Update on the Recent Developments of Checkpoint Inhibitors

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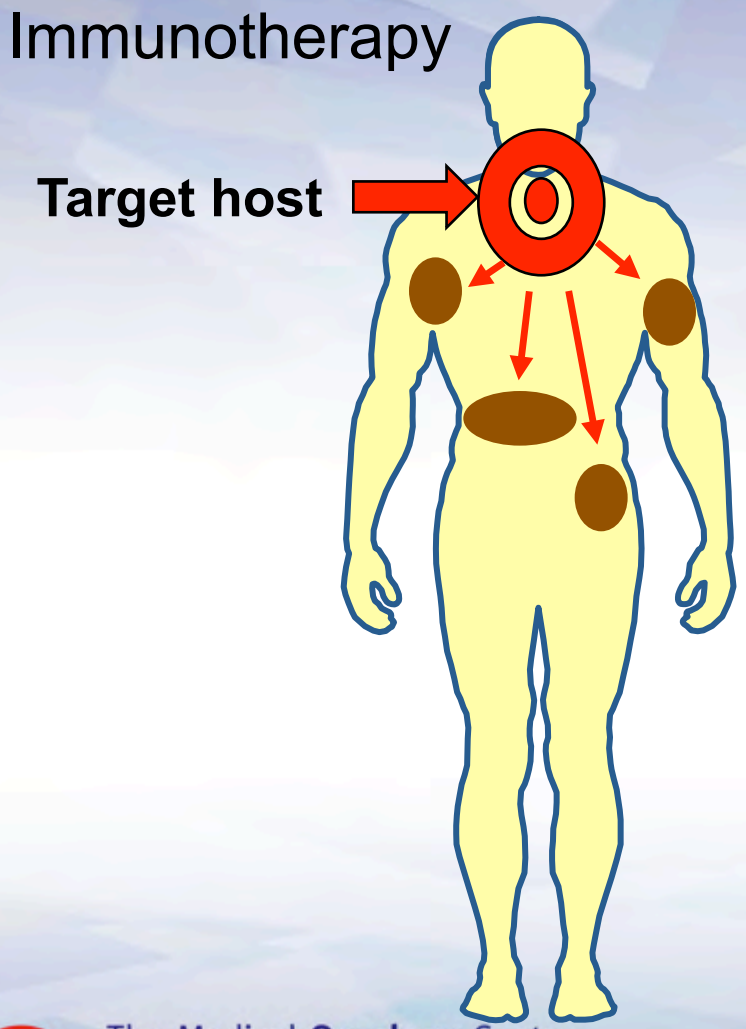
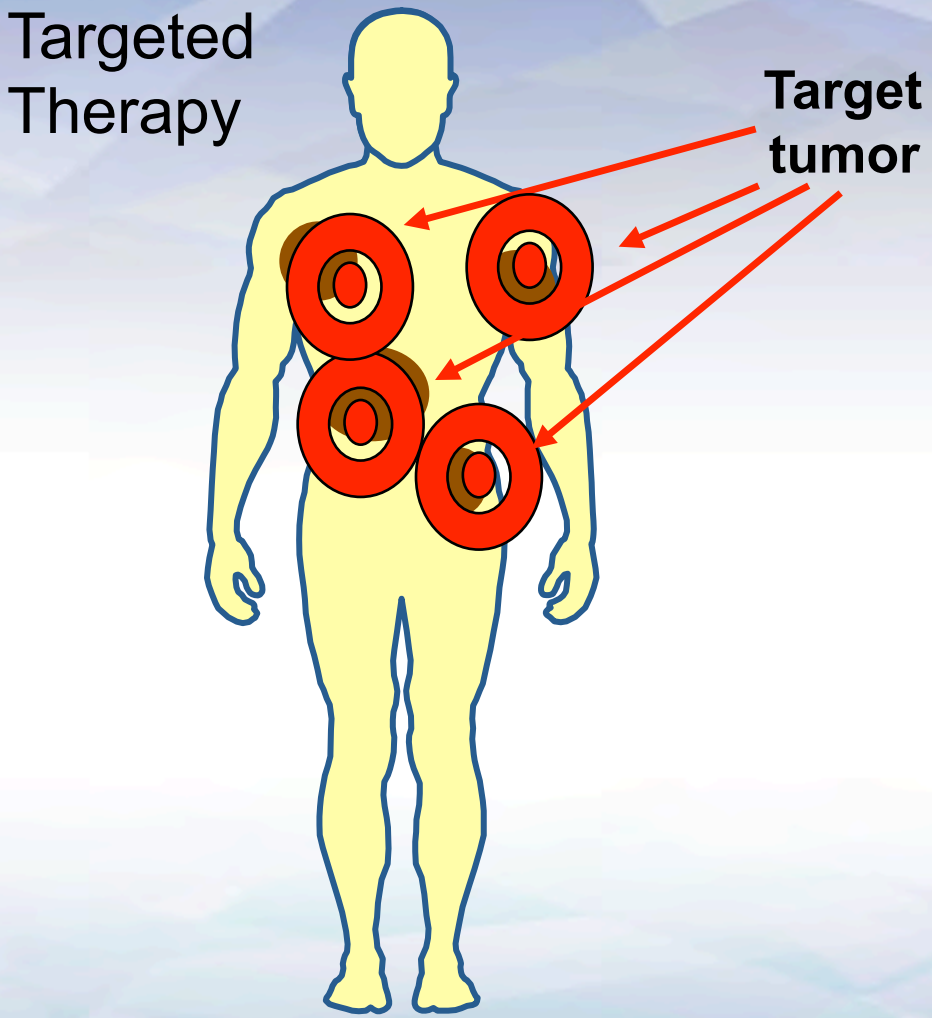
Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Contract Research*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Merck & Co., Inc	x	x	x						Speakers' bureau
Roche	x	x		x					Speakers' bureau
Sandoz	x	x		x					
Tesaro	x	x	x	x					Speakers' bureau
Teva	x	x							Speakers' bureau
Heron Therapeutics	x	x							
BMS South Africa	x	x	x	X					Speakers' bureau
Novartis South Africa	x	x	x						Speakers' bureau
Amgem South Africa	x	x	x						Speakers' bureau
Bayer South Africa	x	x	x						Speakers' bureau
Merck Serono S.Africa	x	x							
Astellas South Africa	x	x							Speakers' bureau
Sanofi Aventis S. Africa	x	x							
Astra Zeneca S. Africa	x	x							Speakers' bureau
Eli-Lilly South Africa			x						
J & J South Africa	X	X							Speakers' bureau

Two Paradigms for Advancing the Therapy of Metastatic Melanoma





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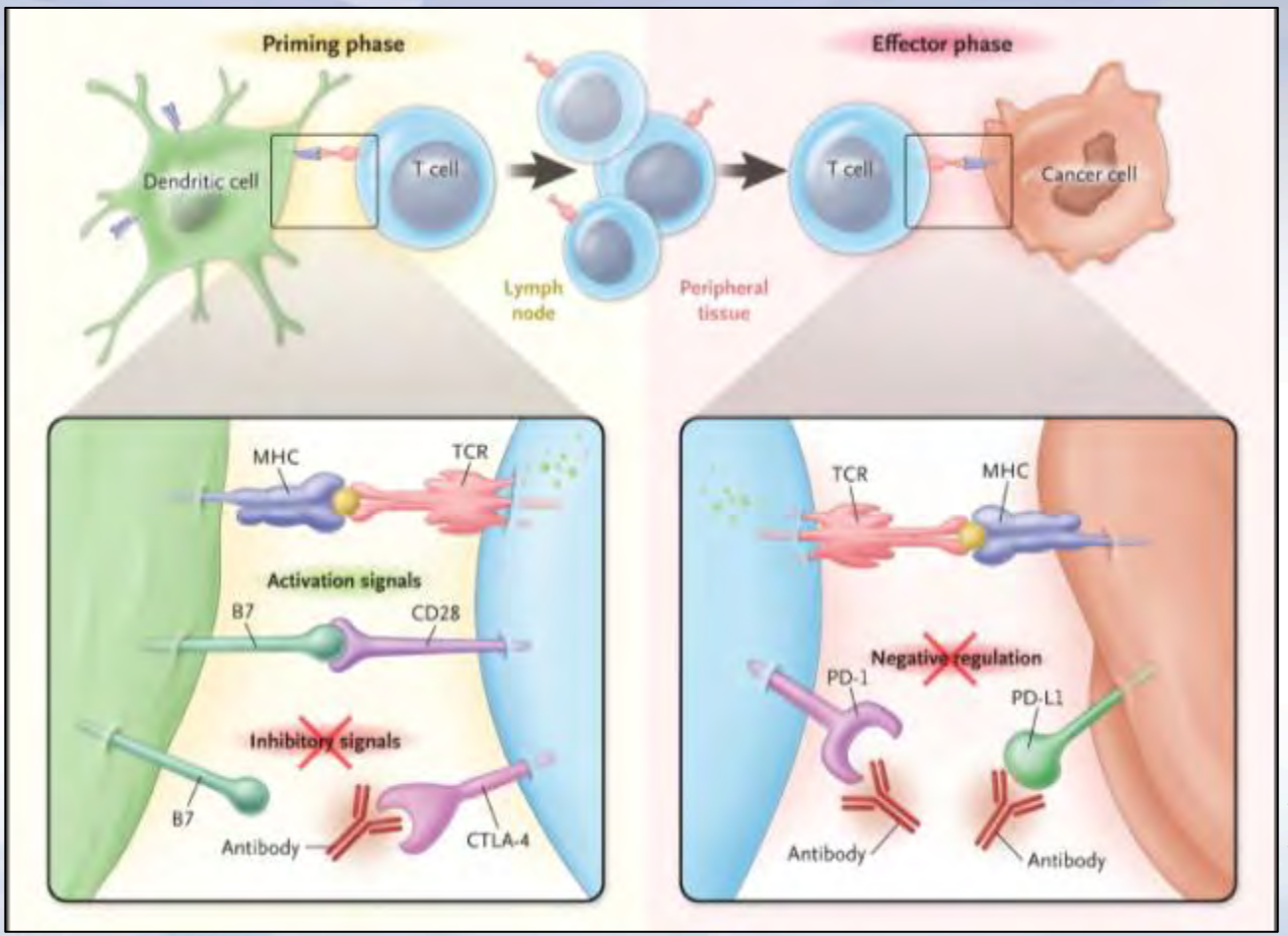
CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

