2015;212(2):139-148.

Preliminary Percent Change From Baseline in Target Lesions
r Time in Patients With SCCHN Treated With Lirilumab + Nivolumab (n = 2



Lirilumab : Ac anti KIR (NK regulation)

The median duration of response was not reached

6 of 29 evaluable patients had a post-baseline assessment.

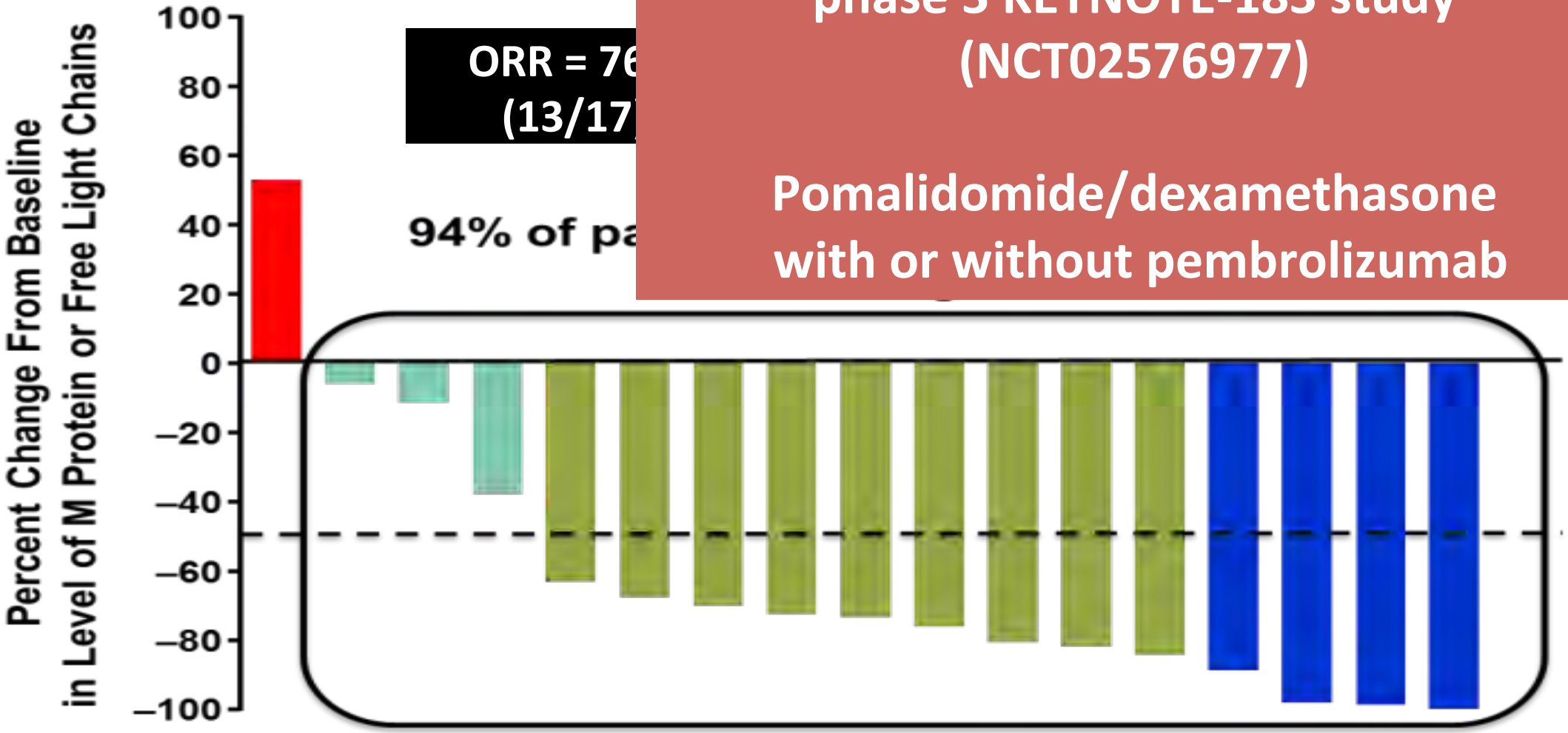
atient with a 37% reduction in target lesion classified as SD. [b] Patient with a 100% reduction in target lesion classified as SD. [c] Patient with a 30% reduction in target lesion classified as PD.

eidner R, et al. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 456.

Lenalidomide + Anti–PD-1 in Multiple Myeloma

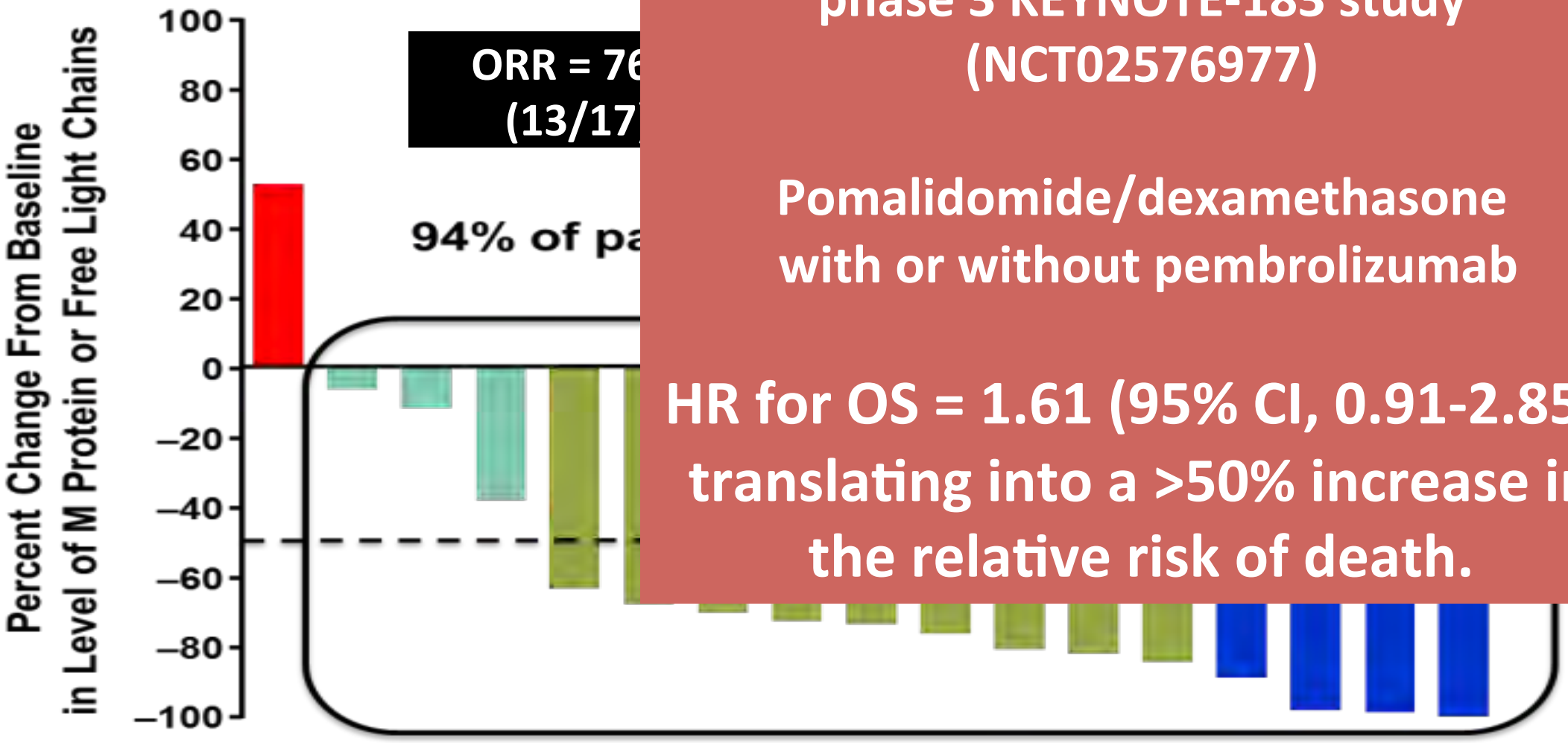
phase 3 KEYNOTE-183 study (NCT02576977)

Pomalidomide/dexamethasone with or without pembrolizumab



an Miguel J, et al. Presented at: 57th American Society of Hematology Annual Meeting; December 5-8, 2015; Orlando, FL. Abstract 505.

Lenalidomide + Anti–PD-1 in Multiple Myeloma



phase 3 KEYNOTE-183 study (NCT02576977)

Pomalidomide/dexamethasone with or without pembrolizumab

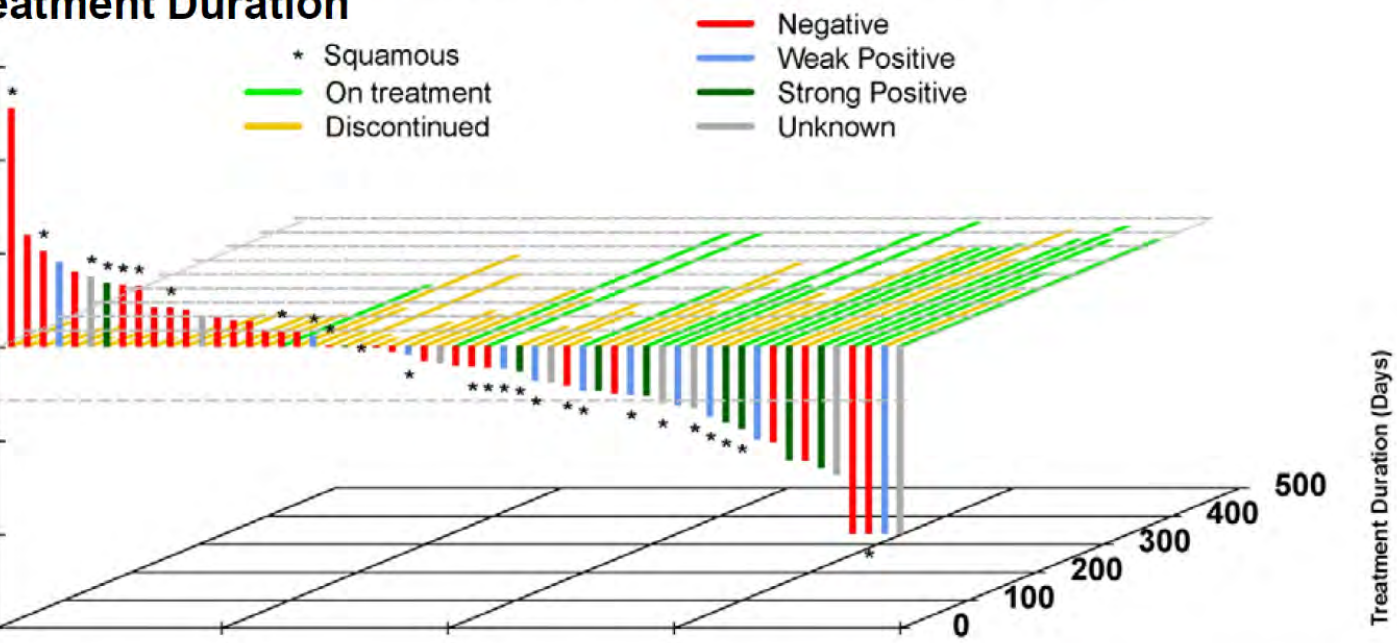
HR for OS = 1.61 (95% CI, 0.91-2.85), translating into a >50% increase in the relative risk of death.

an Miguel J, et al. Presented at: 57th American Society of Hematology Annual Meeting; December 5-8, 2015; Orlando, FL. Abstract 505.

