ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Workshop

Treatment combinations in immuno-oncology

Galatea, floor 2

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Cliniques Universitaires Saint-Luc, Brussels

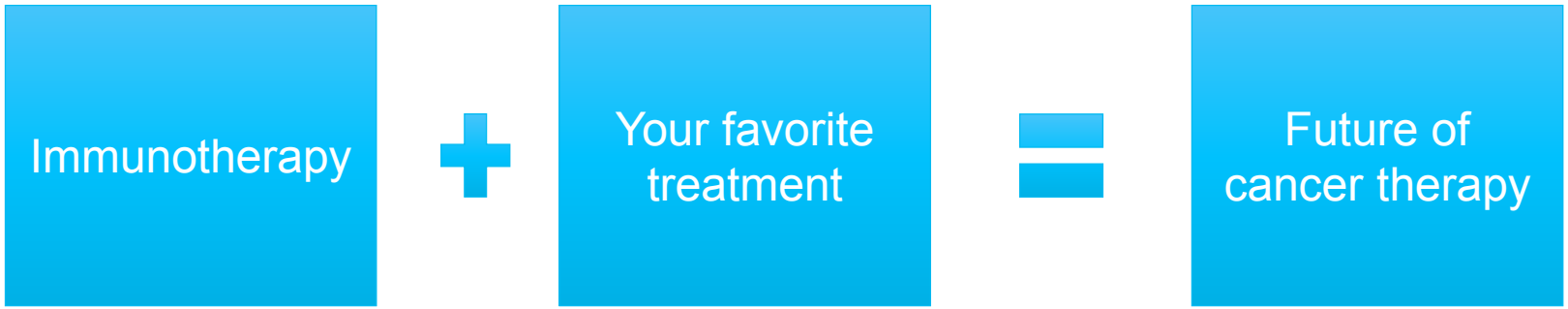
Moderated by

Pierre Coulie

de Duve Institute, University of Louvain

Mercury number IOBE18NP04371-12
Date of preparation: December 2018

Why do we need to combine ?

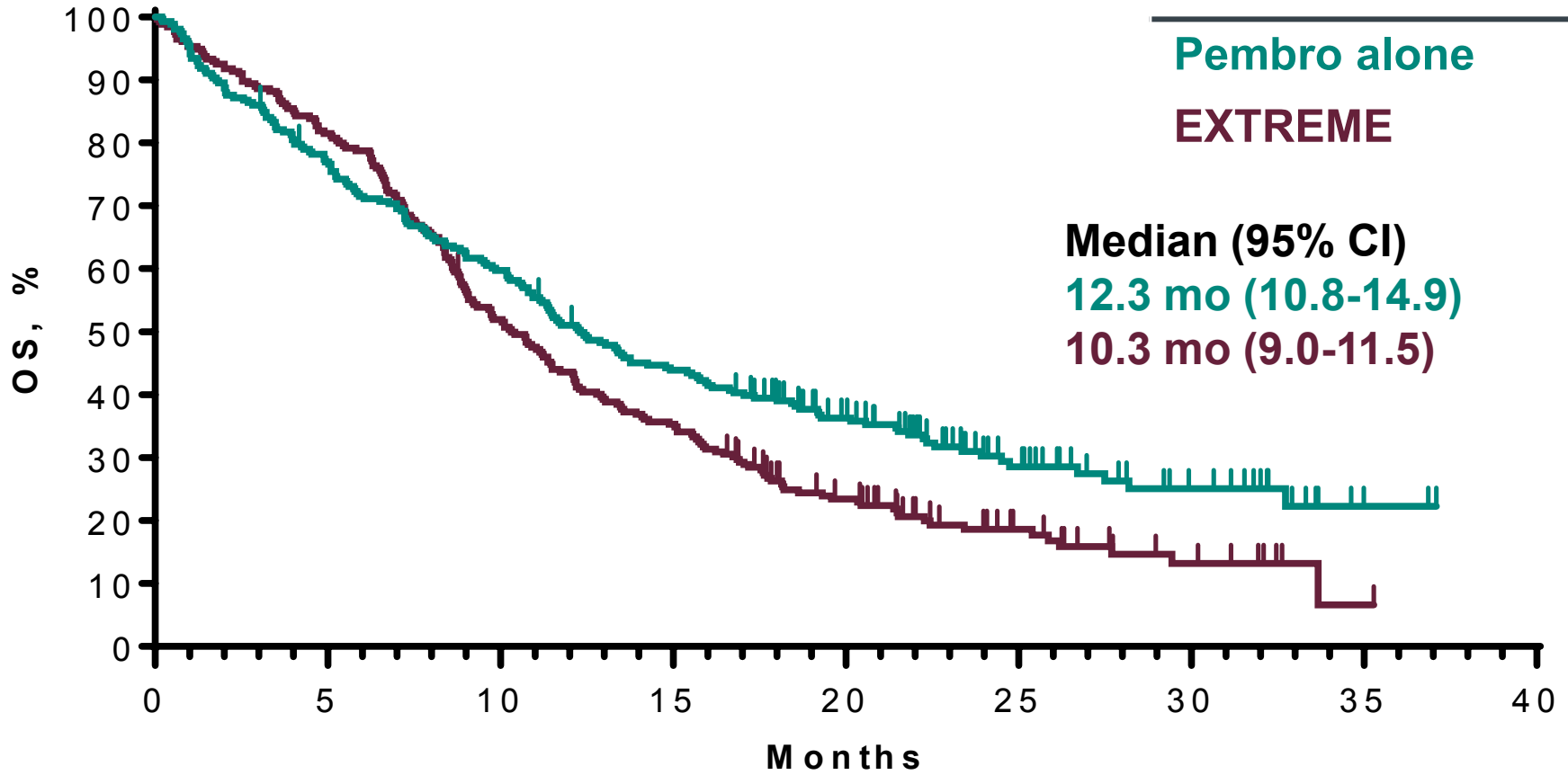


- ✓ To improve treatment outcome
- ✓ To move to the curative treatment

Why do we need to combine ?

	HR (95% CI)	*P*
Pembro alone	0.78 (0.64-0.96)	0.0086
EXTREME		

Median (95% CI)
12.3 mo (10.8-14.9)
10.3 mo (9.0-11.5)



No. at Risk

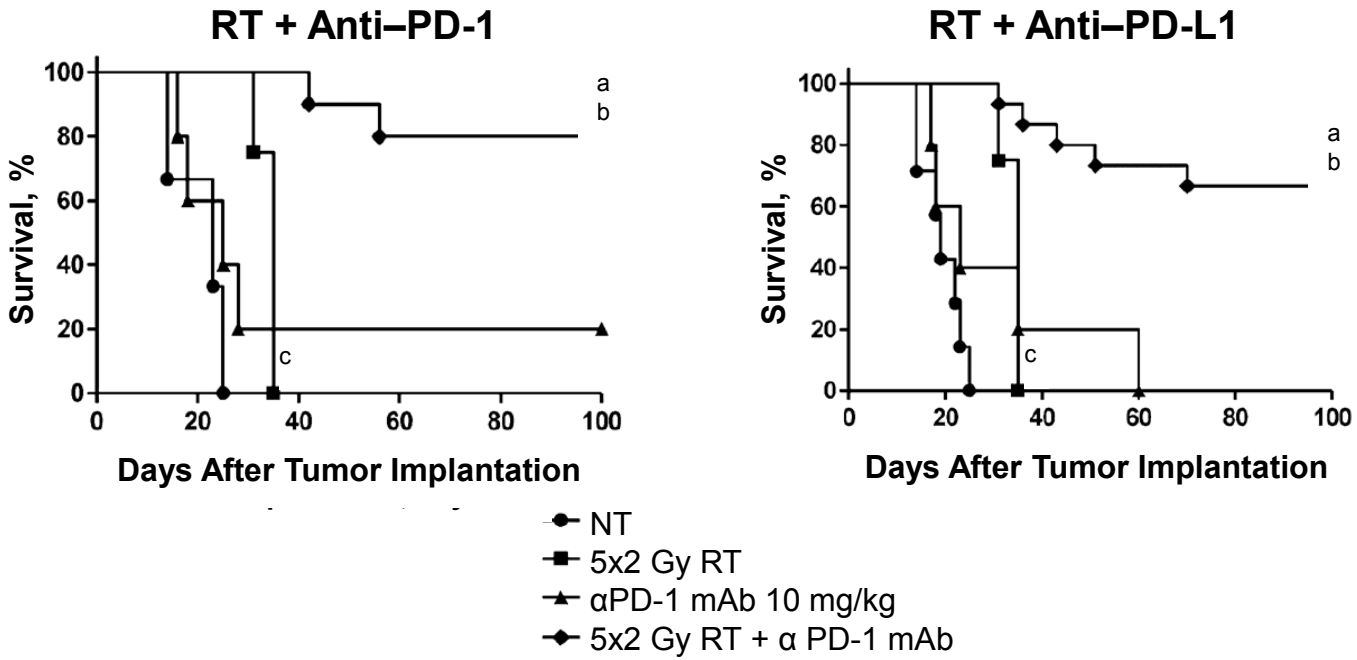
257	196	152	110	74	34	17	2	0
255	207	131	89	47	21	9	1	0

HR, hazard ratio; OS, overall survival.
Burtness et al. Presentation at ESMO 2018. Abstract LBA8_PR.

- Radiation therapy
- Chemotherapy
- Targeted therapy
- Immunotherapy
- (Hormonal treatment)
- (Surgery)

- **Radiation therapy**
- Chemotherapy
- Targeted therapy
- Immunotherapy
- (Hormonal treatment)
- (Surgery)

PD-1/PD-L1 inhibitors synergize with RT



[a] $P < .001$, log-rank (Mantel-Cox) test vs control mice.
[b] $P < .001$, log-rank (Mantel-Cox) test vs monotherapy.
[c] Significance when compared with control mice.

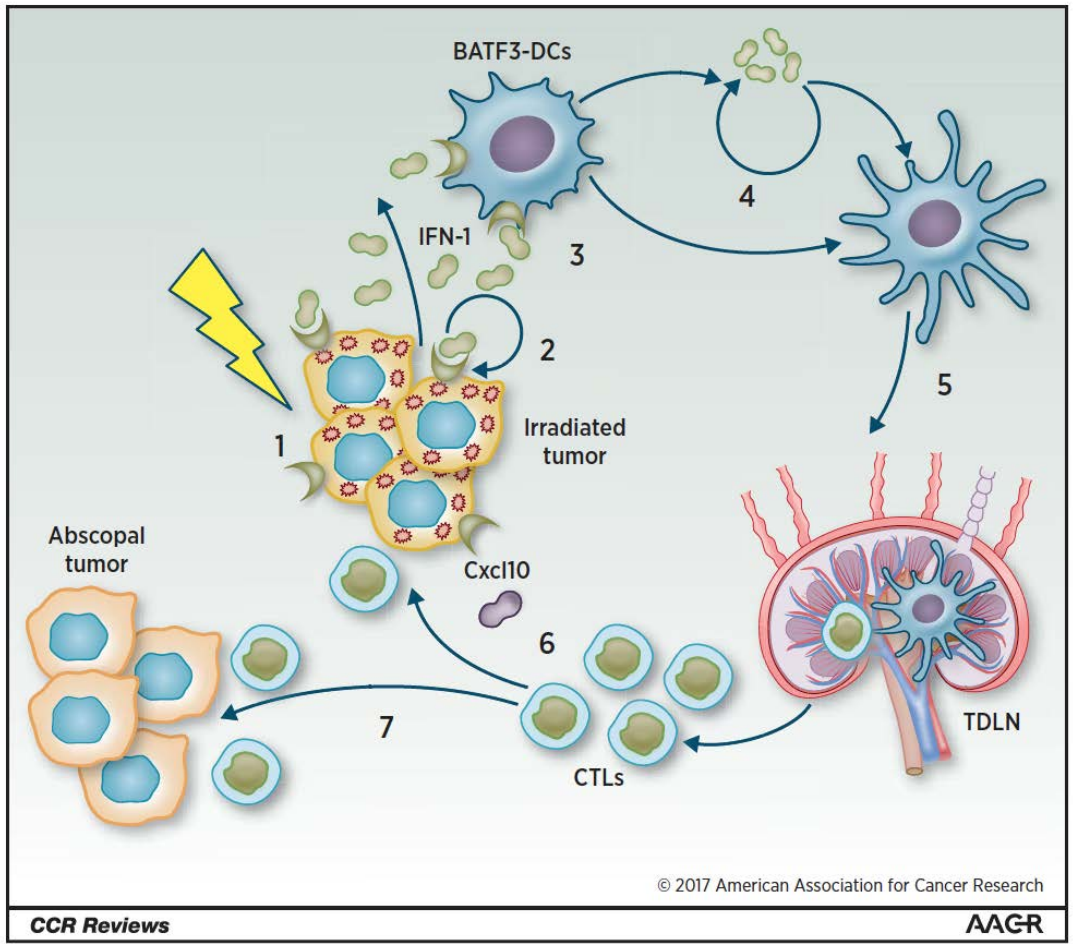
mAb, monoclonal antibody; RT, radiation therapy.
Dovedi SJ et al. Cancer Res 2014;74:19:5458–68.

