Lung Cancer Combination Immunotherapies

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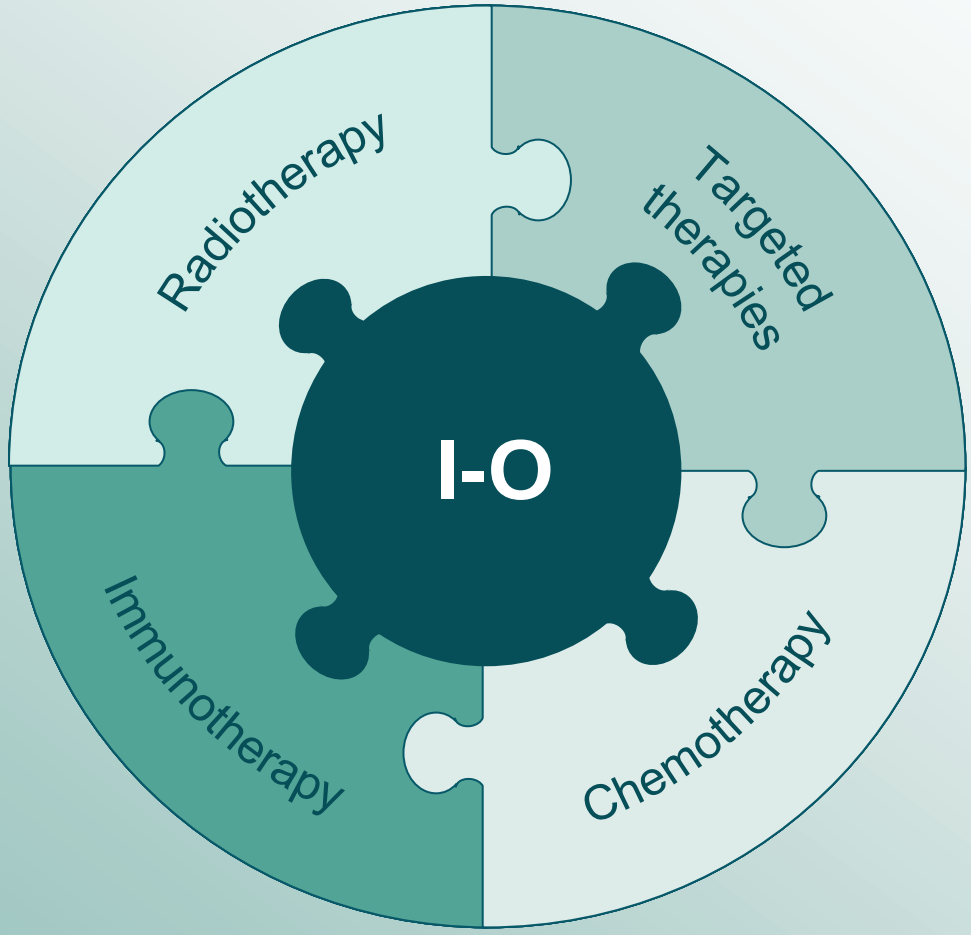
ESMO SYMPOSIUM ON IMMUNO-ONCOLOGY

Disclosure slide

- Bayer Health Care
- Biodesix
- Biothera
- Boehringer Ingelheim
- Bristol Myers-Squibb (BMS)
- Clovis Oncology
- Eisai Inc.
- Genentech/Roche
- GlaxoSmithKline (GSK)
- MedImmune
- Merck
- Novartis
- Peregrine Pharmaceuticals, Inc.
- Pfizer
- Synta Pharmaceuticals Corp.

This includes receipt of grants/research support, receipt of honoraria or consulting fees, and participation in company sponsored speaker's bureaus.

I-O agents have a unique MoA, offering the opportunity for combination with other agents



Drake C. *Ann Oncol.* 2012;23(suppl 8):viii41–viii46; Hannani D, et al. *Cancer J* 2011;17:351–358;
Ménard C, et al. *Cancer Immunol Immunother.* 2008;57:1579–1587; Ribas A, et al. *Curr Opin Immunol.* 2013:25:291–296.

Examples of ongoing combination trials with I-O therapies, many more in development

	Chemotherapy	Radiotherapy	Targeted	Immunotherapy
Nivolumab (anti-PD-1)	+ cisplatin/gemcitabine, cisplatin/pemetrexed or carboplatin/paclitaxel (NCT01454102)	NR	+ bevacizumab or erlotinib (NCT01454102)	+ ipilimumab (NCT01454102) + anti-KIR (NCT01714739) + anti-LAG3 (NCT01968109)
Pembrolizumab (anti-PD-1)	+ cisplatin/pemetrexed or carboplatin/paclitaxel (NCT01840579) + paclitaxel/carboplatin ± bevacizumab (NCT02039674)	NR	+ gefitinib or erlotinib (NCT02039674)	+ ipilimumab (NCT02039674) + INCB024360 (NCT02178722)
MEDI-4736 (anti-PD-L1)	NR	NR	+ gefitinib (NCT02088112) + AZD9291 (NCT02143466)	+ tremelimumab (NCT02000947, NCT02141347)
MPDL3280A (anti-PD-L1)	NR	NR	+ erlotinib (NCT02013219) + cobimetinib (NCT01988896)	+ ipilimumab (NCT02174172)
Ipilimumab (anti-CTLA-4)	Various (NCT00527735; NCT01165216; NCT01285609; NCT01331525; NCT01450761;NCT1454102)	+ stereotactic radiosurgery* (NCT02107755, NCT02239900) + ionizing radiation (NCT02221739)	+ erlotinib or crizotinib (NCT01998126)	+ nivolumab (NCT01454102) + pembrolizumab (NCT02039674)
Tremelimumab (anti-CTLA-4)	NR	NR	+ gefitinib (NCT02040064)	+ MEDI-4736 (NCT02000947)

*Trial in patients with melanoma with metastatic disease to a visceral organ (lung, liver, brain, adrenal, nodal station outside the regional lymph drainage of the primary, vertebral bodies).

NR = no trials reported.

www.clinicaltrials.gov. Accessed June 2014.

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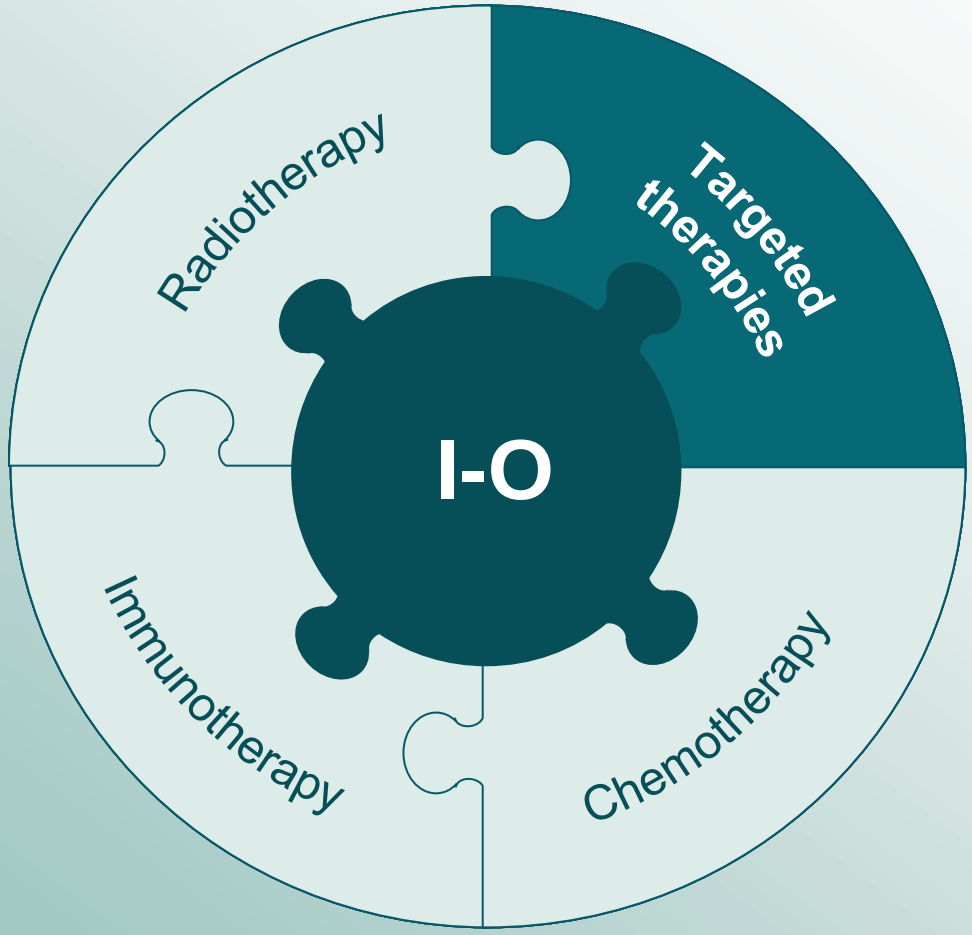

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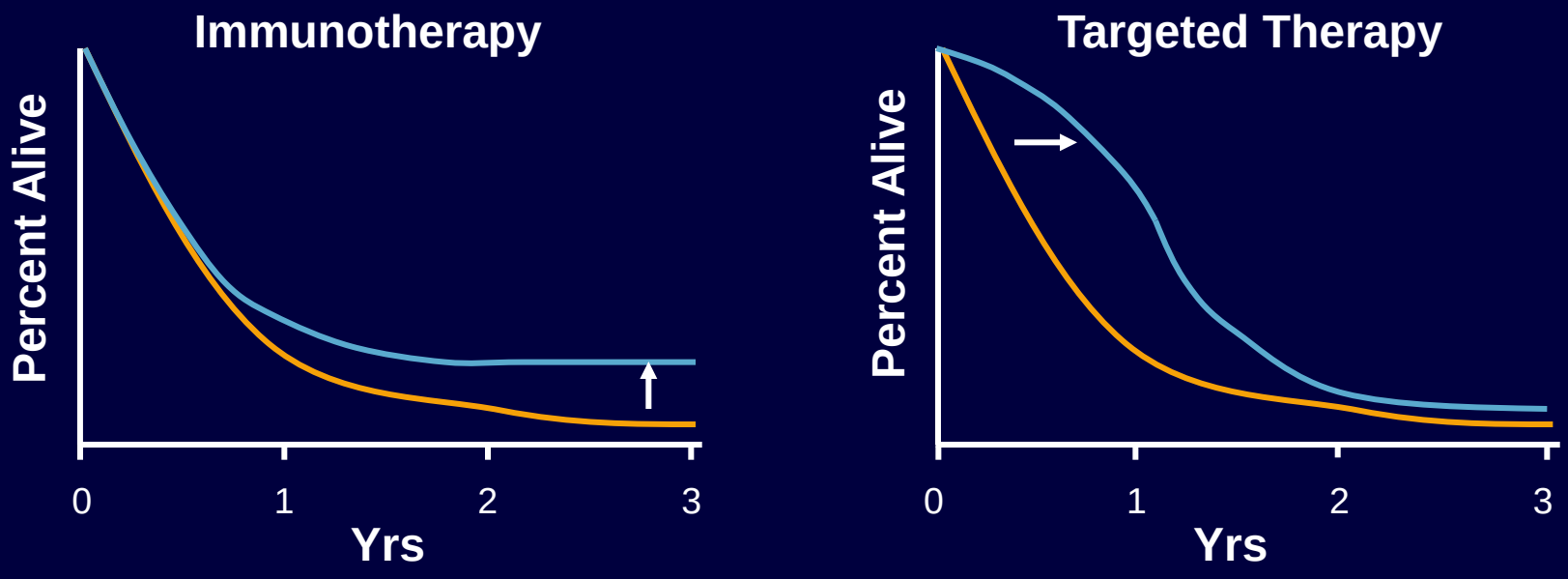
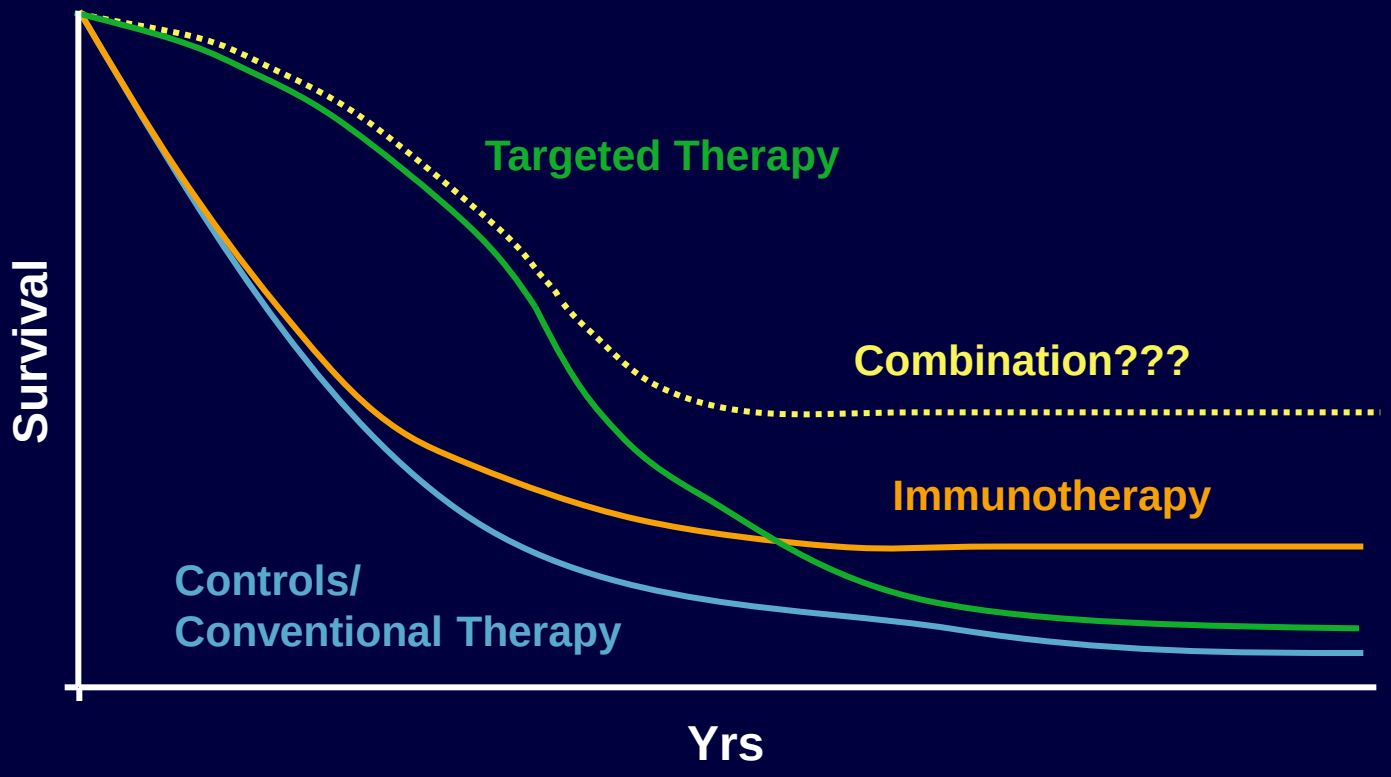
Response Patterns for Immunotherapy Compared With Targeted Therapy



Ribas A, et al. Clin Cancer Res. 2012;18:336-341.

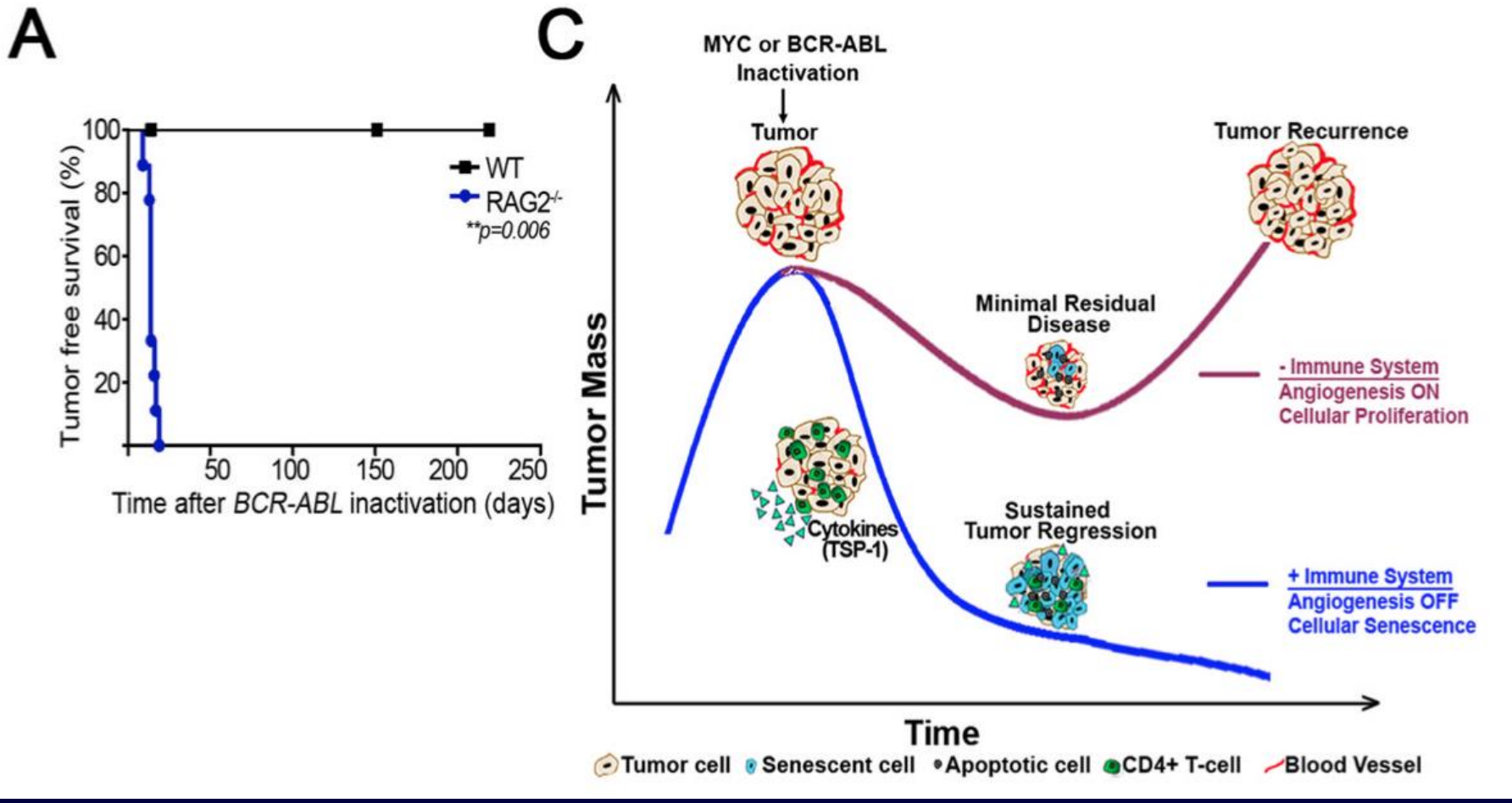
Combining Immunotherapy and Conventional Therapies



Adapted from Ribas A, et al. Clin Cancer Res. 2012;18:336-341.

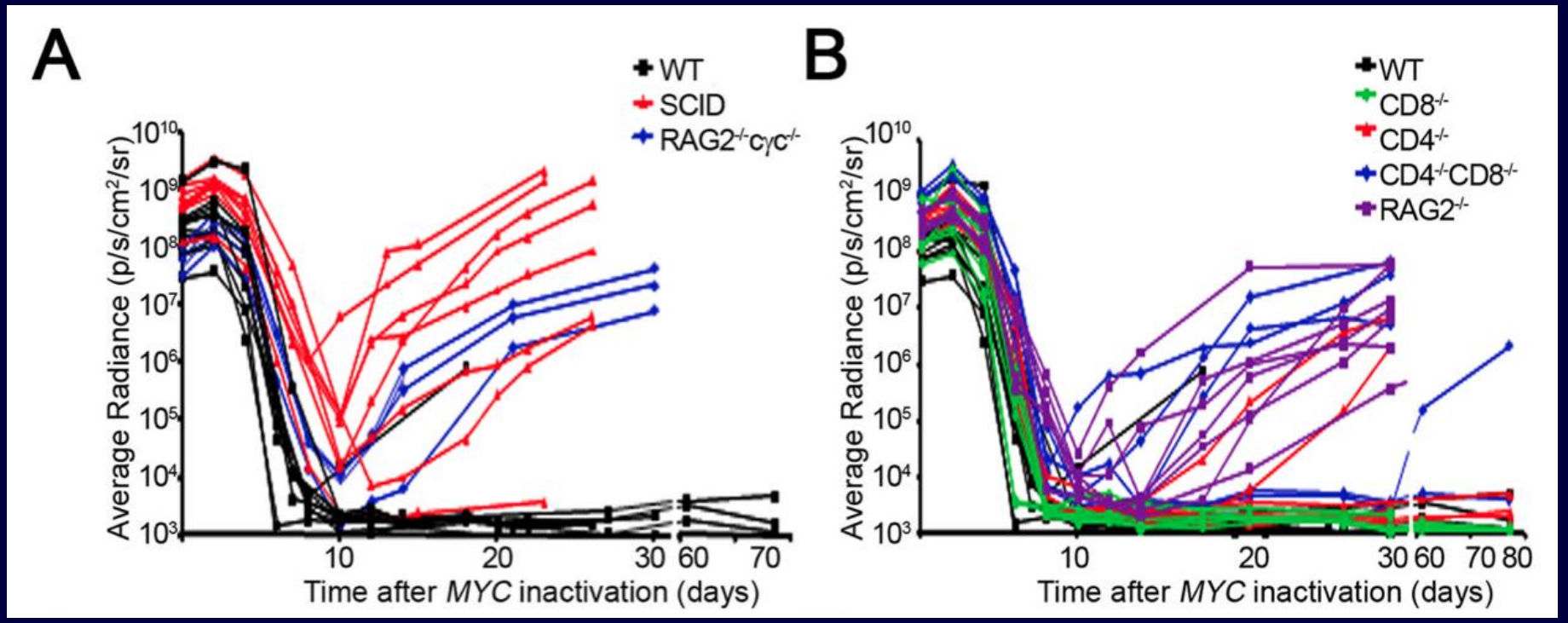
Is the immune system relevant in tumors with “driver oncogenes”?