DA Alerts Healthcare Professionals and Oncology Clinical Investigators about Two Clinical Trials on Hold Evaluating KEYTRUDA® embrolizumab) in Patients with Multiple Myeloma. https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm. Accessed August 31, 2017.

PEMBROLIZUMAB – NECITUMUMAB (Ab EGFR)

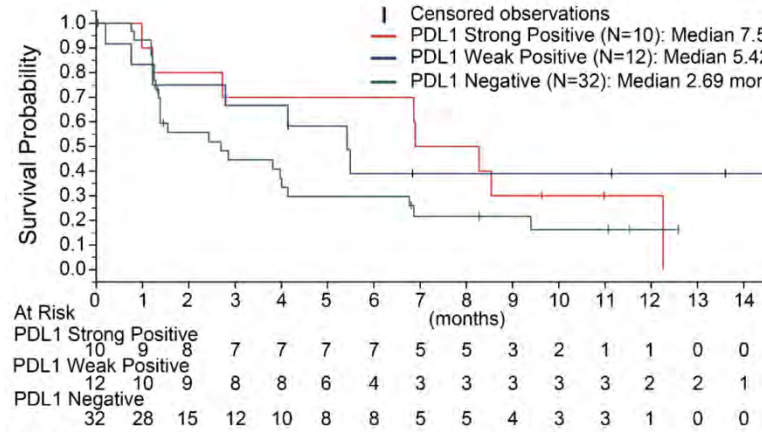
e 1. Best Percent Change from Baseline in Tumor Size
eatment Duration



ORR = 23%

N=64

PDL1- 50% / ~50% squ an



Note: PDL1 status Unknown group was not included in this plot because this group does provide any relevant interpretation

Immunotherapy 1st line in EGFR-mutant

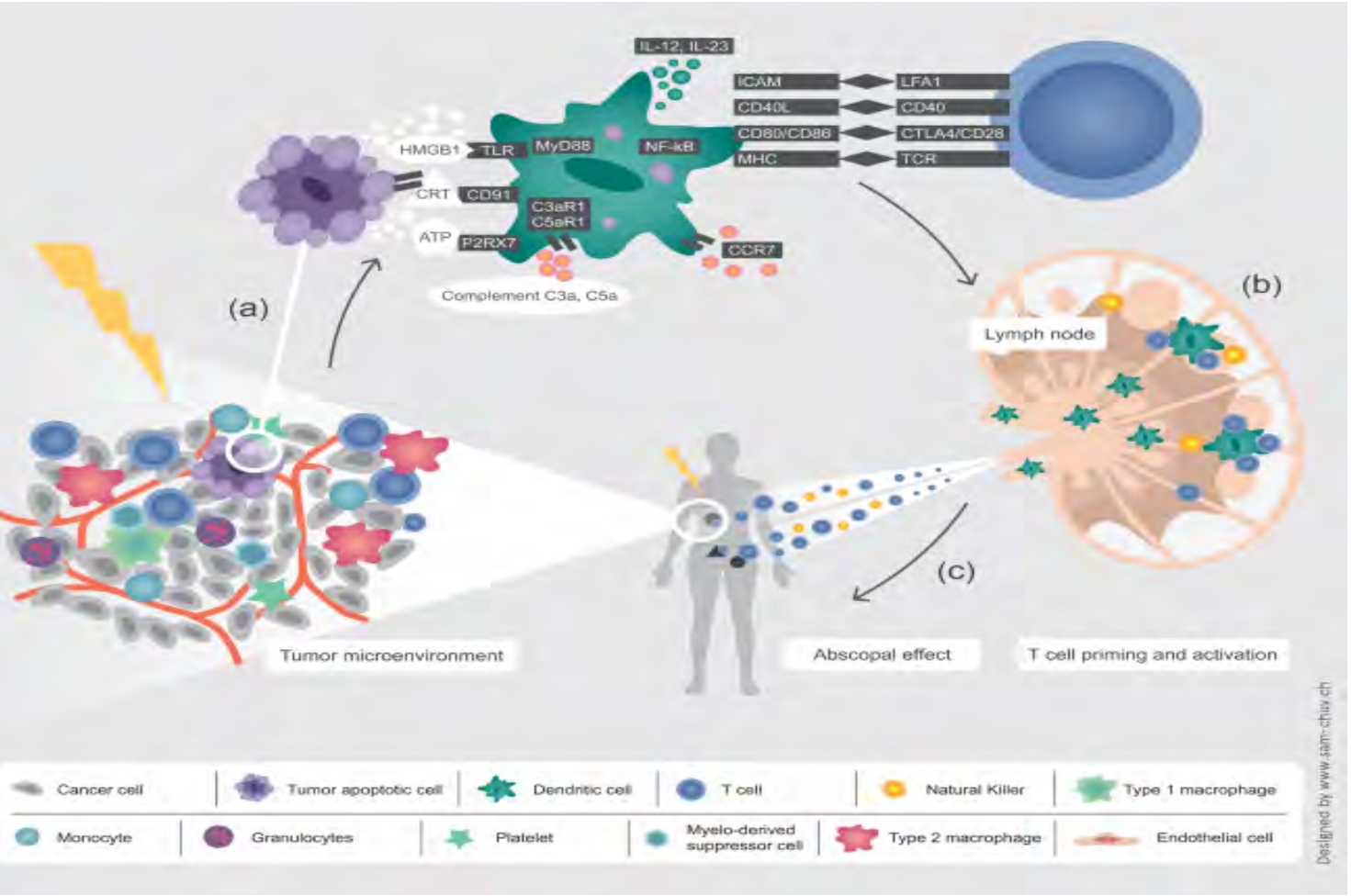
- **Erlotinib and Atezolizumab phI (NCT02013219)**
  - N=20. ORR: 75%. PFS 11.3 mo. Grade 3-4 AE's: 39%

- **Osimertinib + Immune checkpoint inhibitors?**
  - **TATTON phI** (NCT02143466), **CAURAL phIII** (NCT02454933)
  - TATTON:
    - ORR *T790M* + *vs.* -: 67% *vs*. 21%, and 70% in 1st line treatment,
    - 26% and 64% of ILD in 2nd and 1st line, respectively .

EGFR TKI alone as 1st line treatment in ph III, ORR: ~ 70%, PFS: ~ 9-13 months

Ahn – ELCC 2016 (A136O) * Rudin – WCLC 2016 (A5215) * Gibbons – JTO 2016* Reguart – Future Oncol 2015