- Immune checkpoint blockade includes agents targeting the negative regulators CTLA-4 and PD-1
- CTLA-4 attenuates the early activation of naive and memory T cells in the lymph nodes
  - Agents targeting CTLA-4 include ipilimumab and tremelimumab
- In contrast, PD-1 modulates the effector phase of T cell activity in peripheral tissues via interaction with PD-L1 and PD-L2
  - Agents targeting PD-1 include nivolumab and pembrolizumab
  - Agents targeting PD-L1 include atezolizumab, avelumab, durvalumab

Kyi C, et al. FEBS Lett. 2014;588:368-376

CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

CTLA-4 mAbs:
Ipilimumab
Tremelimumab



PD-1 mAbs:
Nivolumab
Pembrolizumab

PD-L1 mAbs:
Atezolizumab
Avelumab
Durvalumab

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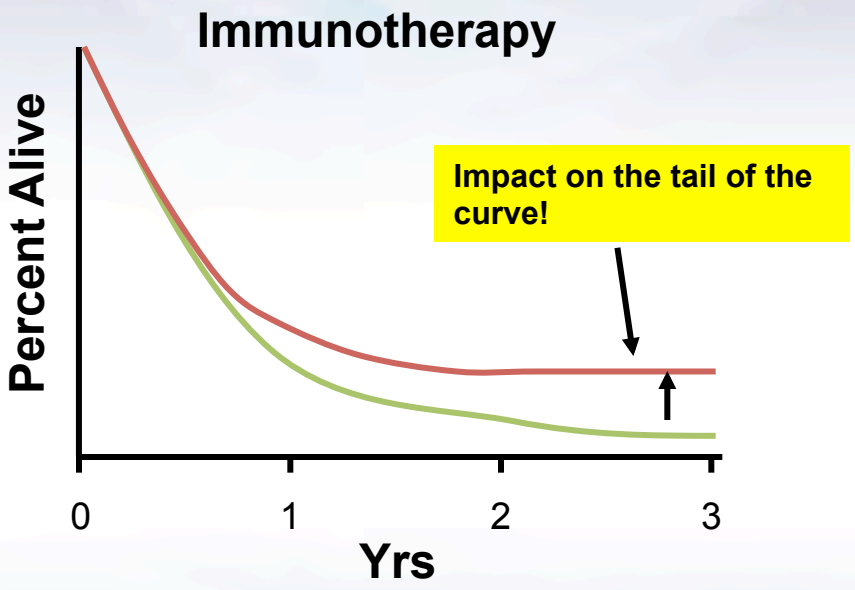
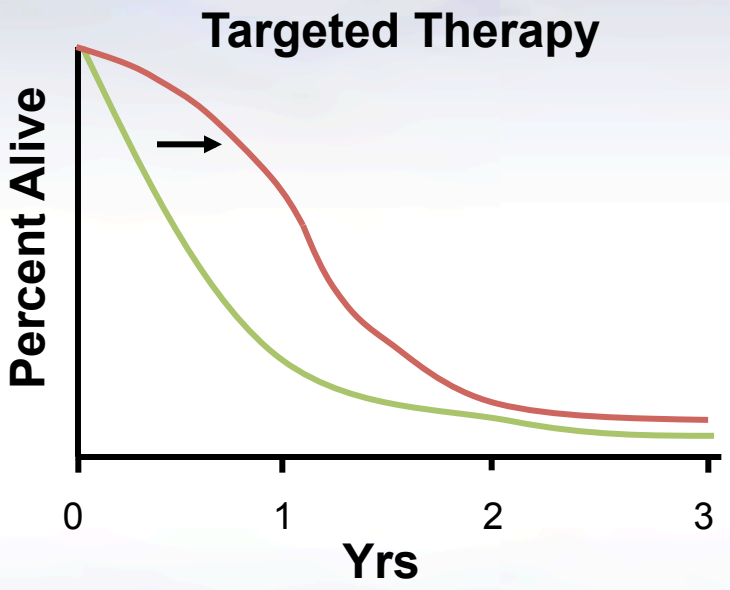
Potential Differences in PD-1 vs PD-L1 Blockade

- Anti-PD-1 and anti-PD-L1 antibodies may have different effects due to distinct mechanisms of action in the inhibitory pathway
- Anti-PD-1 antibodies:
  - Block PD-1 binding to PD-L1 and PD-L2
  - Do not block binding of PD-L1 to B7.1
- Anti-PD-L1 antibodies:
  - Block PD-L1 binding to PD-1 and B7.1
  - Do not block binding of PD-1 to PD-L2

Topalian SL, et al. Curr Opin Immunol. 2012;24:207-212.

Response Patterns for Immunotherapy Compared With Targeted Therapy





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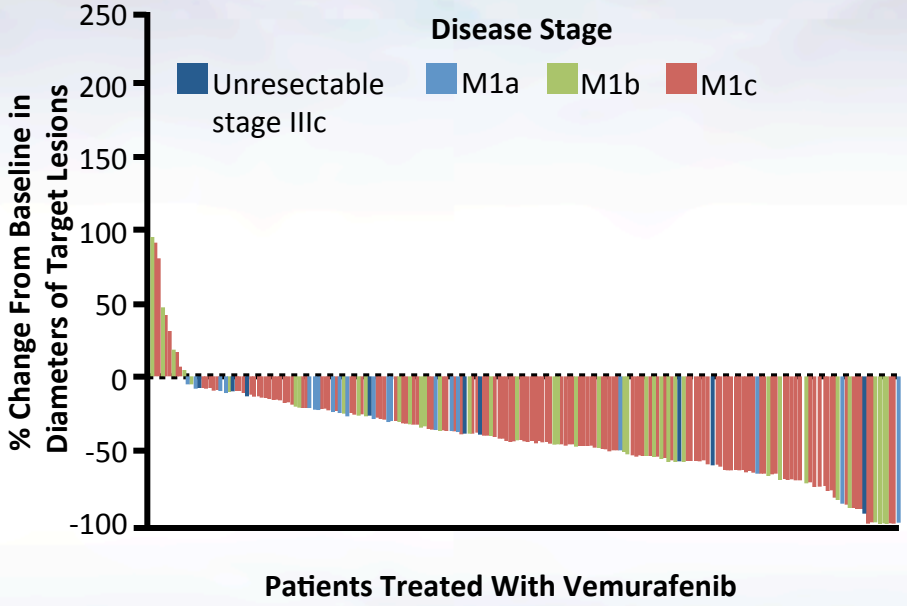
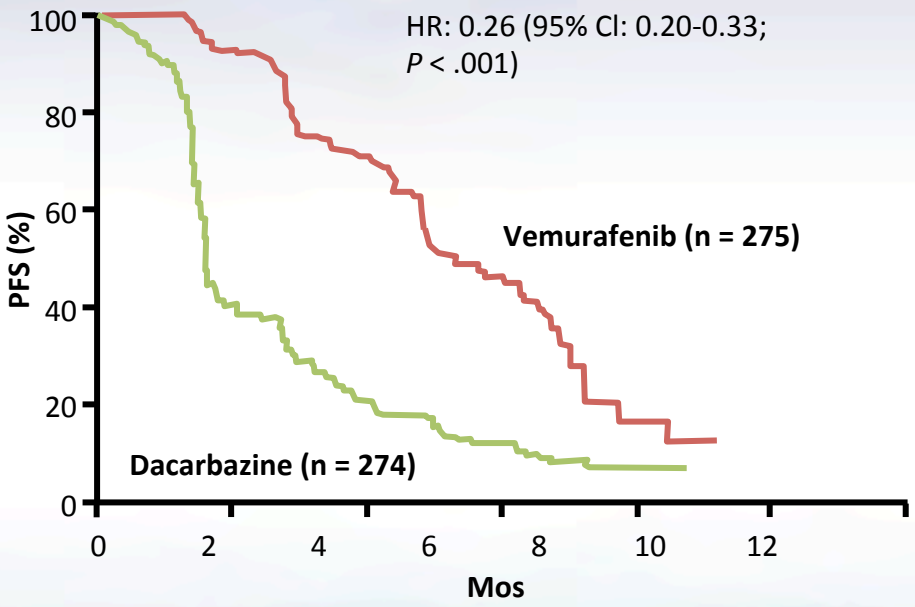
Ribas A, et al. Clin Cancer Res. 2012;18:336-341.

BRIM-3 Phase III Study of Vemurafenib vs DTIC in Melanoma: Response and PFS





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The NEW ENGLAND JOURNAL of MEDICINE

Chapman PB, et al. N Engl J Med. 2011;364:2507-2516.

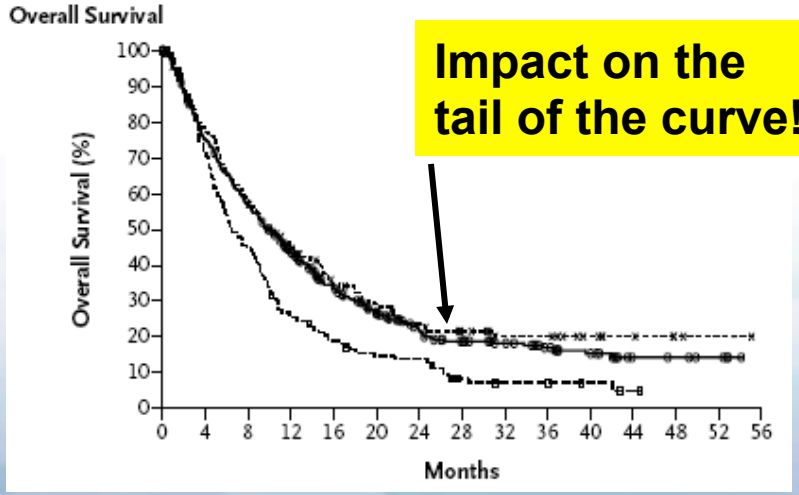
Ipilimumab
The major benefit is in durable tumor regressions

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.