The immune system and “driver oncogenes”



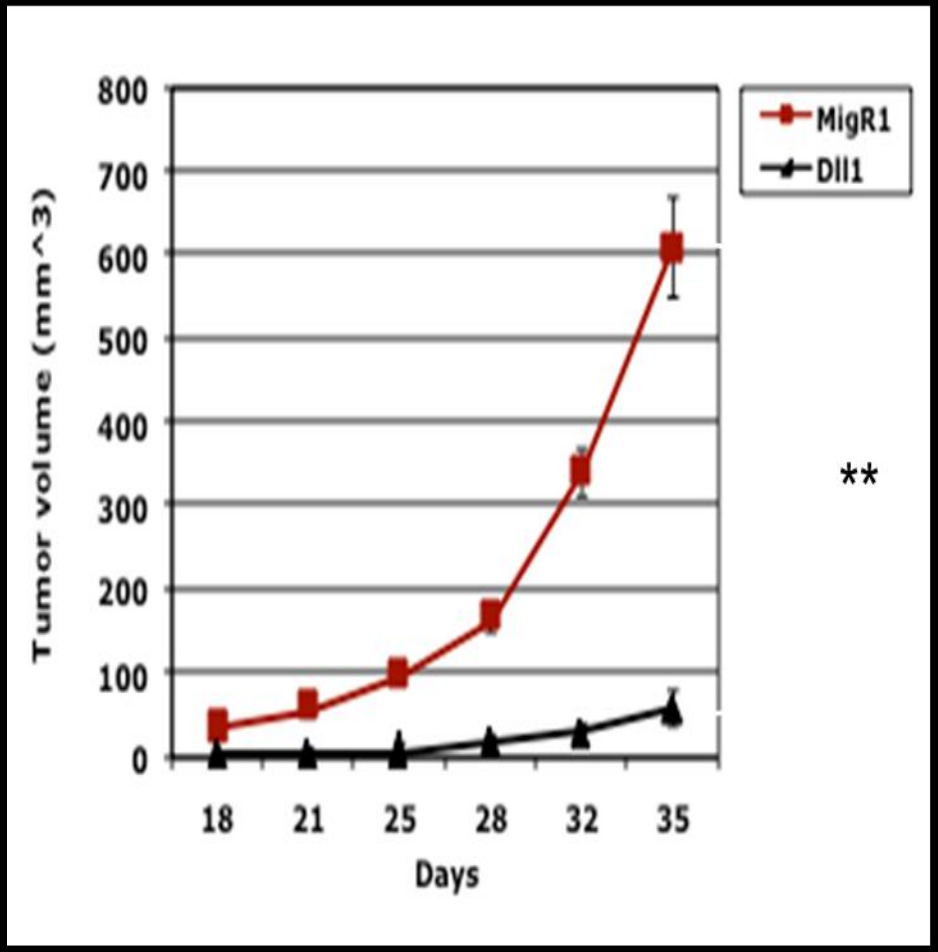
Rakhra and Felsher, Cancer Cell, 2010

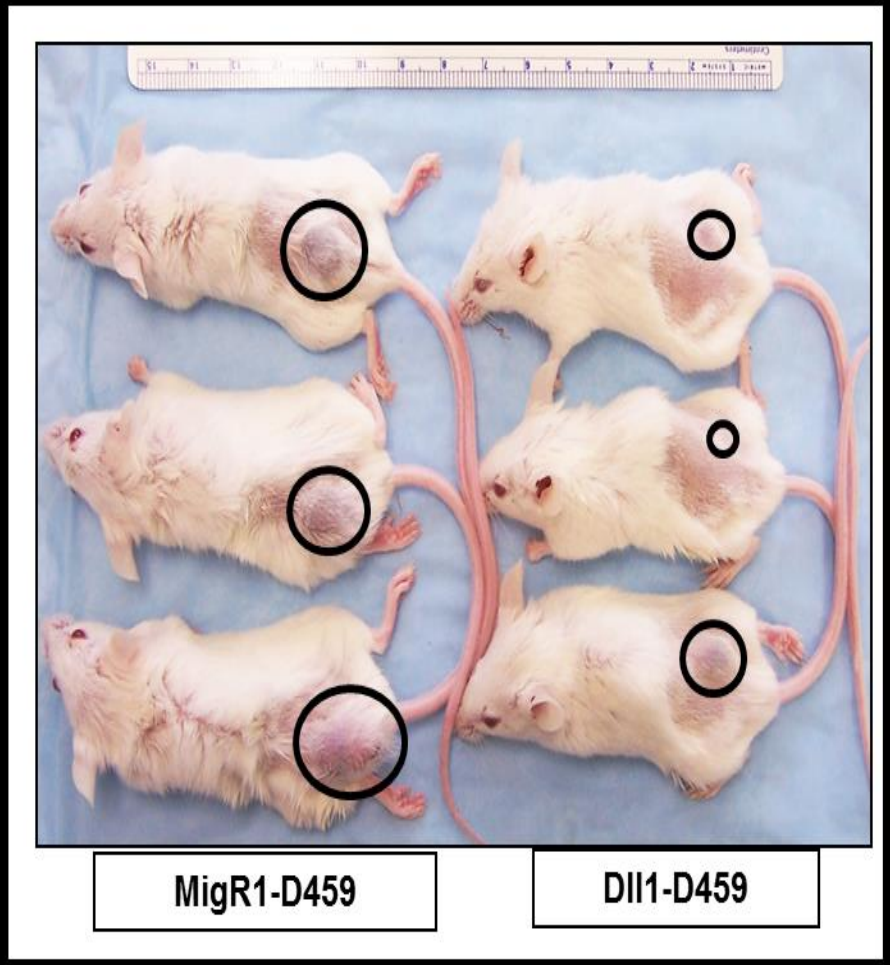
Immune system and MYC



Rakhra and Felsher, Cancer Cell, 2010

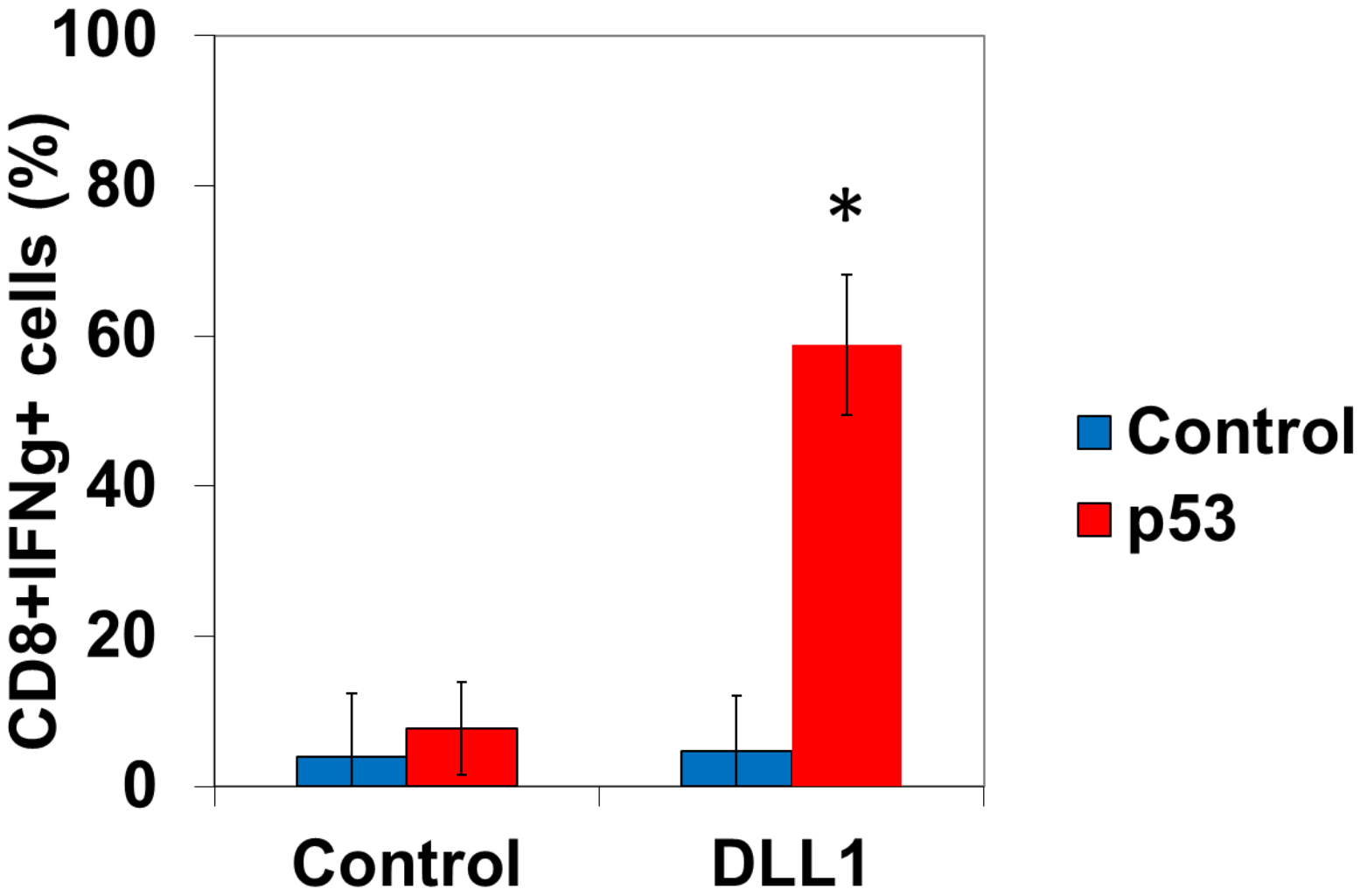
Restoration of DLL-1 in Bone Marrow Inhibits Tumor Growth





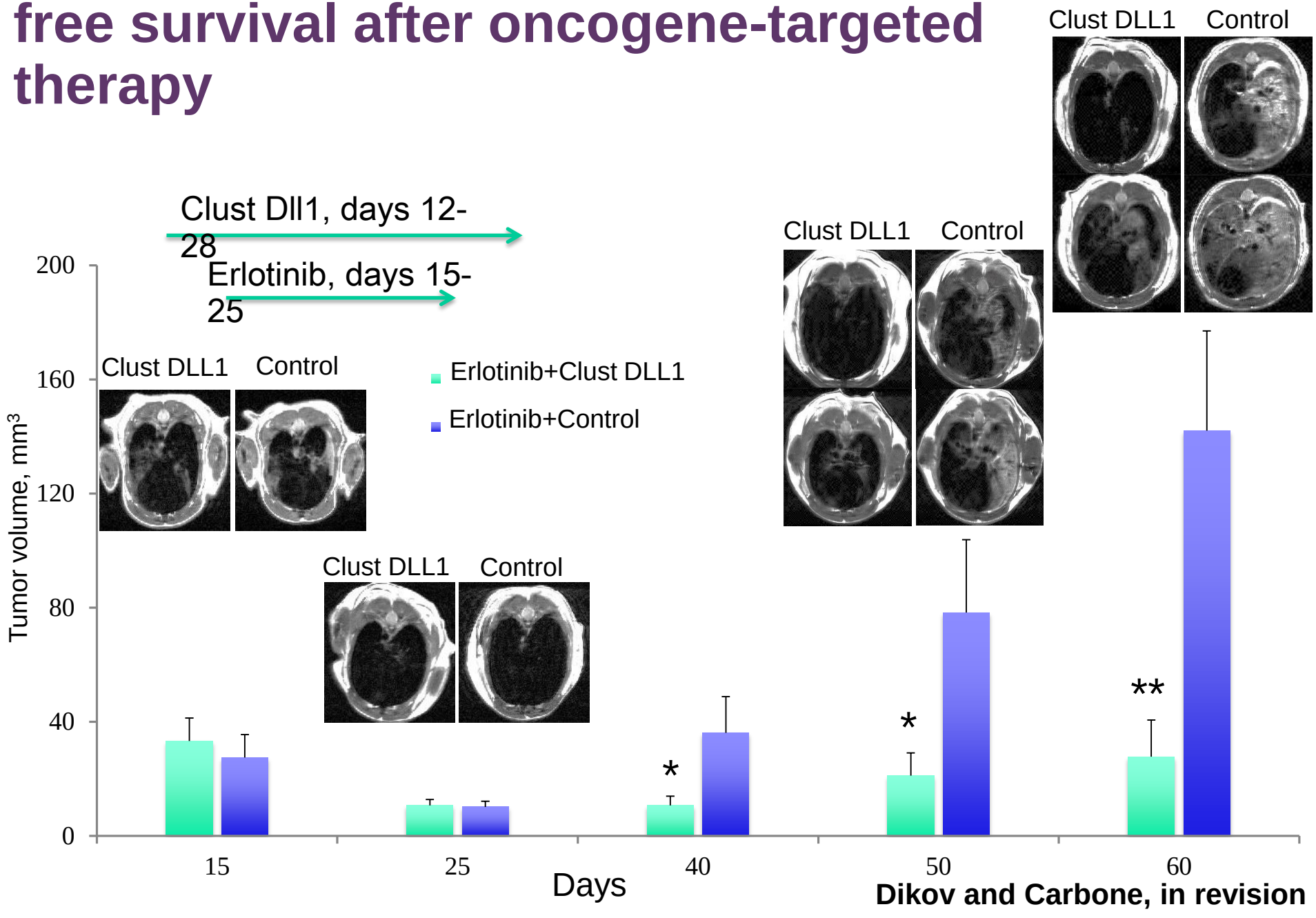
Huang and Carbone, Cancer Research 2011

Induction of Mutant p53-Specific Immune Response by Clustered DLL1



Huang and Carbone, Cancer Research 2011

Clustered DLL1 improves progression-free survival after oncogene-targeted therapy



CA209-012 Study Design: Nivolumab in Combination With Erlotinib

Stage IIIB/IV, EGFR MT, non-squamous NSCLC, no prior chemotherapy for advanced NSCLC and ECOG PS 0 or 1[a,b]

↓

Nivolumab 3 mg/kg IV Q2W + erlotinib 150 mg/day PO until disease progression or unacceptable toxicity[c]

↓

Primary objective: safety and tolerability
Secondary objectives: ORR (by RECIST v1.1)[d] and PFS rate at 24 wks
Exploratory objective: OS

[a]Site-determined EGFR mutation test
[b]Prior use of EGFR TKIs was allowed
[c]Pts were permitted to continue study treatment beyond RECIST v1.1-defined progression if they were considered to be deriving clinical benefit and tolerating study treatment
[d]Response was assessed at the beginning of wks 11, 17, 23, and every 3 months thereafter until disease progression
ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = objective response rate; OS = overall survival; PO = oral administration; Q2W = every two wks; RECIST = Response Evaluation Criteria In Solid Tumors; wks = weeks

Tumor response in NSCLC pts treated with nivolumab plus erlotinib

	Prior treatment with erlotinib (n = 20)	No prior treatment with erlotinib (n = 1)
Confirmed ORR, n (%) [95% CI]	4 (19) [5, 42]	
Ongoing responders, n (%)	2 (67)	1 (100)
Best overall response, n (%) PR[a] SD PD	 3 (15) 9 (45) 8 (40)[b]	 1 (100) 0 0
Response duration by pt, wks	60.1, 64.6+, 70+	83.7+
SD duration by pt, wks	9.9+, 15.7, 22.3, 22.7+, 29.4, 35.9, 49.4, 52.7, 53.0	–
PFS		
PFS rate at 24 wks, % (95% CI)	50 (27, 70)	
Median PFS, wks (range)	29.4 (4.6, 93.1+)	
OS		
18-month OS rate, % (95% CI)	64 (39, 81)	
Median OS, wks (range)	NR (10.7+, 110.3+)	

[a]All PRs were confirmed by a subsequent tumor assessment per RECIST v1.1
[b]Includes one pt with an unconventional "immune-related" response
+ = censored; CI = confidence interval; NR = not reached

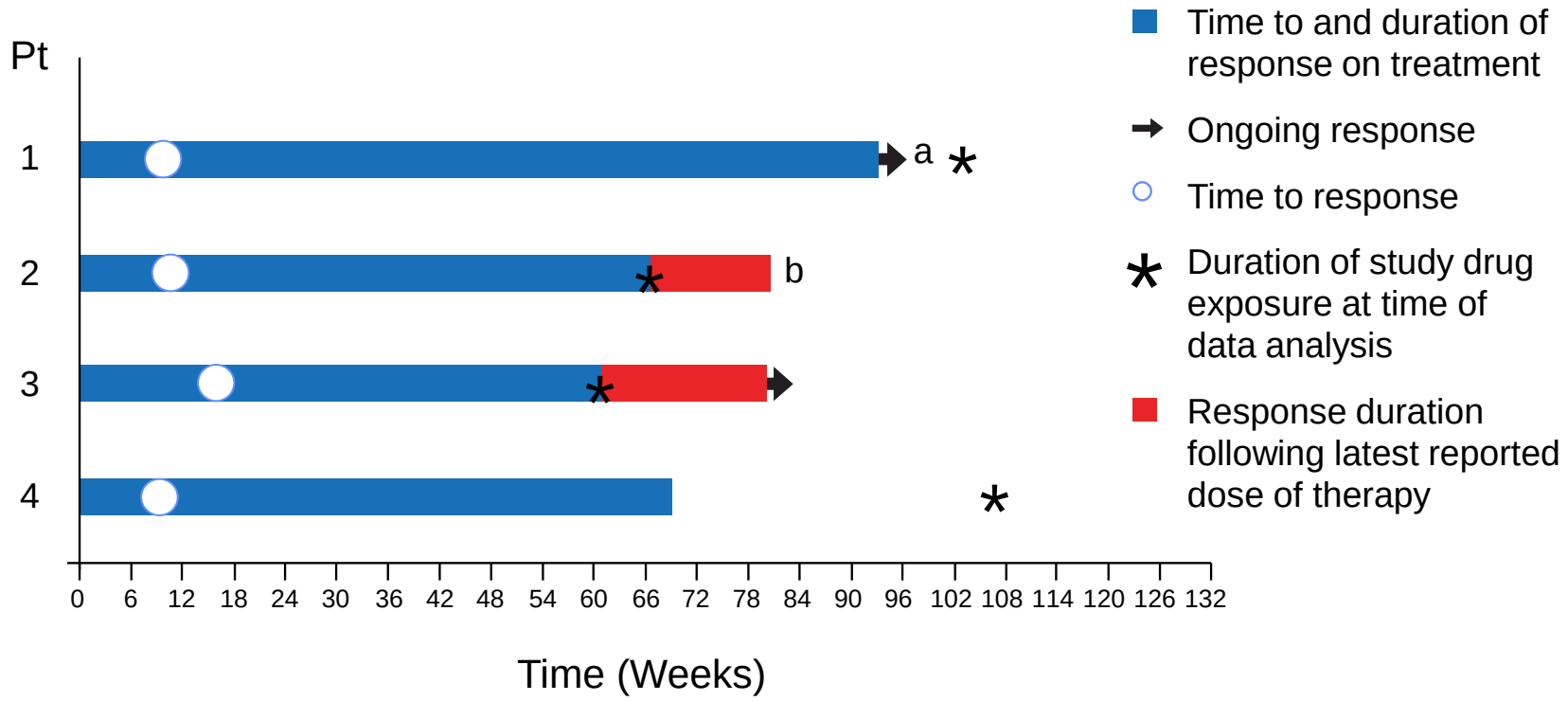
Characteristics of Pts With Tumor Regression on Nivolumab Plus Erlotinib

Pt	EGFR MT	PFS (wks)[a]		Rebiopsy	Nivolumab + erlotinib (n = 21)	
		Prior erlotinib	Prior afatinib/ cetuximab		Treatment duration (wks)	PFS[b] (wks)
1	DEL19	90	n/a	T790M+	66+	80
2	DEL19	40	15	T790M–	61	80+
3[c]	L858R	26	n/a	T790M–	108+	69
4[d]	L858R/ S768I	n/a	n/a	n/a	104+	93+
5[e]	L858R	55	34	T790M+	104+	9