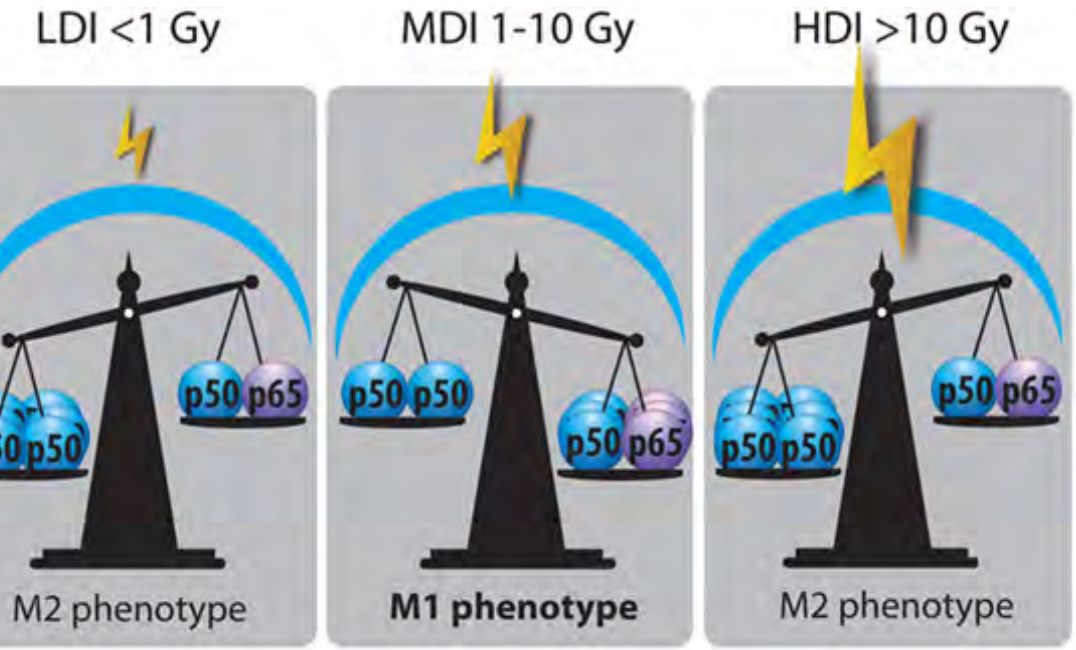
IO-RT: Lung

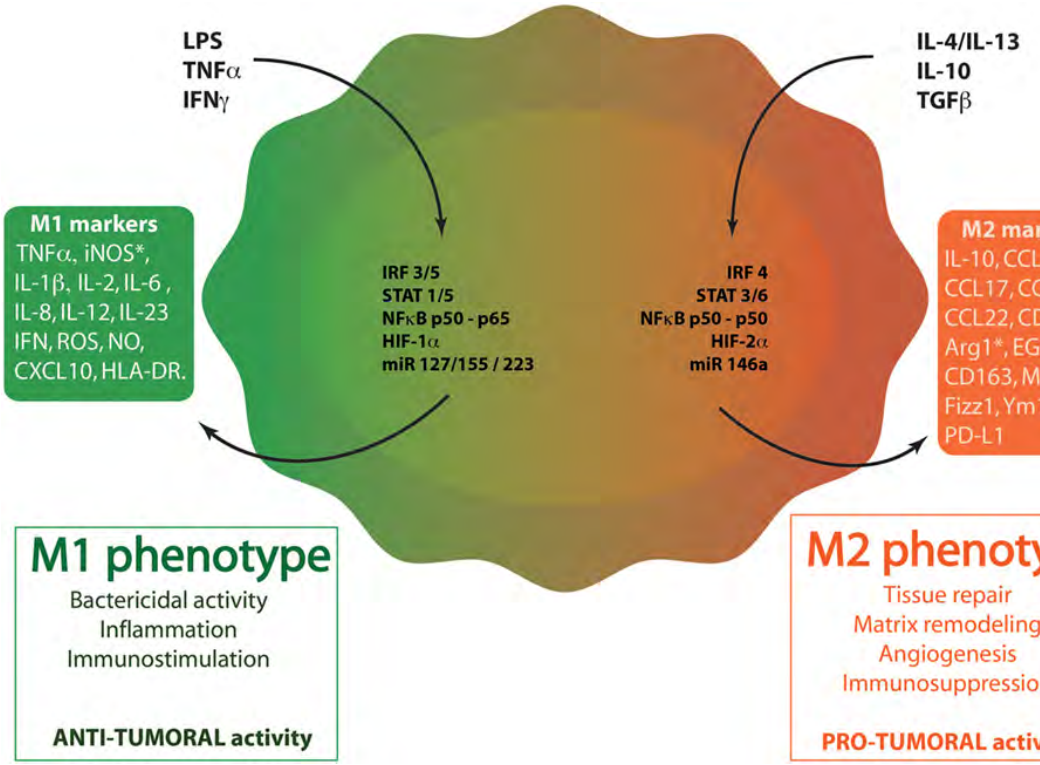


- In situ vaccination
- T-cell priming
- Trafficking, infiltration, and killing

et al. *CA Cancer J Clin.* 2017;67(1):65-85.

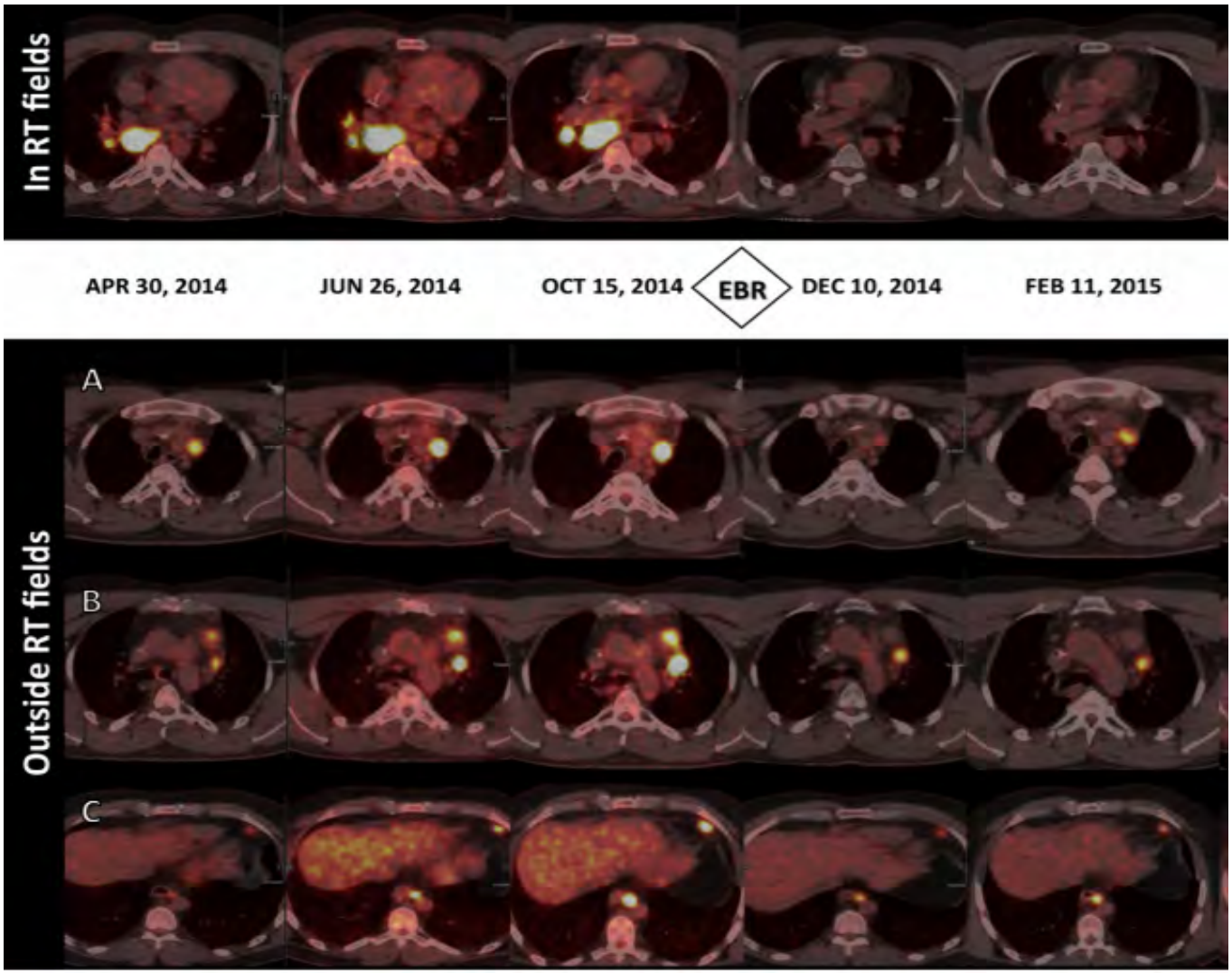
IO-RT: Lung





t al. *Front Immunol.* 2017;8:828.

Abscopal Effect in a Patient With Hodgkin Lymphoma Treated by PD-1 Antibody

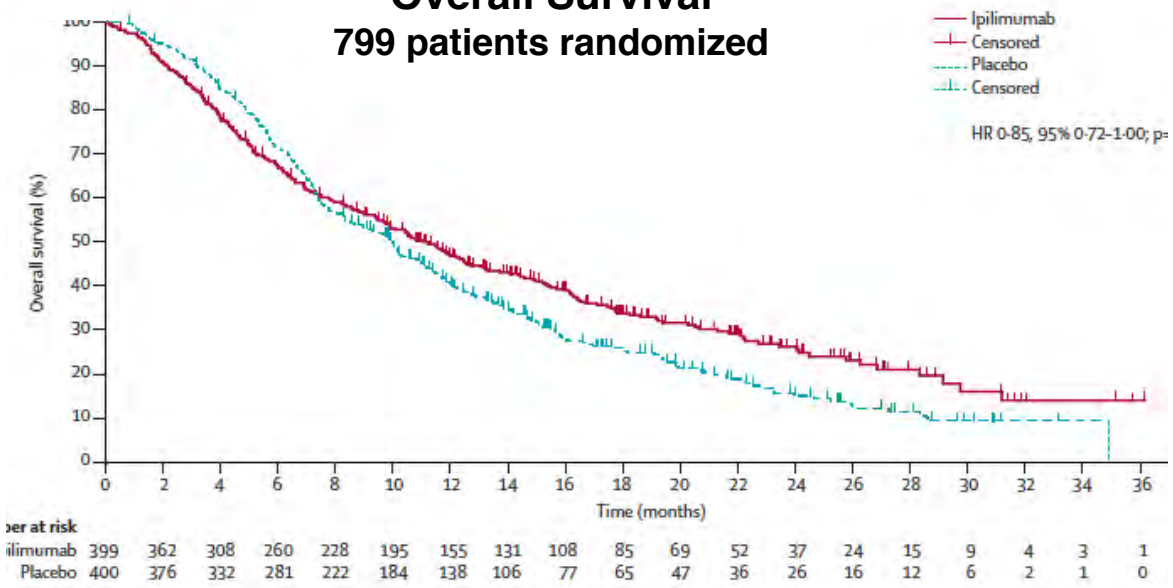


ichot JM, et al. *Eur J Cancer*. 2016;66:91-94.

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043 a multicentre, randomised, double-blind, phase 3 trial

*Eugene D Kwon, Charles G Drake, Howard I Scher, Karim Fizazi, Alberto Bossi, Alfons J M van den Eertwegh, Michael Krainer, Nadine Houede, Ricardo Santos, Hakim Mahammedi, Siobhan Ng, Michele Maio, Fabio A Franke, Santhanam Sundar, Neeraj Agarwal, Andries M Bergman, Tudor E Ciuleanu, Ernesto Korbenfeld, Lisa Sengeløv, Steinbjorn Hansen, Christopher Logothetis, Tomasz M Beer, M Brent McHenry, Paul Gag David Liu, Winald R Gerritsen, for the CA184-043 Investigators**