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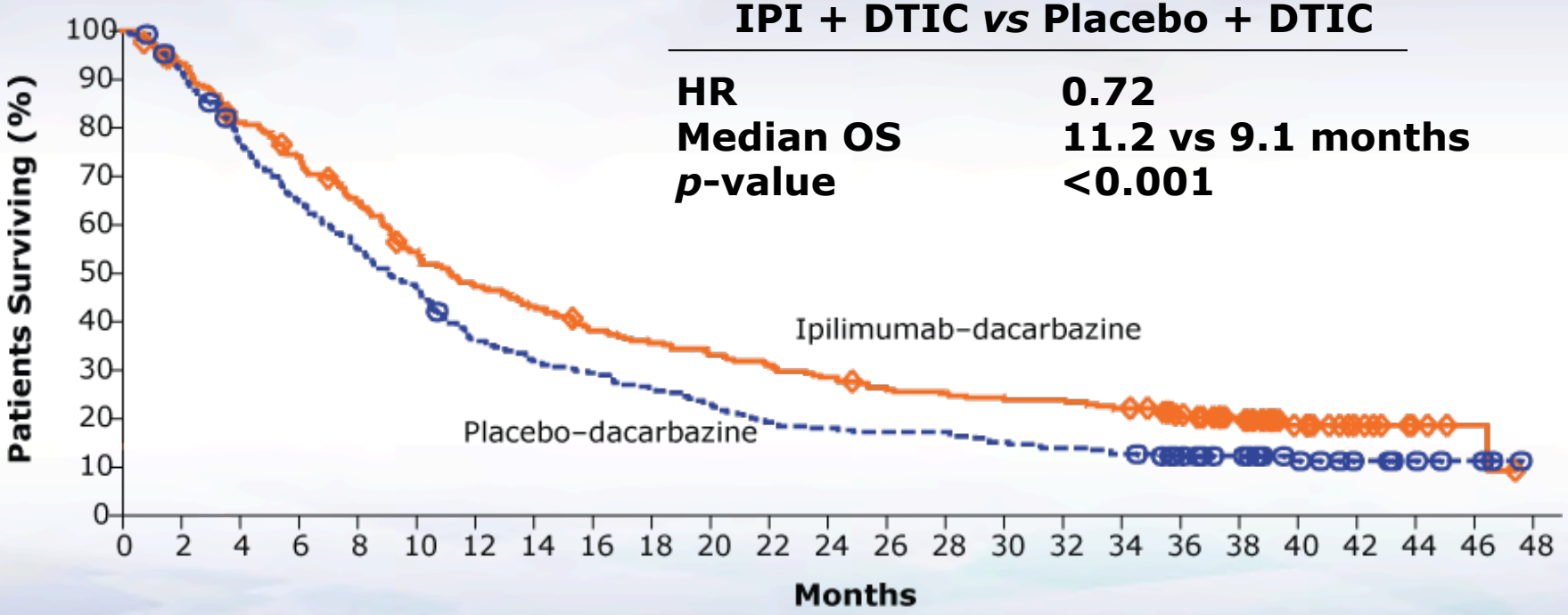
Study 024: Overall Survival

IPI + DTIC

Placebo + DTIC

IPI + DTIC *vs* Placebo + DTIC	
HR	**0.72**
Median OS	**11.2 vs 9.1 months**
***p*-value**	**<0.001**



Robert C et al. *N Engl J Med* 2011;

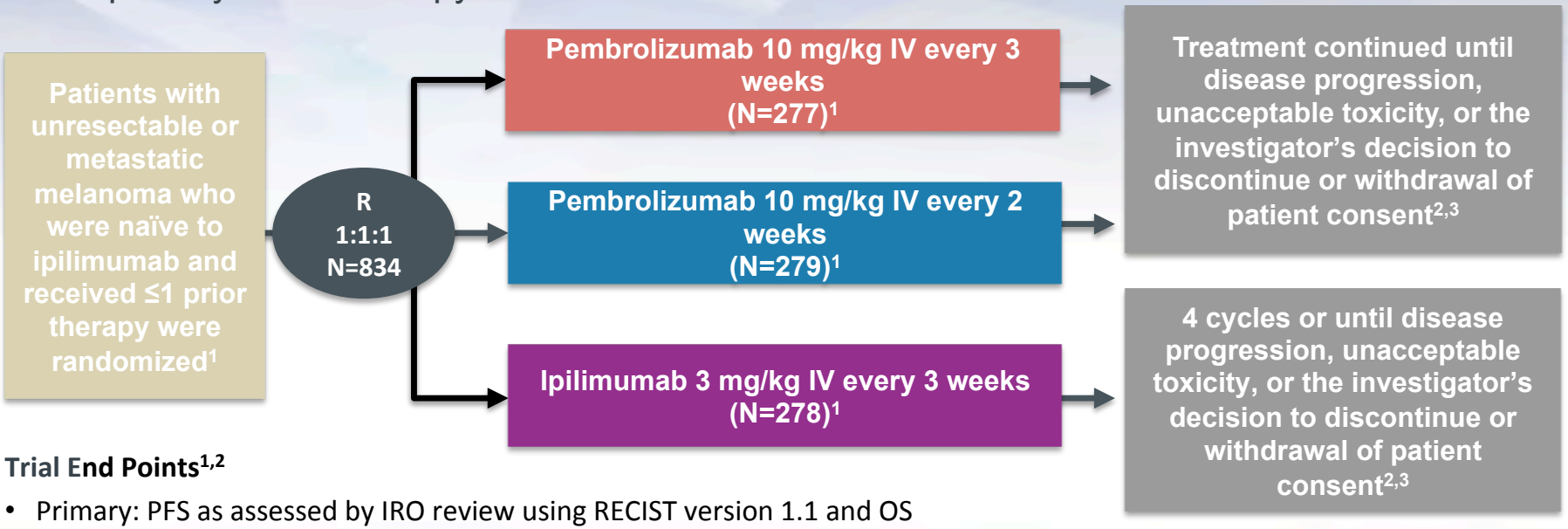
Select Adverse Events and Immune-Related Adverse Events

All Adverse Events, Regardless of Cause	IPI + DTIC (n=247)		Placebo + DTIC (n=251)	
	Total	Gr 3/4	Total	Gr 3/4
Diarrhea	36.4%	4.0%	24.7%	0
Rash	24.7%	1.2%	6.8%	0
Increased AST	29.1%	18.2%	5.6%	1.2%
Increased ALT	33.2%	21.9%	5.6%	0.8%
Immune-Related Adverse Events				
Increased AST	26.7%	17.4%	3.2%	0.4%
Increased ALT	29.1%	20.7%	4.4%	0.8%

Robert C et al. *N Engl J Med* 2011

KEYNOTE-006: Pembrolizumab vs Ipilimumab

- Open-label, multicenter, randomized, controlled, phase 3 trial included patients with unresectable or metastatic melanoma who were naïve to ipilimumab and received no or one prior systemic therapy[1]

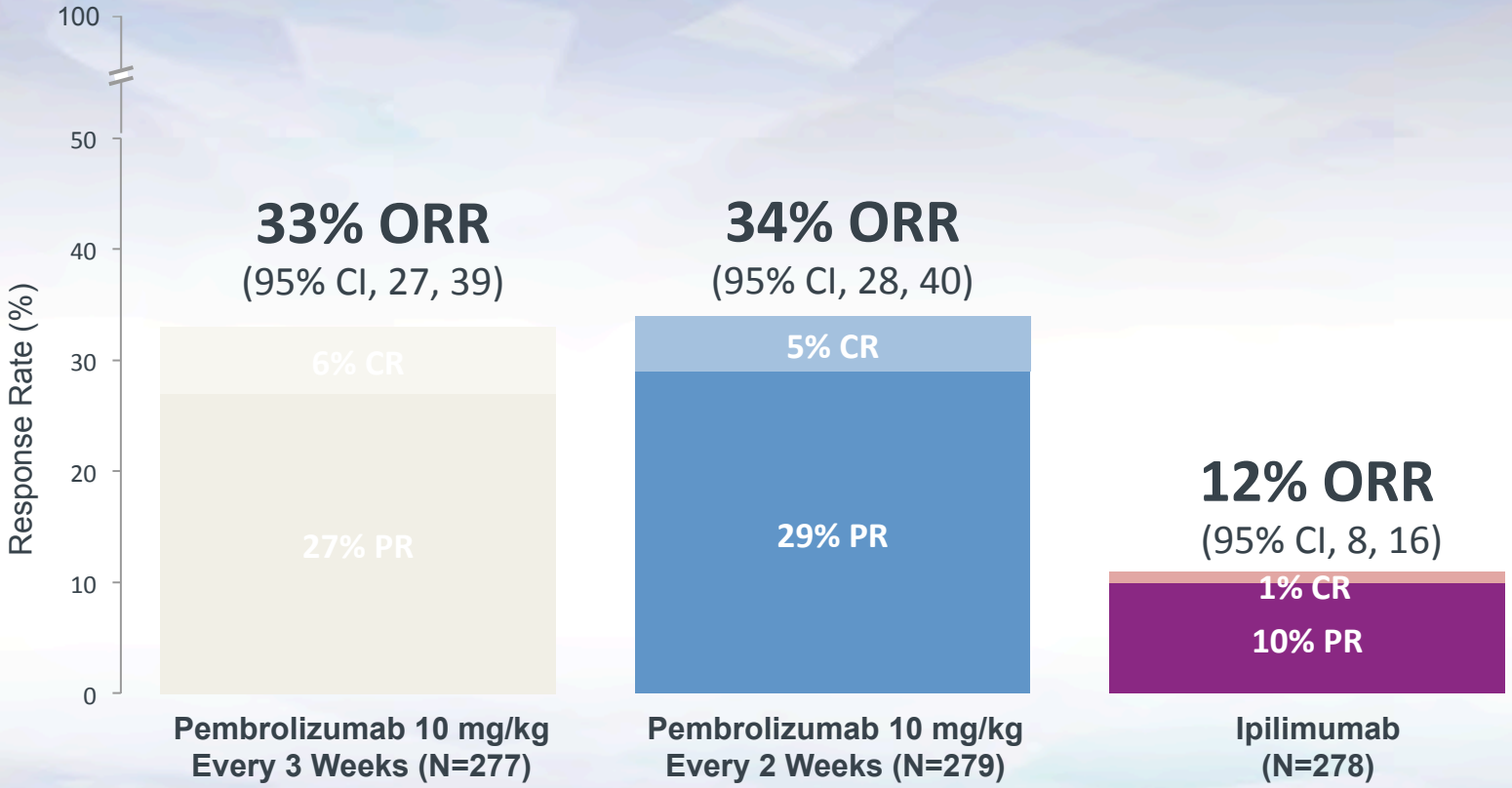


Trial End Points[1,2]

- Primary: PFS as assessed by IRO review using RECIST version 1.1 and OS
  - PFS was assessed at first interim analysis. All patients were followed for at least 6 months[b]
  - OS was assessed at second interim analysis. All patients were followed for at least 9 months or when the minimum follow-up duration was 12 months, whichever occurred first[c]
- Selected Secondary: ORR

KEYNOTE-006: Overall Response Rate With Pembrolizumab

Greater ORR with pembrolizumab10 mg/kg every 3 weeks vs ipilimumab[1,a,b]



Analysis cutoff date: 3 September 2014.