Immune effects of radiation therapy

- RT can generate T cells specific for tumor-associated antigens by inducing immunogenic cell death
- RT can overcome T-cell exclusion from the tumor
- RT can improve the recognition and killing of cancer cells by CD8+ T cells

Vanpouille-Box C et al. Clin Cancer Res 2018;24:2:259–265.

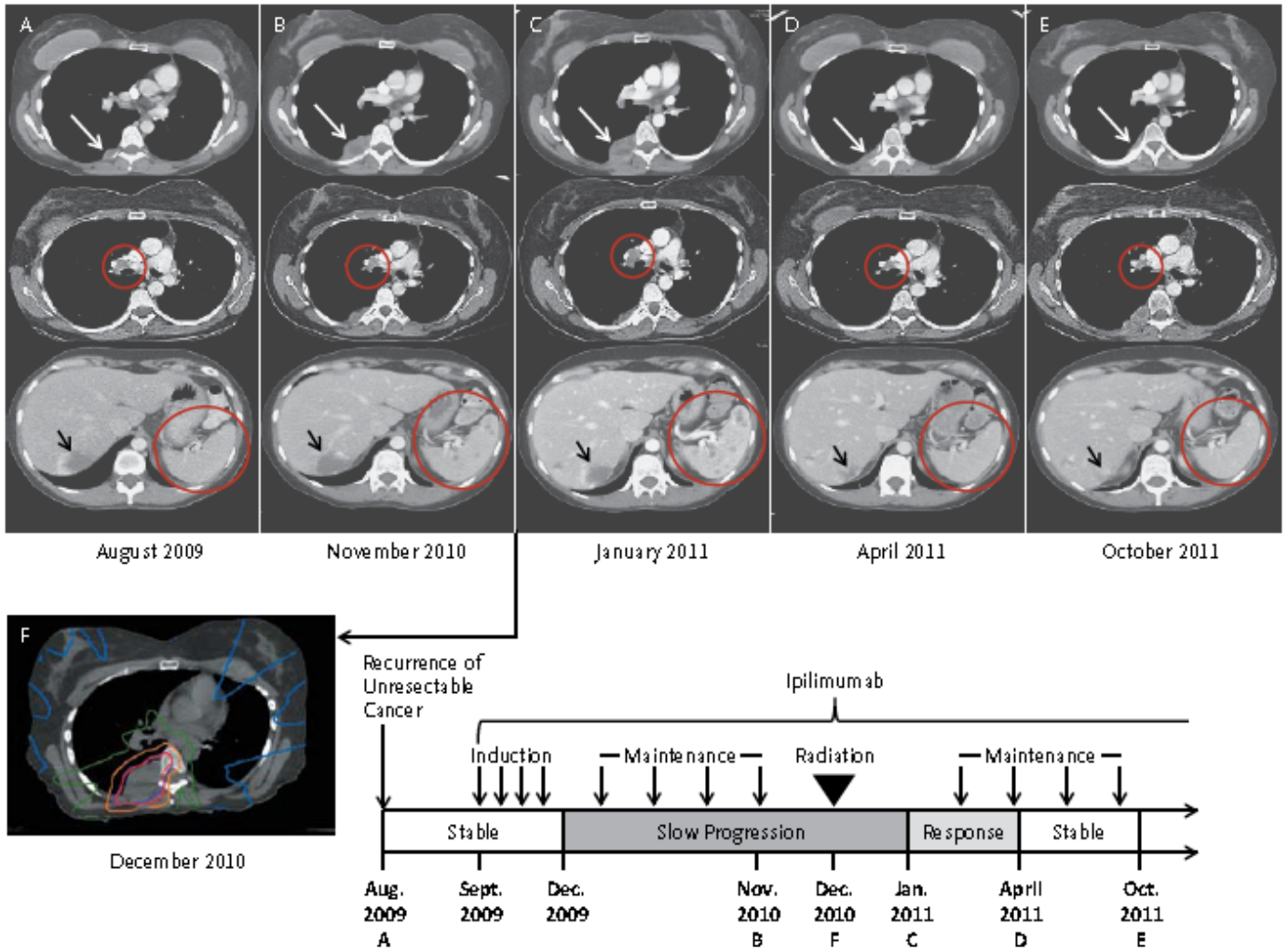
Immune effects of radiation therapy are dependent on the dose and schedule



- ✓RT leads double stranded DNA accumulation, which stimulates
  - the production of IFN-1 (STING)
  - INF stimulated chemokines (Cxcl10)
- ✓INF-1 promotes the recruitment and activation of DCs
- ✓DCs migrate to the lymph node to prime naive CD8+T-cells
- ✓CTLs home to the irradiated tumors (Cxcl10) and distant metastases (abscopal)
- ✓**This is observed in mouse models with 8 Gy 3x but not 20 Gy 1x**
- ✓**More research is needed**

CD, cluster of differentiation; CTLs; cytotoxic T lymphocyte; DCs, dendritic cells; Gy, gray unit; STING, stimulator of interferon genes; TDLN, tumour-draining lymph node; Vanpouille-Box, Clin Cancer Res 2017.

Abscopal effect ?



Postow et al, N Engl J Med 2012;366:925–931.

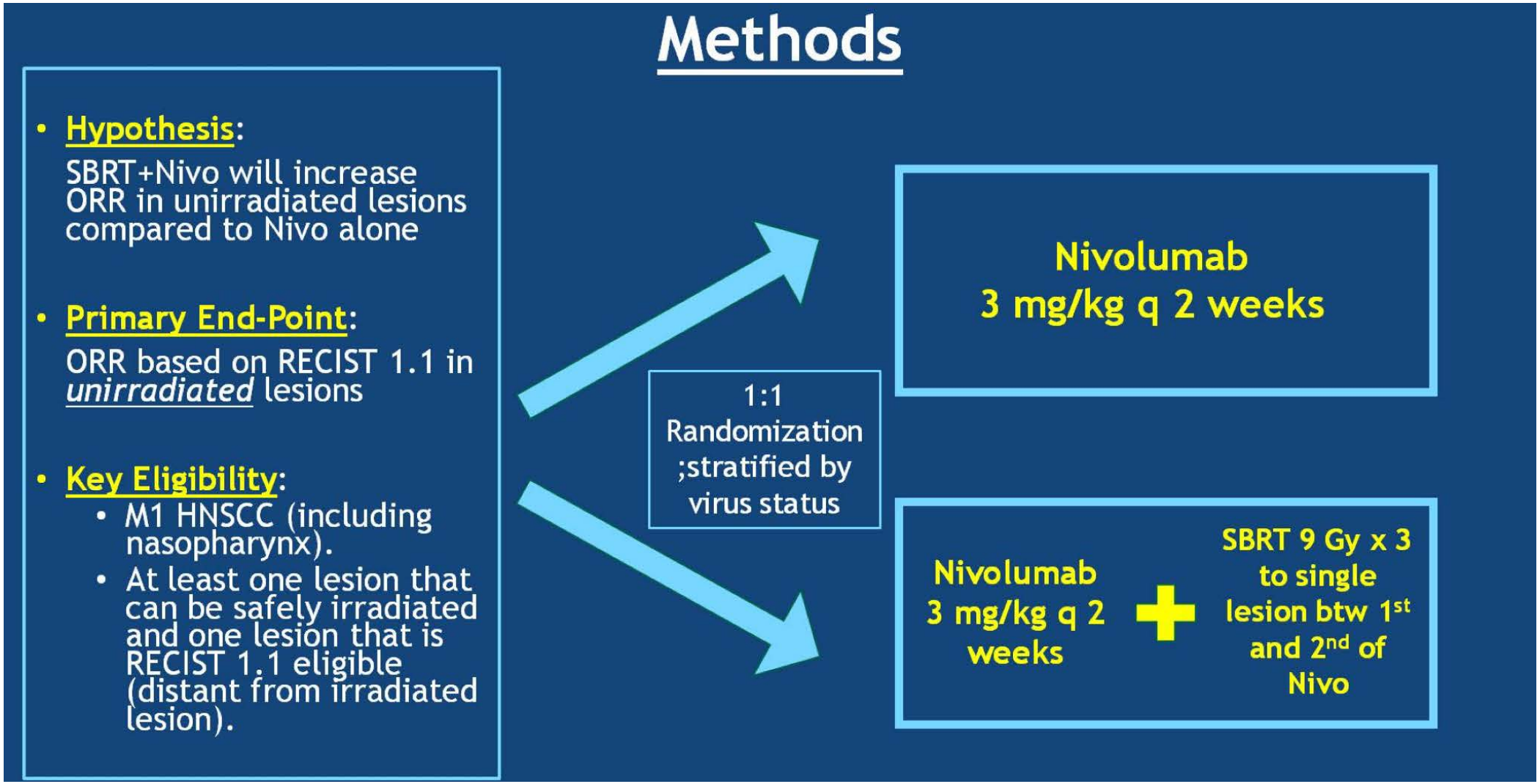
Abscopal effect ?

- Systematic review : studies published between 1960 and 2014
- 51 patients who had an abscopal effect.

- Abscopal effects were observed:
  - median of 5 months after RT (range, 1-24 months),
  - median response duration of 13 months (range, 3-39 months).
  - median RT dose was 32 Gy.
  - 5 abscopal effects were achieved with a combined immunotherapy-RT approach

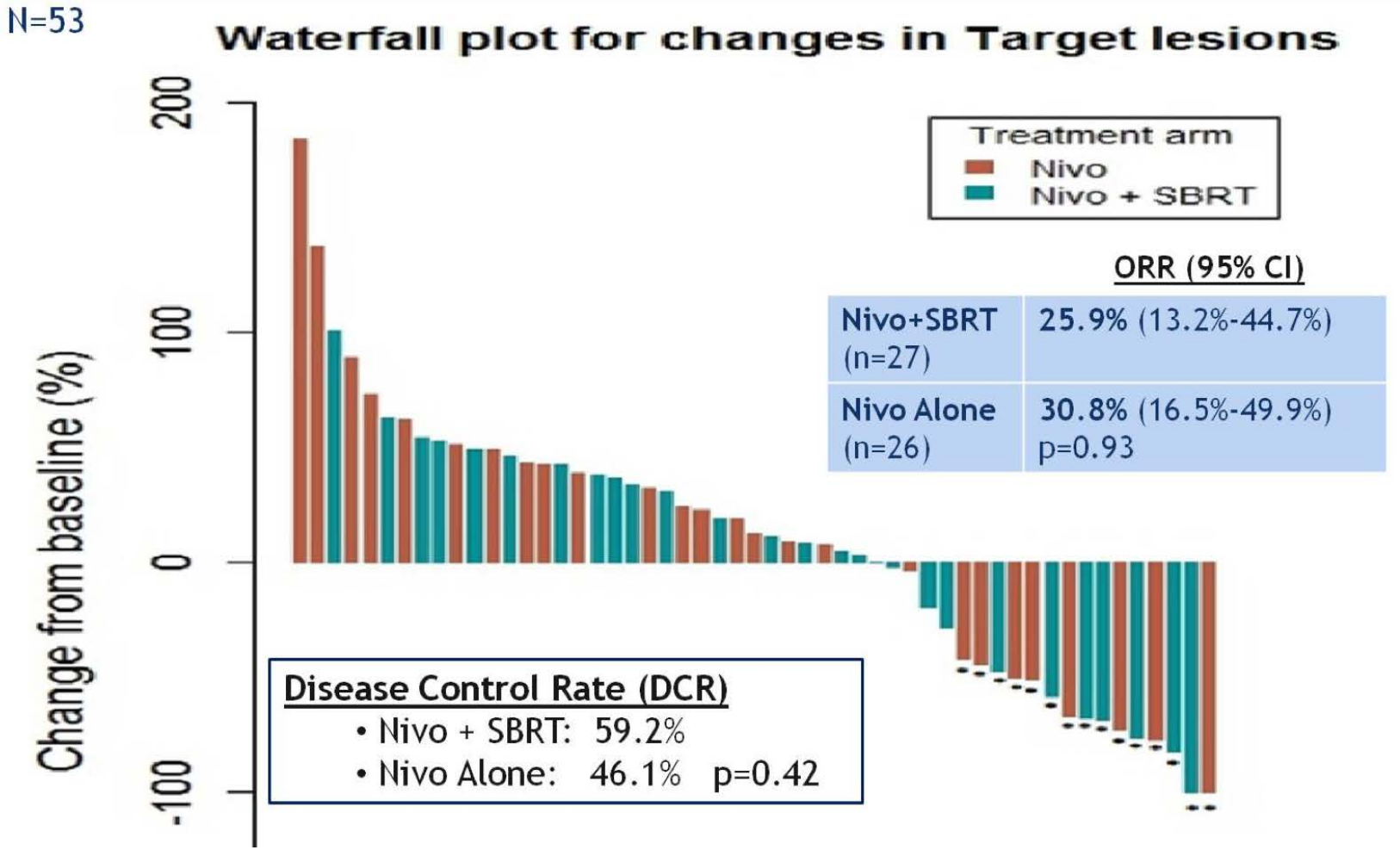
Gy, gray unit; RT, radiation therapy.
Reynders et al. Cancer Treat Rev. 2015;41:6:503–10.