Overall Survival
799 patients randomized



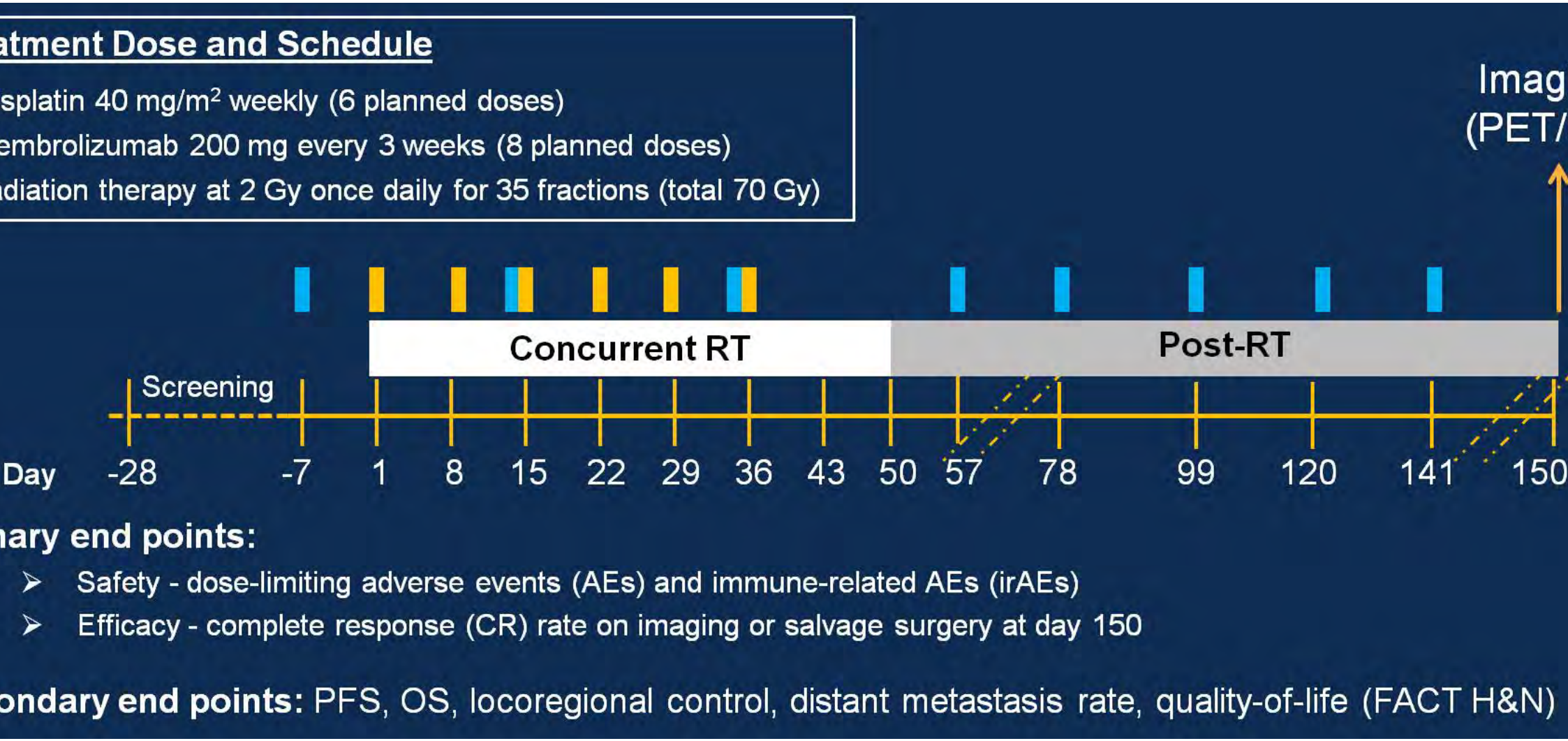
Study powered to detect a 4 month difference in median overall survival (15.8 months versus 12.0 months)

Radiotherapy

Site:	Bone metastases
Dose:	8 Gy, single fraction
Time:	Radiotherapy within 2 days from ipilimumab, then anytime during ipilimumab

won ED, et al. *Lancet Oncol*. 2014;15(7):700-712.

IO – RT in H&N



nary end points:

- Safety - dose-limiting adverse events (AEs) and immune-related AEs (irAEs)
- Efficacy - complete response (CR) rate on imaging or salvage surgery at day 150

ondary end points: PFS, OS, locoregional control, distant metastasis rate, quality-of-life (FACT H&N)

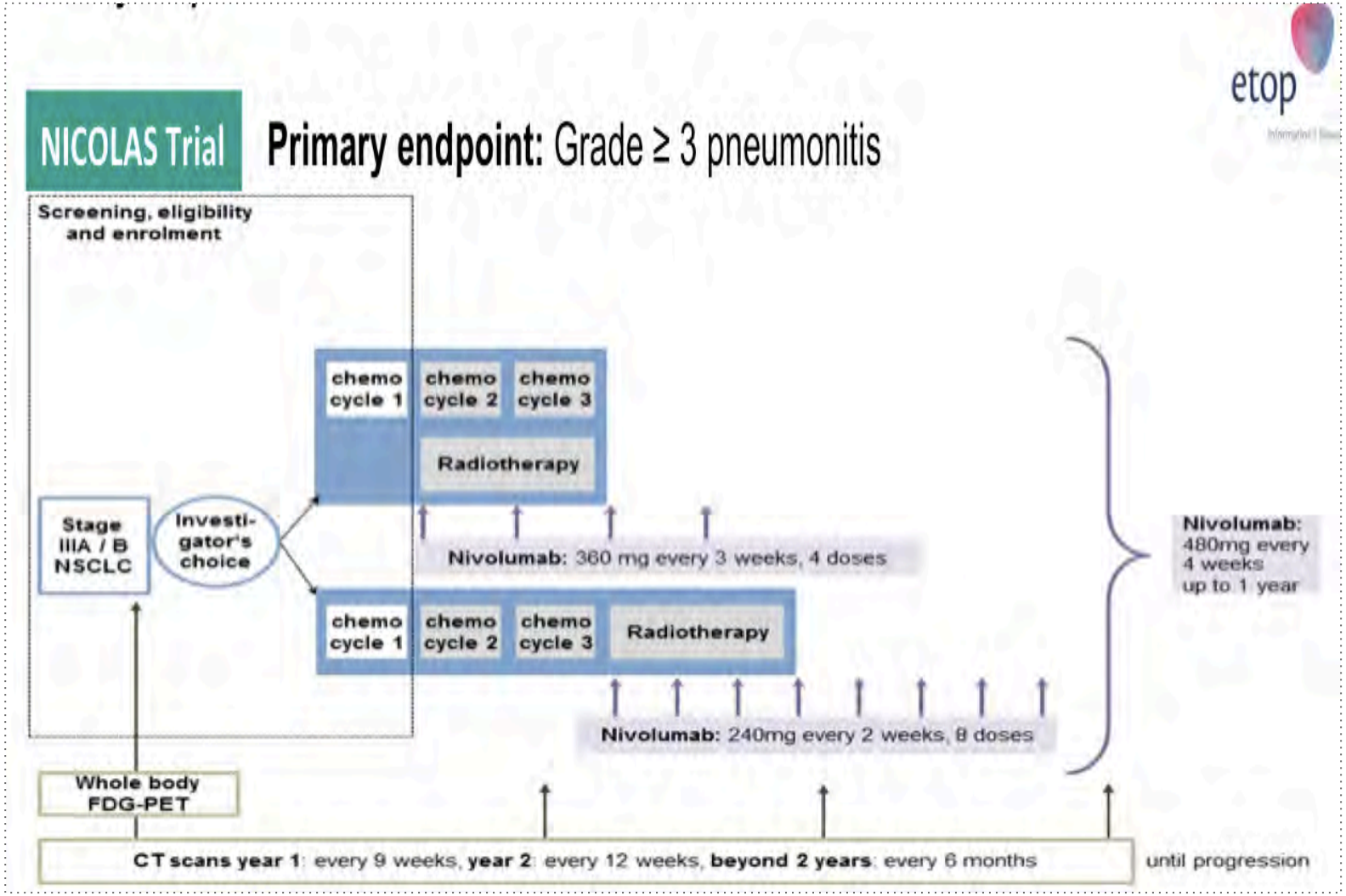
owell, ASCO 2017

IO – RT in H&N

AE	All Grades	Grade 3	Grade 4
Dysphagia	26 (96%)	12 (44%)	
Mucositis (oral/pharyngeal)	26 (96%)	8 (30%)	None
Dermatitis radiation	22 (81%)	4 (15%)	
Weight loss	22 (81%)	4 (15%)	
Neutropenia	17 (63%)	9 (33%)	1(4%)
Anemia	25 (93%)	4 (15%)	None
Thrombocytopenia	11 9(41%)	2 (7%)	
Hyponatremia	20 (74%)	5 (19%)	None
Hypomagnesemia	17 (63%)	1 (4%)	
Hypophosphatemia	12 (44%)	4 (15%)	1 (4%)

owell, ASCO 2017

IO + RT NSCLC



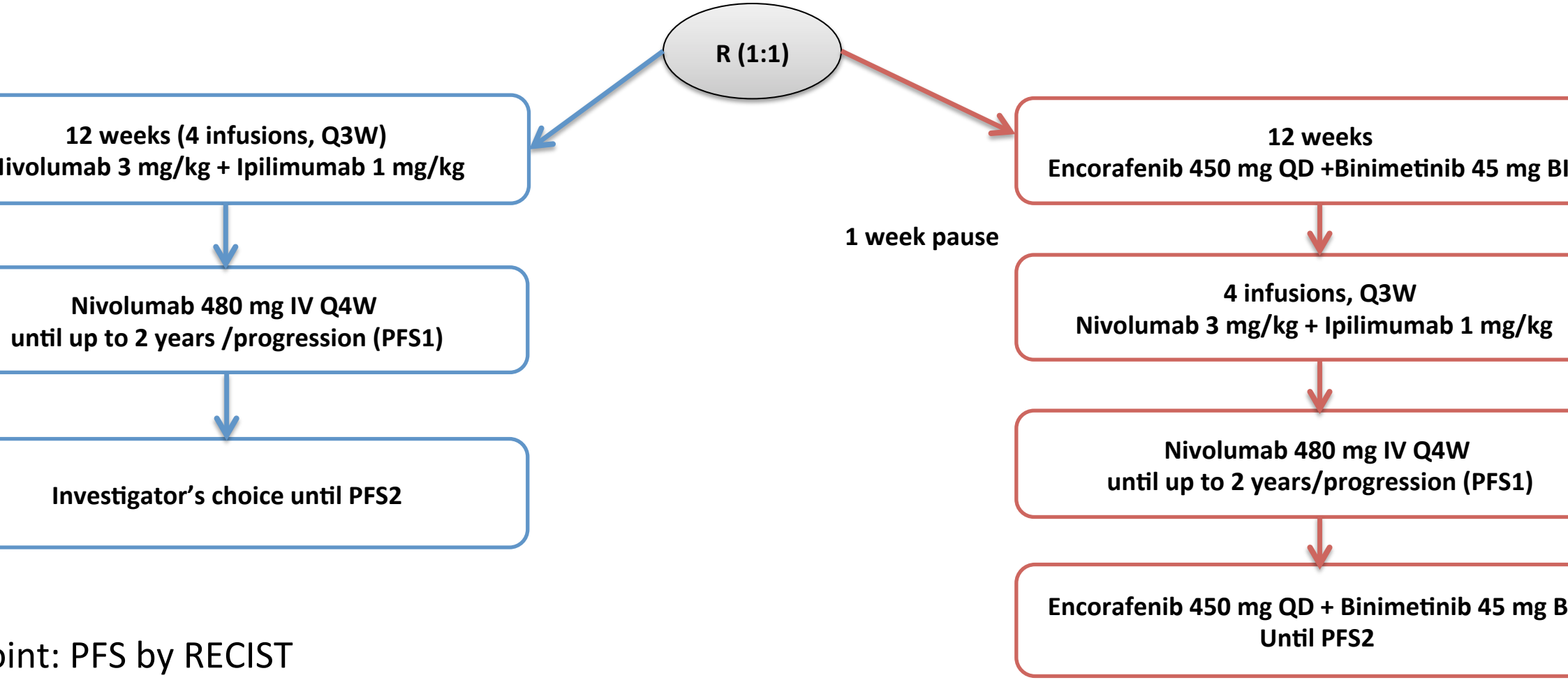
NCT02402920. phase I. N=80 LD/ED-SCLC.
CTRT + Pembrolizumab