[a]Investigator-reported PFS
[b]Tumor assessments were performed until disease progression, including after discontinuation of treatment
[c]Pt continues trial therapy after excision of solitary site of growth, with sustained response at other sites
[d]Erlotinib-naïve pt
[e]Pt with PD by RECIST v1.1; however, this pt exhibited an unconventional "immune-related" response, with a 51% reduction in target lesions (maximum decrease) after initial progression in non-target lesions
+ = ongoing; n/a = not available

Results(cont)

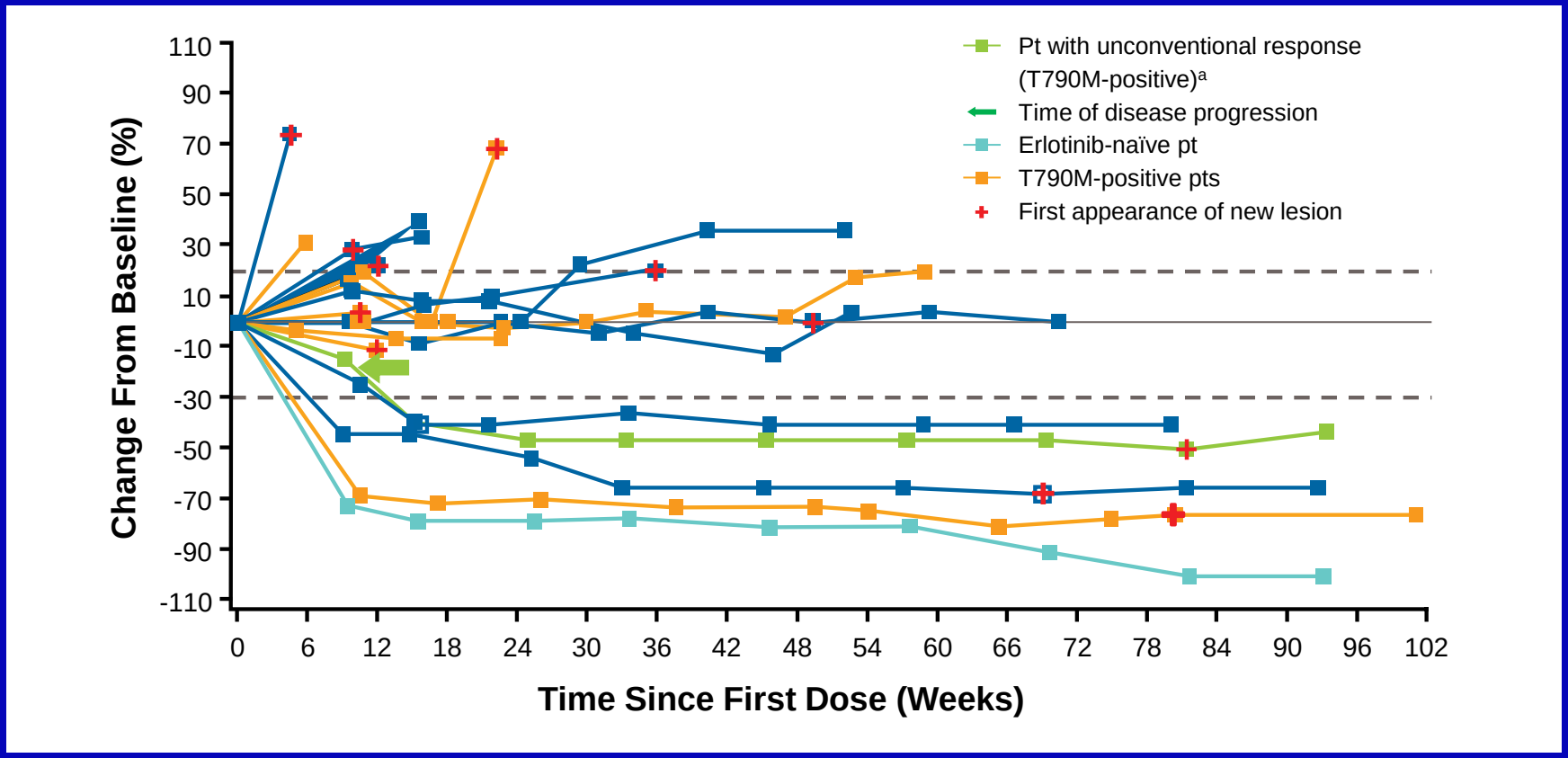
Characteristics of Response in NSCLC Pts Treated With Nivolumab Plus Erlotinib



[a]Erlotinib-naïve pt
[b]T790M-positive pt

Percent Changes in Target Lesion Tumor Burden in NSCLC Pts Treated With Nivolumab Plus Erlotinib

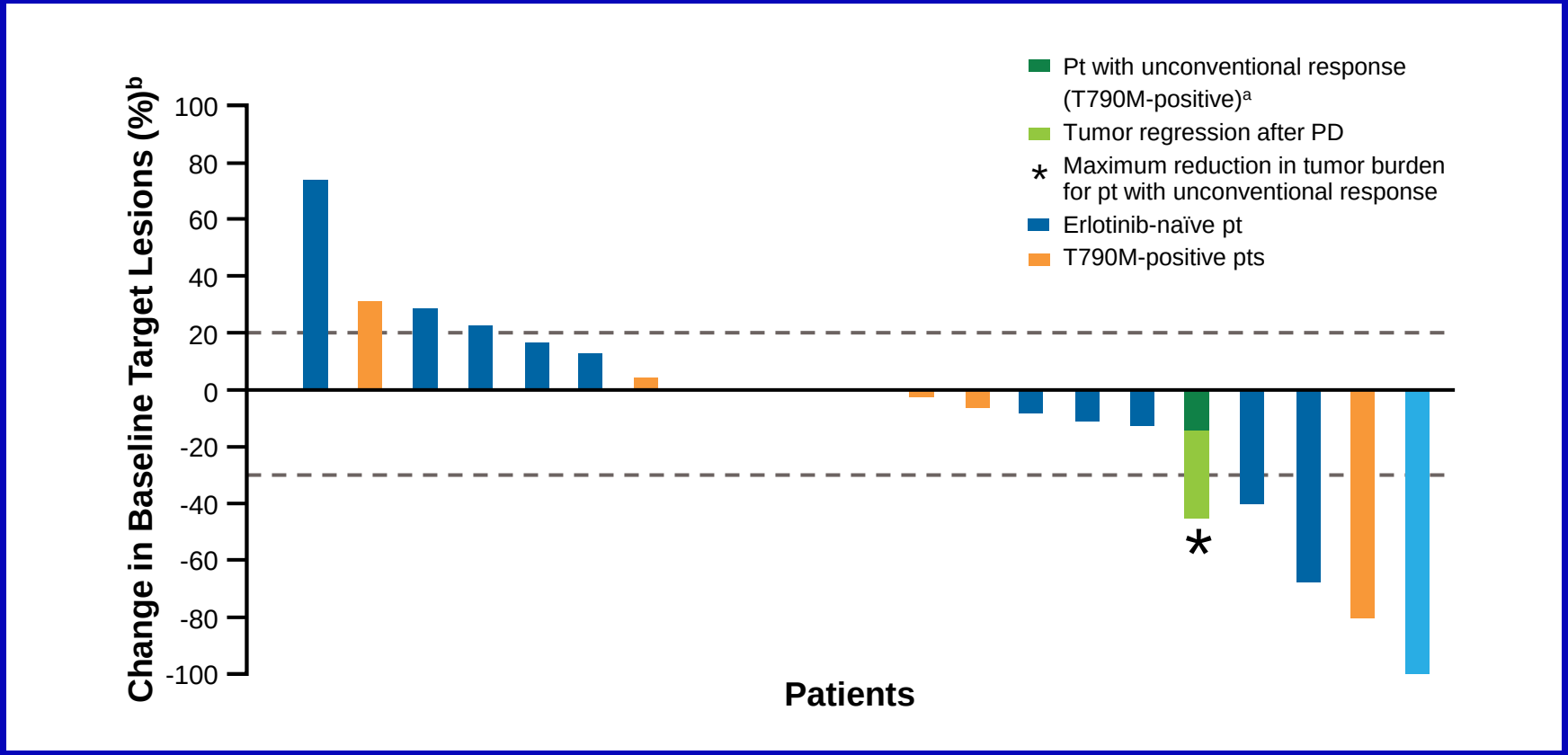
Percent Change in Target Lesions From Baseline



[a]One pt exhibited an unconventional "immune-related" response (ongoing), with a 51% reduction in target lesions (maximum decrease) after initial progression in non-target lesions (included here as having PD)
[b]Only includes pts with baseline target lesion(s) and at least one complete post baseline target lesion assessment

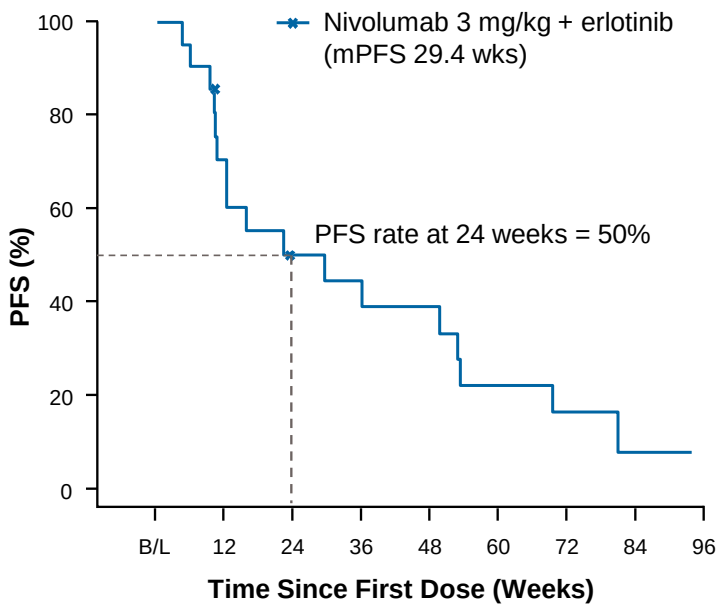
Percent Changes in Target Lesion Tumor Burden in NSCLC Pts Treated With Nivolumab Plus Erlotinib

Best percent change in target lesion tumor burden from baseline



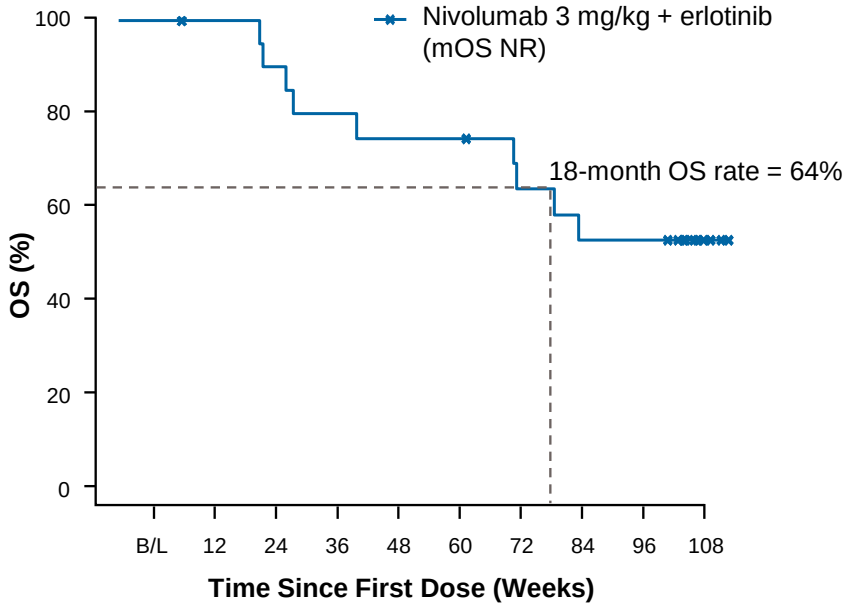
[a]One pt exhibited an unconventional "immune-related" response (ongoing), with a 51% reduction in target lesions (maximum decrease) after initial progression in non-target lesions (included here as having PD)
[b]Only includes pts with baseline target lesion(s) and at least one complete post baseline target lesion assessment

PFS and OS in NSCLC Pts Treated With Nivolumab Plus Erlotinib



Number of Pts at Risk

Nivolumab + erlotinib	21	14	9	7	7	4	3	1	0



Number of Pts at Risk

Nivolumab + erlotinib	21	20	20	16	15	15	13	10	10	2

B/L = baseline; mOS = median OS; mPFS = median PFS

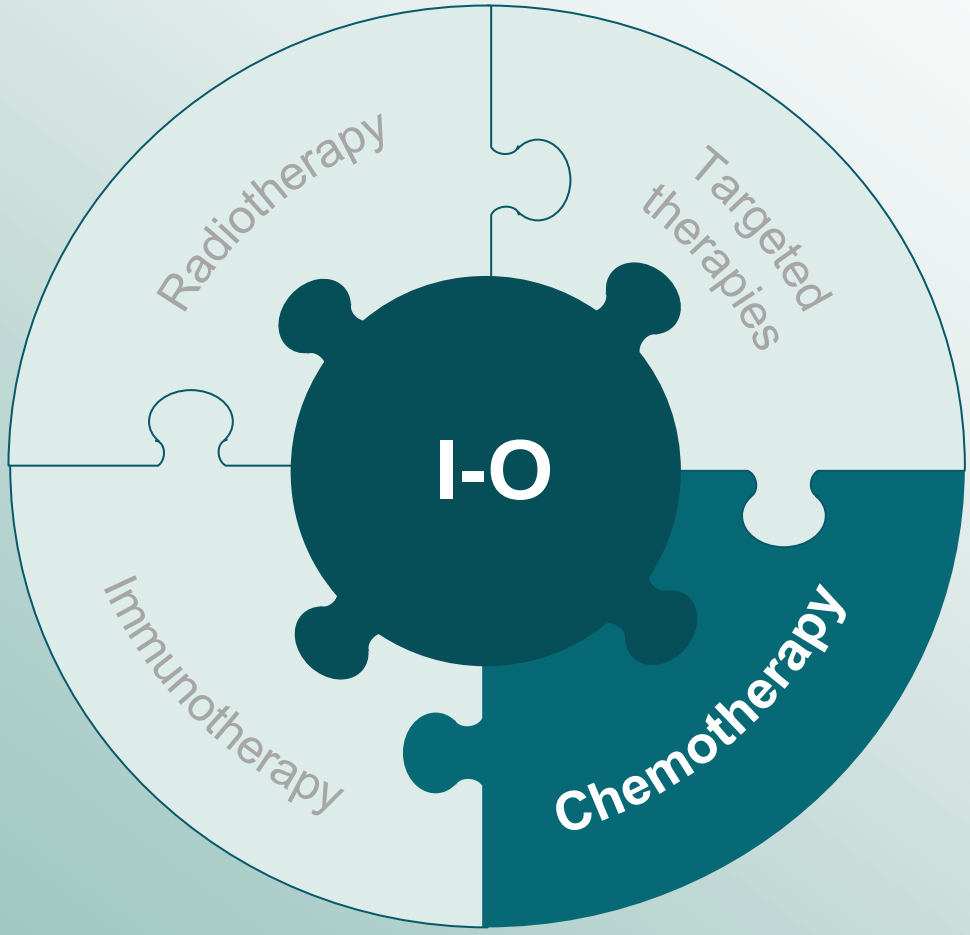
Safety

- Most treatment-related adverse events (AEs) were low grade
- No grade 4 or 5 AEs were reported
- One pt (5%) had grade 1 pneumonitis
- Treatment-related diarrhea (n = 2, both grade 3), increased aspartate aminotransferase (AST) (n = 1, grade 3), increased alanine aminotransferase (ALT), flushing, and tubulointerstitial nephritis (n = 1 each, grade 2) led to discontinuation of study medication in 4 pts (19%)
  - One pt had both grade 3 diarrhea and grade 2 flushing
- At the time of analysis, 9 pts had died, including 8 due to disease progression and 1 due to an unknown cause

Erlo-Nivo combination conclusions

- Treatment with nivolumab plus erlotinib may provide durable clinical benefit in chemotherapy-naïve, EGFR MT pts previously treated with EGFR TKI therapy
  - Observed duration of response and prolonged SD are encouraging relative to other available therapies for such pts
  - Responses were seen across EGFR MT subtypes, including pts with/without T790M mutations
- Nivolumab in combination with erlotinib was associated with a safety profile that reflected additive toxicities of the individual agents and was manageable using safety algorithms
- These findings support further evaluation of anti-PD-1 and EGFR inhibitor combinations in this pt population

I-O agents have a unique MoA, offering the opportunity for combination with other agents



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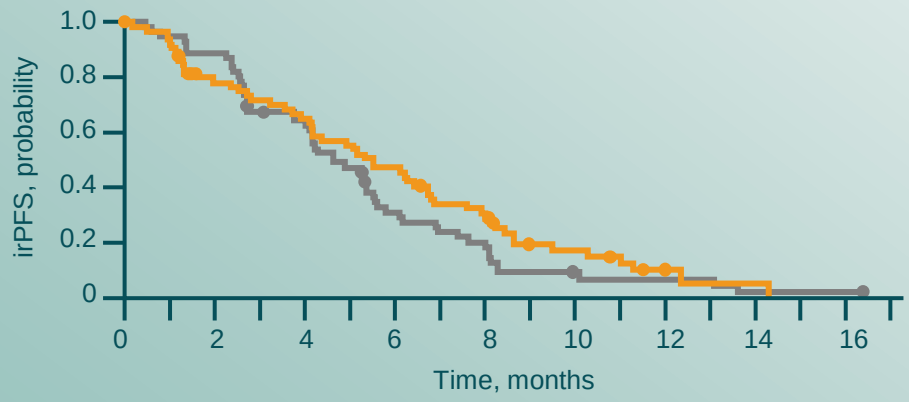
Anti-CTLA-4 plus chemotherapy as 1st-line treatment: ipilimumab plus carboplatin/paclitaxel as an example

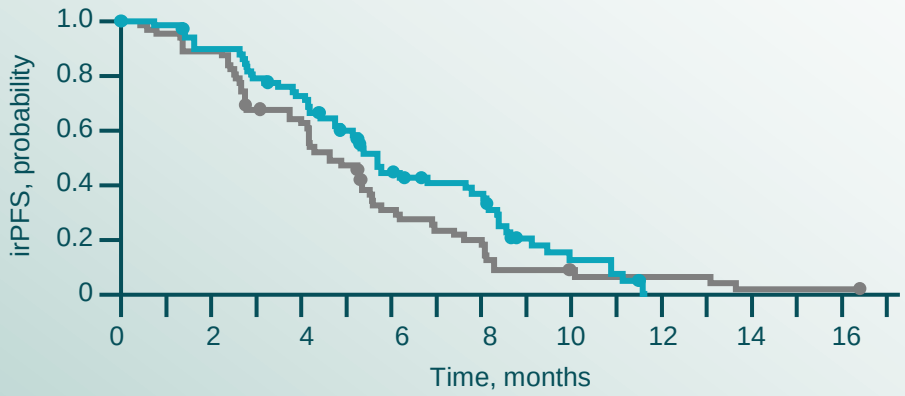
CA184-041: phase 2 study results, no prior therapy for lung cancer, stage IIIB/IV NSCLC, ECOG PS ≤1, all histologies

Ipilimumab + concurrent chemotherapy



	Events/ patients	Median irPFS, months	95% CI	HR	*P*- value
Placebo	56/66	4.63	4.14, 5.52		
Ipilimumab	55/70	5.52	4.17, 6.74	0.81	0.13

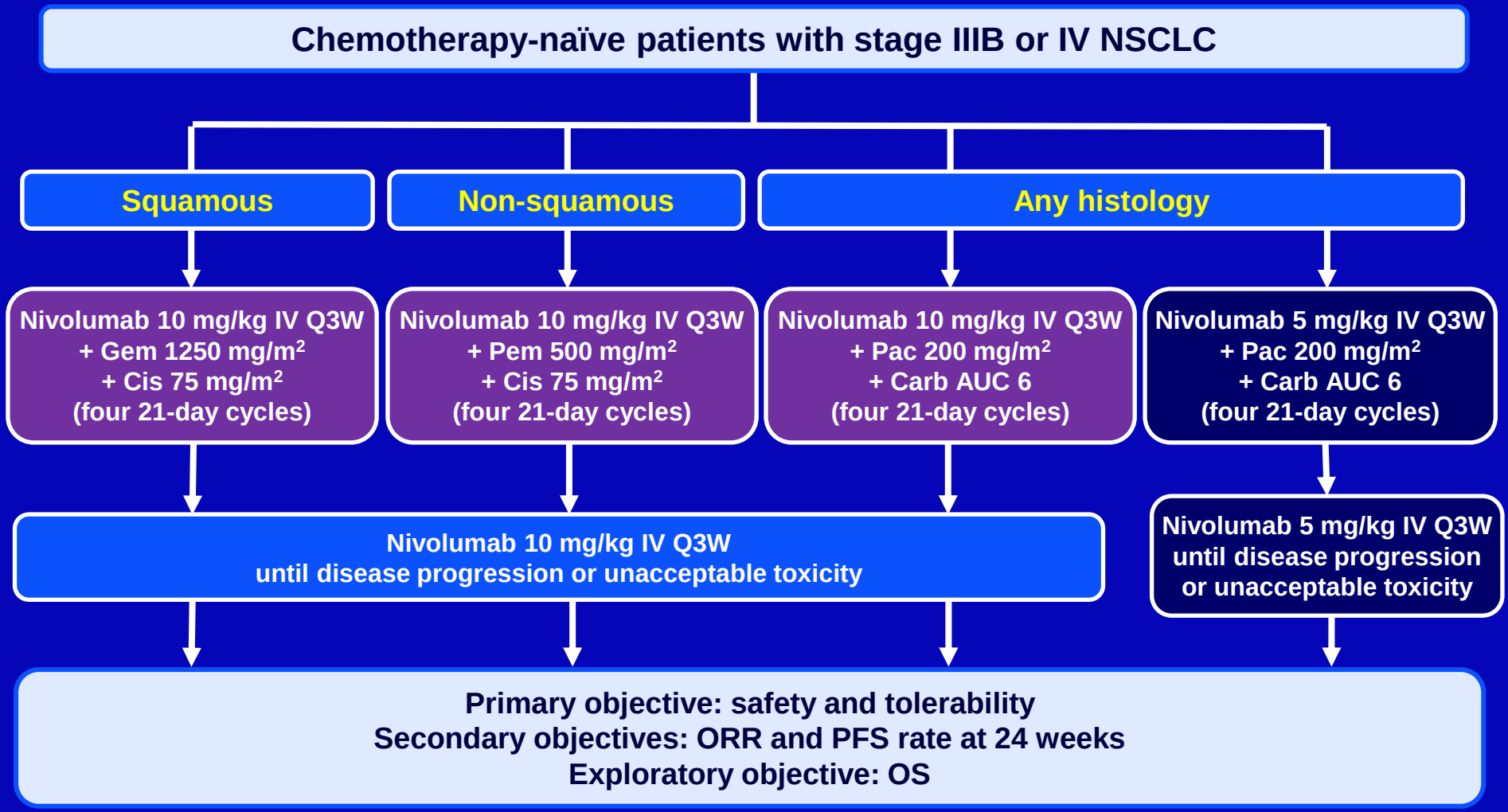
Ipilimumab + phased chemotherapy



	Events/ patients	Median irPFS, months	95% CI	HR	*P* -value
Placebo	56/66	4.63	4.14, 5.52		
Ipilimumab	54/68	5.68	4.76, 7.79	0.72	0.05

Lynch T, et al. *J Clin Oncol*. 2012;30:2046–2054.