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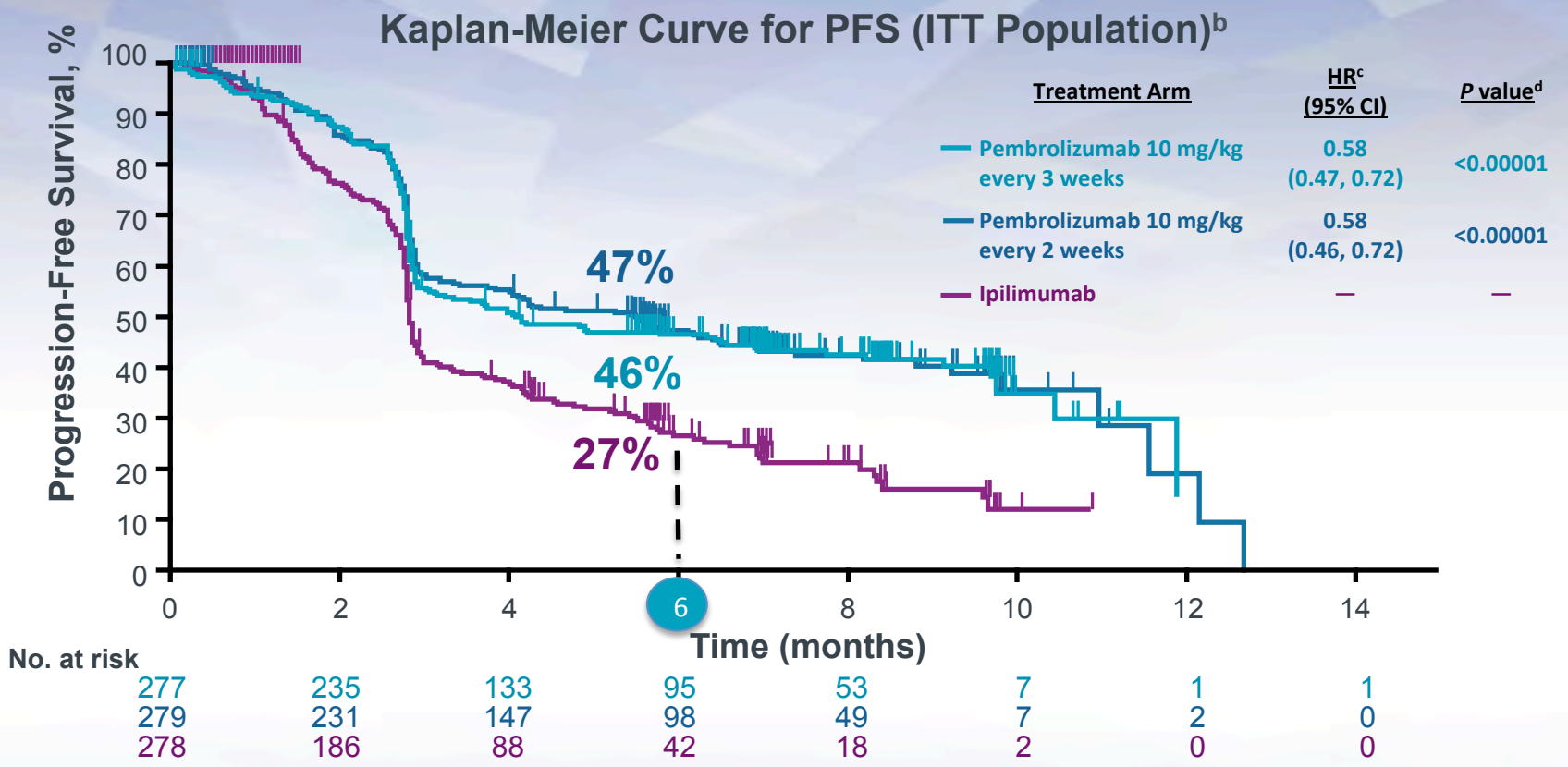
KEYNOTE-006: Estimated PFS With Pembrolizumab



- 42% reduction in the risk of death with pembrolizumab10 mg/kg every 3 weeks vs ipilimumab
- 42% reduction in the risk of death with pembrolizumab10 mg/kg every 2 weeks vs ipilimumab

Analysis cutoff date: 3 September 2014.

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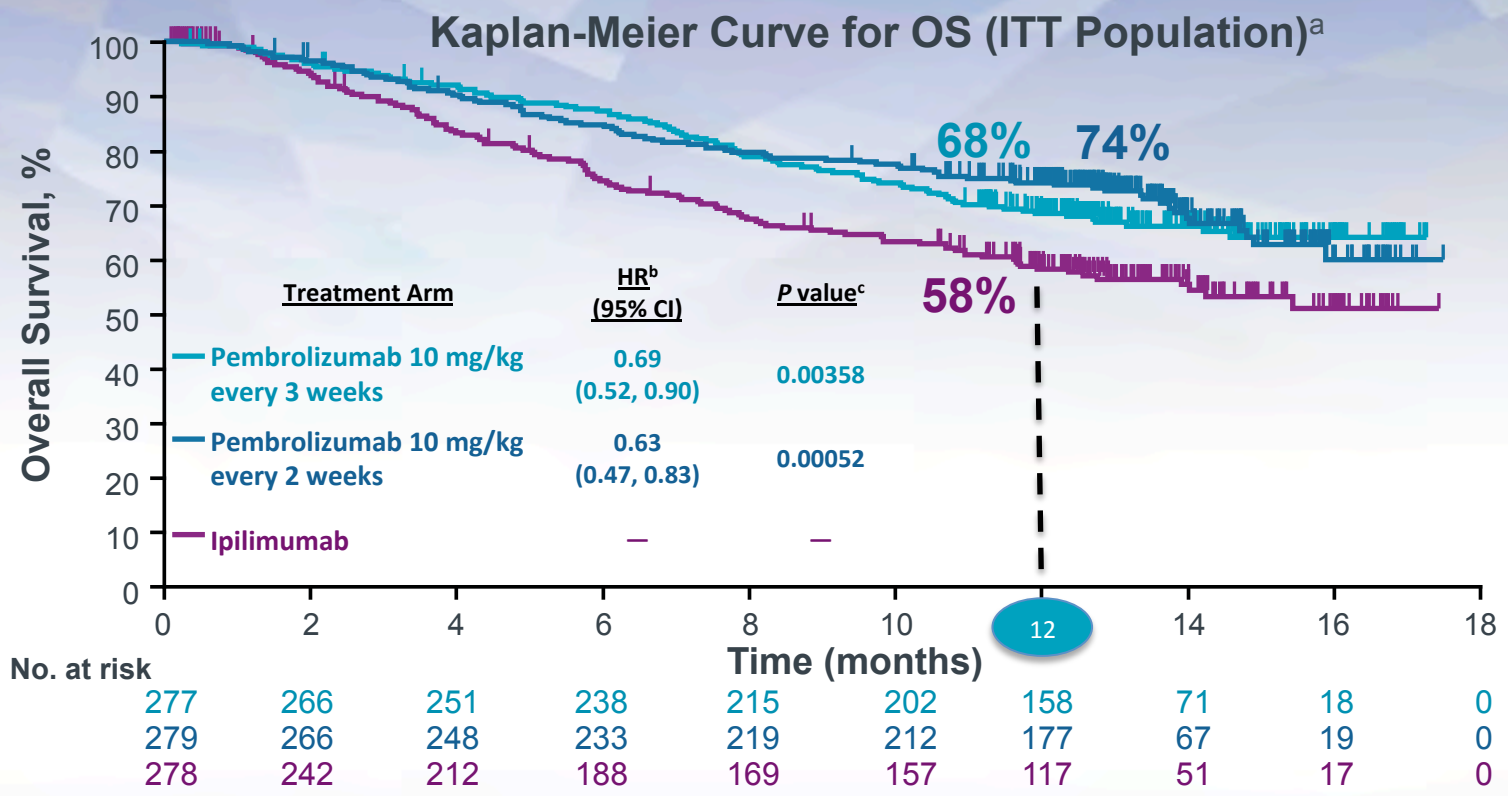
Robert C et al, for the KEYNOTE-006 investigators. *N Engl J Med*. 2015;372(26):2521-2532.

KEYNOTE-006: Estimated OS With Pembrolizumab



- 31% reduction in the risk of death with KEYTRUDA 10 mg/kg every 3 weeks vs ipilimumab
- 37% reduction in the risk of death with KEYTRUDA 10 mg/kg every 2 weeks vs ipilimumab
- The recommended dose of KEYTRUDA is 2 mg/kg every 3 weeks[1]

Analysis cutoff date: 3 March 2015.