The Future

- Better use of IO
  - Learn the sequence IO vs other treatment (academic study)
  - Learn when to stop and de-escalade

Sequence with TKI? EORTC Phase II Study *1612-MG*

Unresectable or metastatic (7th edition AJCC stage IIIC/IV) melanoma, BRAF V600E mut (N = 270)

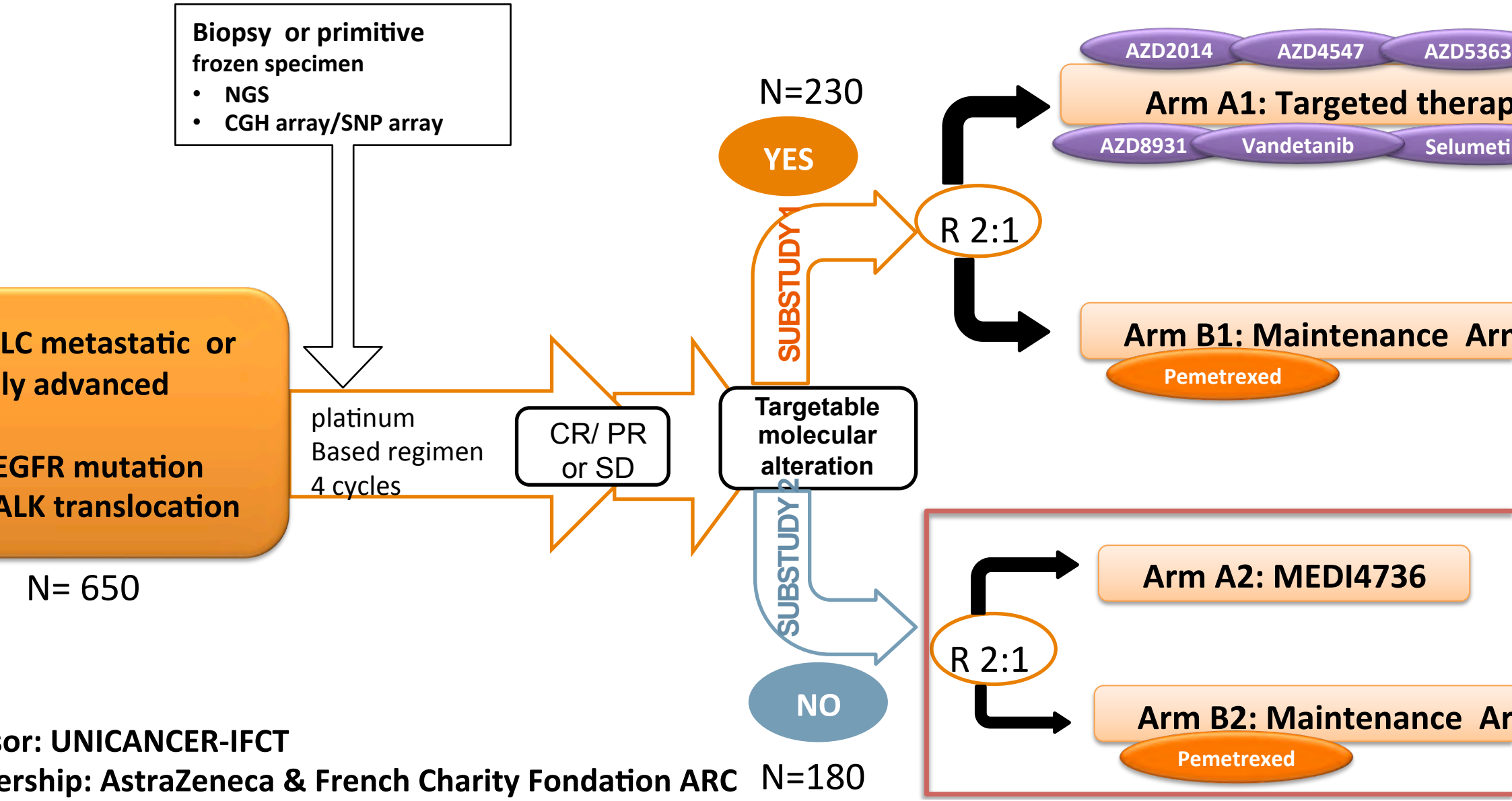


oint: PFS by RECIST

Robert

SAFIR02 Lung – IFCT 1301

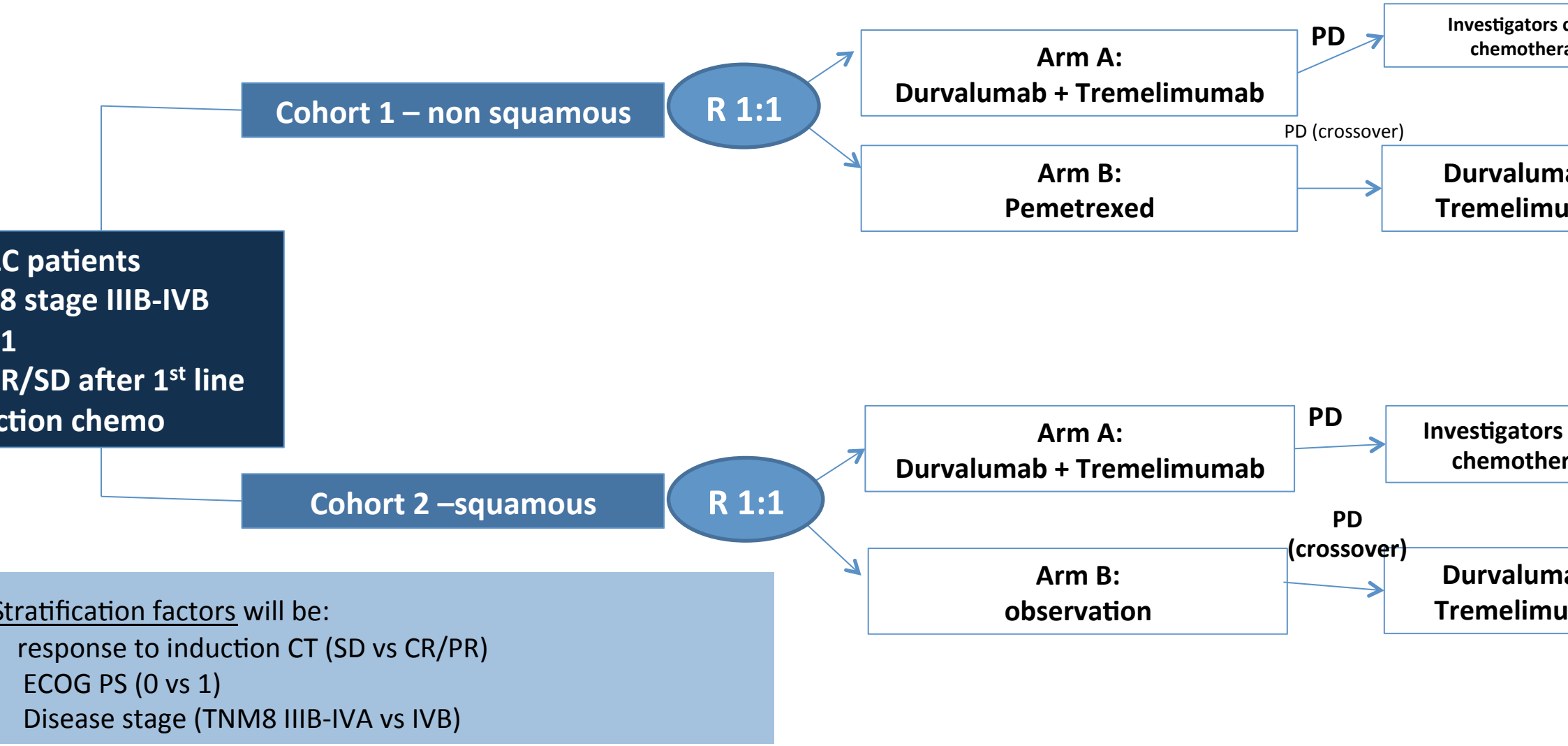
PIs: B Besse & F Barlesi



sor: UNICANCER-IFCT

ership: AstraZeneca & French Charity Fondation ARC

EORTC 1643



Stratification factors will be:

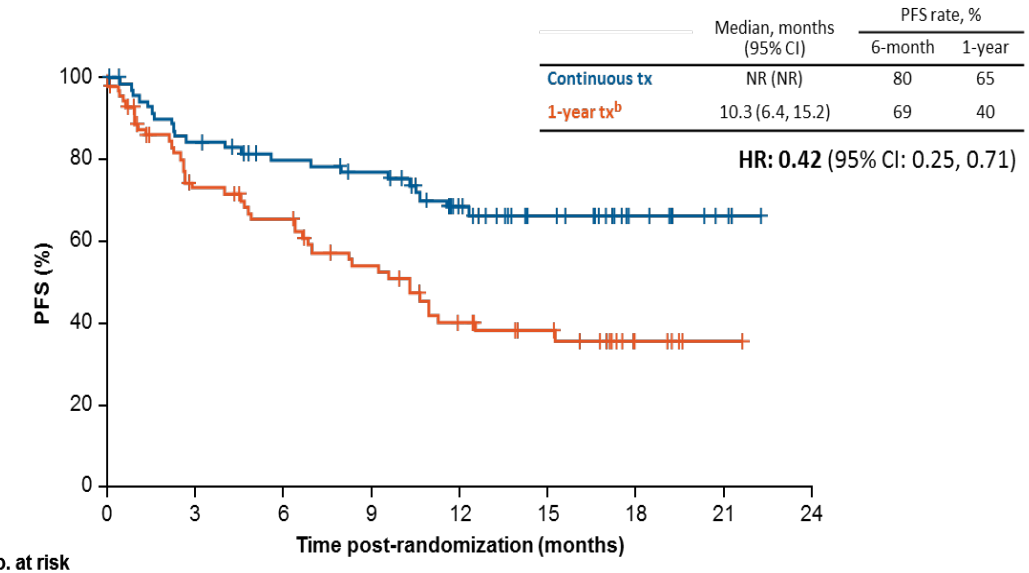
- response to induction CT (SD vs CR/PR)
- ECOG PS (0 vs 1)
- Disease stage (TNM8 IIIB-IVA vs IVB)