CA209-012 (CheckMate 012) Study Design: Nivolumab in Combination With Chemotherapy



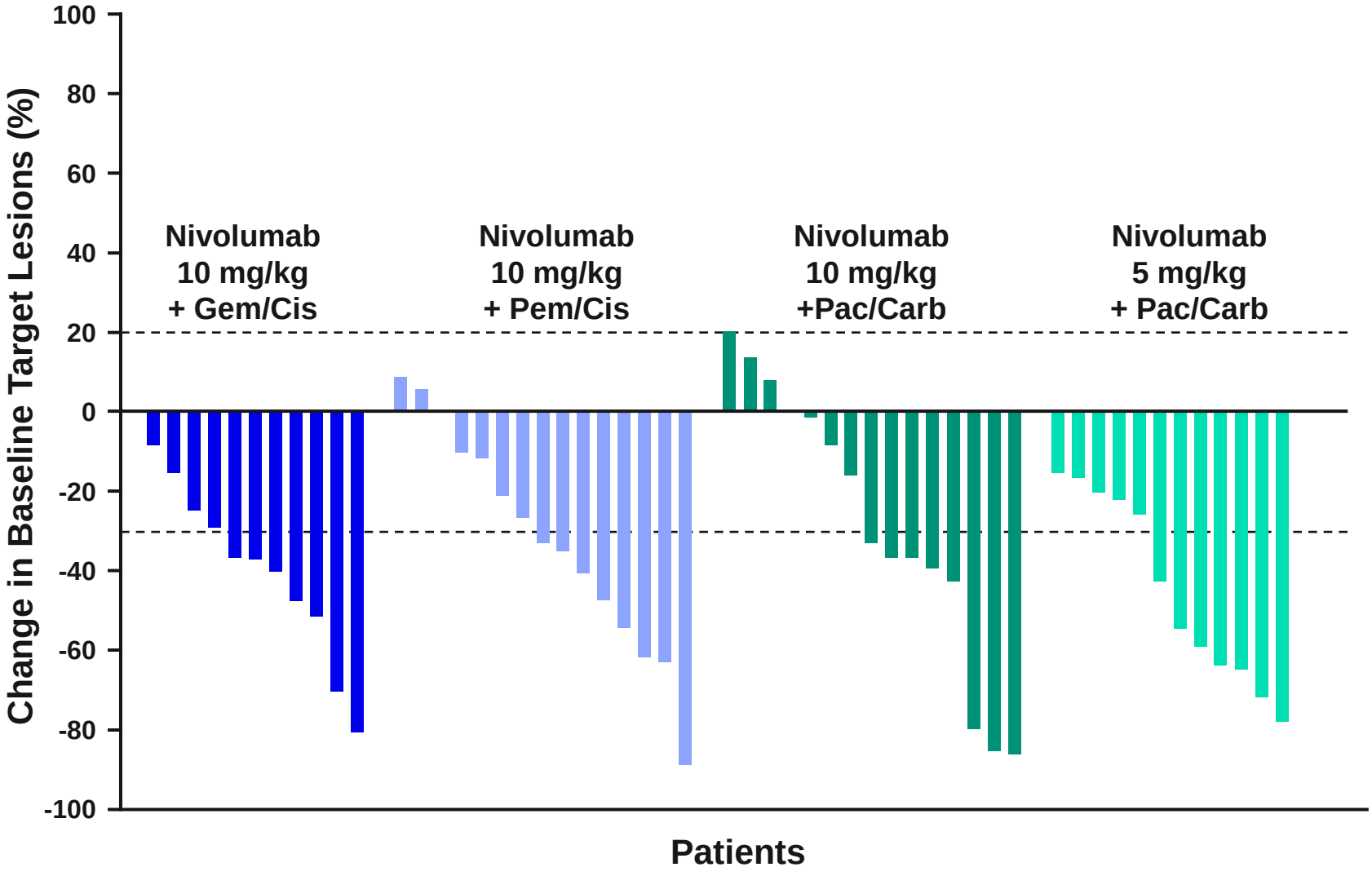
Carb = carboplatin; Cis = cisplatin; Gem = gemcitabine; ORR = objective response rate; OS = overall survival; Pac = paclitaxel; Pem = pemetrexed; PFS = progression-free survival; Q3W = every three weeks

Efficacy Endpoints

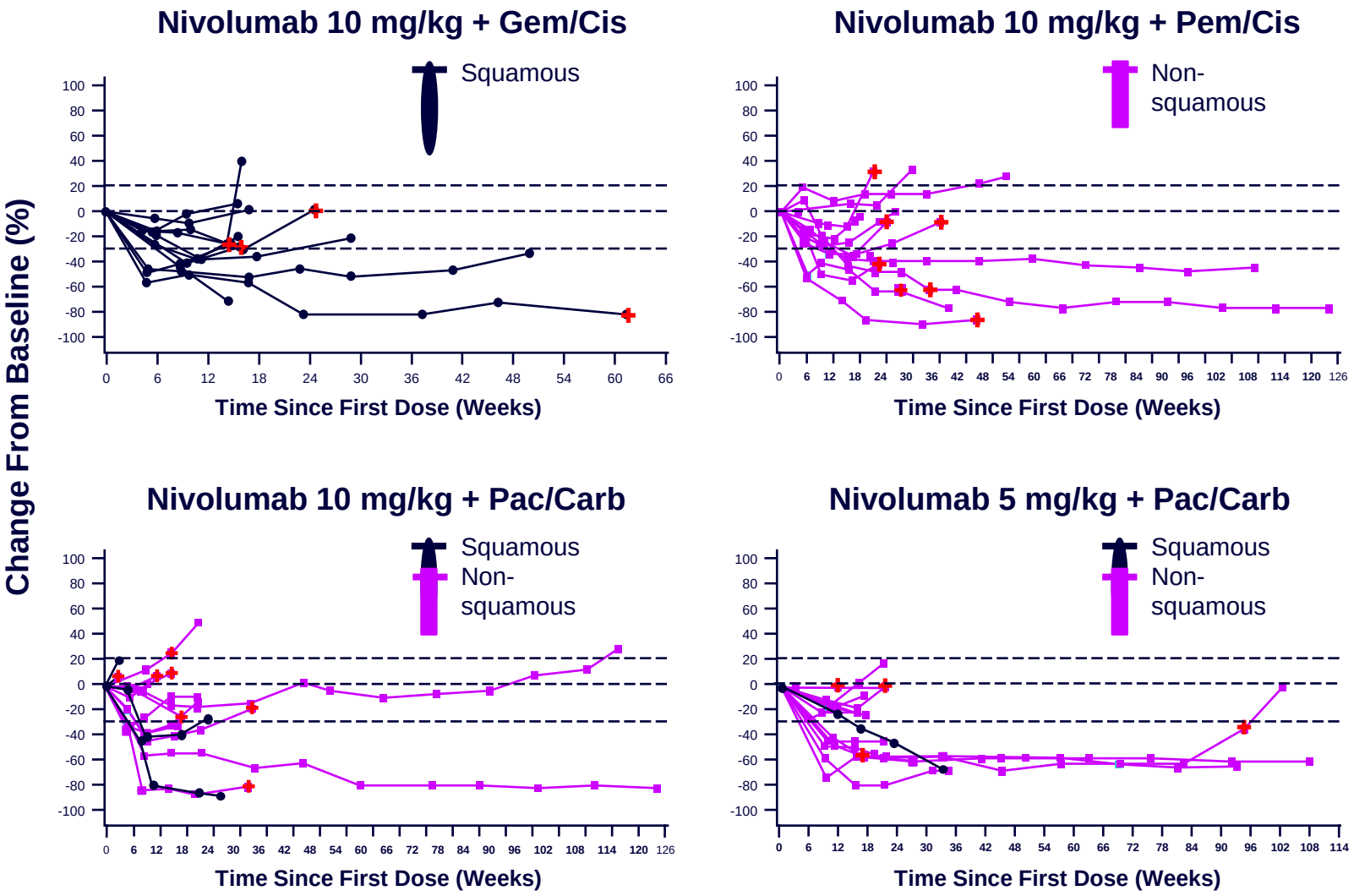
	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg
	Gem/Cis (n = 12)	Pem/Cis (n = 15)	Pac/Carb (n = 15)	Pac/Carb (n = 14)
ORR, %	33	47	47	43
SD, %	58	47	27	43
18-month OS rate, %	33	60	40	86
Median OS, weeks	51	83	65	NR

NR = not reached

Best Percent Change in Target Lesions



Percent Change in Target Lesions



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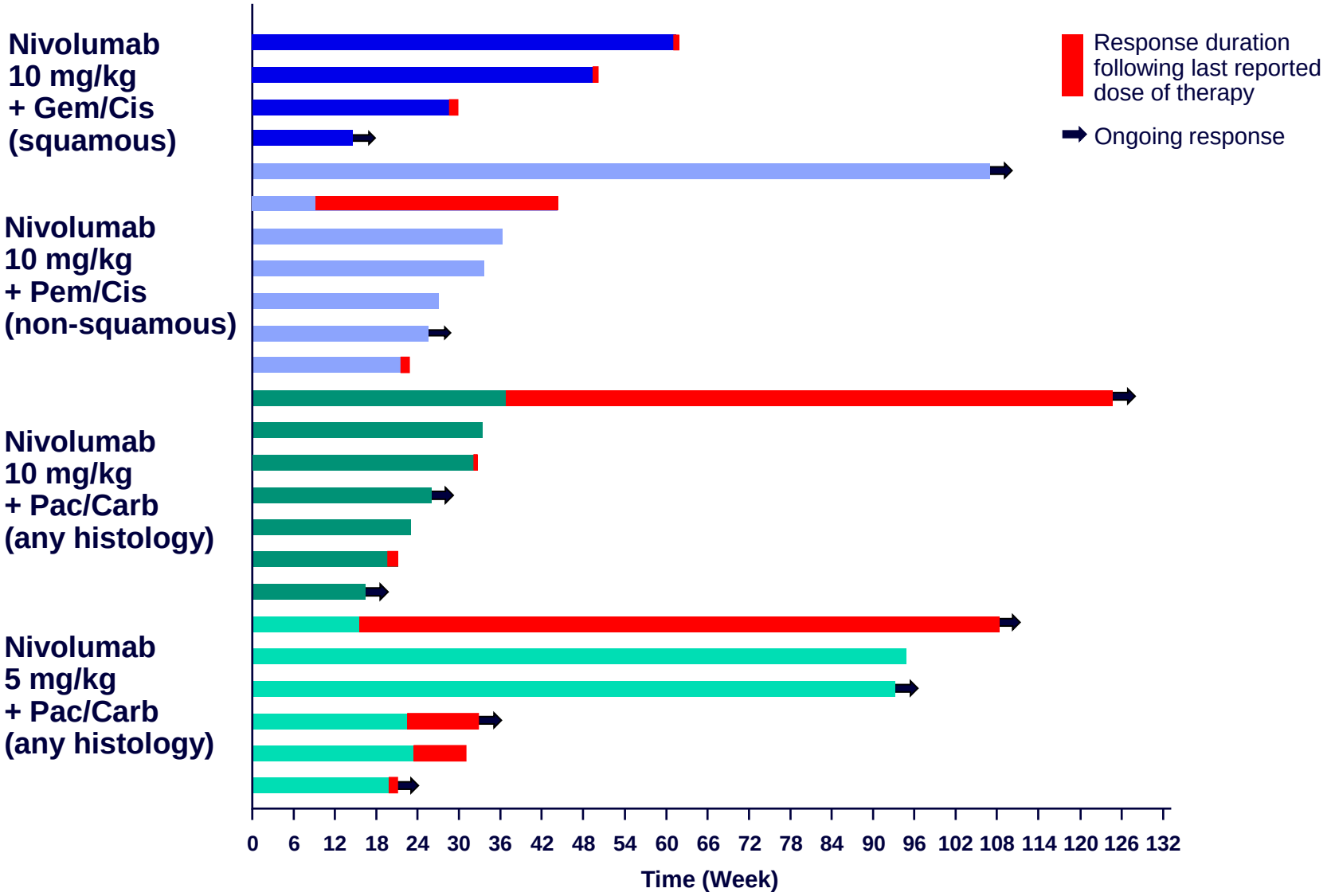
Responses Can Persist Following Treatment Discontinuation



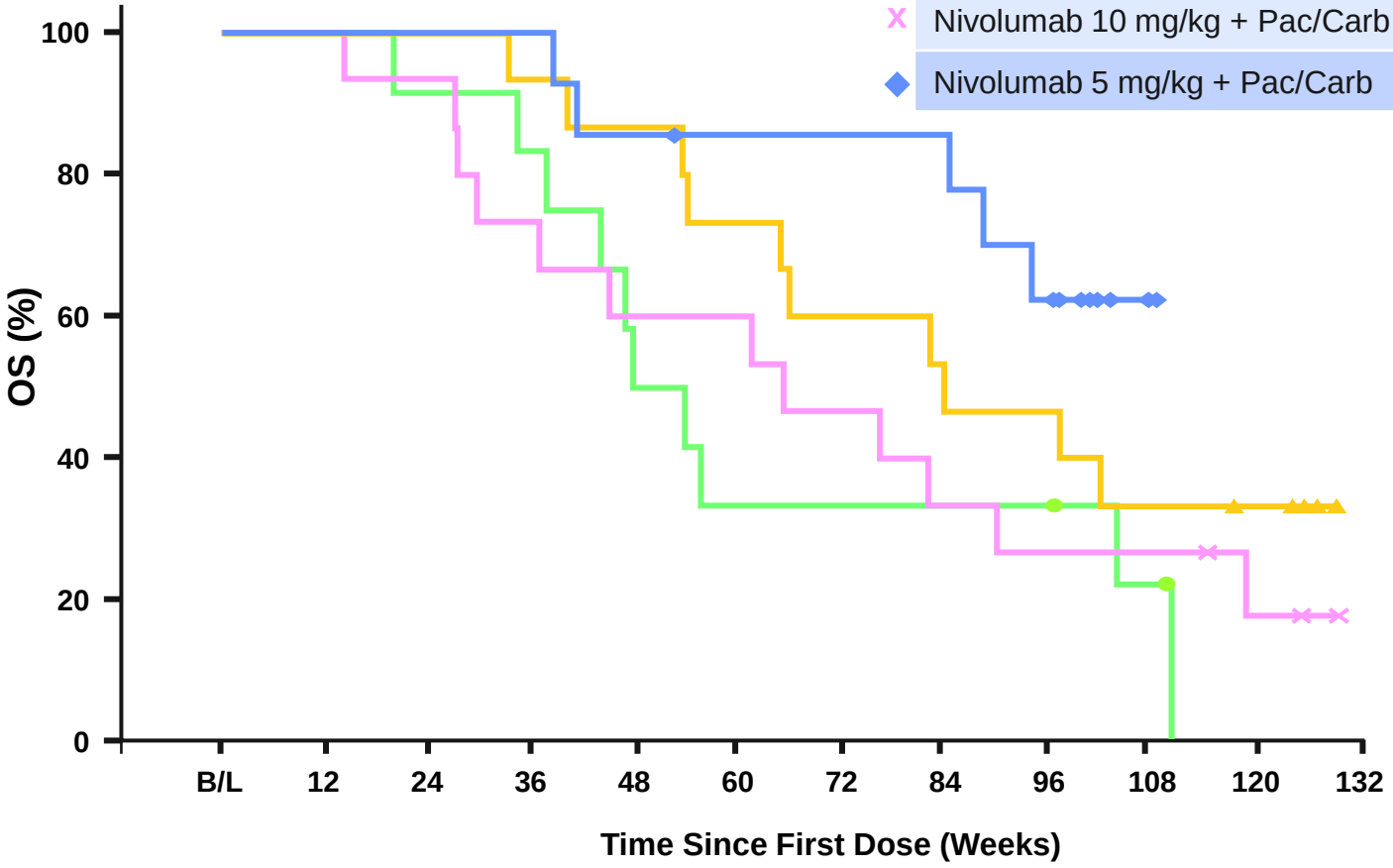
Efficacy Endpoints According to Baseline PD-L1 Expression

	Baseline PD-L1 expression[a]	
	PD-L1^{+}	PD-L1^{-}
Samples sufficient for analysis, n	17	27
ORR,[b] %	53	41
18-month OS rate, %	59	51
Median OS, weeks	88	83

[a]Positivity defined as tumor cell membrane staining with ≥5% expression in a minimum of 100 evaluable cells
[b]Confirmed PRs or CRs only (per RECIST v1.1)

Overall Survival by Treatment Arm

Regimen	mOS (wks)
Nivolumab 10 mg/kg + Gem/Cis	51
Nivolumab 10 mg/kg + Pem/Cis	83
Nivolumab 10 mg/kg + Pac/Carb	65
Nivolumab 5 mg/kg + Pac/Carb	NR