Abscopal effect ? Head and neck cancer



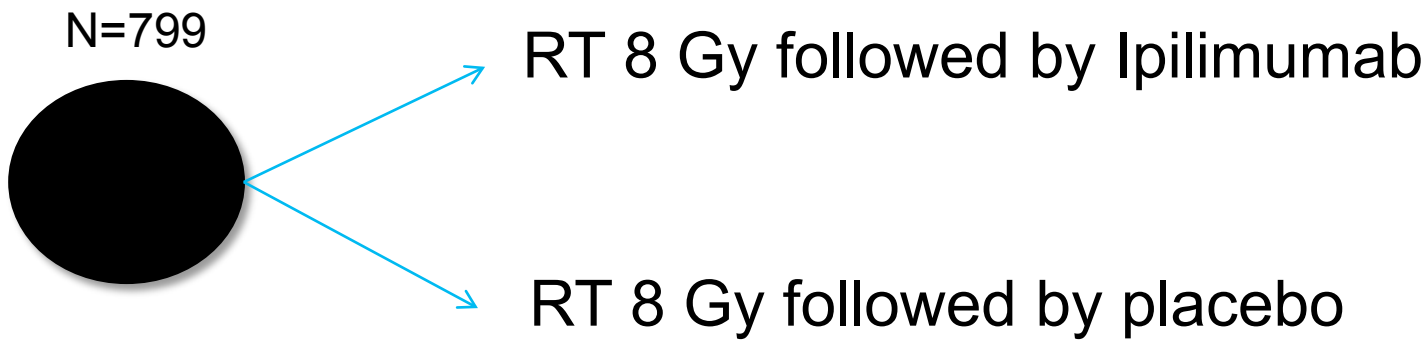
Gy, gray unit, HNSCC, head and neck squamous cell carcinoma; Nivo, nivolumab; ORR, overall response rate; SBRT, stereotactic body radiation therapy.
McBride et al. Abstract 2018 ASCO annual meeting.

Abscopal effect ? Head and Neck cancer



DCR, disease control rate; Nivo, nivolumab; ORR, overall response rate; SBRT, stereotactic body radiation therapy.
McBride et al. Abstract at 2018 ASCO annual meeting.

Metastatic castrate-resistant prostate cancer

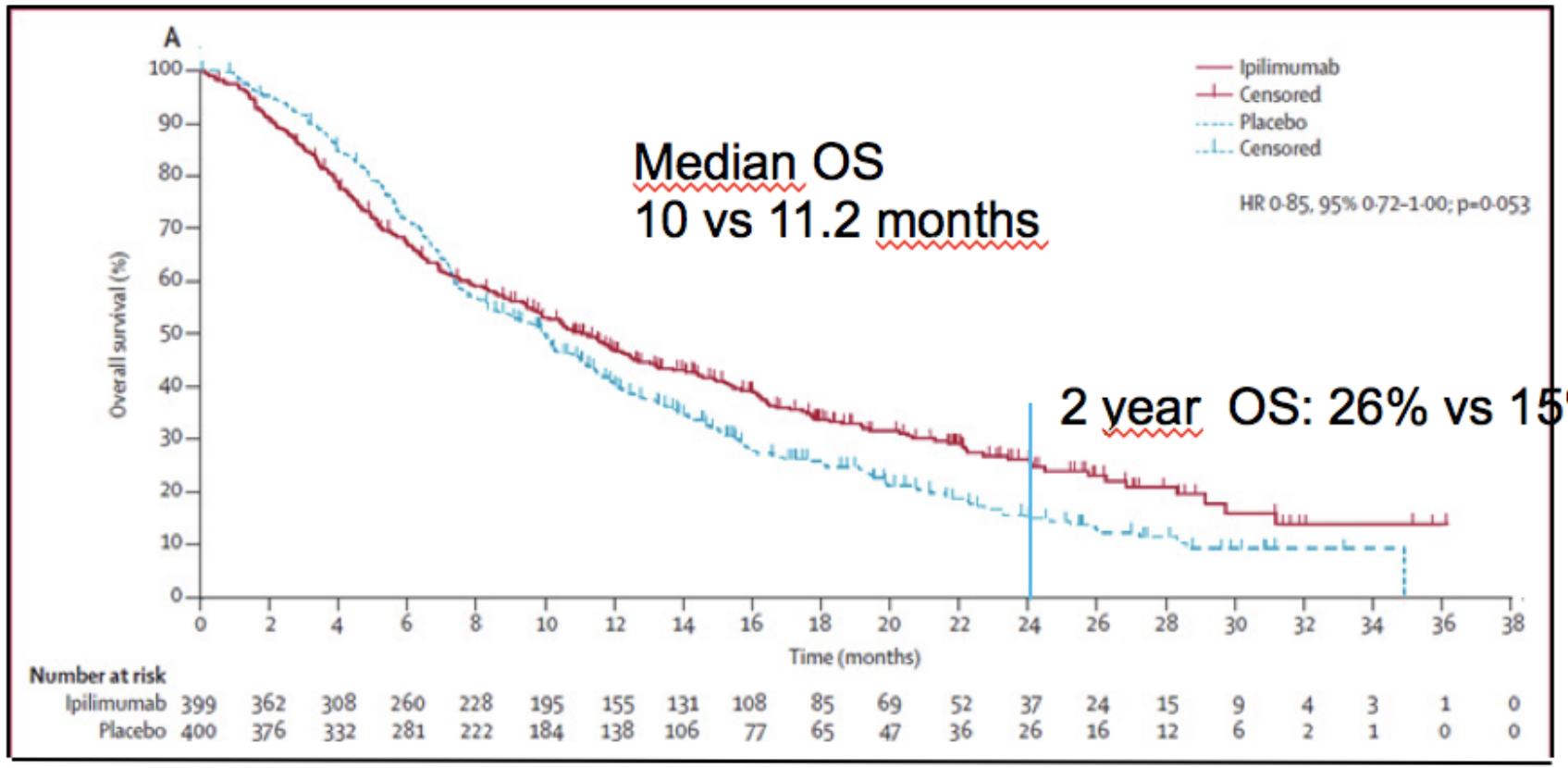


Primary endpoint: Overall survival

Radiotherapy:
- 8 Gy in one fraction,
- on one to five bone metastases,
- within two days before radiotherapy

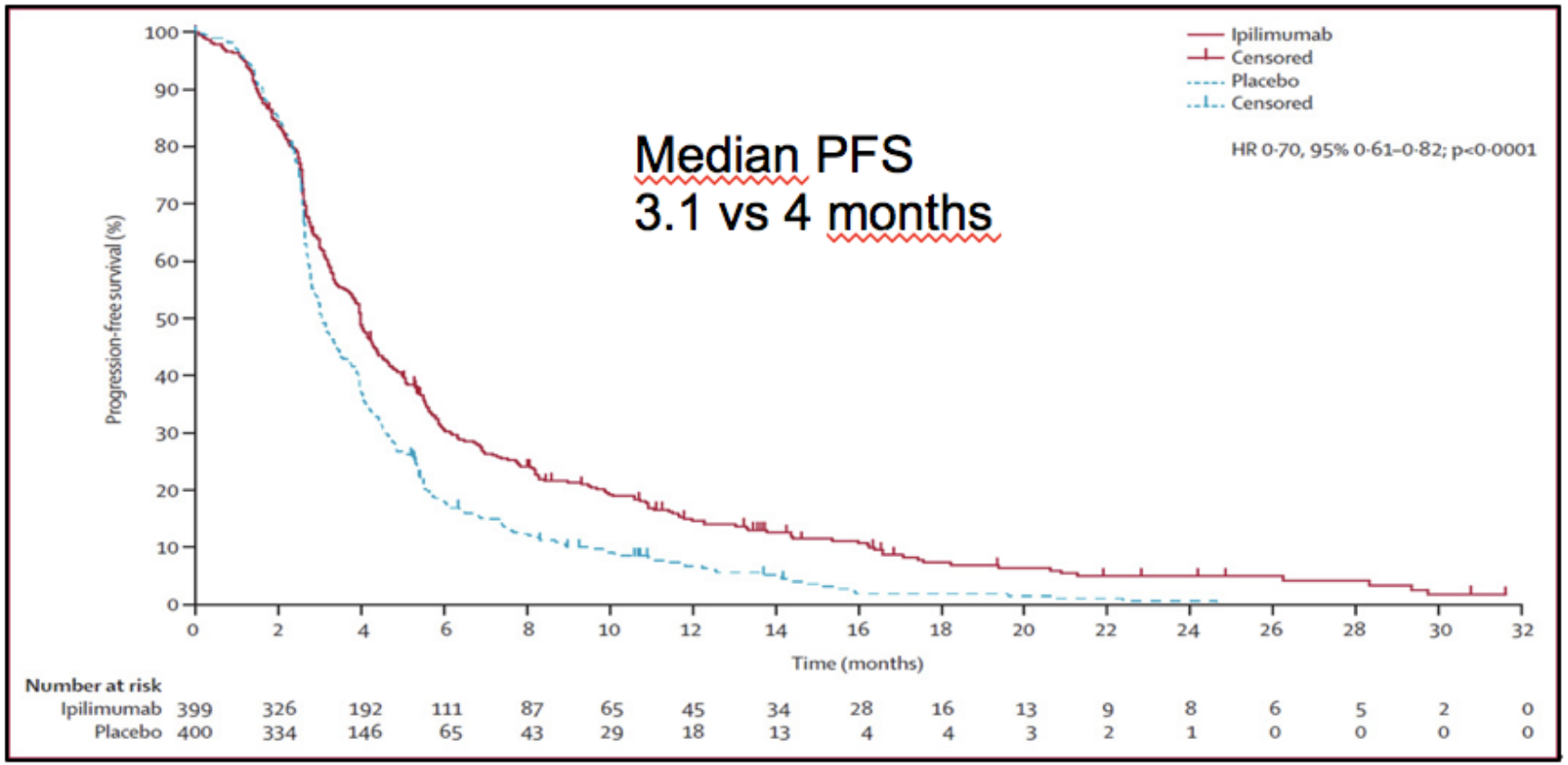
Gy, gray unit; RT, radiation therapy.
Kwon et al. Lancet Oncology 2014;5:7:700–712.

Metastatic castrate-resistant prostate cancer



HR, hazard ratio, OS, overall survival.
Kwon et al. Lancet Oncology 2014;5:7:700–712.

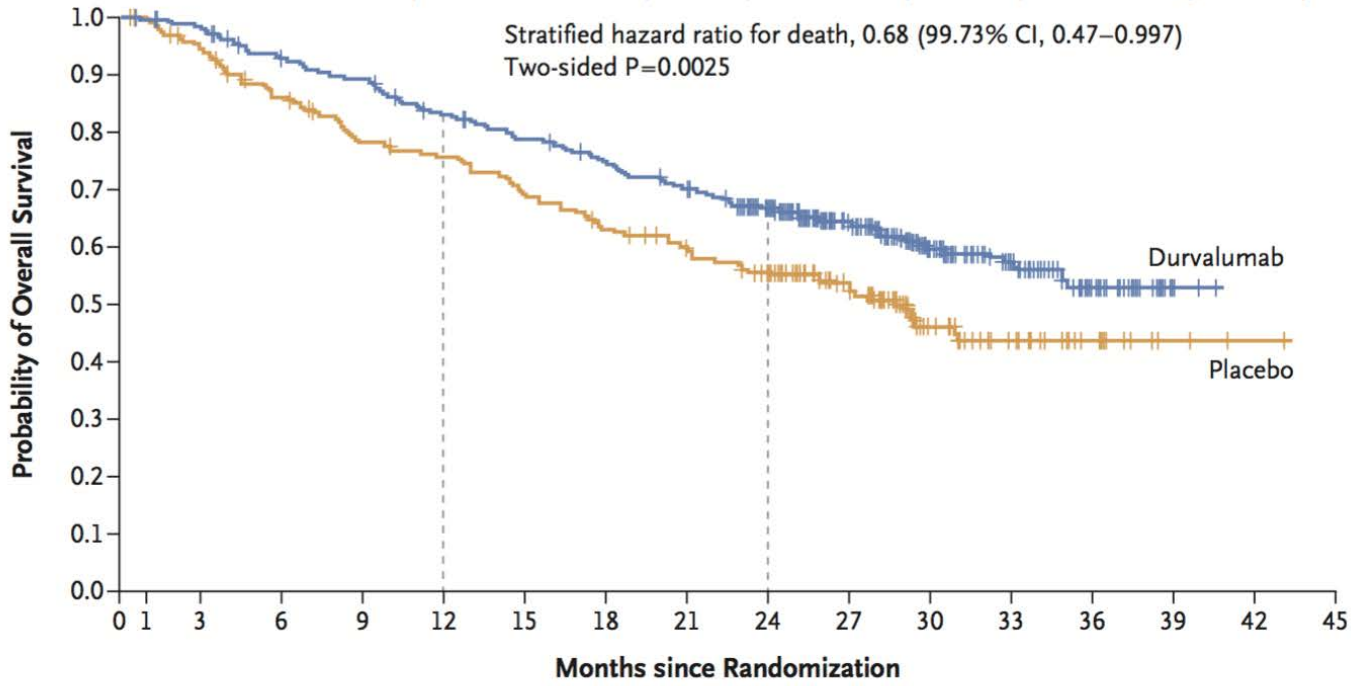
Metastatic castrate-resistant prostate cancer



HR, hazard ratio; PFS, progression-free survival.
Kwon et al. Lancet Oncology 2014;5:7:700–712.