The Future

- Better use of IO
  - Learn the sequence IO vs other treatment (academic study)
  - Learn when to stop and de-escalade

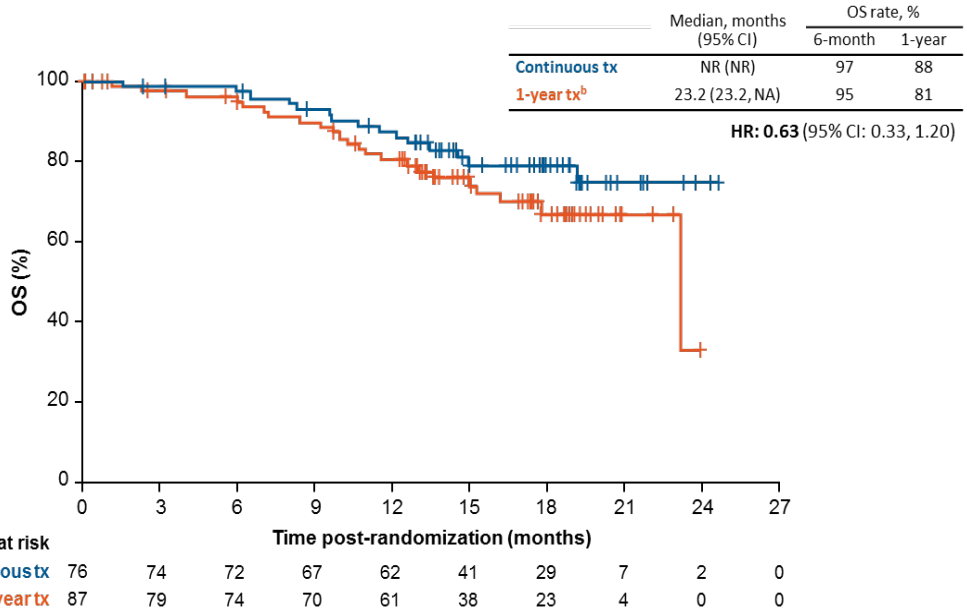
CheckMate 153: Continuous vs 1-Year Nivolumab (NSCLC, second-line+, n = 168)

PFS From Randomization



[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD
NR = not reached; tx = treatment

OS From Randomization



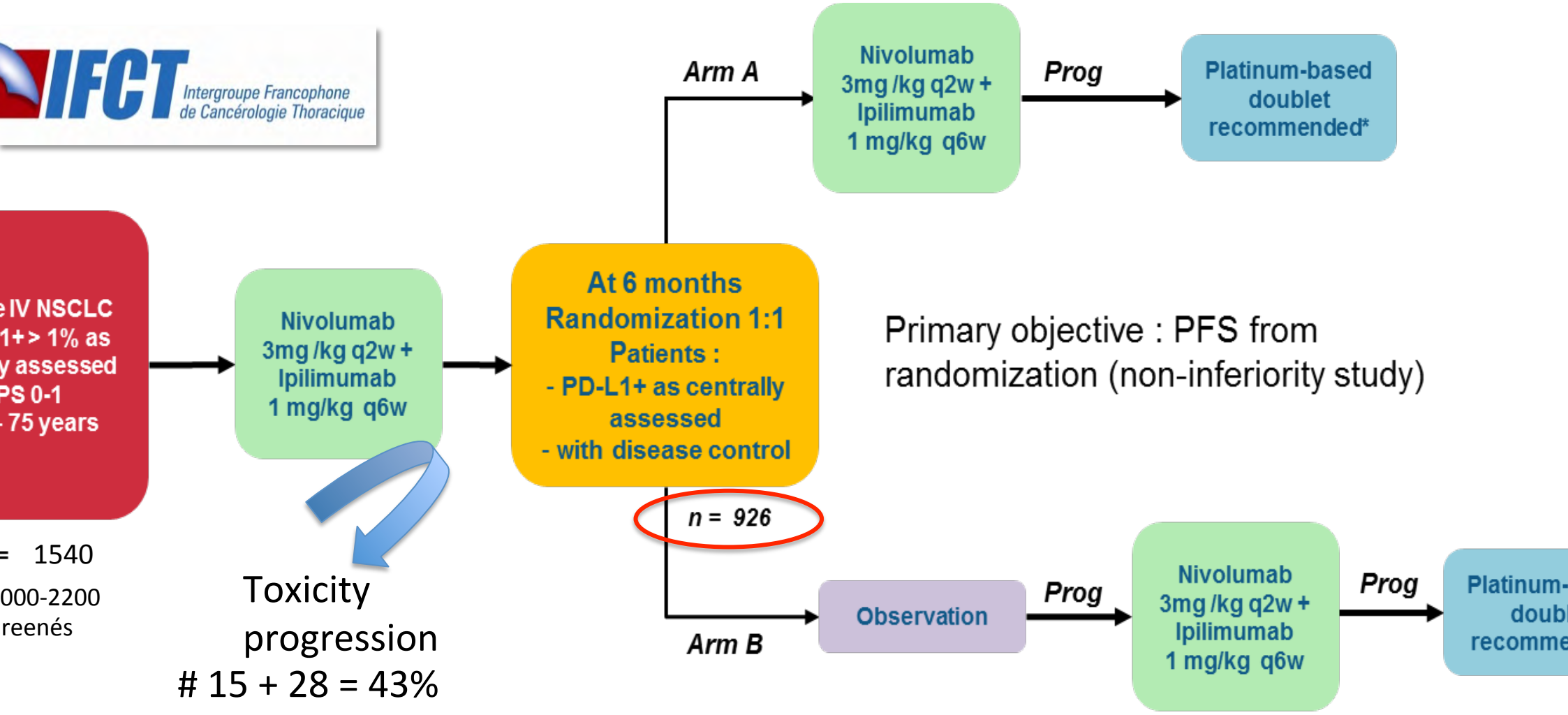
[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD

al. ESMO 2017. Abstract 12970.

IFCT-1701 – DICIPLE

Double **I**mmune **C**heckpoint **I**nhibitors in **P**D-L1-positive stage IV non-small **L**ung **C**anc**E**r

IFCT Intergroupe Francophone de Cancérologie Thoracique



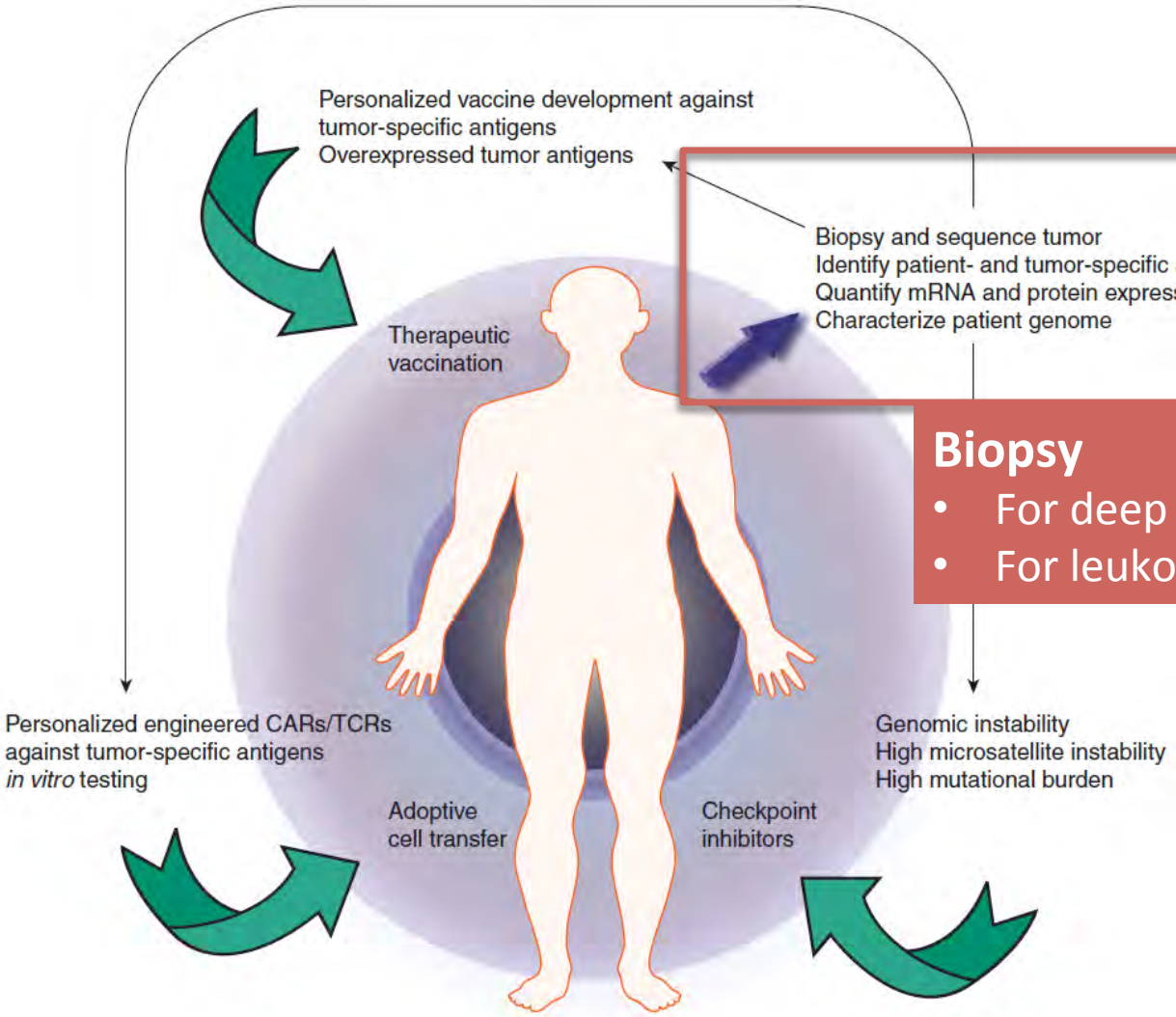
Primary objective : PFS from randomization (non-inferiority study)

tification factors:
ology (SCC vs. Non-SCC)
king status (ever smoker vs. never smoker)
1 centrally-assessed IHC: ≥ 50% vs. < 50%