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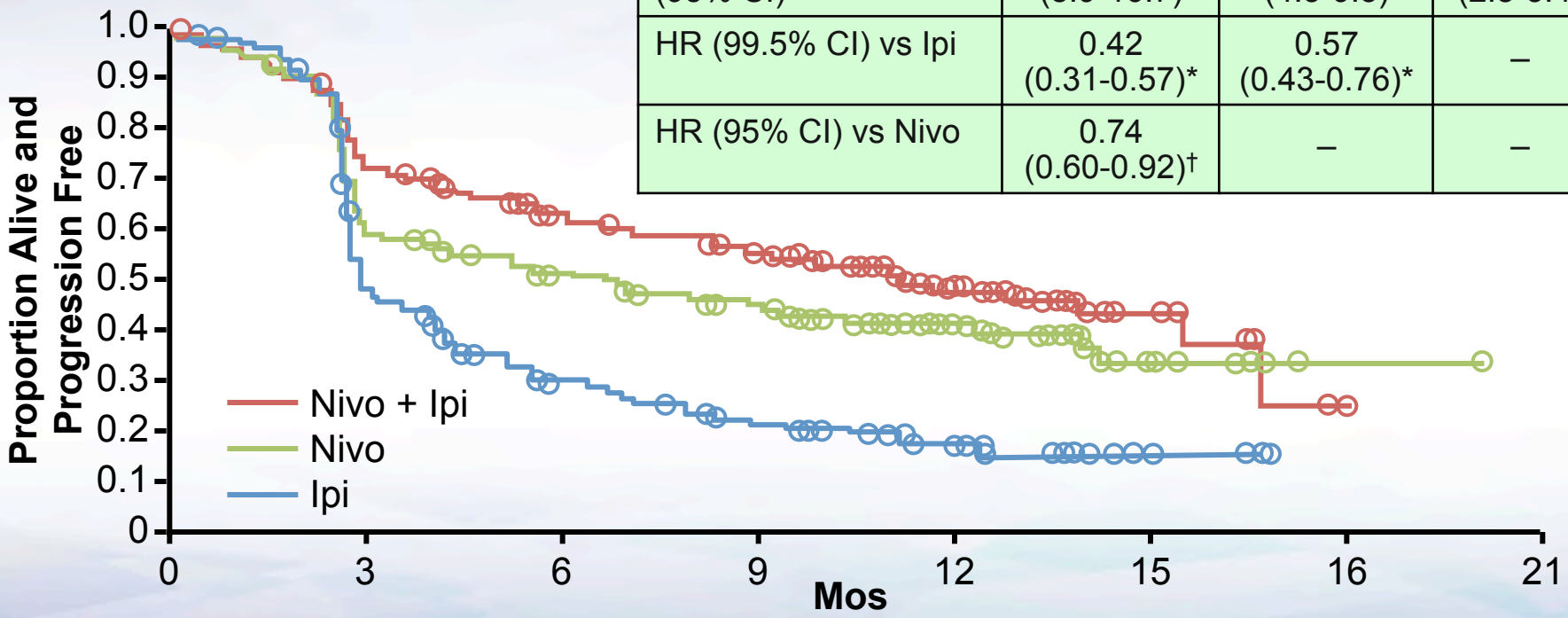
Robert C et al, for the KEYNOTE-006 investigators. *N Engl J Med*. 2015;372(26):2521-2532.

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone

	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median PFS, mos (95% CI)	11.5 (8.9-16.7)	6.9 (4.3-9.5)	2.9 (2.8-3.4)
HR (99.5% CI) vs Ipi	0.42 (0.31-0.57)*	0.57 (0.43-0.76)*	–
HR (95% CI) vs Nivo	0.74 (0.60-0.92)†	–	–



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Wolchok JD, et al. ASCO 2015. Abstract LBA1. *Reprinted with permission*.

Nivolumab vs Docetaxel in Previously Treated Advanced NSCLC: Phase III Trials

CheckMate 017[1]

Pts with stage IIIb/IV SQ NSCLC, 1 prior platinum-based treatment, ECOG PS 0/1 (N = 272)

- Nivolumab 3 mg/kg IV q2w (n = 135)
- Docetaxel 75 mg/m^2 IV q3w (n = 137)

→ ***Until disease progression or unacceptable toxicity***

CheckMate 057[2]

Pts with stage IIIB/IV non-SQ NSCLC who failed 1 prior platinum-based treatment, ECOG PS 0/1 (N = 582)

- Nivolumab 3 mg/kg IV q2w (n = 292)
- Docetaxel 75 mg/m^2 IV q3w (n = 290)

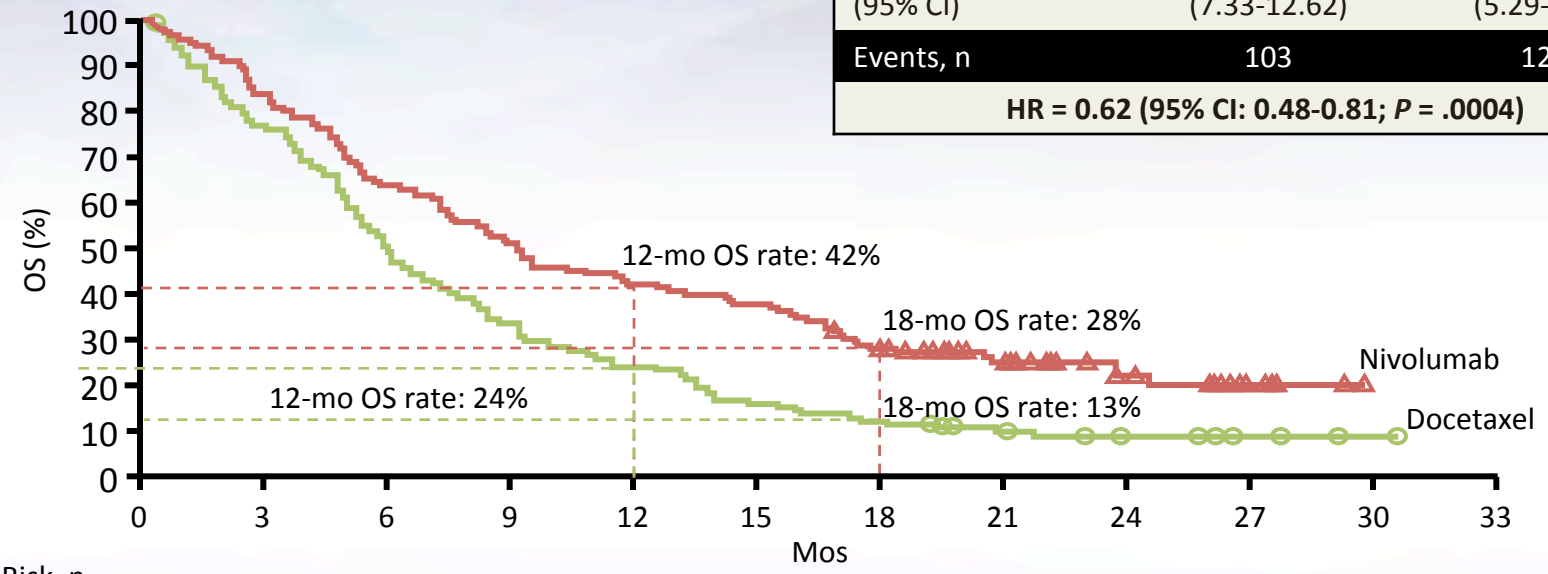
→ ***Until disease progression or unacceptable toxicity***

Primary endpoint (both trials): OS

1. Brahmer J, et al. N Engl J Med. 2015;373:123-135.
2. Borghaei H, et al. N Engl J Med. 2015;373:1627-1639.

Nivolumab vs Docetaxel in Advanced SQ NSCLC (CheckMate 017): OS

	Nivolumab (n = 135)	Docetaxel (n = 137)
Median OS, mos (95% CI)	9.2 (7.33-12.62)	6.0 (5.29-7.39)
Events, n	103	122
HR = 0.62 (95% CI: 0.48-0.81; *P* = .0004)		



Pts at Risk, n												
Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	3	1	0

Minimum follow-up for survival: 18 mos

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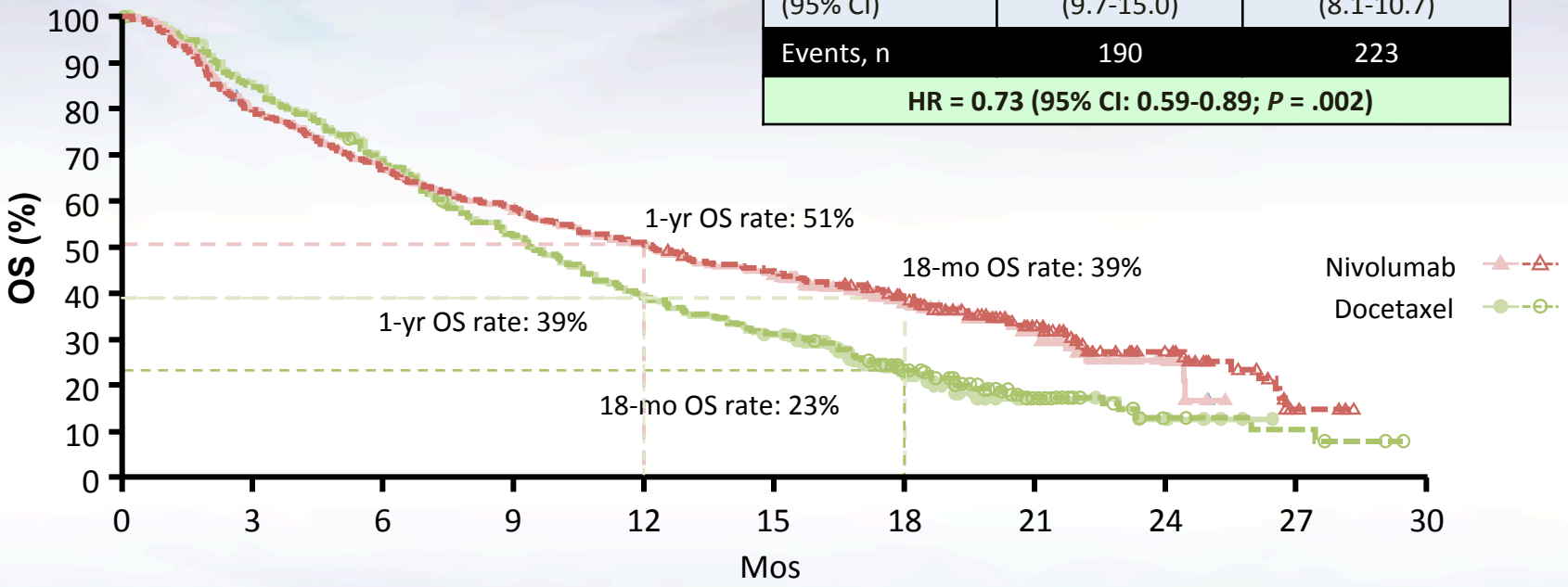
Reckamp K, et al. WCLC 2015. ORAL02.01.