Durvalumab after chemoradiation in NSCLC (Stage 3)

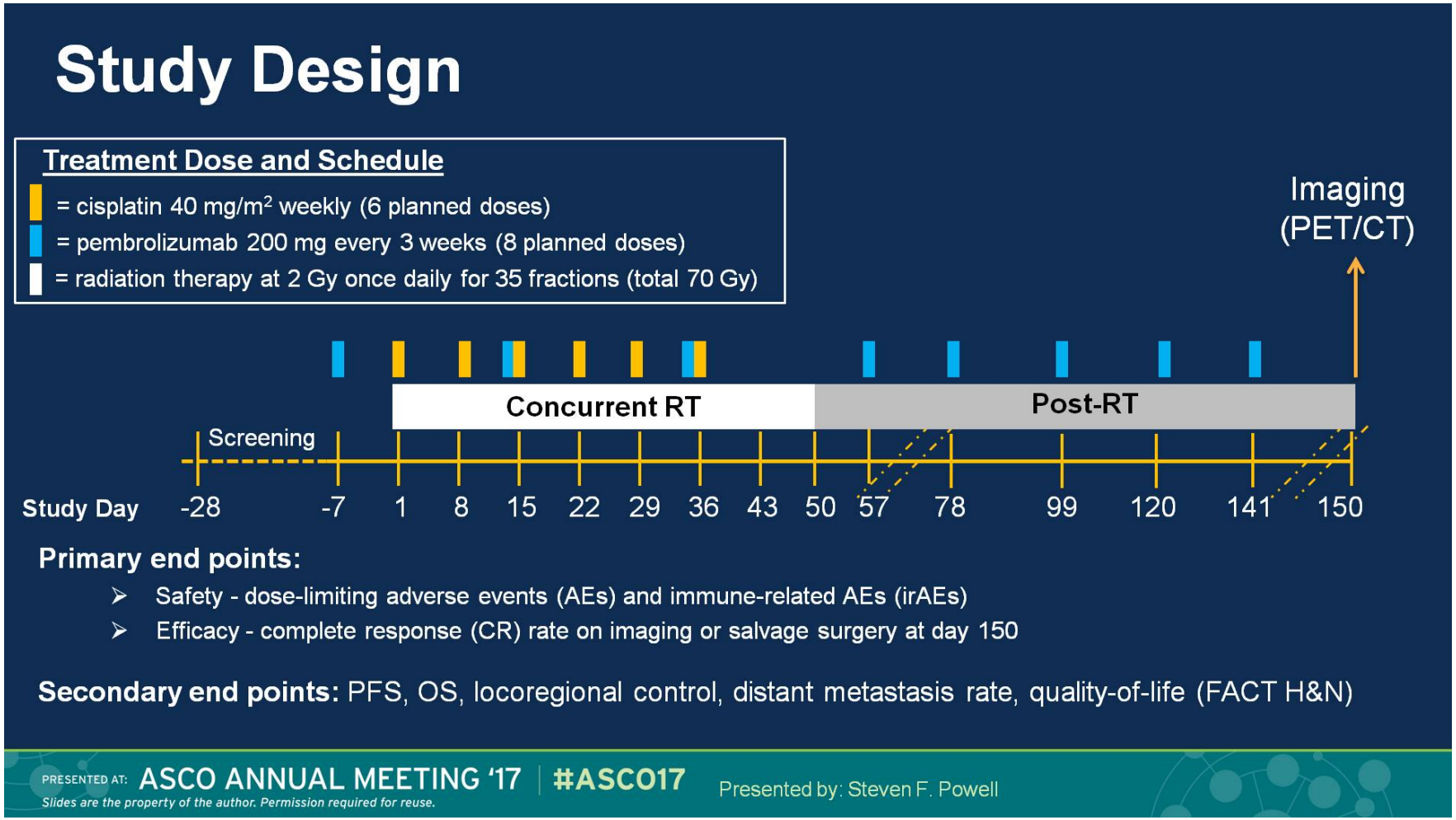
	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



No. at Risk															
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

CI, confidence interval; Mo, month, NR, not recorded; NSCLC, non-small cell lung cancer.
Antonia et al. N Engl J Med 2018.

Sequence: rarely investigated



AE, adverse event; CT, computerised tomography; Gy, gray unit; irAE, immune-related AE; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; RT, radiation therapy
Powell S et al. Presentation at 2017 ASCO Annual Meeting

- Radiation therapy
- **Chemotherapy**
- Targeted therapy
- Immunotherapy
- (Hormonal treatment)
- (Surgery)

Taxanes, anthracyclines, Oxaliplatin, 5-FU (T-cell activation)

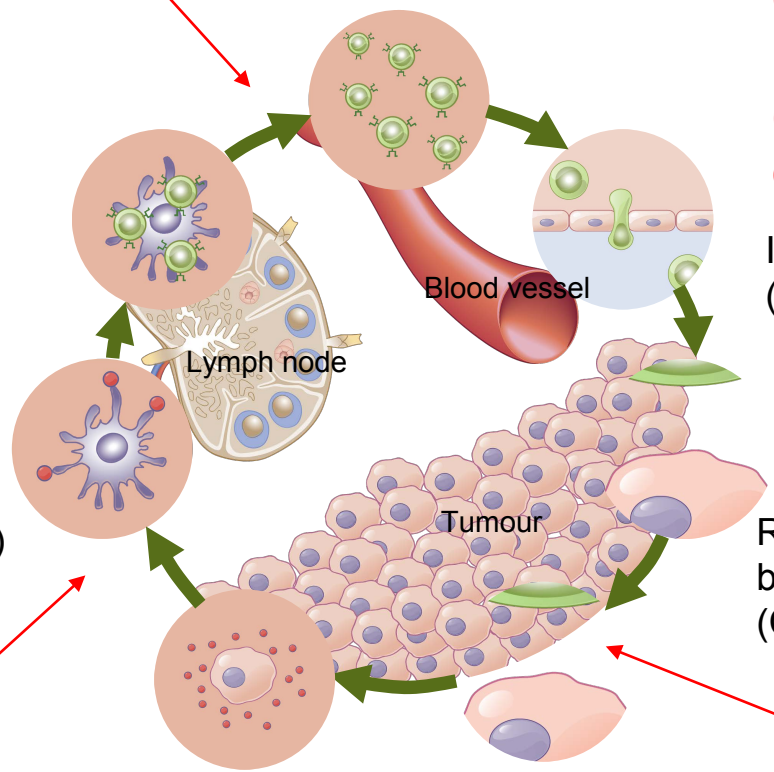
Gemcitabine, Cyclophosphamide Taxanes, Bleomycin (Inhibition of regulatory T cells)

Trafficking of T cells to tumours

Cyclophosphamide Fludarabine (Generation of memory T cells)

Priming and activation (APCs and T cells)

Paclitaxel, Gemcitabine (Antigen presentation)



Infiltration of T cells into tumours (CTLs, endothelial cells)

Cancer antigen presentation (dendritic cells/APCs)

Recognition of cancer cells by T cells (CTLs, cancer cells)

Cisplatin, 5-FU (Target destruction)

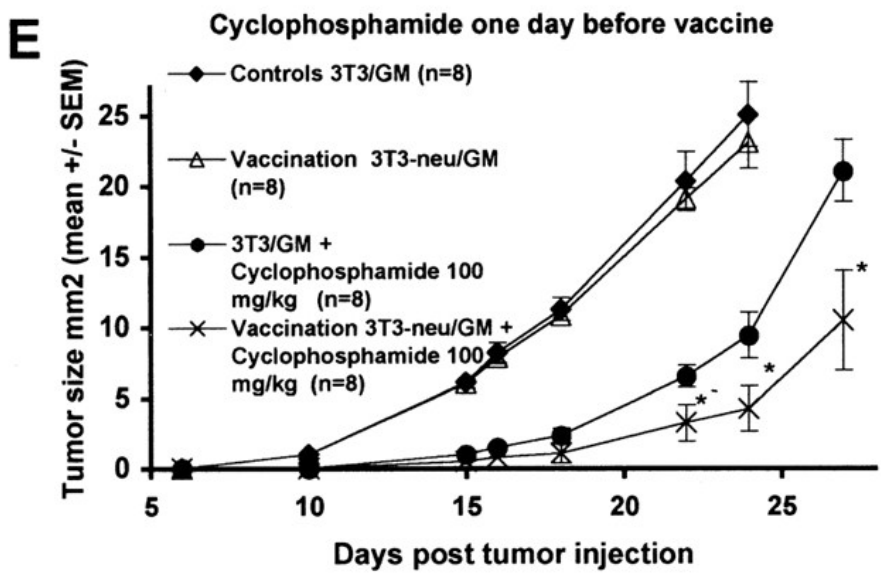
Oxaliplatin, Anthracyclines (Antigen processing)

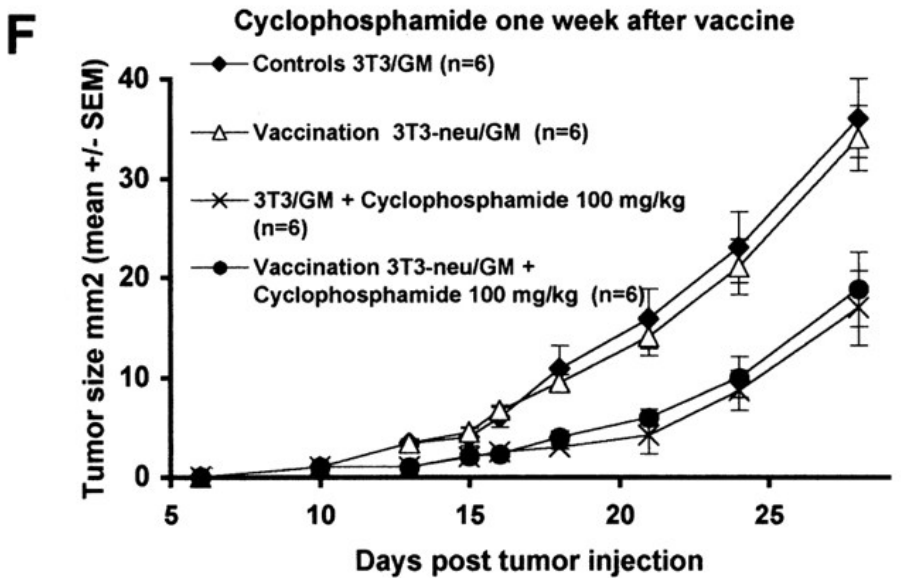
Release of cancer cell antigens (cancer cell death)

Killing of cancer cells (immune and cancer cells)