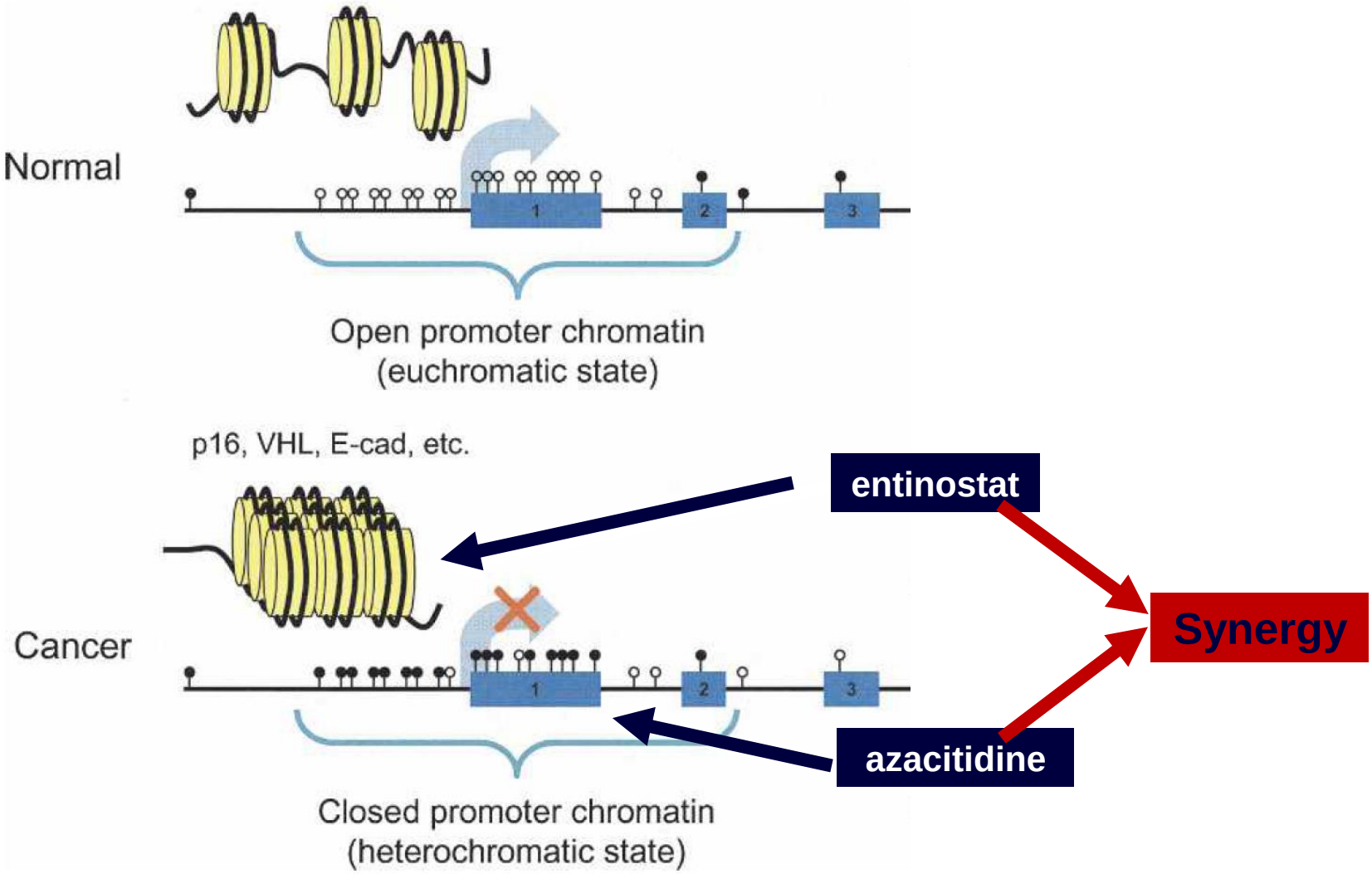


Chemo-Nivo conclusions

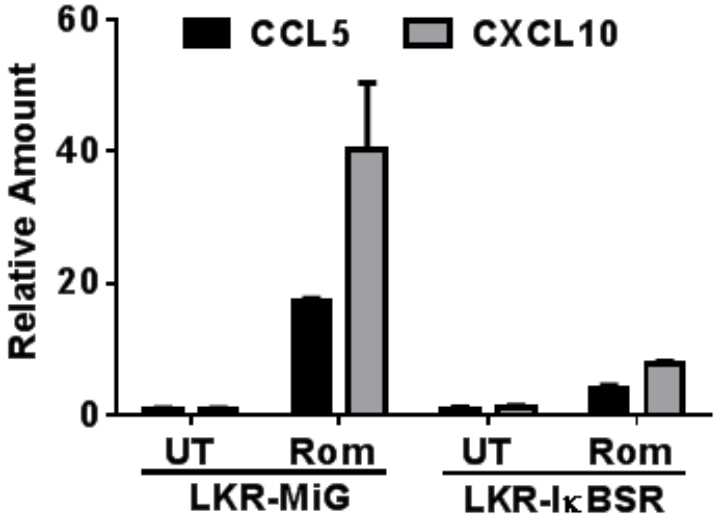
- ORR for nivolumab plus chemotherapy in 1st-line treatment of patients with advanced NSCLC are similar to those previously reported for chemotherapy alone
- Nivolumab 5 mg/kg Q3W in combination with paclitaxel/carboplatin may provide clinical benefit beyond nivolumab monotherapy or single modality chemotherapy
  - Encouraging 18-month OS rate of 86% with a lack of progressive disease at first restaging
- Responses were observed regardless of tumor PD-L1 expression
- Nivolumab plus chemotherapy demonstrates a manageable safety profile, reflecting additive toxicities of individual agents
- These data support further evaluation of nivolumab 5 mg/kg Q3W in combination with chemotherapy

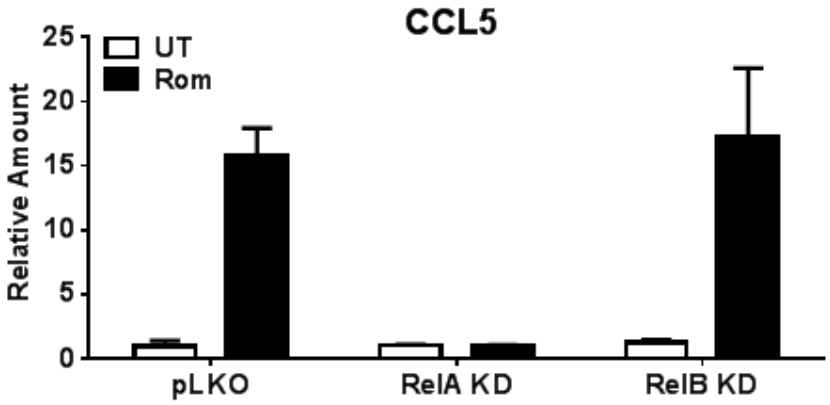
Epigenetic Priming for Chemotherapy and PD-1 Blockade

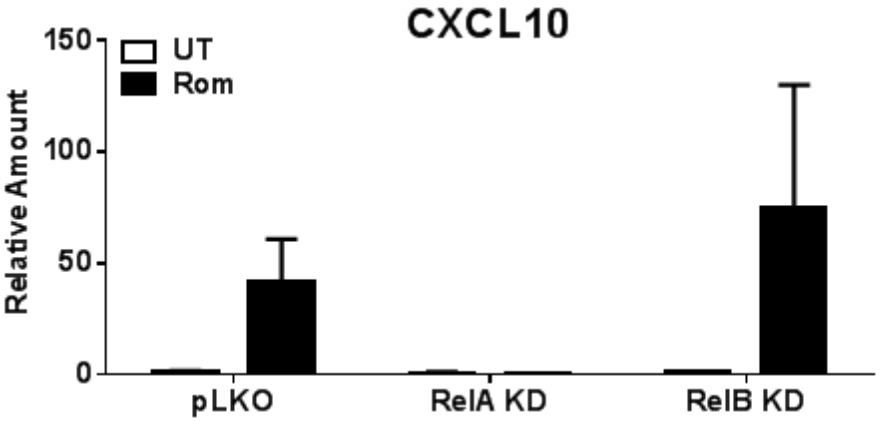
Tumor-intrinsic effects of combination epigenetic therapy



Romodepsin-induced T cell chemokine expression is NF-κB-dependent (mouse LKR-13 lung cancer cell line)

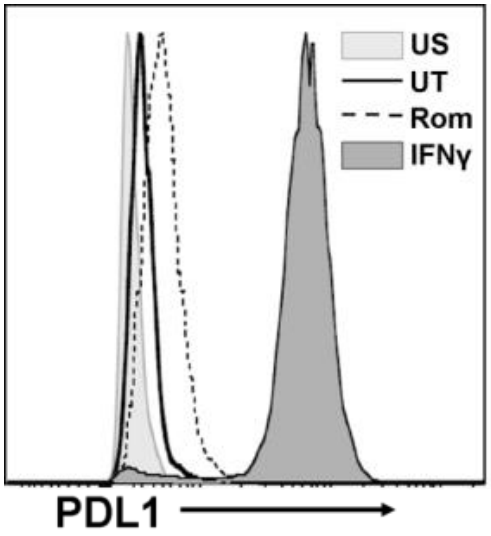


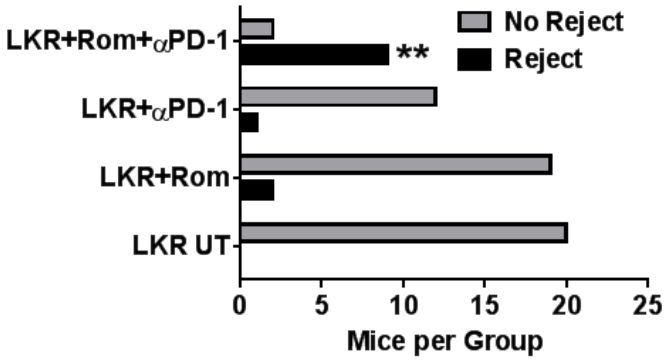


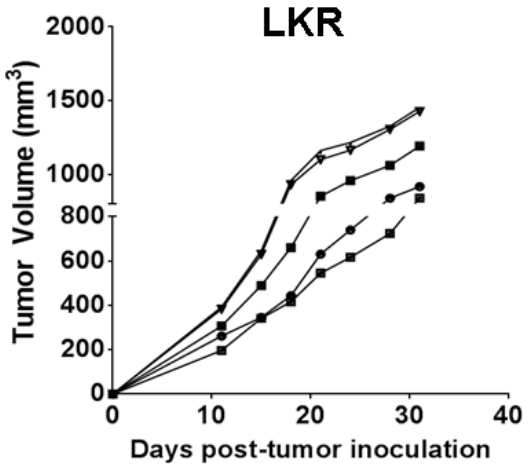


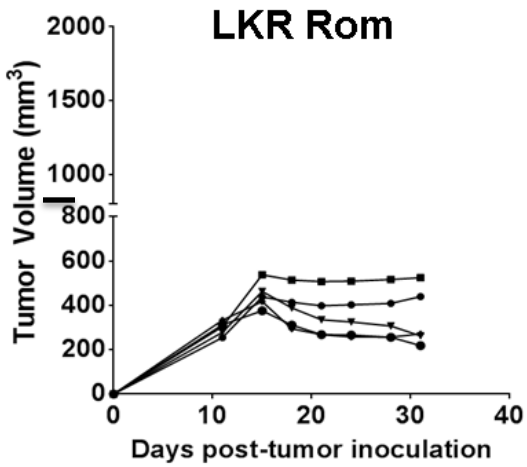
Amer Beg, unpublished

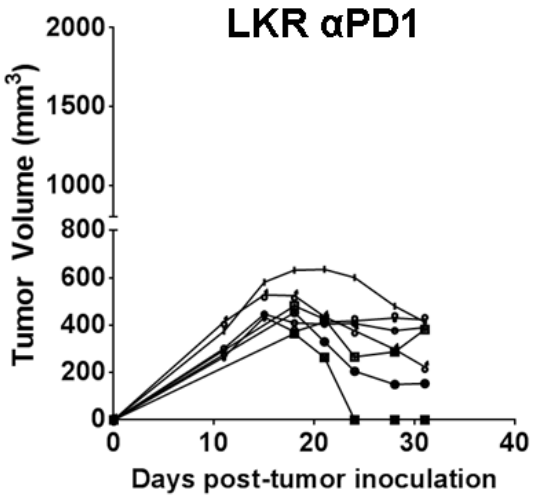
Romidepsin enhances response to anti-PD-1 (day 15, 17, 19)

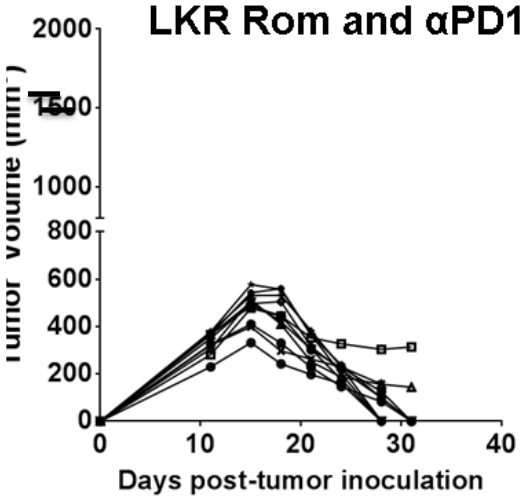






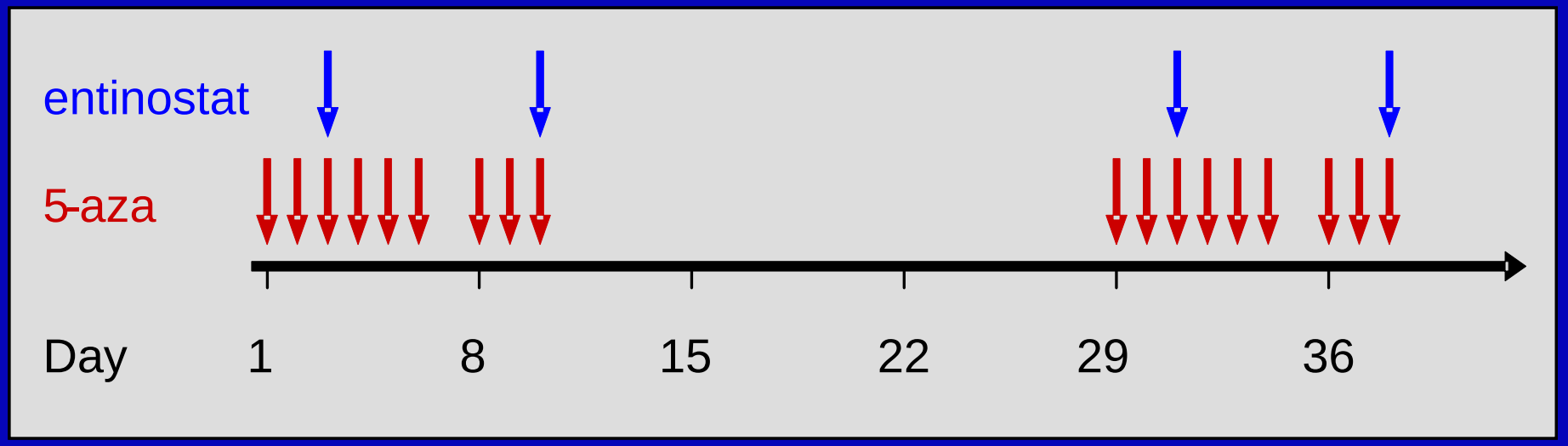






Amer Beg, unpublished

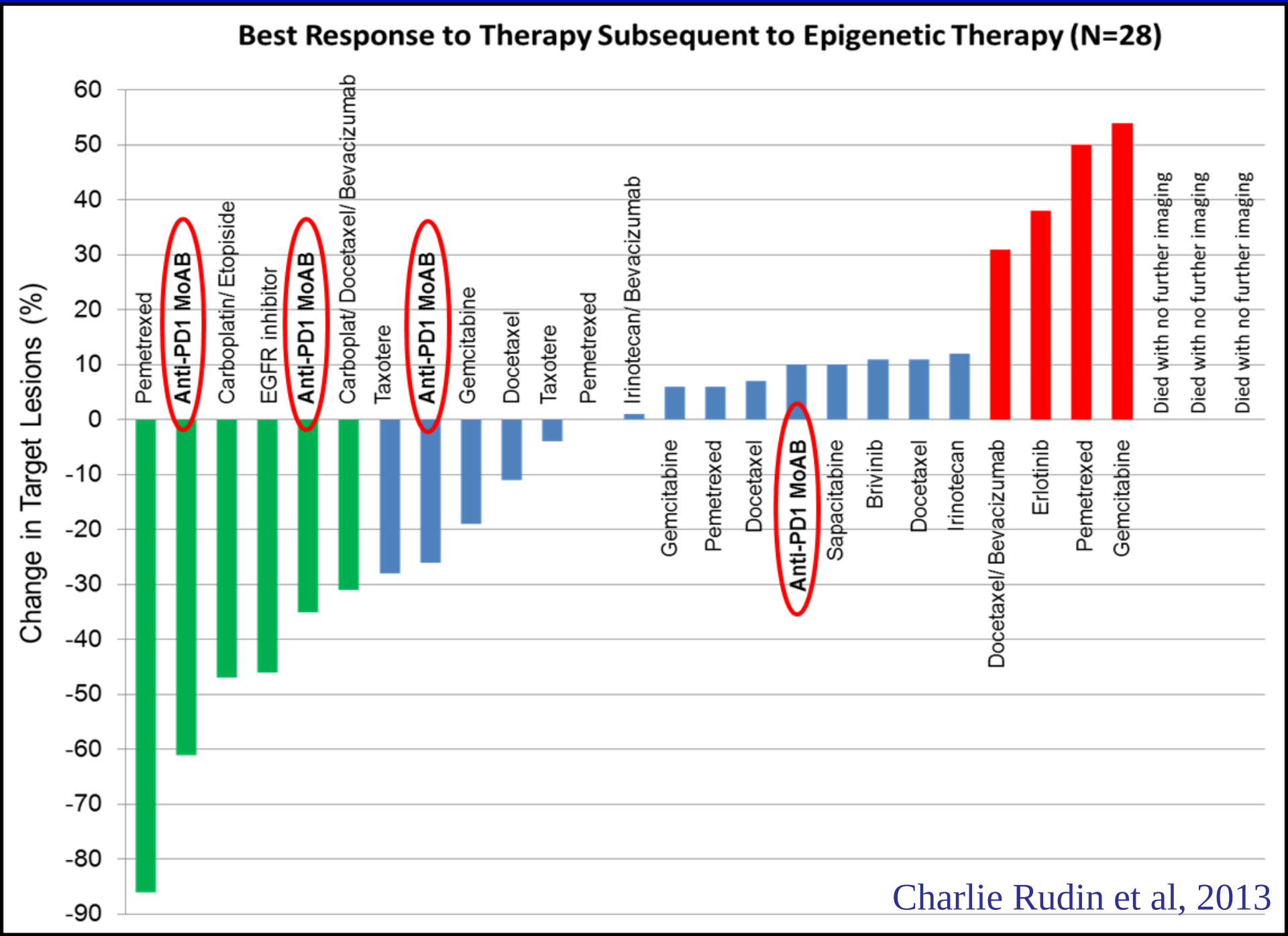
Epigenetic lung cancer study - trial schema



- Single-arm phase II
- Simon two-stage design
- 5AC dosing = 40 mg/m^2 SQ daily on days 1-6 and 8-10
- Entinostat dosing = 7 mg PO days 3 & 10
- Cycle length = 28 days
- 3% RR, Median Survival 8.6 months