Nivolumab vs Docetaxel in Advanced Non-SQ NSCLC (CheckMate 057): OS

	Nivolumab (n = 292)	Docetaxel (n = 290)
Median OS, mos (95% CI)	12.2 (9.7-15.0)	9.4 (8.1-10.7)
Events, n	190	223
HR = 0.73 (95% CI: 0.59-0.89; *P* = .002)		



Minimum follow-up for 12-mo OS rate: 13.2 mos;
for 18-mo OS rate: 17.1 mos

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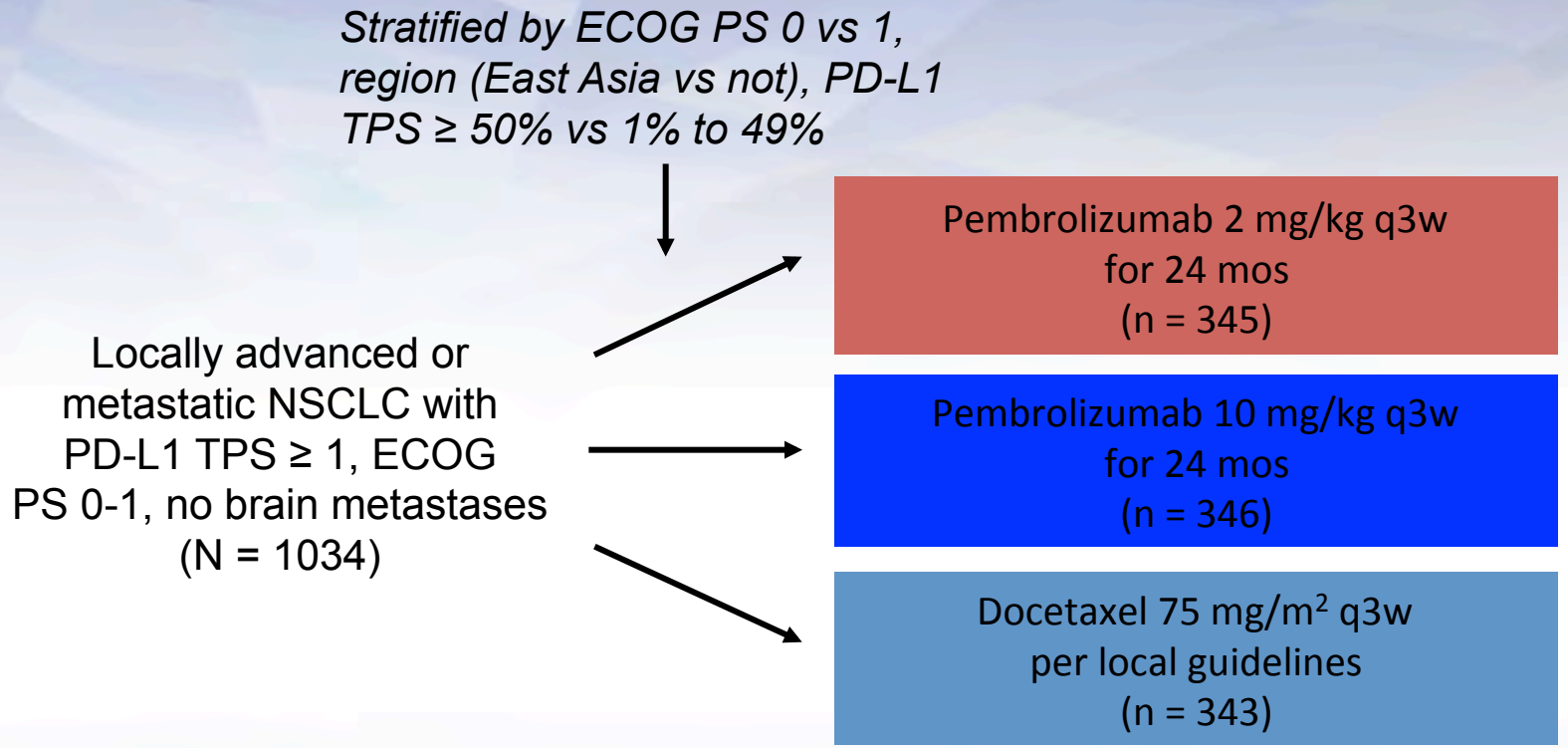
Horn L, et al. ESMO 2015. Abstract 3010.
Borghaei H, et al. N Engl J Med. 2015;373:1627-1639.

Pembro vs Doc in Previously Treated PD-L1+ Advanced NSCLC (KEYNOTE-010)



- Primary endpoints*: PFS, OS
- Secondary endpoints*: ORR, DoR, safety

*In both the PD-L1 TPS ≥ 1% and ≥ 50% populations.

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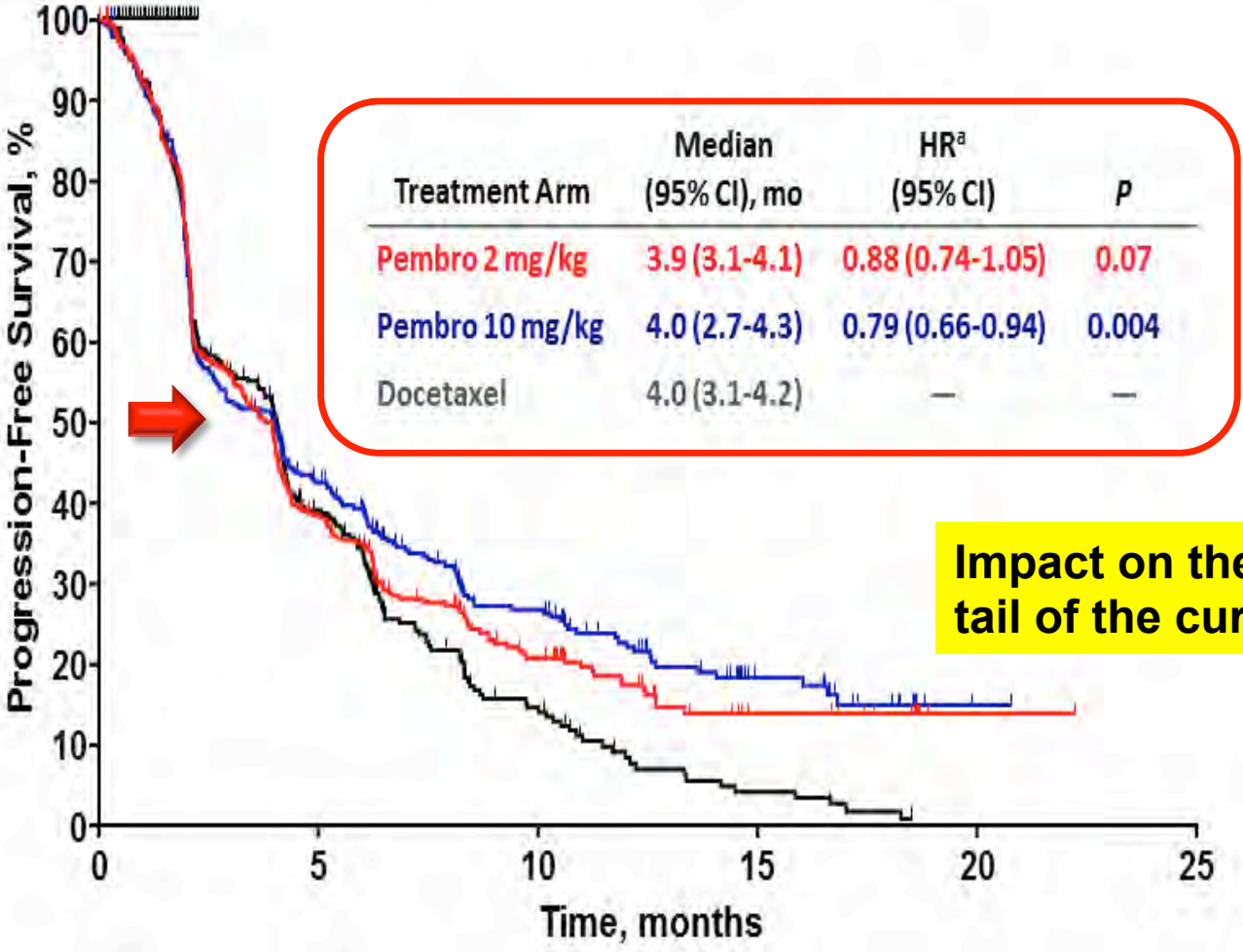
Herbst R, et al. Lancet. 2015;[Epub ahead of print].