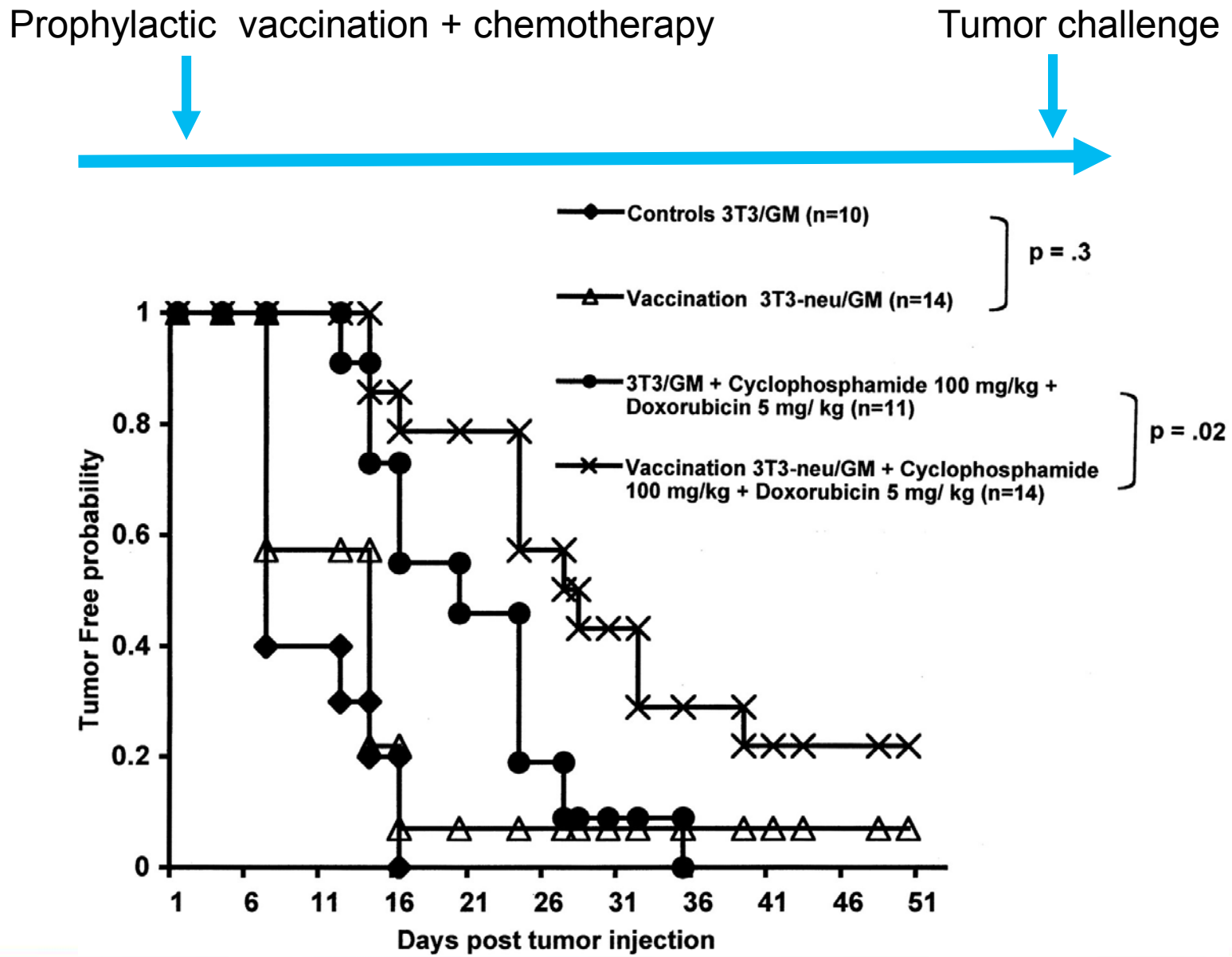
APCs, antigen-presenting cells; CTL, cytotoxic T lymphocyte; 5-FU, 5-fluorouracil.
Chen DS et al. Immunity 2013; Zitvogel et al. Nature Reviews

Immune effects of chemotherapy are dependent on the dose and schedule



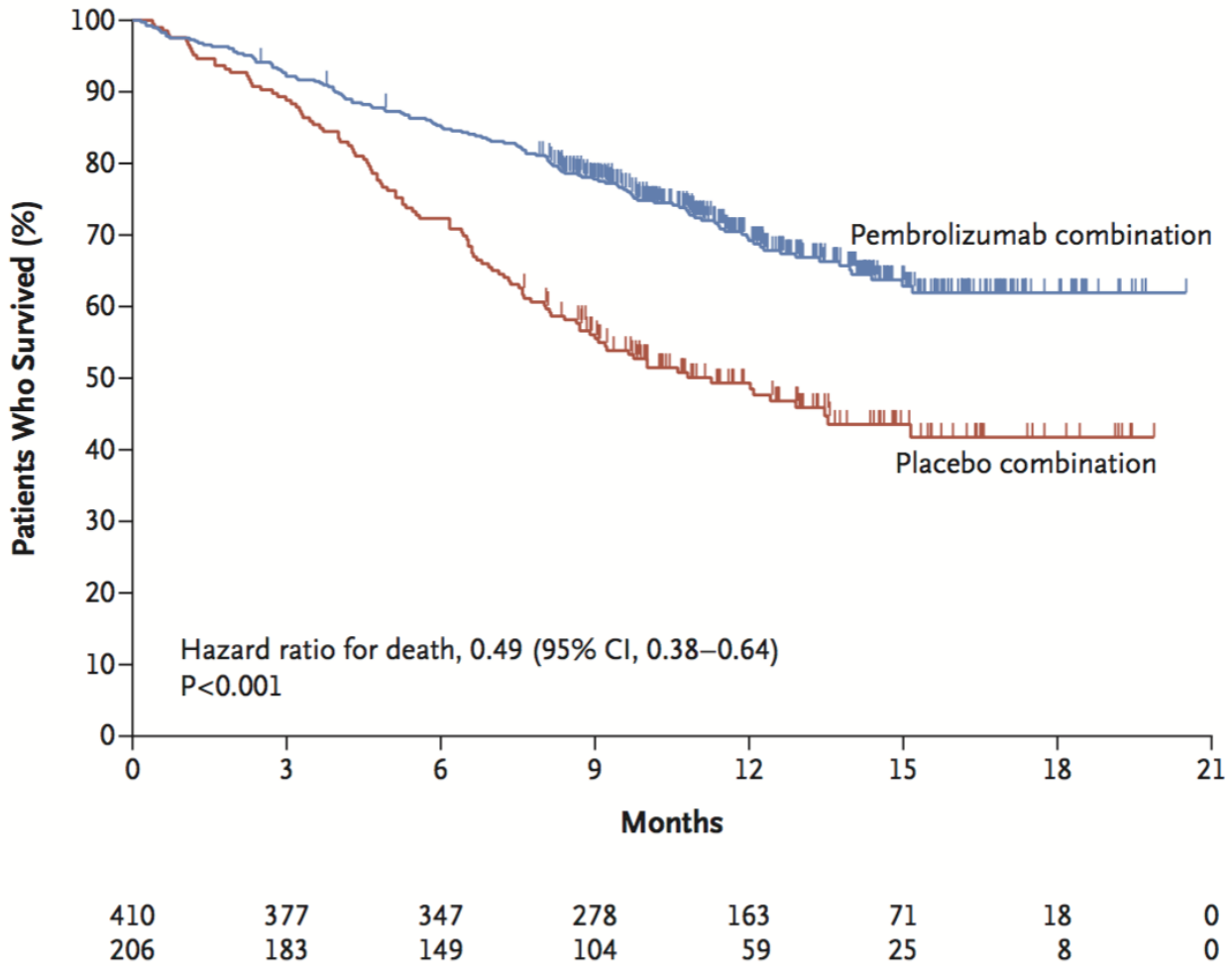


GM, genetically modified; SEM, standard error of the mean.
Machiels et al. Cancer Research 2001;61:3689–97.

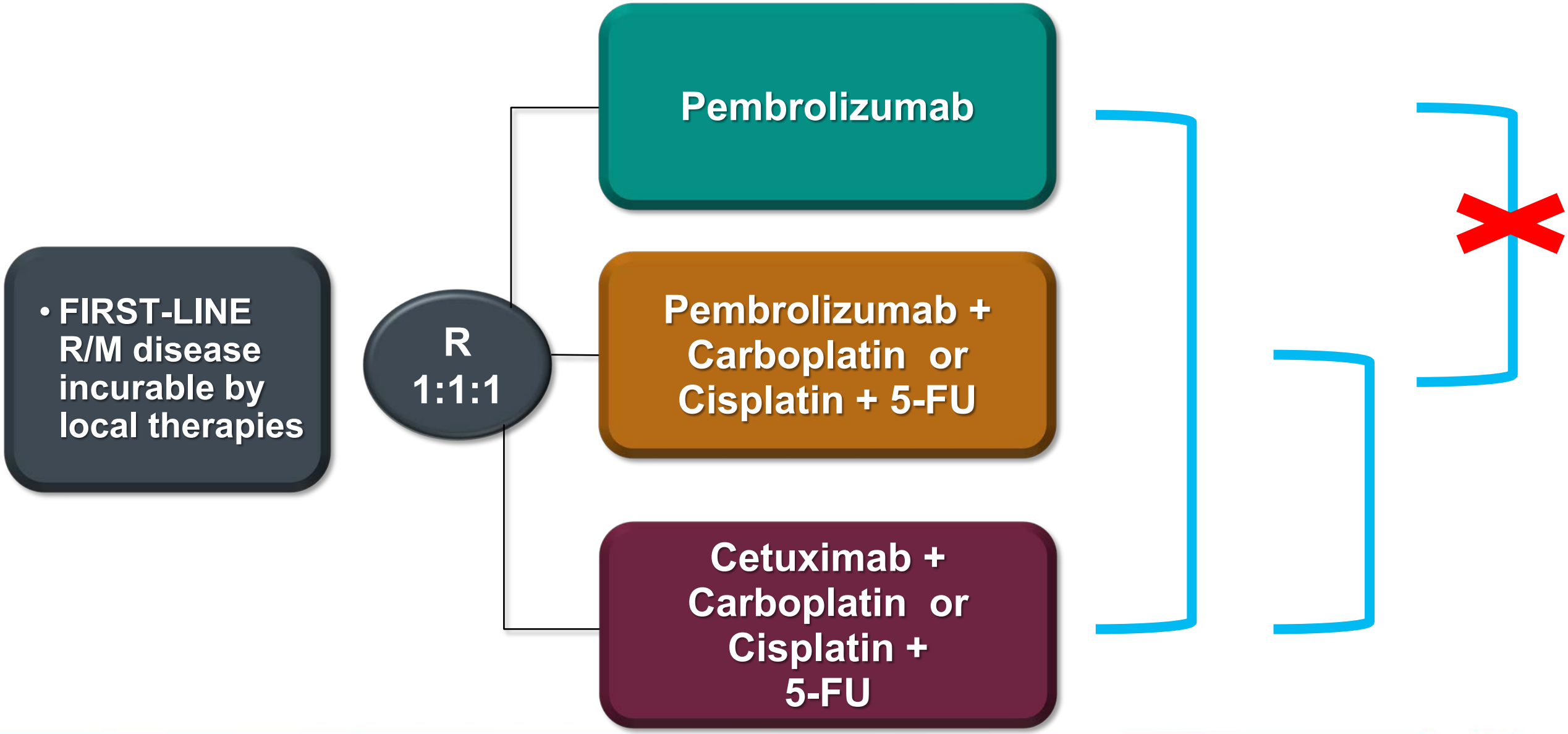


GM, genetically modified; SEM, standard error of the mean.
Machiels et al. Cancer Research 2001;61:3689–97.

Chemotherapy + pembrolizumab in NSCLC

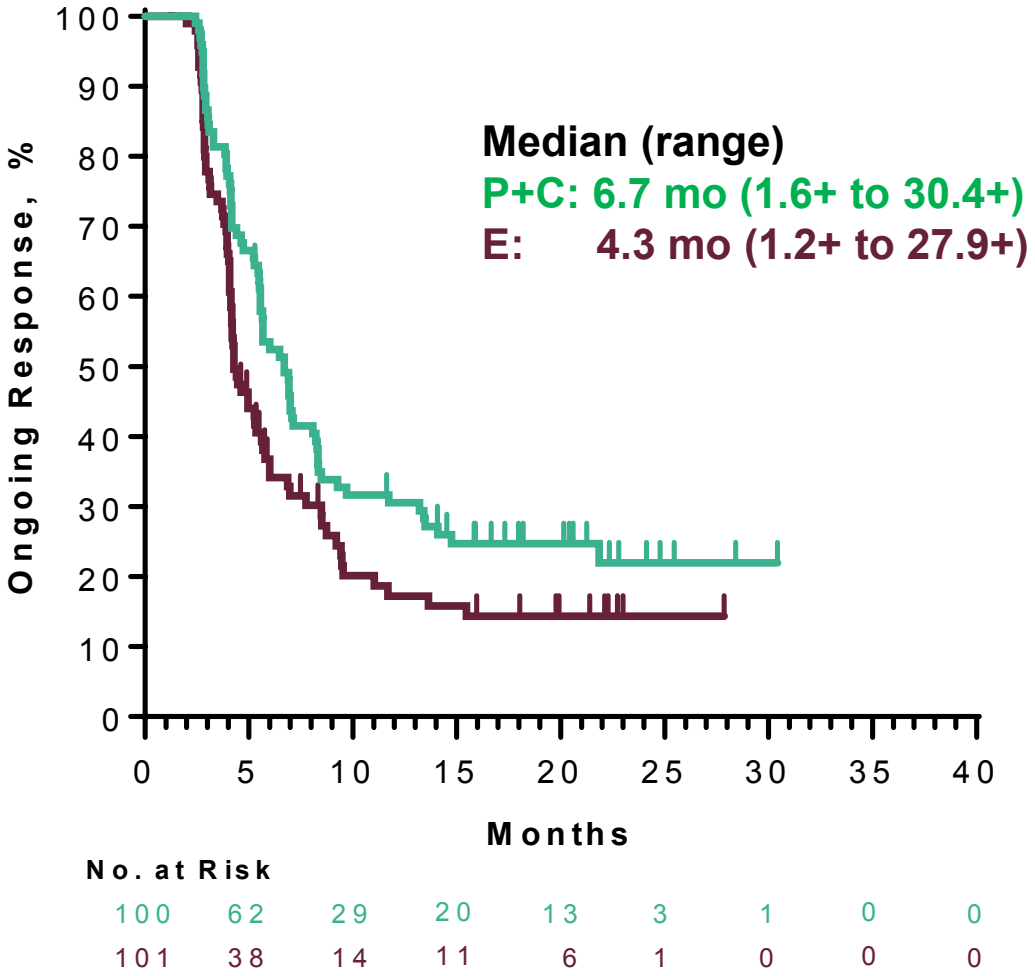


CI, confidence interval; NSCLC, non-small cell lung cancer.
Gandhi et al. N Engl J Med 2018;378:22:2078–92.