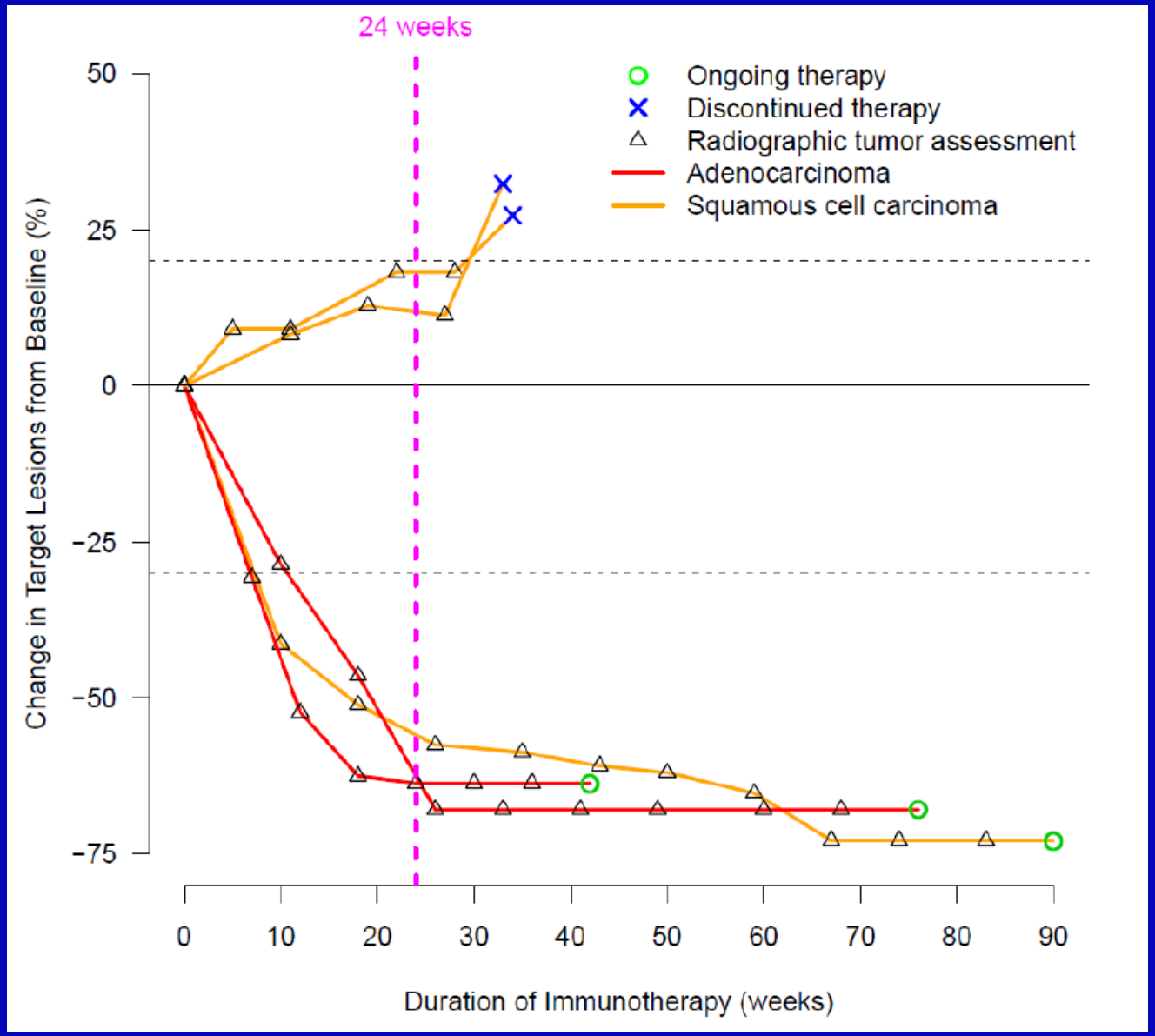
Juergens R et al Cancer Disc 2011

STAND UP TO CANCER



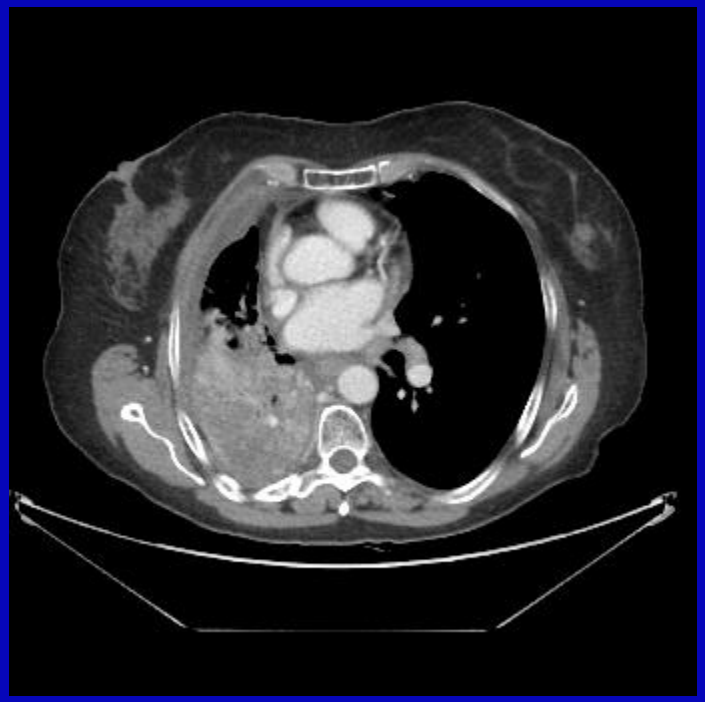
Charlie Rudin et al, 2013

Immunotherapy After Epigenetic Therapy

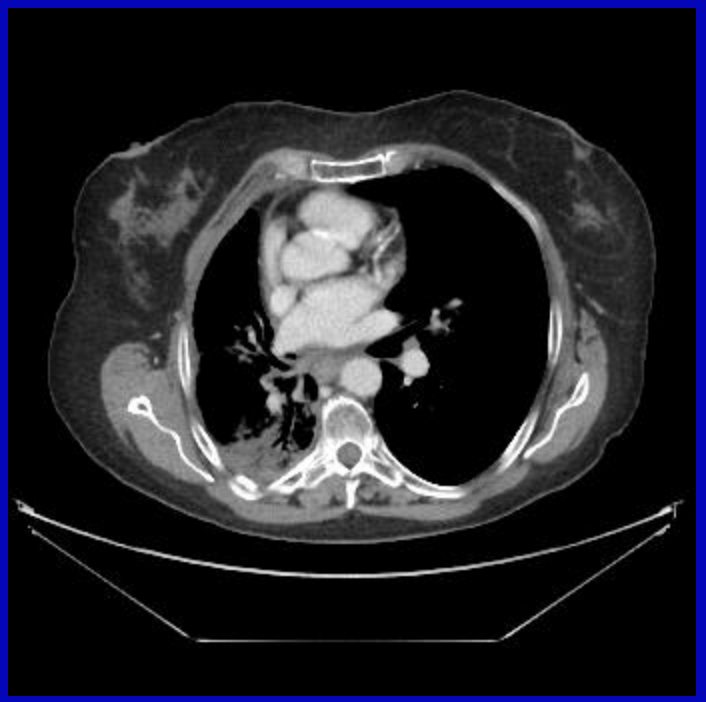


Epigenetic Therapy Followed by Anti-PD-L1: An example of response

10/2011



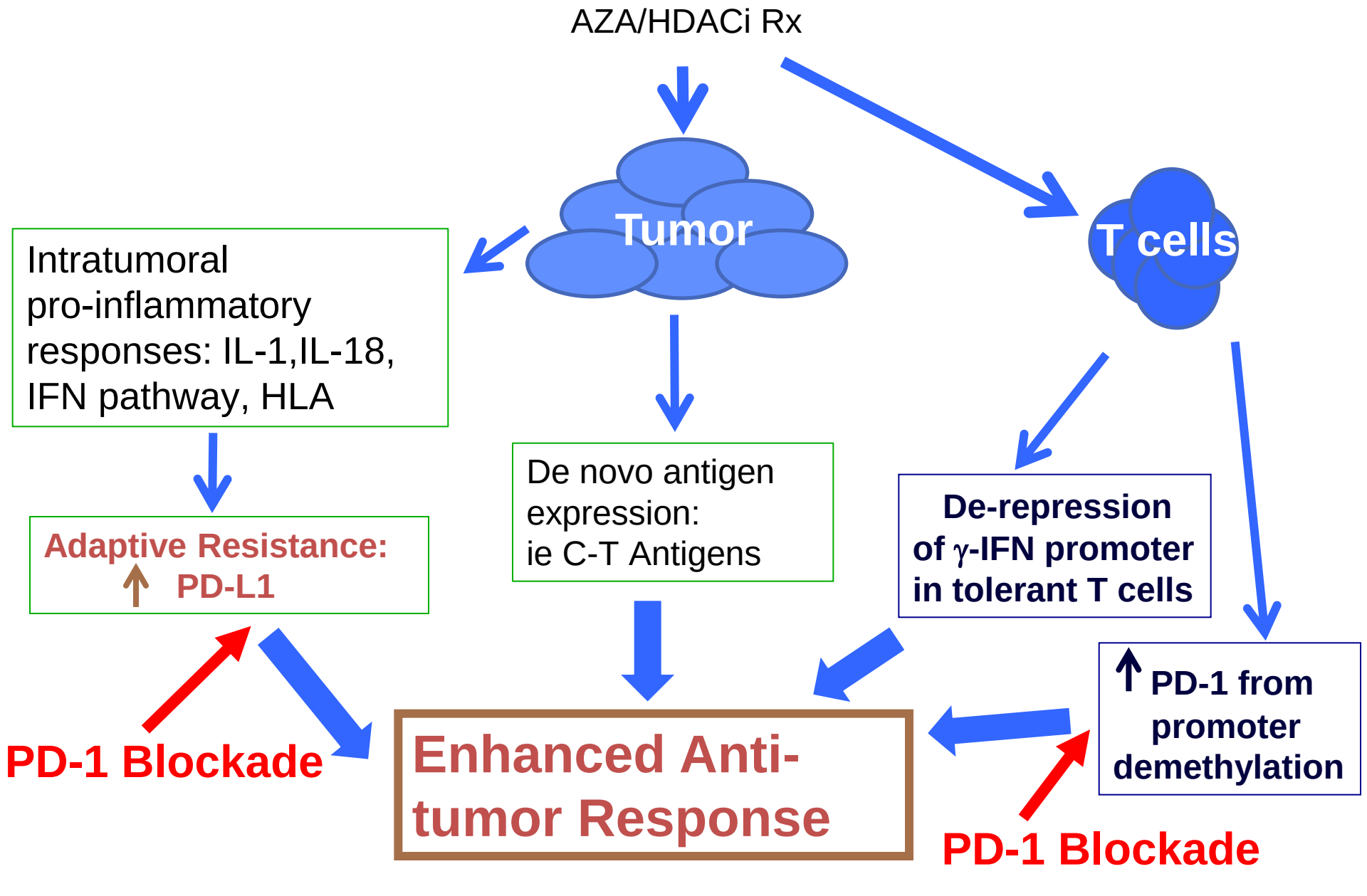
12/2011



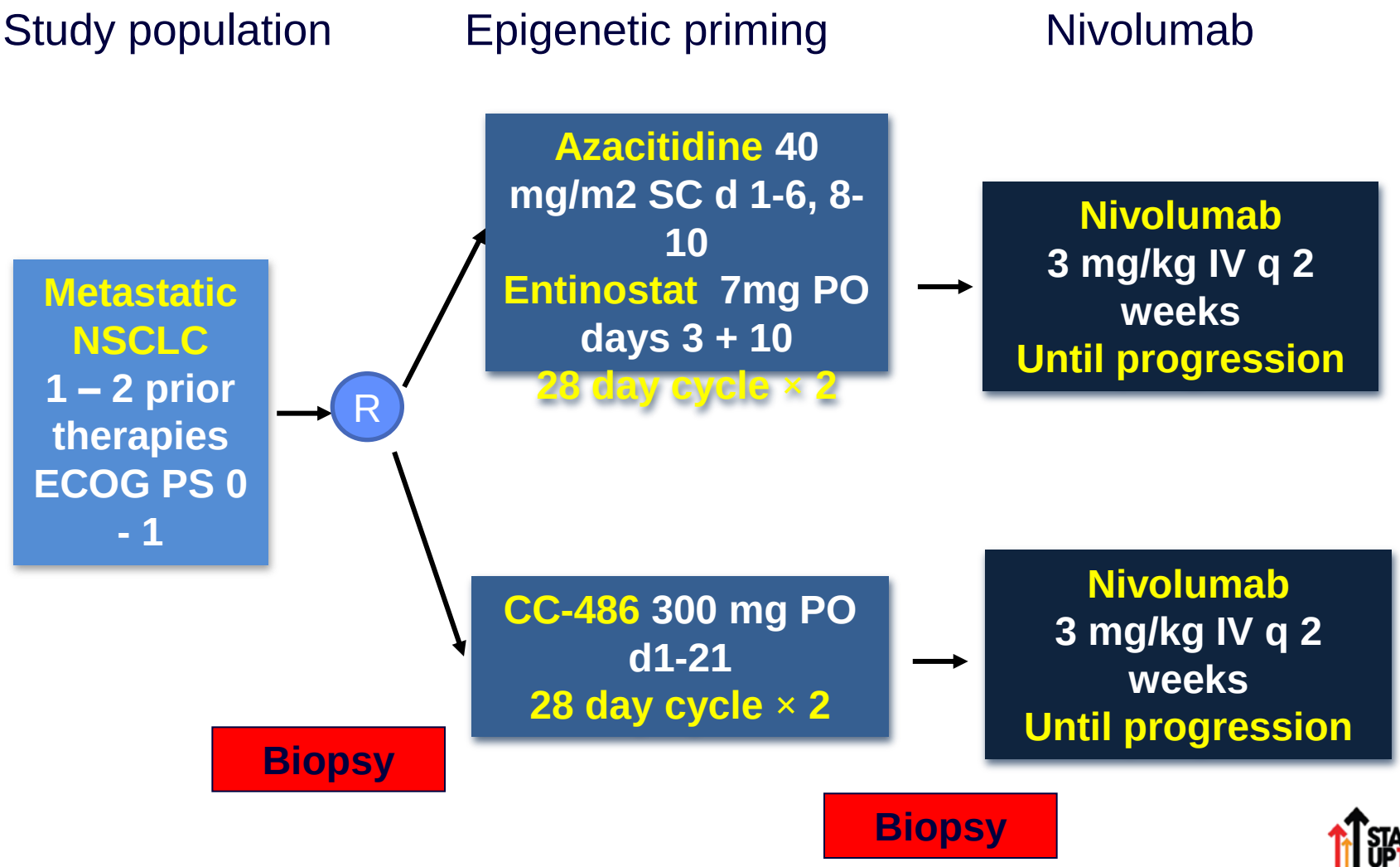
Pt 010-6084 – History 64 y/o Diagnosed with IIIB adenoca Rx with XRT+ Tax/carbo, pemetrexed + carbo, Entinostat + 5aza x 6 cycles

M. Brock, C. Rudin, J. Brahmer, S. Baylin

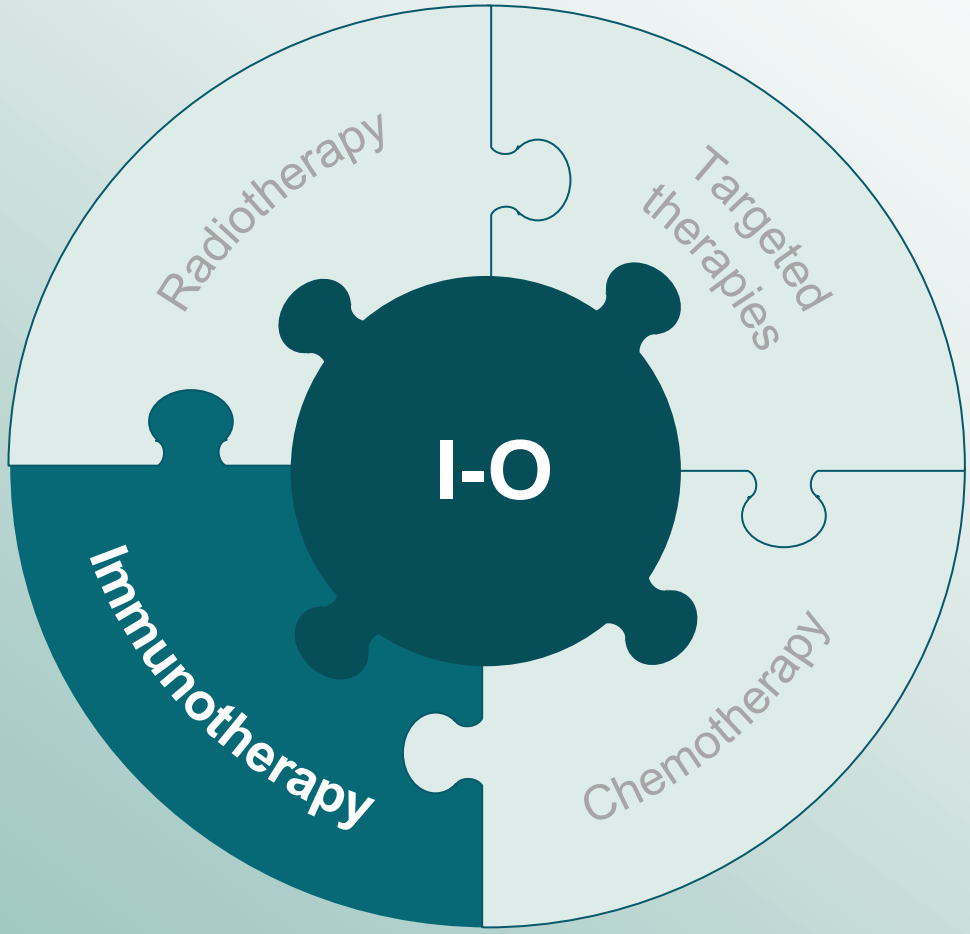
Synergy between Epigenetic Modulation and PD-1 pathway blockade - Unleashing the Perfect Storm against Tumors



Epigenetic Priming Study Design

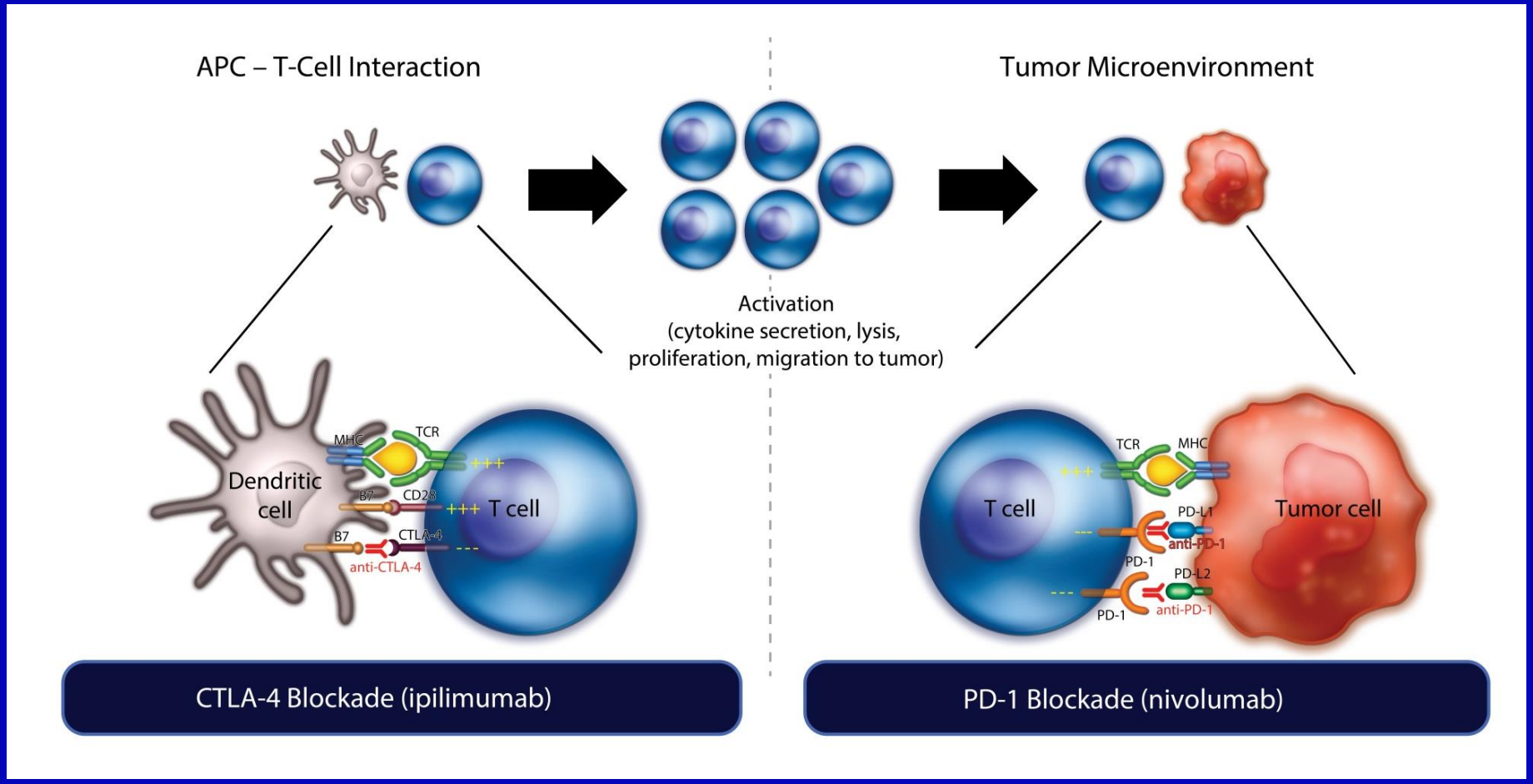


I-O agents have a unique MoA, offering the opportunity for combination with other agents



Drake C. *Ann Oncol.* 2012;23(suppl 8):viii41–viii46; Hannani D, et al. *Cancer J* 2011;17:351–358;
Ménard C, et al. *Cancer Immunol Immunother.* 2008;57:1579–1587; Ribas A, et al. *Curr Opin Immunol.* 2013:25:291–296.

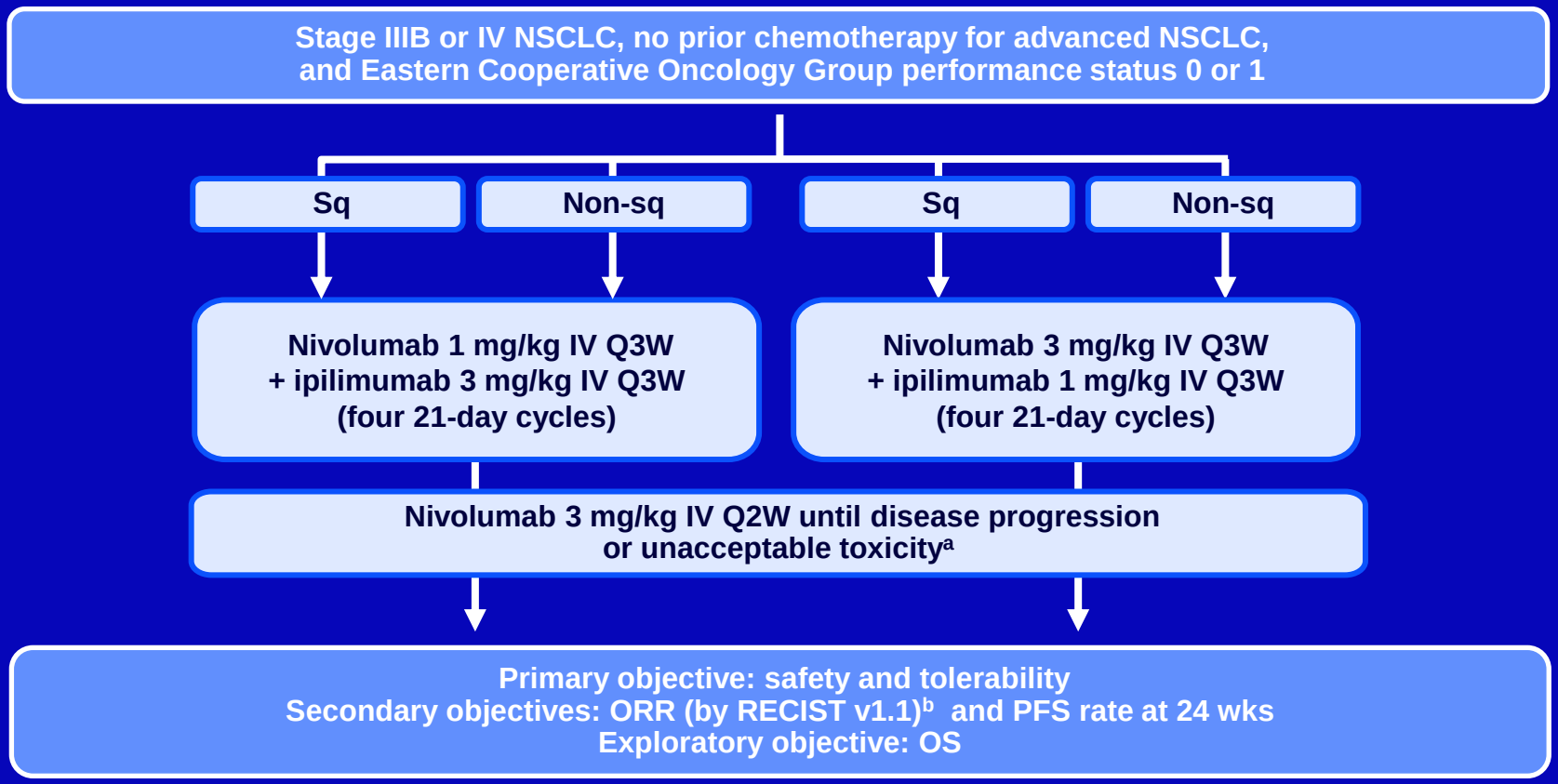
Mechanism of Action of PD-1 and CTLA-4 Blockade



MHC = major histocompatibility complex; TCR = T-cell receptor

Brahmer JR, et al. *J Clin Oncol* 2010,Wang C, et al. *Cancer Immunol Res* 2014, Pardoll DM. *Nat Rev Cancer* 2012;12:252–64.