The Future

- Better use of IO
  - Learn the sequence IO vs other treatment (academic study)
  - Learn when to stop and de-escalade
- Next gen IO: personalized IO (CAR-T, individual vaccine)

Personalized IO

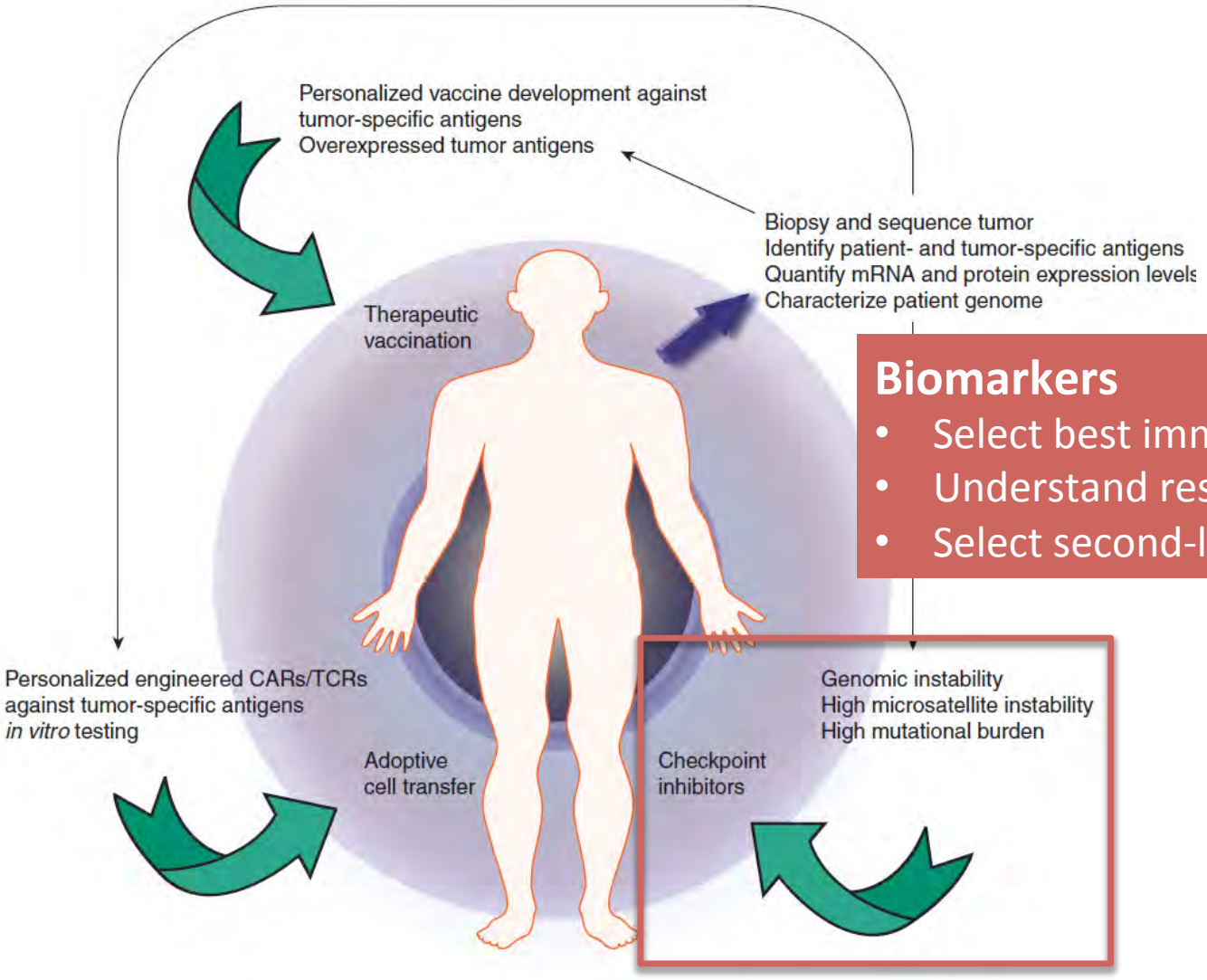


Biopsy

- For deep tumor cell analysis
- For leukocyte assessment

han TA. *Cancer Discov.* 2016;6(7):703-713.