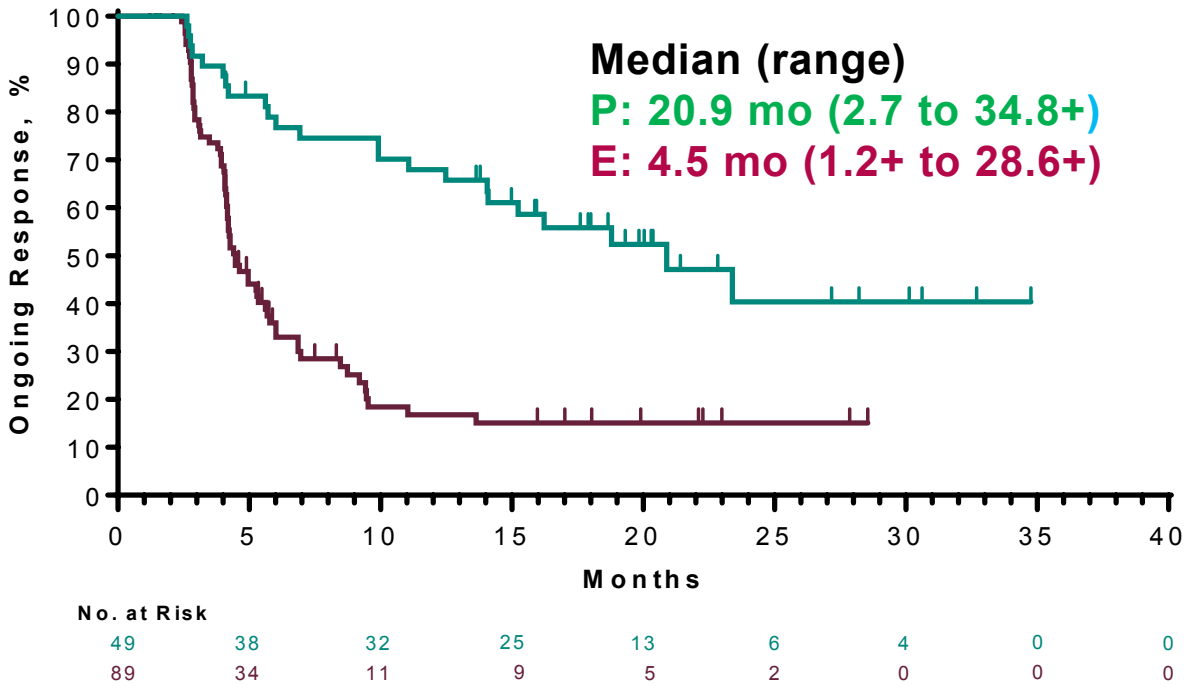


R/M, recurrent or metastatic; R, randomised; 5-FU, 5-fluorouracil.
Adapted from Burtness et al. Presented at ESMO 2018, Munich, Germany; Abstract LBA8-PR.

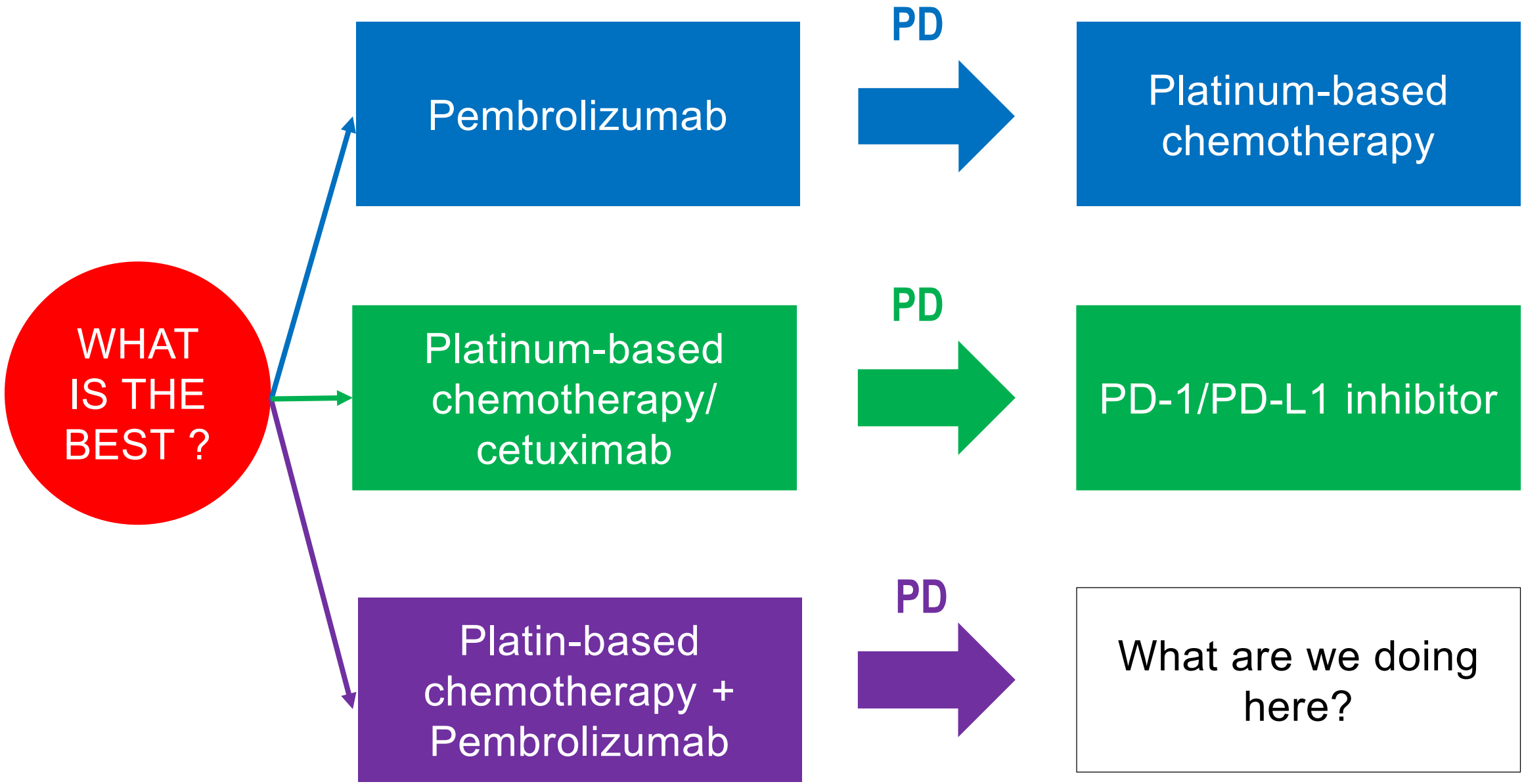
Duration of response
Total population, P+C



Duration of response
CPS ≥ 1, Pembro



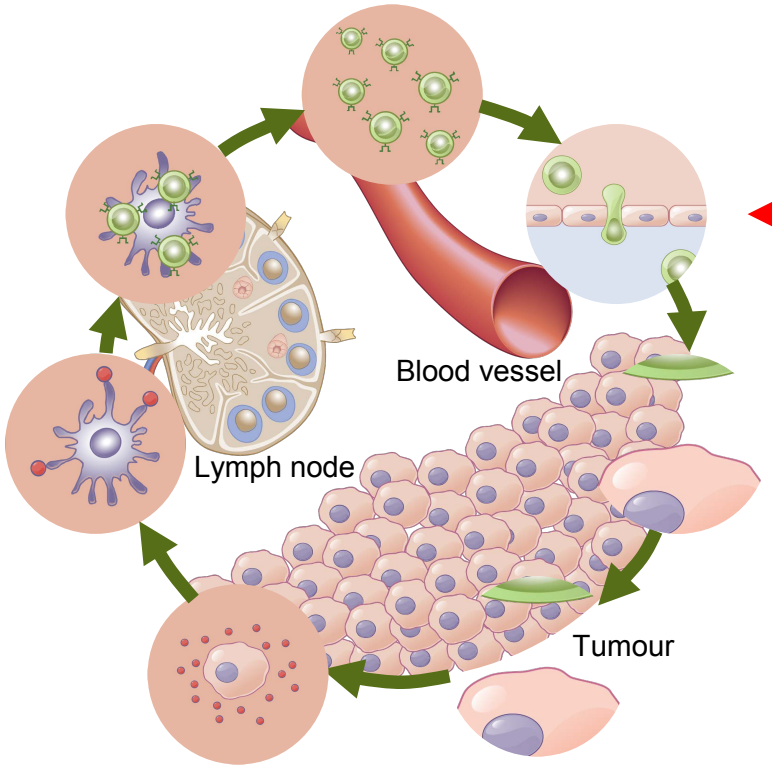
C, chemotherapy; CPS, combined positive score; MO, month; P, pembrolizumab.
Adapted from Burtness et al. Presented at ESMO 2018, Munich, Germany; Abstract LBA8-PR.



Adapted from Burtness et al. Presented at ESMO 2018, Munich, Germany; Abstract LBA8-PR.

- Radiation therapy
- Chemotherapy
- **Targeted therapy**
- Immunotherapy
- (Hormonal treatment)
- (Surgery)