PFS (RECIST v1.1, Central Review)
PD-L1 TPS ≥ 1%

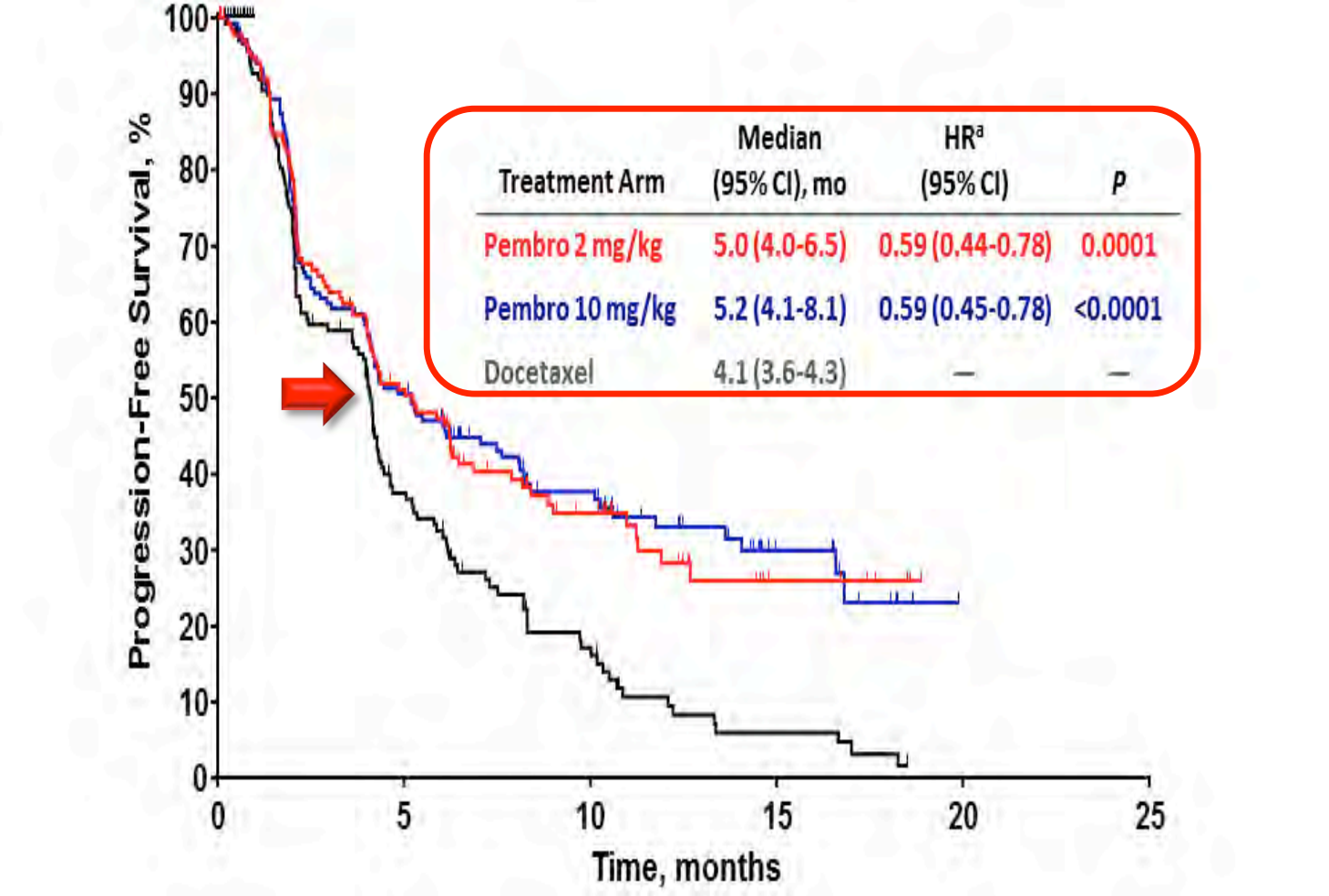


Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	3.9 (3.1-4.1)	0.88 (0.74-1.05)	0.07
Pembro 10 mg/kg	4.0 (2.7-4.3)	0.79 (0.66-0.94)	0.004
Docetaxel	4.0 (3.1-4.2)	—	—

Impact on the tail of the curve!

Improved Quality of Response With Higher PD-L1 Level

PFS (RECIST v1.1, Central Review)
PD-L1 TPS ≥ 50%



Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	5.0 (4.0-6.5)	0.59 (0.44-0.78)	0.0001
Pembro 10 mg/kg	5.2 (4.1-8.1)	0.59 (0.45-0.78)	<0.0001
Docetaxel	4.1 (3.6-4.3)	—	—

KEYNOTE-024: Select Adverse Events

Adverse event, n (%)	Pembrolizumab (N = 154)		Chemotherapy (N = 150)	
	All grades	Grade ≥3	All grades	Grade ≥3
Diarrhea	22 (14.3)	6 (3.9)	20 (13.3)	2 (1.3)
Fatigue	16 (10.4)	2 (1.3)	43 (28.7)	5 (3.3)
Pyrexia	16 (10.4)	0	8 (5.3)	0
Immune-mediated adverse event				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)
Severe skin reaction	6 (3.9)	6 (3.9)	0	0
Colitis	3 (1.9)	2 (1.3)	0	0

Reck M et al. *N Engl J Med* 2016;375(19):1823-33.

Atezolizumab vs Docetaxel in NSCLC (POPLAR): All-Comer Phase II Study

Stratified by PD-L1 IHC expression (0 vs 1 vs 2 vs 3), histology (squamous vs nonsquamous), prior chemotherapy regimens (1 vs 2)

Metastatic or locally advanced NSCLC (2L/3L), PD on prior platinum-based treatment (N = 287)

Atezolizumab
1200 mg IV q3w
until loss of clinical benefit
(n = 144)

Docetaxel
75 mg/m^2 IV q3w
until PD
(n = 143)

- Primary objective
  - Estimate OS by PD-L1 expression
- Secondary objectives
  - Estimate PFS, ORR, DoR by PD-L1 expression
  - Evaluate safety

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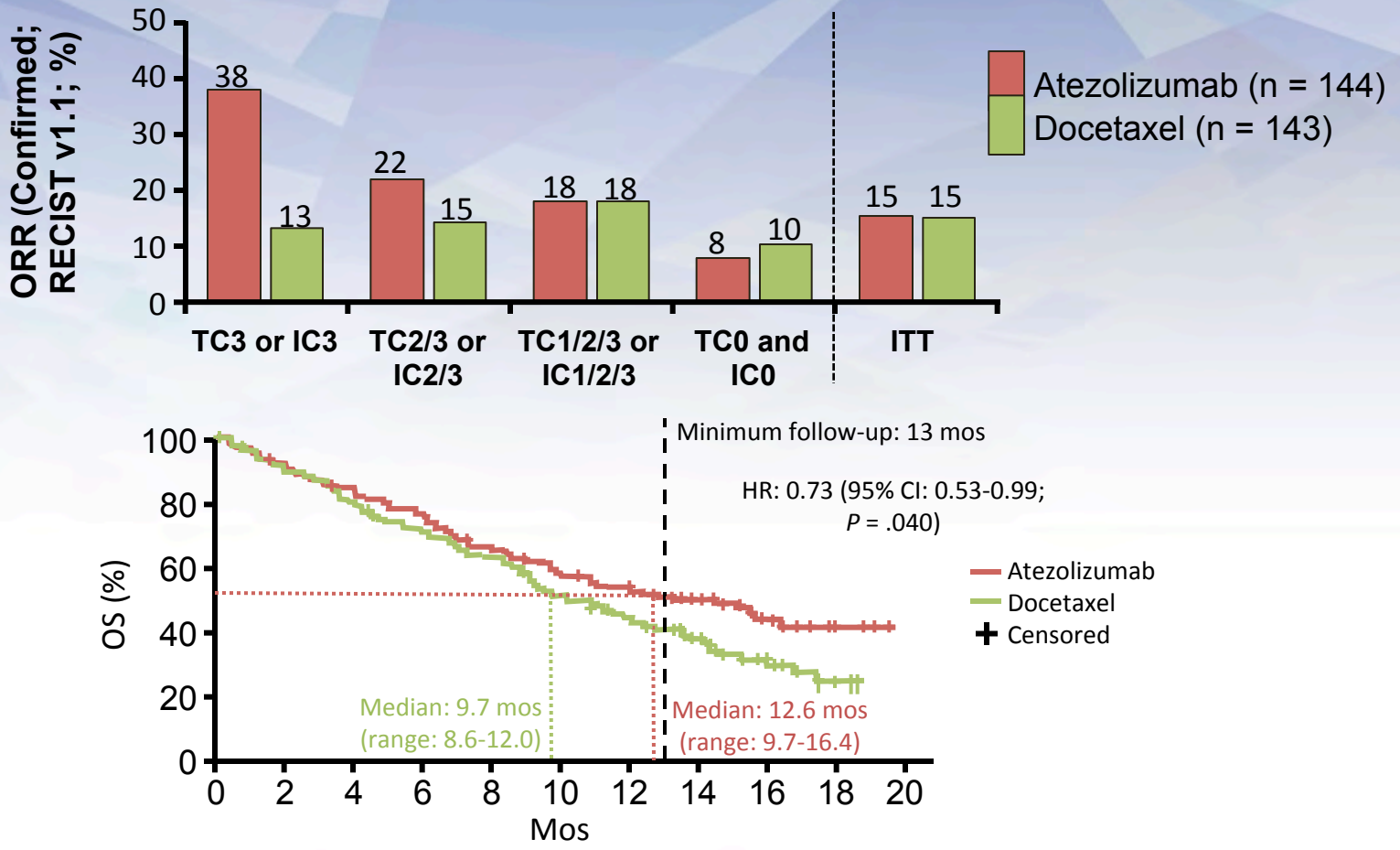
Fehrenbacher L, et al. Lancet. 2016. [epub ahead of print].