CA209-012 Study Design: Nivolumab Plus Ipilimumab

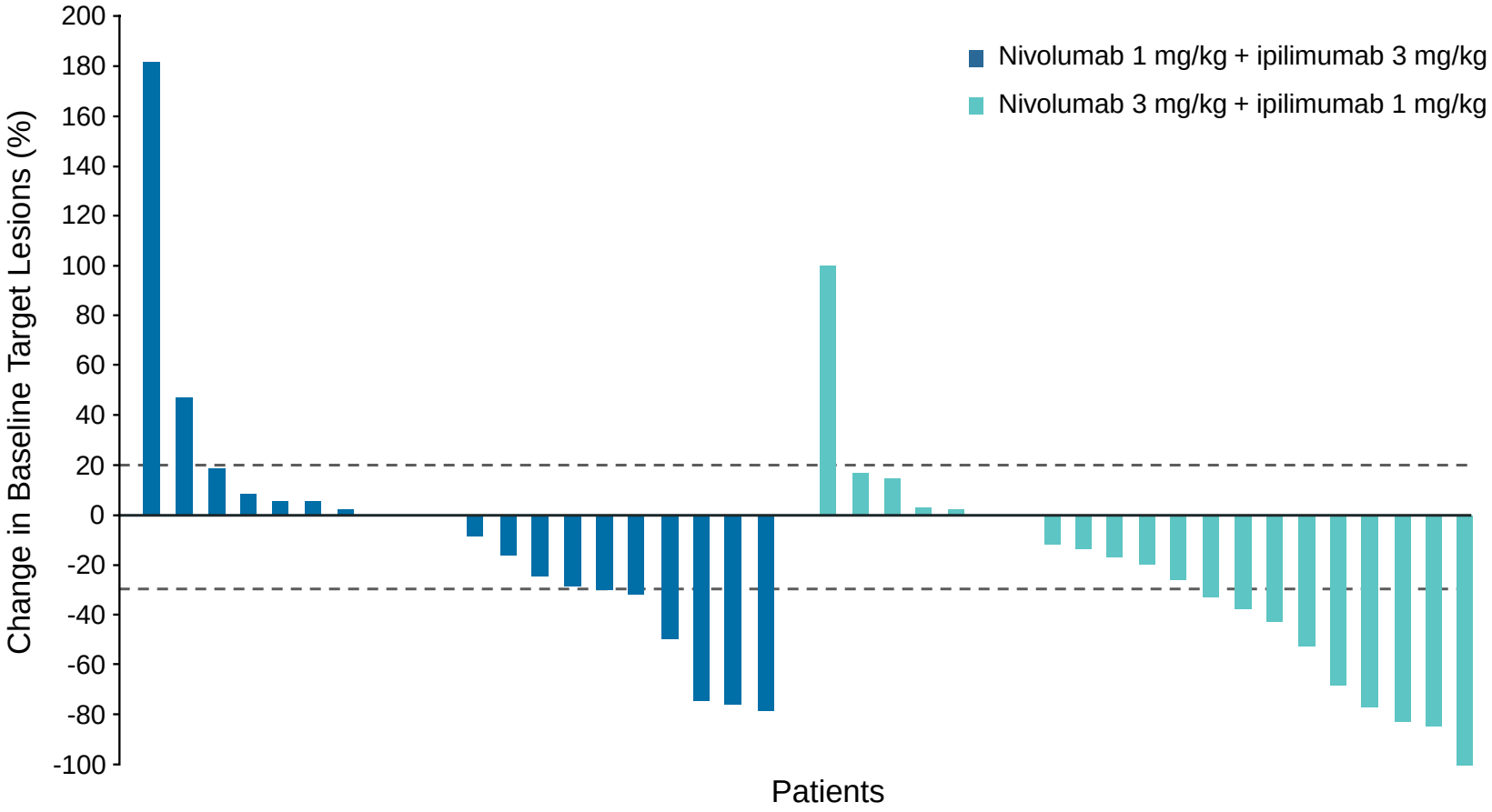


[a]Pts were permitted to continue study treatment beyond RECIST v1.1-defined progression if they were considered to be deriving clinical benefit and tolerating study treatment

[b]Response was assessed at wks 10, 17, and 23, and every 3 months thereafter until disease progression

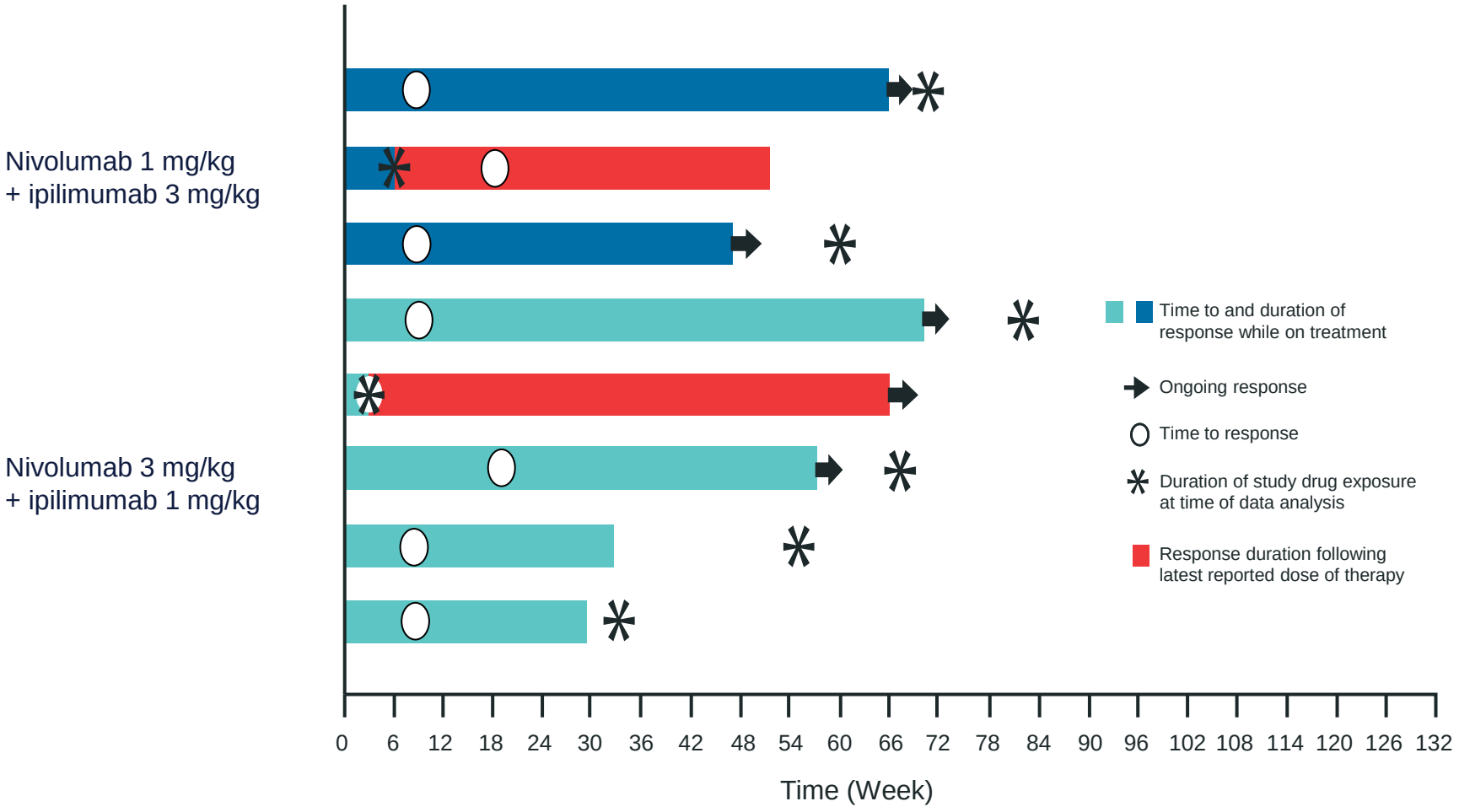
non-sq = non-squamous; Q2W = every two wks; Q3W = every three wks; RECIST = Response Evaluation Criteria In Solid Tumors; sq = squamous; wks = weeks

Best Percent Change in Target Lesion Tumor Burden From Baseline in NSCLC Pts Treated With Nivolumab Plus Ipilimumab

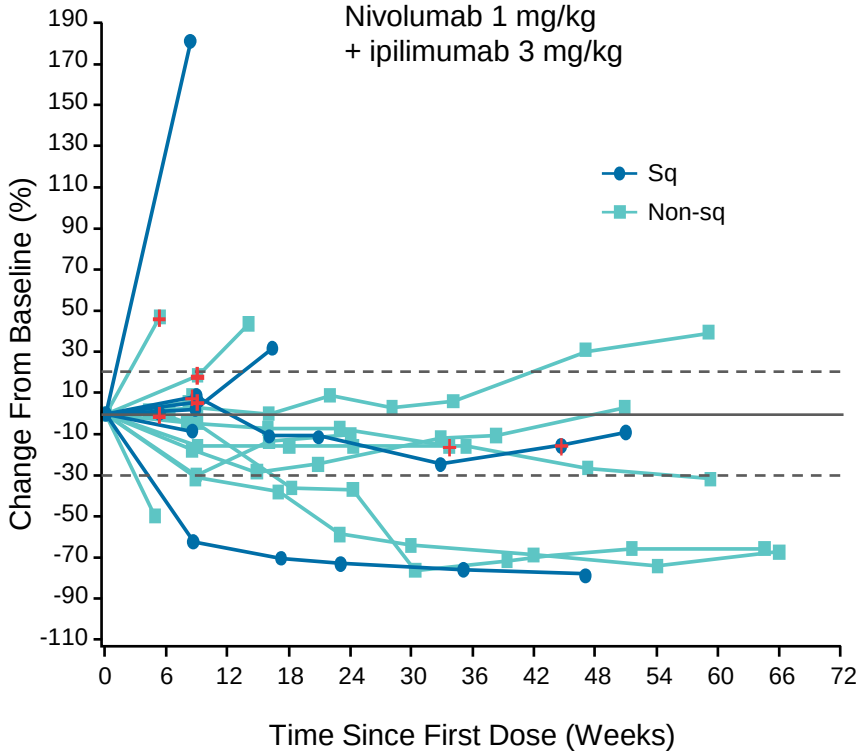


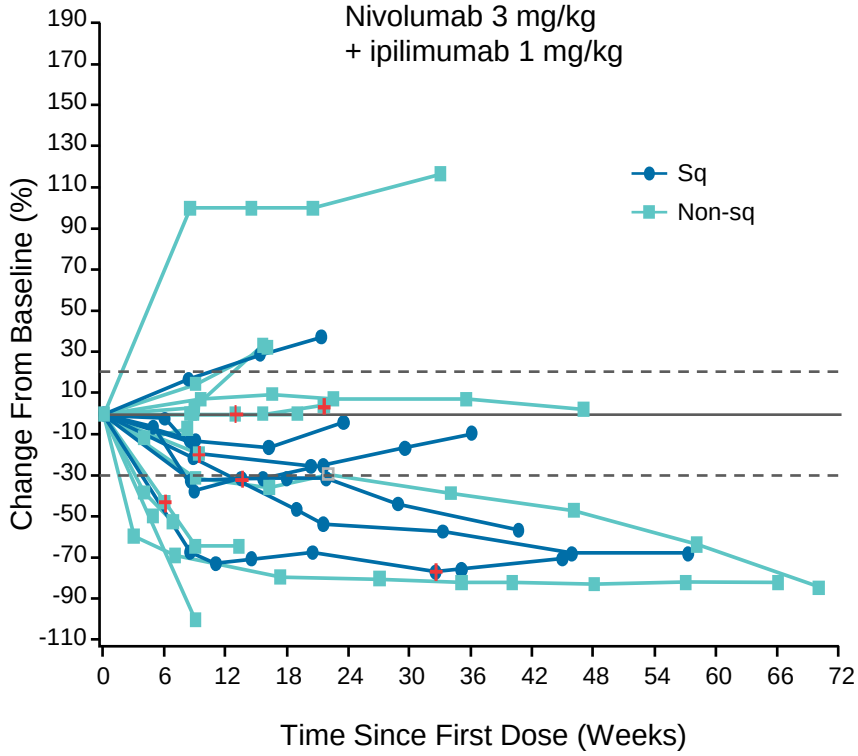
Only includes pts with baseline target lesion and ≥1 post-baseline target lesion assessment with non-missing value

Characteristics of Response by Treatment Arm in NSCLC Pts Treated With Nivolumab Plus Ipilimumab



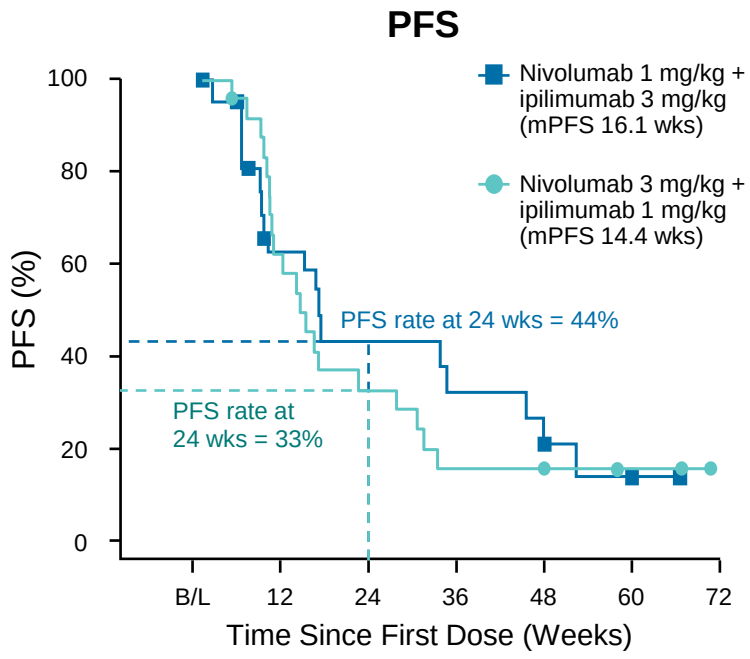
Percent Changes in Target Lesion Tumor Burden From Baseline in NSCLC Pts Treated With Nivolumab Plus Ipilimumab





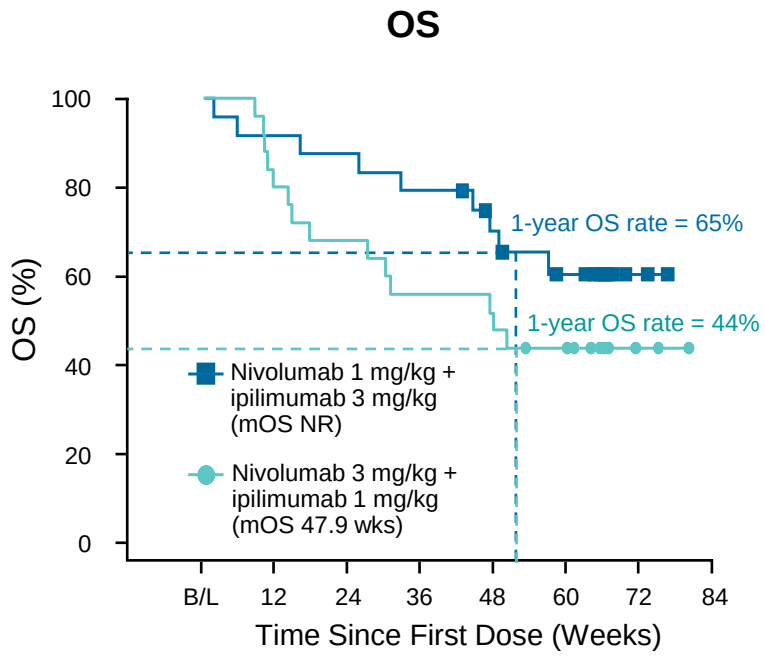
+ first appearance of new lesion

PFS and OS in NSCLC pts Treated With Nivolumab Plus Ipilimumab



Number of Pts at Risk

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	24	10	8	6	3	1	0
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	25	14	8	4	3	2	0

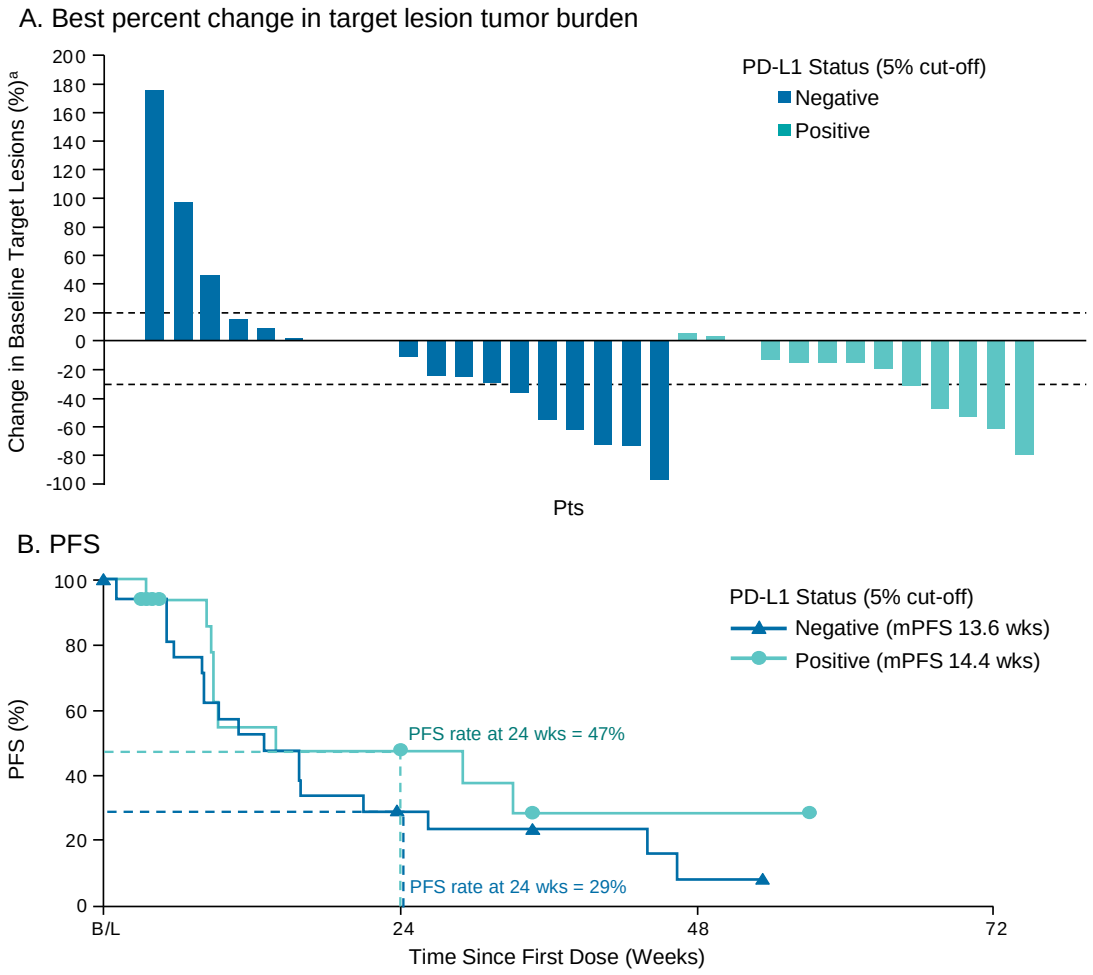


Number of Pts at Risk

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	24	22	21	19	15	11	2	0
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	25	20	17	14	12	10	2	0

mOS = median OS; mPFS = median PFS

Percent Changes in Target Lesion Tumor Burden and PFS by PD-L1 Status in NSCLC Patients Treated With Nivolumab Plus Ipilimumab