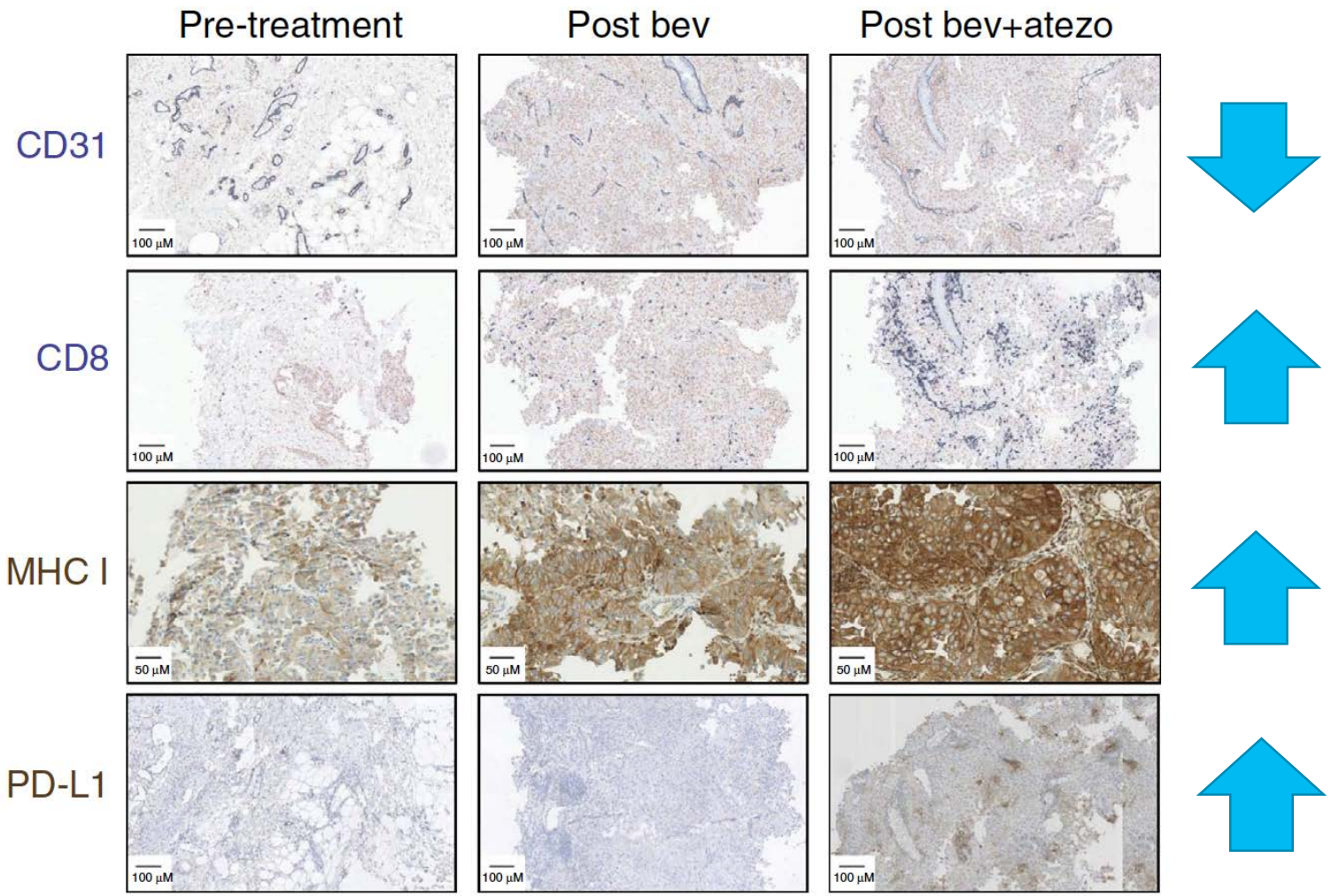
Anti-VEGF and T-cell infiltration



Infiltration of T cells enhanced by VEGF blockade

VEGF, vascular endothelial growth factor.
Chen DS et al. Immunity 2013;39.

Anti-VEGF and T-cell infiltration



Atezo, atezolizumab ; Bev, bevacizumab; CD, cluster of differentiation; MHC I, major histocompatibility complex ; PD-L1, programmed death-ligand ; VEGF, vascular endothelial growth factor.
Wallin et al. Nature Communications 2016.

Anti-VEGF and anti-CTLA4

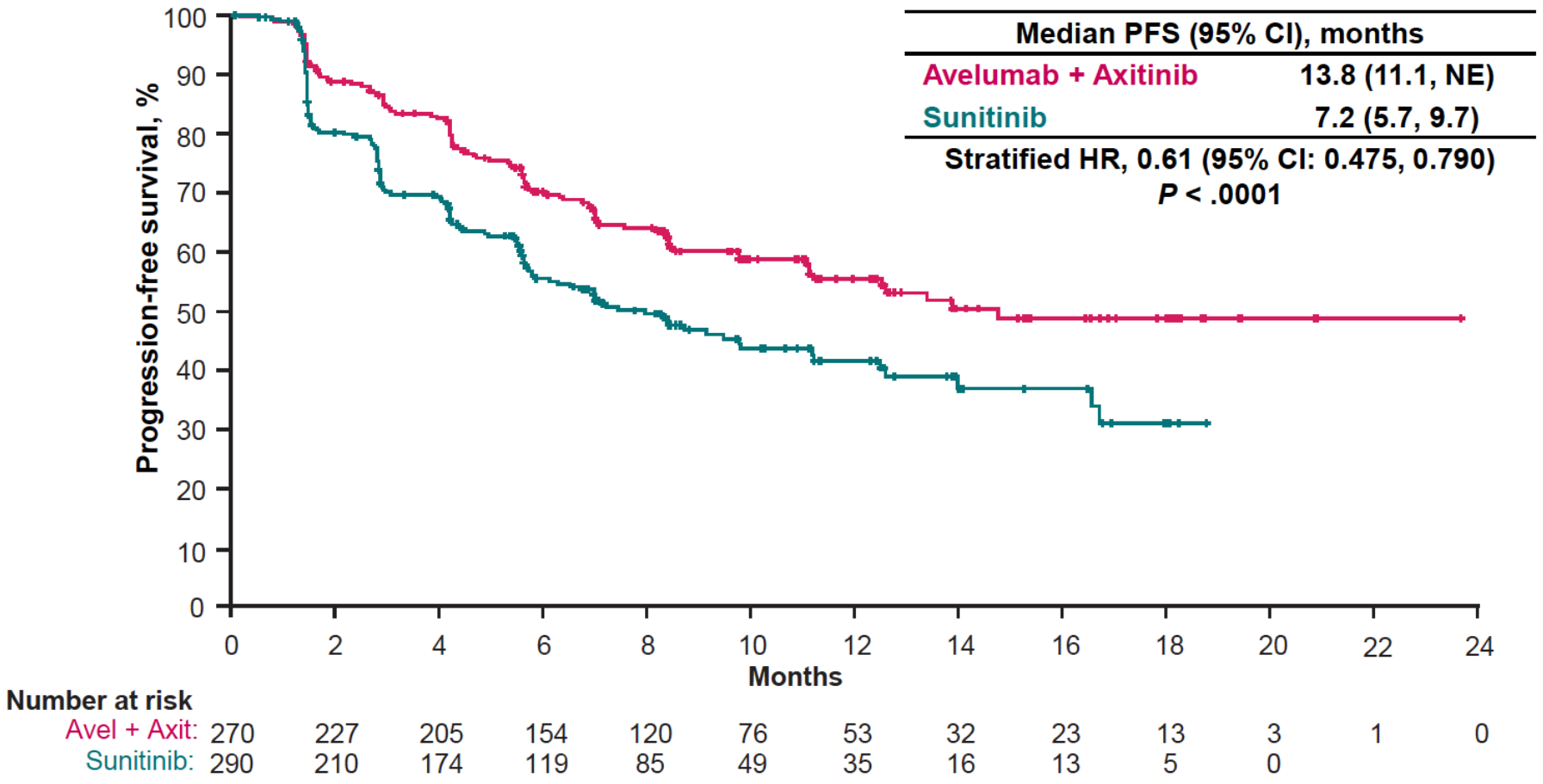
	Tremelimumab 6mg/kg + sunitinib 50 mg (n = 5)	Tremelimumab 6mg/kg + sunitinib 37.5 mg (n = 7)	Tremelimumab 15mg/kg + sunitinib 37.5 mg (n = 6)
DLTs	2/5	1 death	3/6

DLTs = Mostly acute renal failure

This combination is not recommended

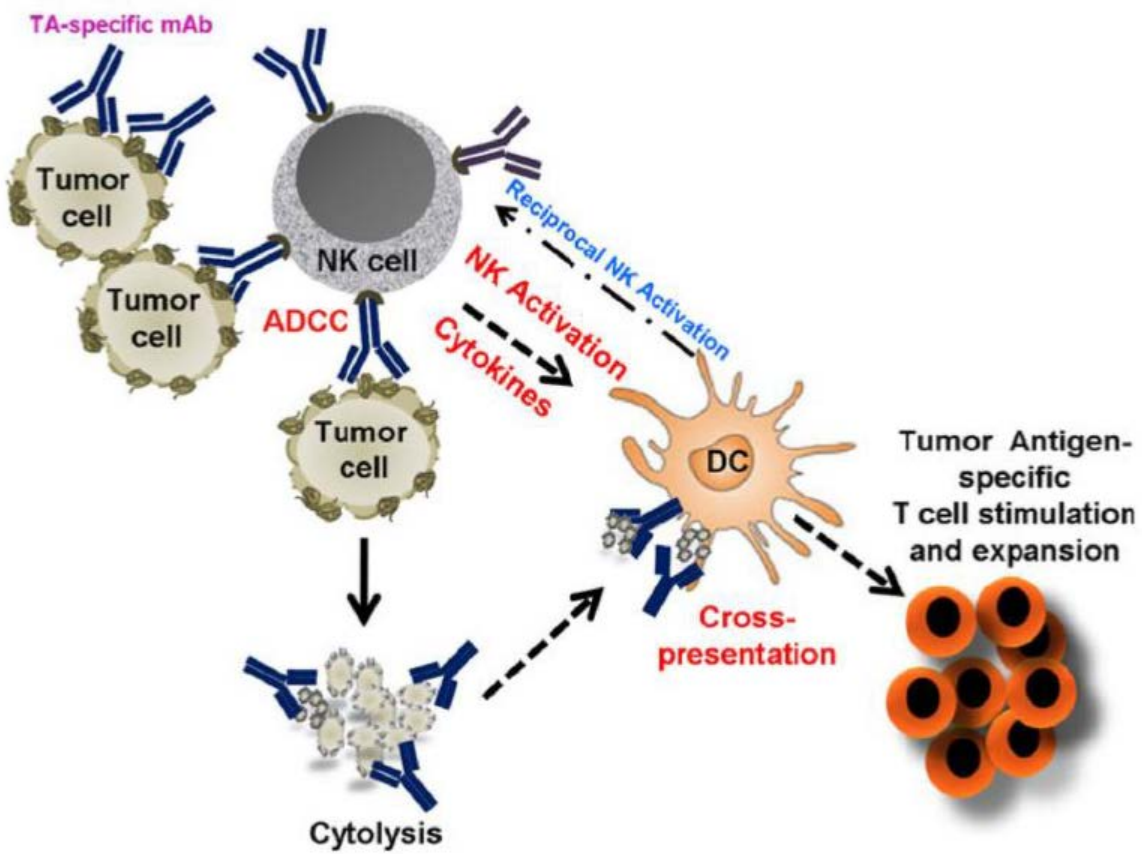
DLT, domino liver transplantation; VEGF, vascular endothelial growth factor.
Rini et al. Cancer. 2011;117:4:758–67.

Anti-VEGF and anti-PD-L1: renal cell carcinoma



NE, not estimable.
Motzer et al. Presentation at ESMO 2018.

Cetuximab



Cetuximab may enhance:

- PD1 + TIM3 + TIL[1]
- CTLA4 + Treg that could block NK activity[2]

Possible synergy between cetuximab and immune checkpoints

ADCC, antibody-dependent cellular toxicity; NK, natural killer.

1. Jie et al. Cancer Immunol Res 2017;5:5:408–16. 2. Jie et al. Cancer Res 2015 75:11:2200–10.

RT + ipilimumab + cetuximab

STUDY DESIGN

Standard, 3+3 Phase I Design

PROTOCOL THERAPY	Week of Treatment									
	1	2	3	4	5	6	7	8	11	14
IMRT 70-74 Gy, standard fractionation		X	X	X	X	X	X	X		
Cetuximab 400 mg/m^2 load then 250 mg	X	X	X	X	X	X	X	X		
Ipilimumab Cohort -1: 1 mg/kg Cohort 1 **(start)**: 3 mg/kg Cohort 2: 10 mg/kg					X			X	X	X

DOSE-LIMITING TOXICITY:

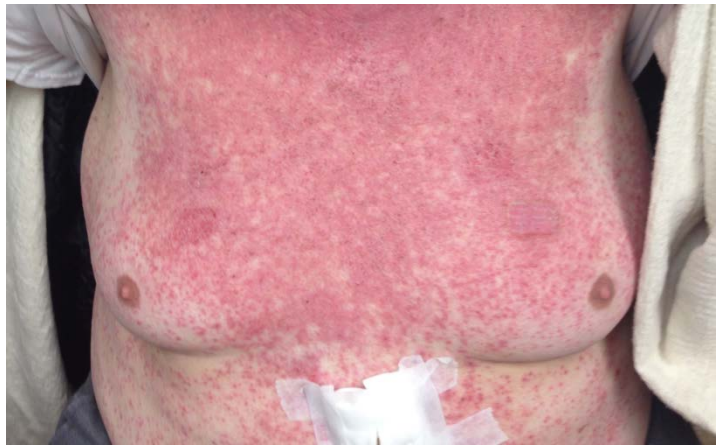
- Any grade 4 toxicity (except in-field radiation dermatitis or asymptomatic, correctable lab abnormality)
- Any grade ≥ 3 immune-related AE (irAE) requiring ≥ 2 weeks of systemic immunosuppression
- Any toxicity at least partially attributable to ipilimumab resulting in the delay of IMRT completion by ≥ 10 fractions

IMRT, intensity-modulated radiation therapy; irAE, immune-related adverse event..
Bauman et al. Poster presentation at ESMO 2016.