Personalized IO

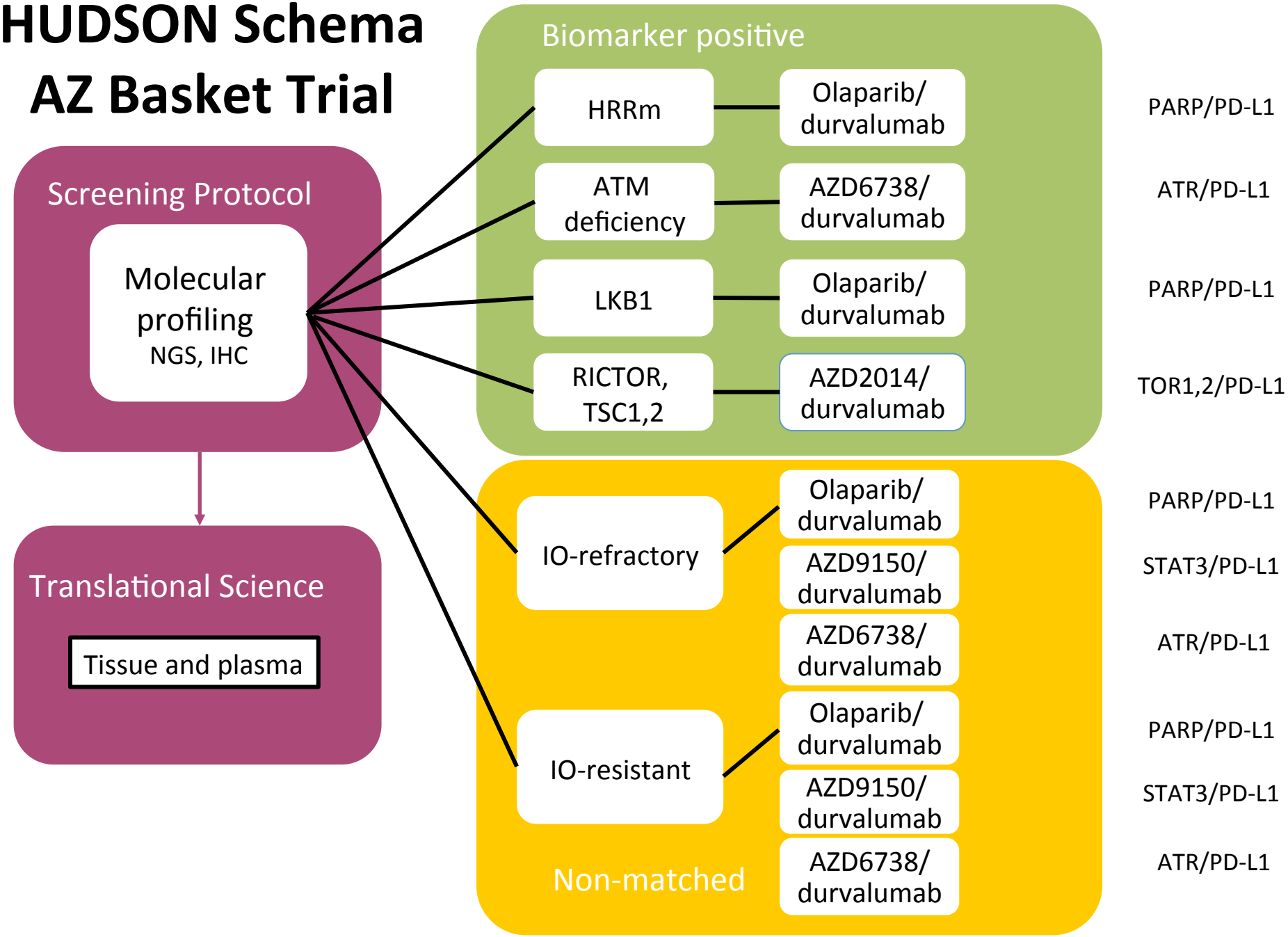


Biomarkers

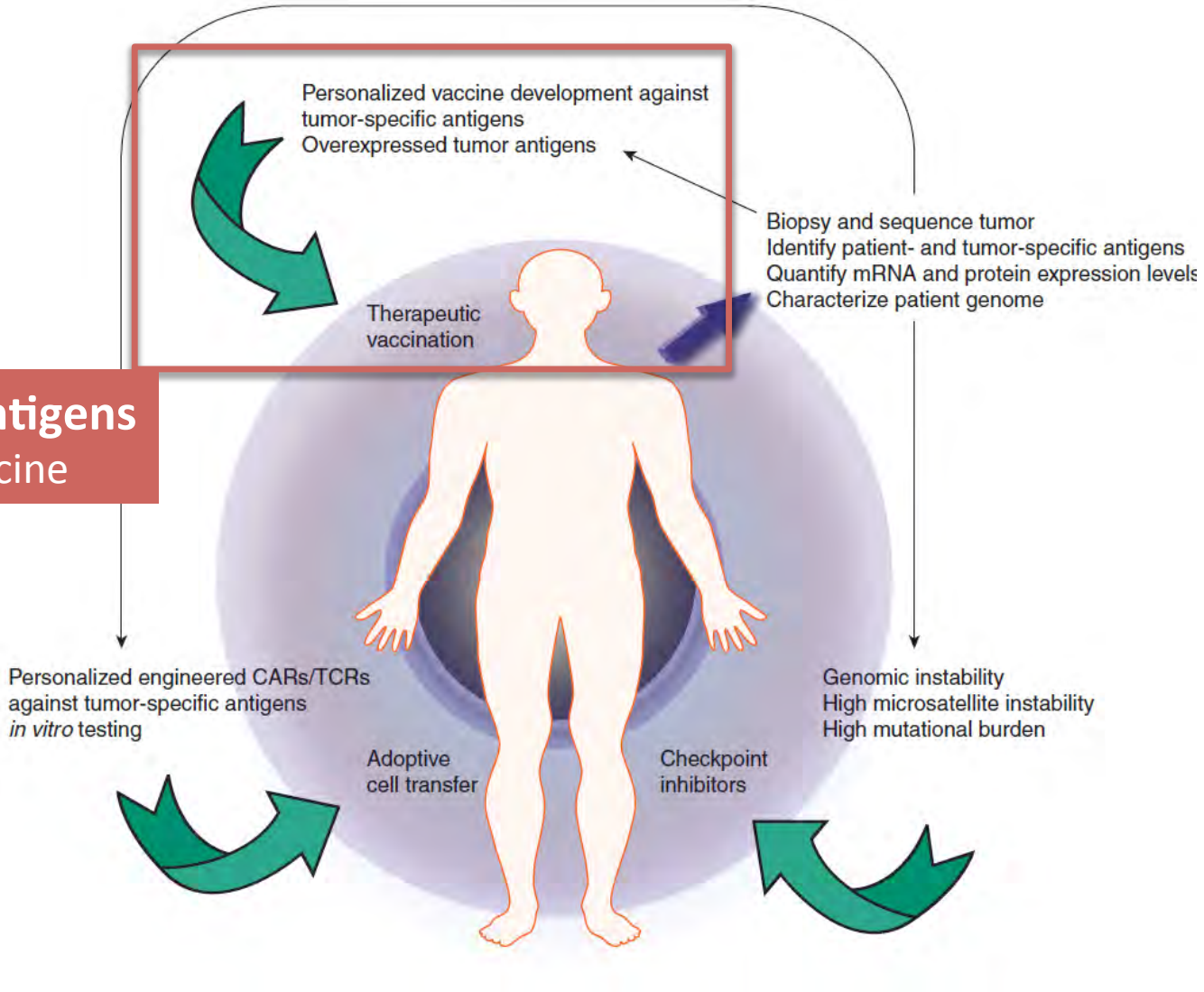
- Select best immune checkpoint inhibito
- Understand resistance
- Select second-line IO

han TA. *Cancer Discov.* 2016;6(7):703-713.

HUDSON Schema
AZ Basket Trial



Personalized IO



Analyze tumor antigens

- Personalized vaccine

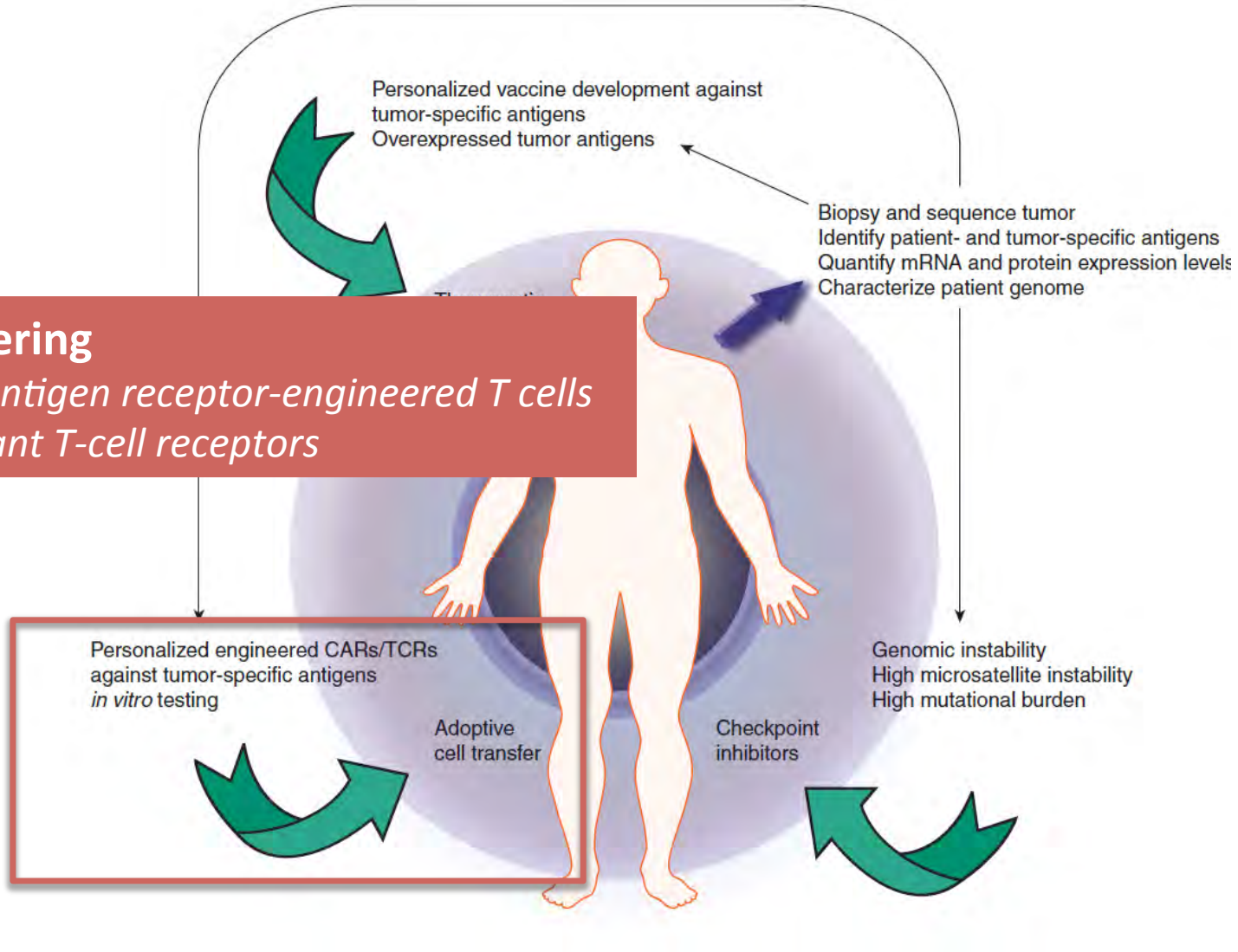
han TA. *Cancer Discov.* 2016;6(7):703-713.

Personalized IO

kocyte engineering

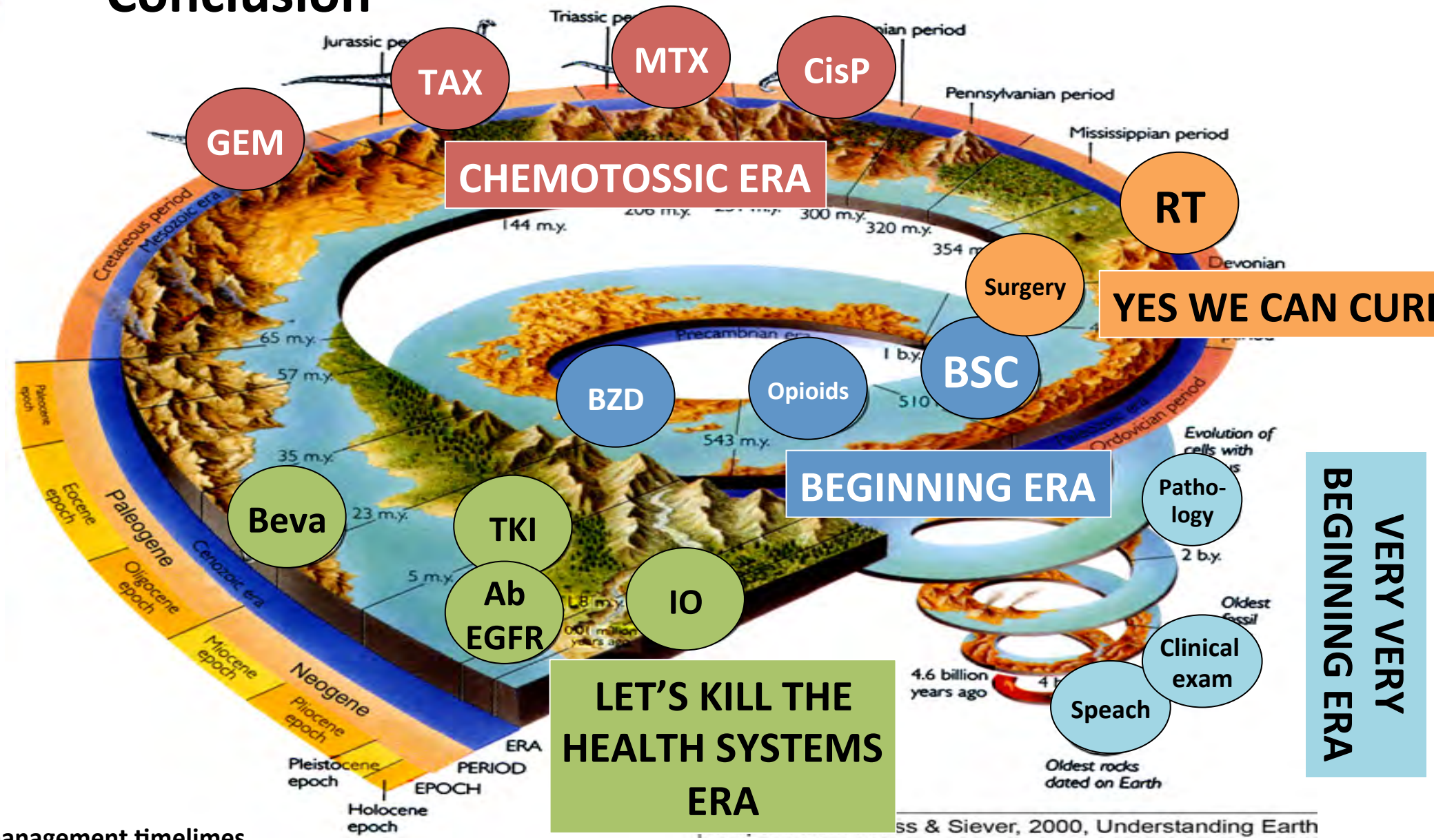
ARs – *Chimeric antigen receptor-engineered T cells*

CRs – *Recombinant T-cell receptors*



han TA. *Cancer Discov.* 2016;6(7):703-713.

Conclusion



ss & Siever, 2000, Understanding Earth

ancer management timelimes

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