[a]Only includes pts with baseline target lesion and at least on-baseline target lesion assessment with missing value

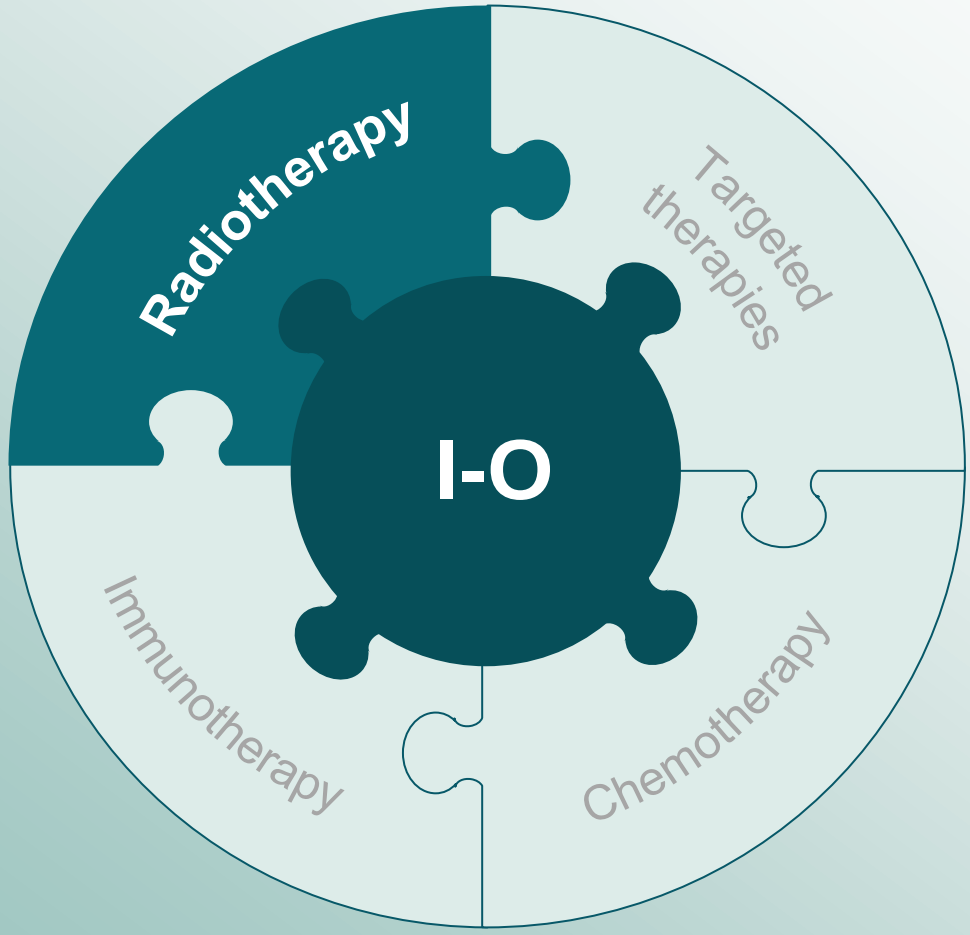
Safety

- Adverse events (AEs) were managed using well established safety guidelines
- The majority of toxicity occurred during the induction phase (nivolumab + ipilimumab Q3W for four cycles) as compared with the maintenance phase
  - Across arms, grade 3–4 AEs were reported in 32–50% of pts and 21–27% of pts during induction and maintenance, respectively

Ipi-Nivo conclusions

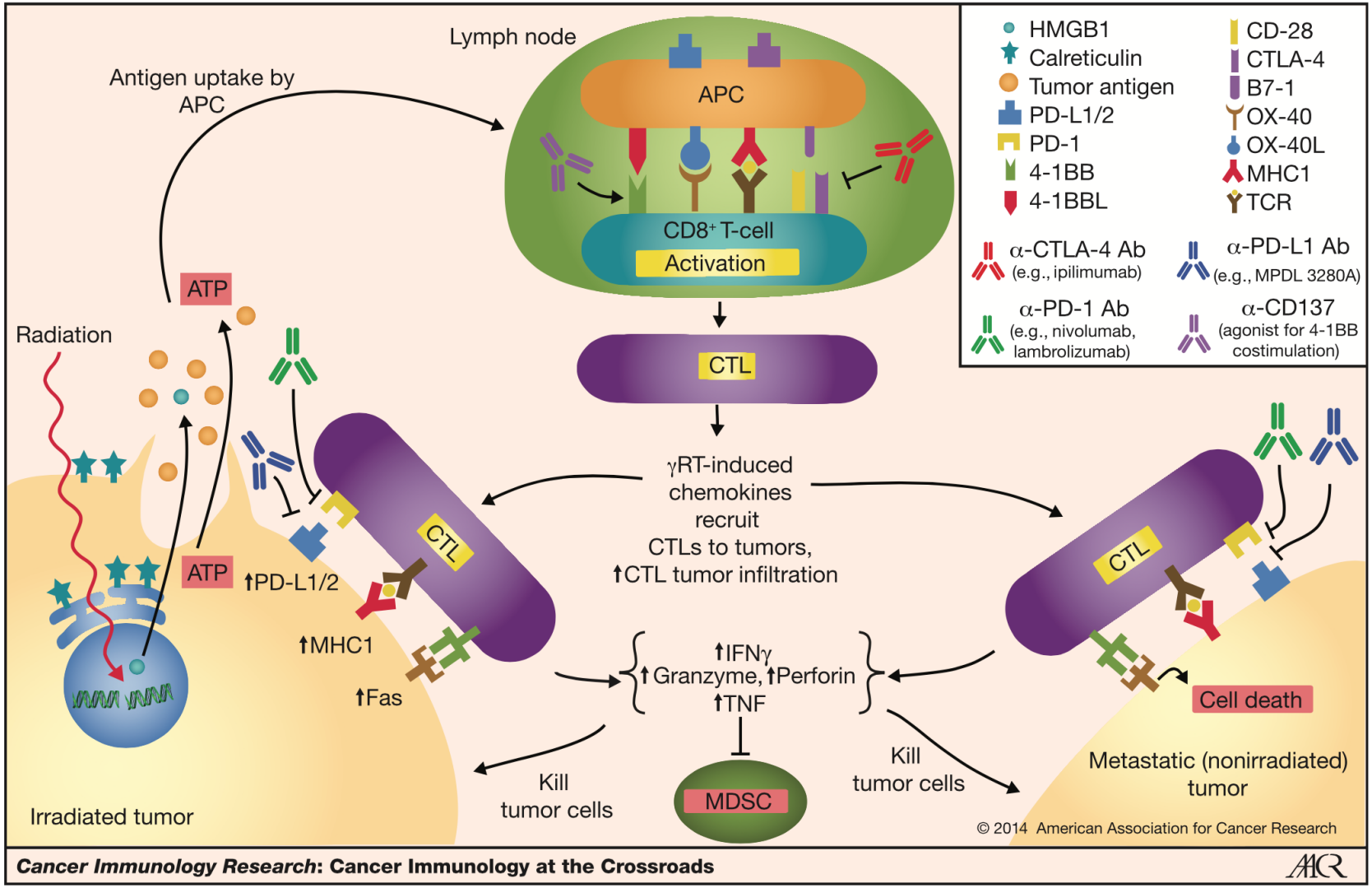
- Treatment with nivolumab plus ipilimumab was associated with a safety profile that was managed using well-established safety guidelines
- The nivolumab plus ipilimumab regimen provided durable responses as first-line treatment for pts with advanced NSCLC, regardless of histology
- Activity was observed with nivolumab plus ipilimumab in PD-L1^{+} and PD-L1^{-} pts
- The safety and clinical activity of nivolumab plus ipilimumab will be further assessed at additional specified doses and schedules

I-O agents have a unique MoA, offering the opportunity for combination with other agents



Drake C. *Ann Oncol.* 2012;23(suppl 8):viii41–viii46; Hannani D, et al. *Cancer J* 2011;17:351–358;
Ménard C, et al. *Cancer Immunol Immunother.* 2008;57:1579–1587; Ribas A, et al. *Curr Opin Immunol.* 2013:25:291–296.

Radiation and Immunotherapy



Tang et al, Cancer Immunol Res, 2(9); 831–8. 2014

Potential of anti-CTLA-4 plus radiation: ipilimumab in one patient with melanoma as an example

- The target and other lesions regressed
- Regression of distant lesions may be due to an enhanced systemic response

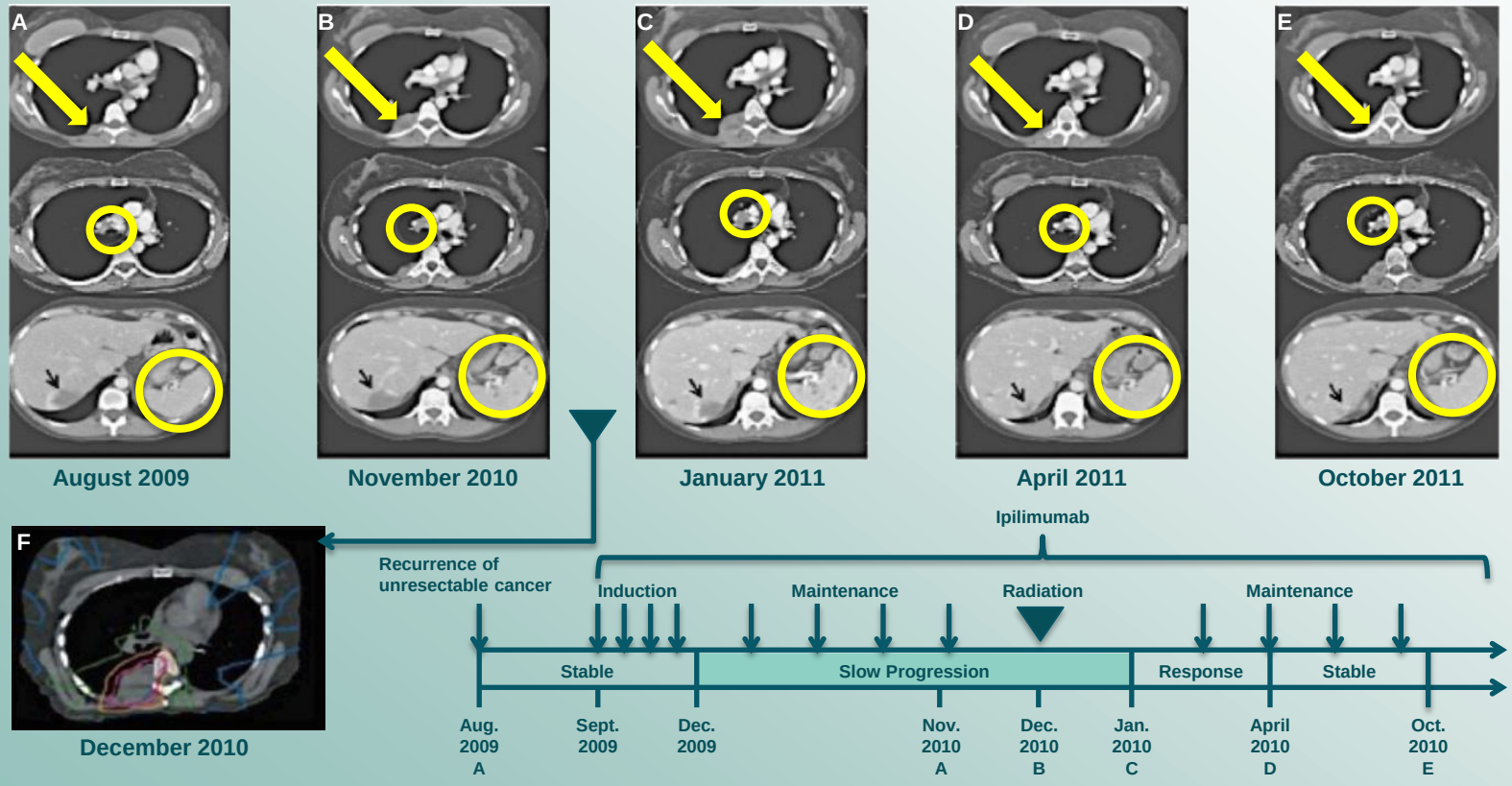
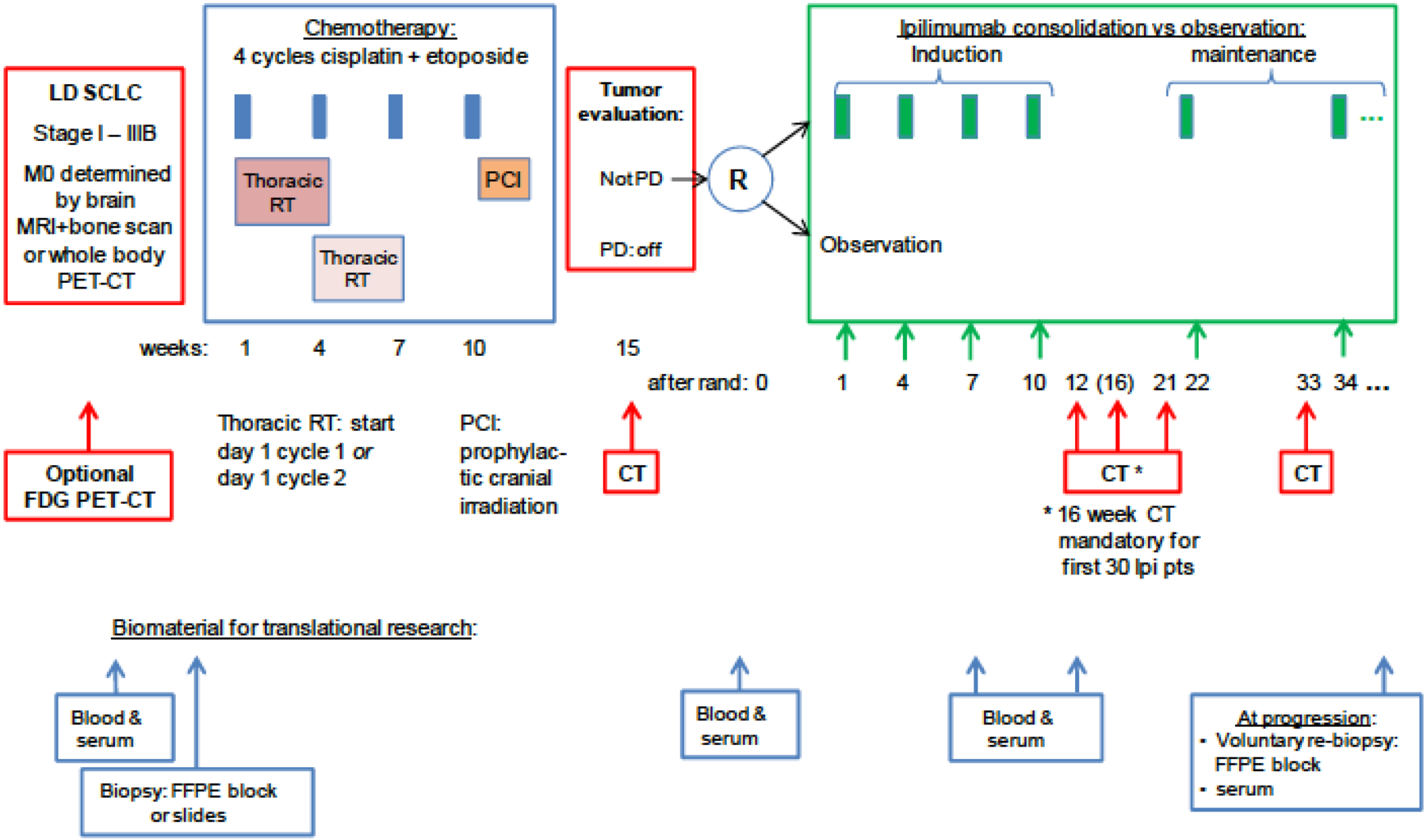


Figure adapted from Postow M, et al. *N Engl J Med. 2012*;366(10): 925–931.

STIMILI: A randomized phase II trial of consolidation ipilimumab vs placebo in limited-stage SCLC after chemoradiotherapy



- Biomarker collaboration: G Coukos, Lausanne

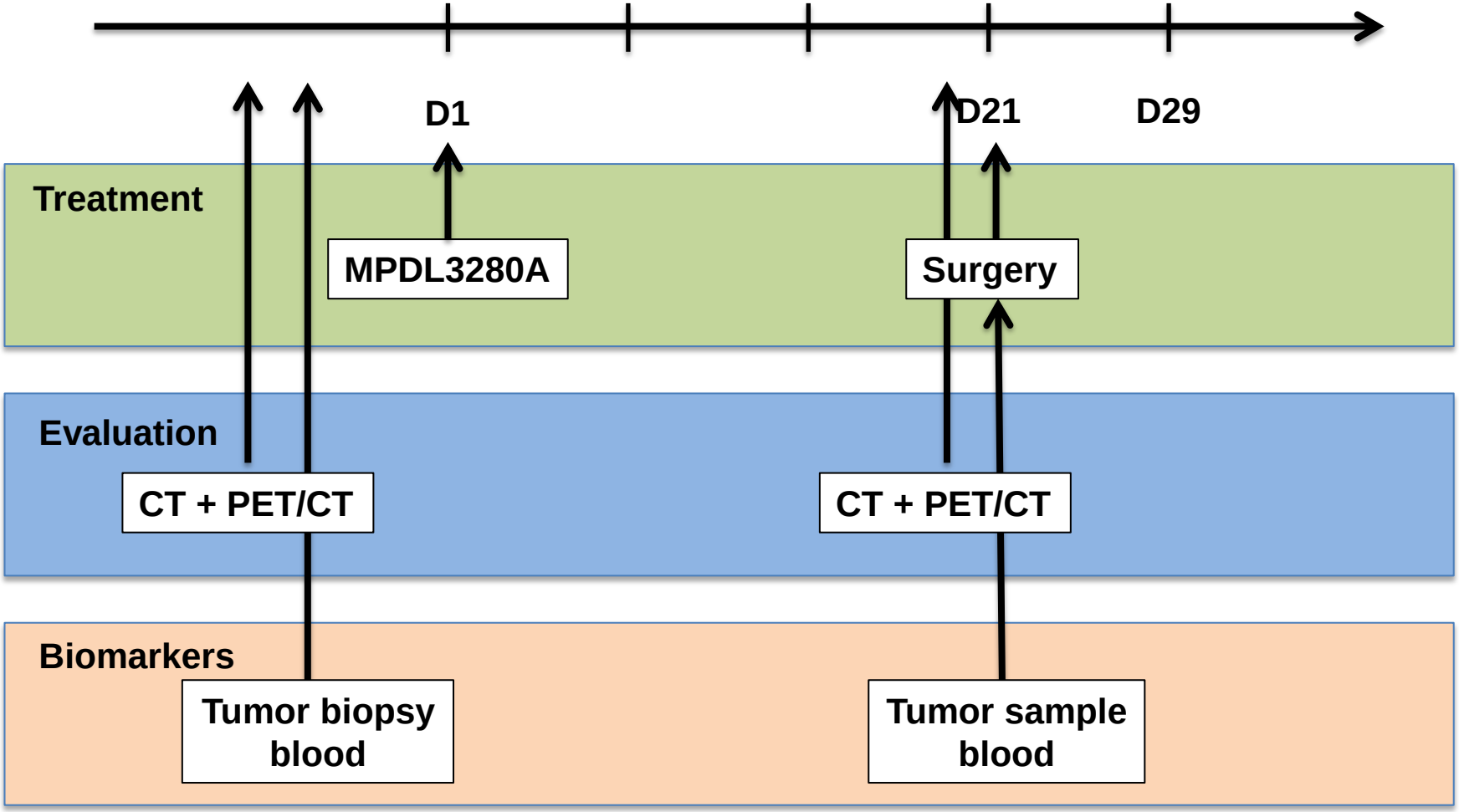
Early Stage disease

Combination with surgery

Early Stage Disease: Neoadjuvant therapy

SOC pre-operative evaluation

SOC adjuvant therapy



If no progression is seen at D20 CT, an additional 2 cycles are given before surgery

Combinations and new directions

- Combinations are being studied with
  - PD-1 and anti-CTLA4 or other immune modulators
  - PD-1 and chemotherapies, first and later lines
  - PD-1 and targeted therapies, up-front or upon resistance
  - Neoadjuvant/Adjuvant
  - Radiation therapy
  - Vaccines
  - Other biologics, e.g. bevacizumab

Summary

- Immunotherapy has clear activity in lung cancer as a single agent
- Modest and manageable side-effects that differ from other therapies enable the testing of combinations
- Many combinations are being tested with promising results