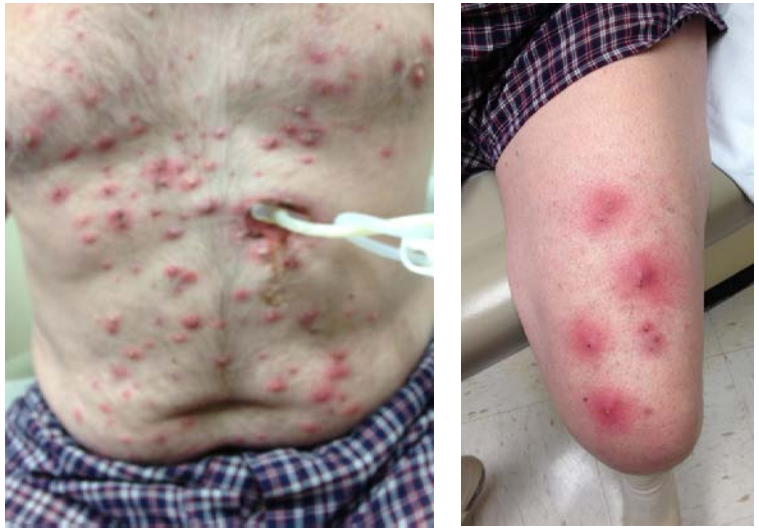
RT + ipilimumab + cetuximab

Dose-Limiting Toxicity

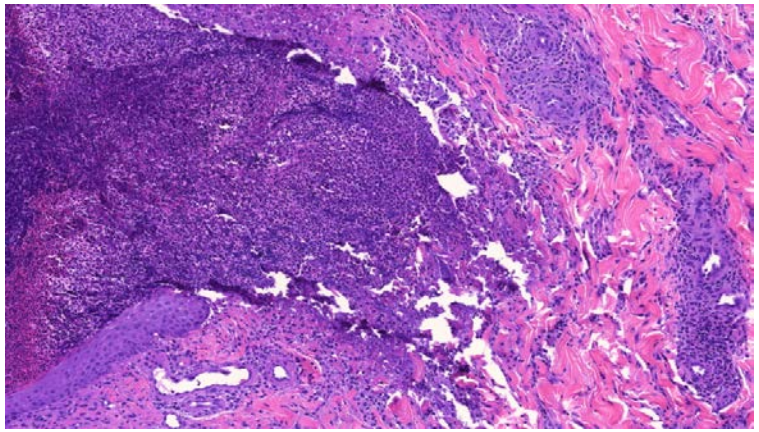
- Two of 6 patients in Cohort 1 (ipilimumab 3 mg/kg) experienced dermatologic immune-related AEs qualifying as DLTs



B. Autoimmune Dermatitis



A. Perforating Folliculitis



Bauman et al. Poster presentation at ESMO 2016.

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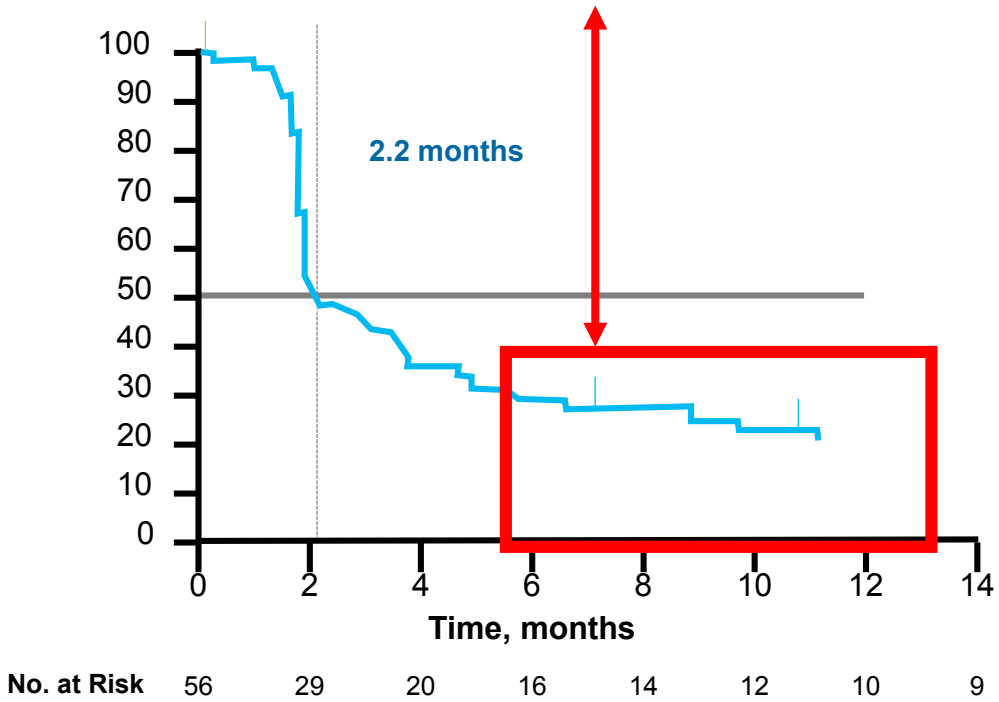
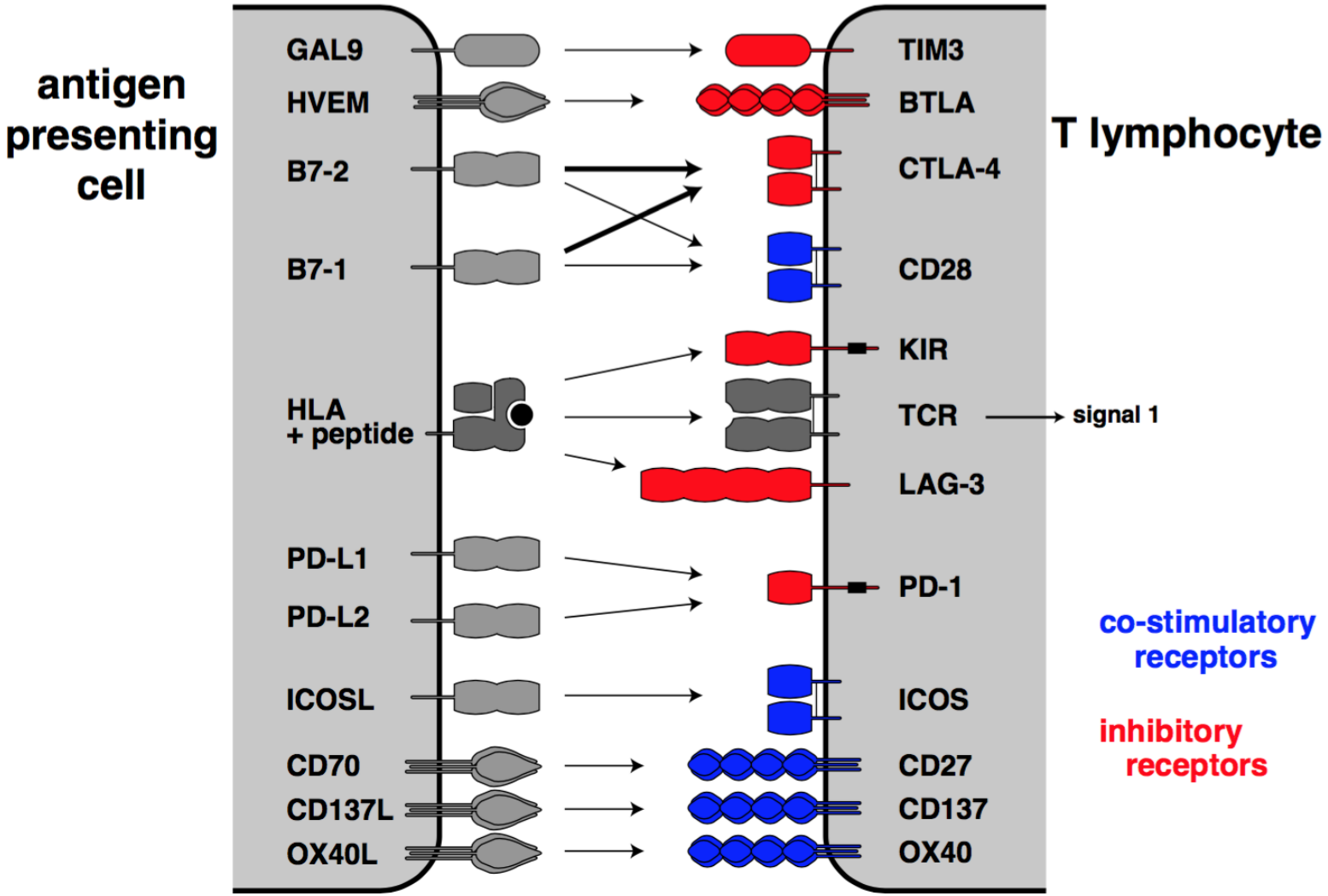
- (Surgery)



Seiwert et al. Lancet Oncol;2016:17:956–65.



Slide provided courtesy of S. Lucas and P. Coulie.

Immunosuppressive mechanisms

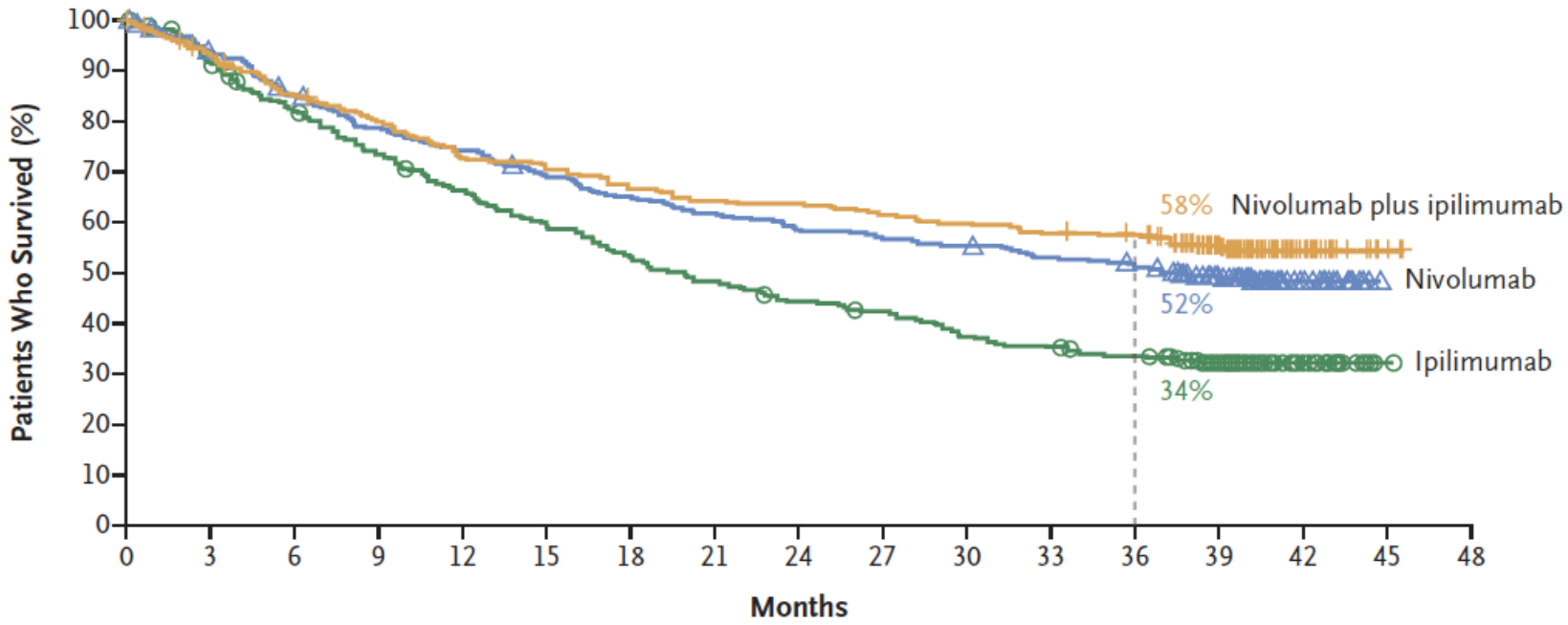
T-cell-intrinsic mechanisms
- CTLA-4/B7
- PD-1/PD-L1

Suppression by tumor cells
- PD-L1, FasL
- Depletion in tryptophane (IDO, …)
- Secretion of immunosuppresive factor (TGF beta, ...)

Suppression by other cells
- Regulatory T cells (Tregs)
- Myeloid-derived suppressive cells (MDSCs)
- Tumor associated macrophages (TAMs)

IDO, indoleamine-2,3-dioxygenase; TGF-β, tumour necrosis factor beta.
Slide provided courtesy of S. Lucas and P. Coulie.

Nivolumab + ipilimumab in melanoma



No. at Risk																	
Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

Wolchok et al. N Engl J Med 2017;377:1345–56.

Conclusions

- Scientific rationale to combine immunotherapy with the other cancer treatment modalities
- Treatment sequences not properly investigated
- Be careful with some new combinations


ImmunoScience Academy
Partnering for Education & Optimizing Treatment in ImmunoScience

Thank you

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