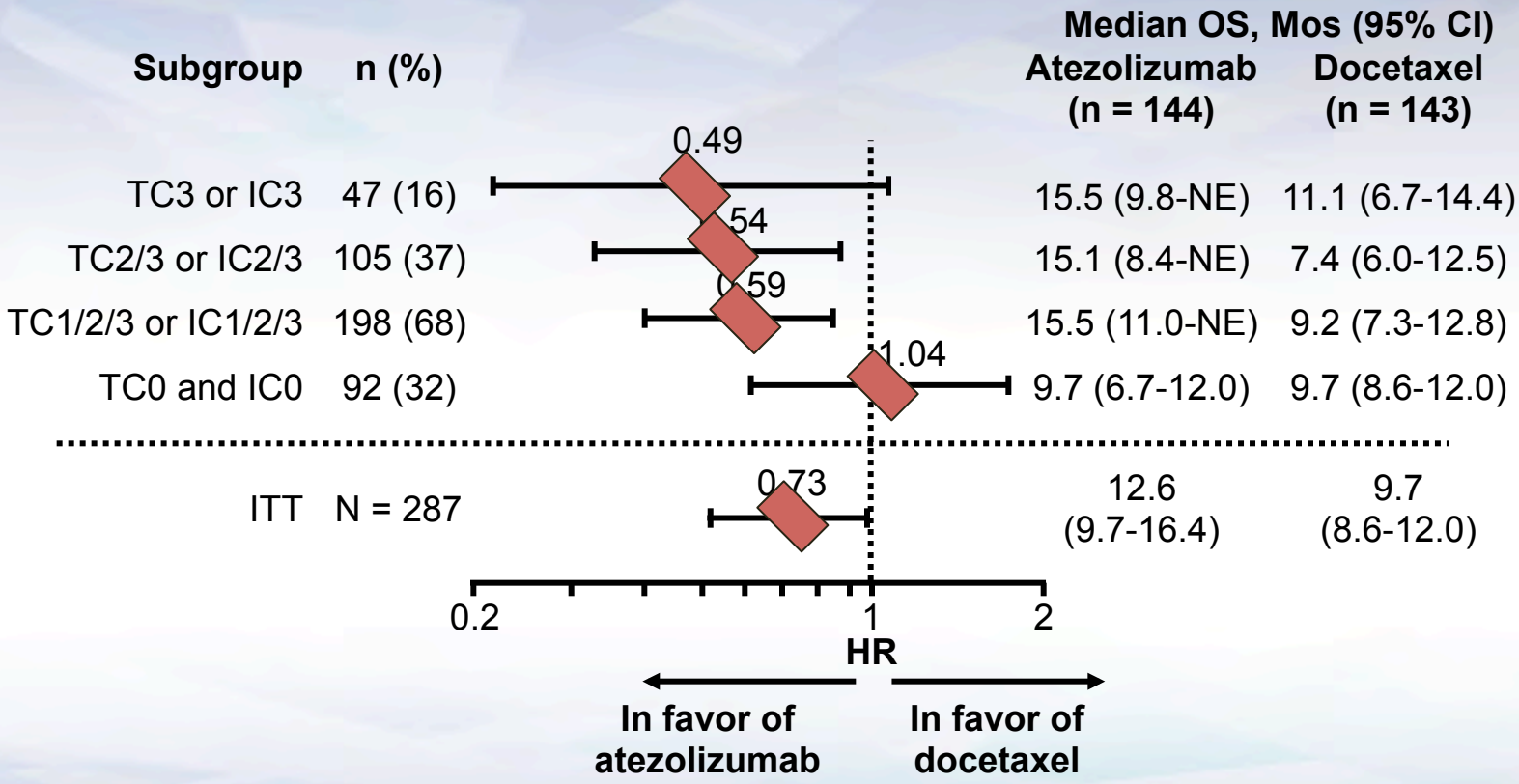
POPLAR: ORR and OS



- Event/pt ratio: 60% (54% for atezolizumab, 66% for docetaxel)

Spira AI, et al. ASCO 2015. Abstract 8010.
Fehrenbacher L, et al. Lancet. 2016. [epub ahead of print].

POPLAR: OS by PD-L1 Expression



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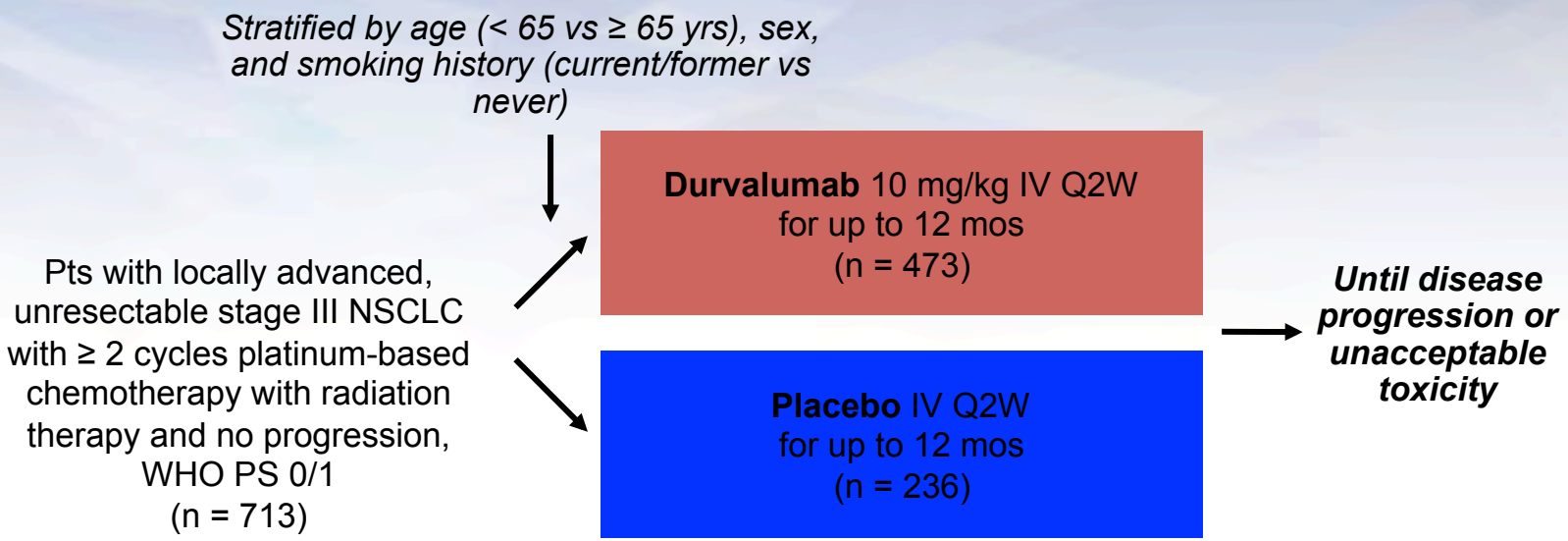
Vansteenkiste J, et al. ESMO 2015. Abstract 14LBA.
Fehrenbacher L, et al. Lancet. 2016. [epub ahead of print]

PACIFIC: Durvalumab vs Placebo After Concurrent CRT in Unresectable Stage III NSCLC

Interim analysis of international, randomized, double-blind, placebo-controlled phase III trial



- Primary endpoints
  - PFS: ≥ 95% power for detecting HR of 0.67 with 458 events
  - OS: 85% power for detecting HR of 0.73 with 491 events

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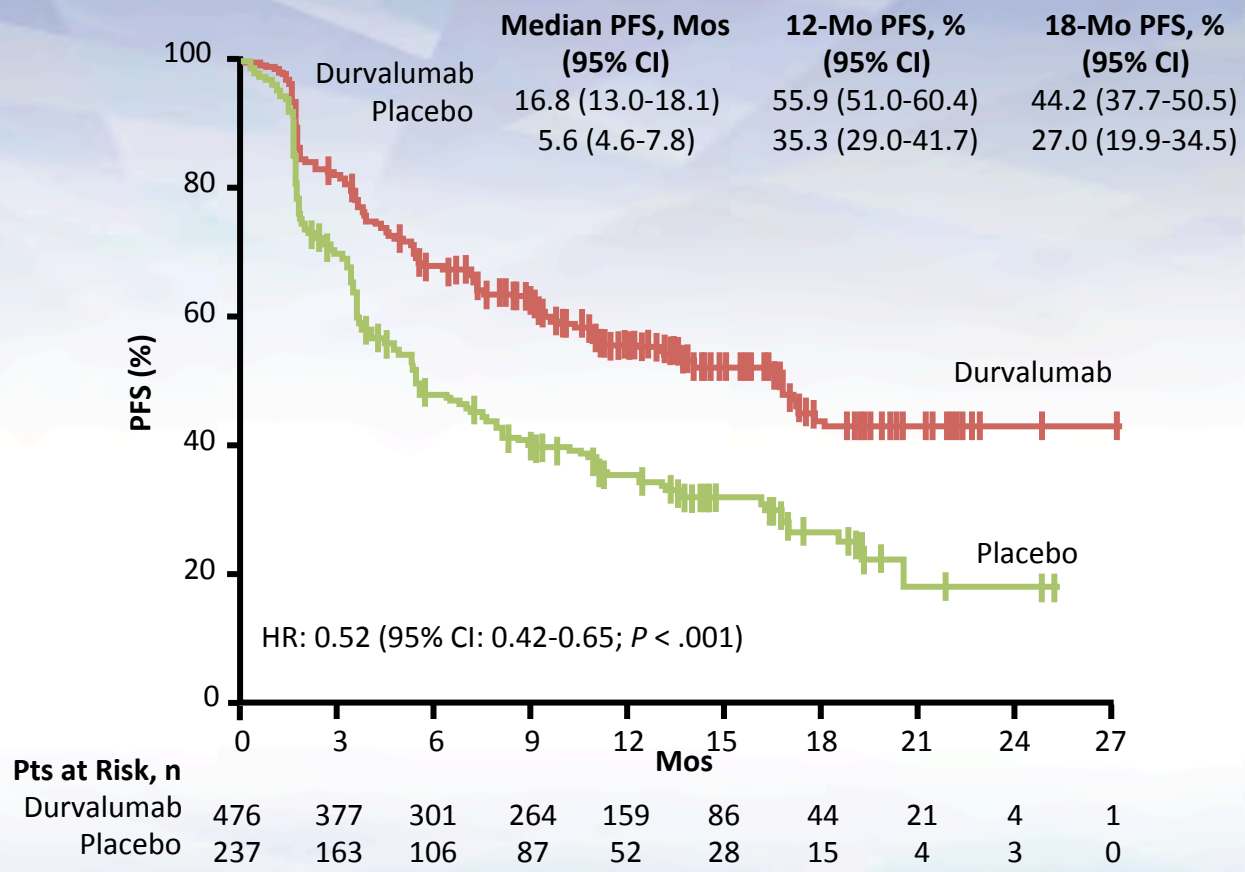
Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929.

PACIFIC: PFS by BICR in ITT Population (Primary Endpoint)



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Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929.

PACIFIC

Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N = 475)		Placebo (N = 234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

PACIFIC: PFS by BICR in ITT Population (Primary Endpoint)

- Durvalumab is now an FDA-approved option for stage III unresectable NSCLC after chemoradiation
  - HR 0.52
  - PFS 16.8 vs 5.8 mo
  - OS data not yet available
- Patient selection
- Toxicity assessment and management

Table 1. Reported (PACIFIC) or ongoing trials with immune checkpoint inhibitor immunotherapy in patients with unresectable stage III non-small cell lung cancer (NSCLC).

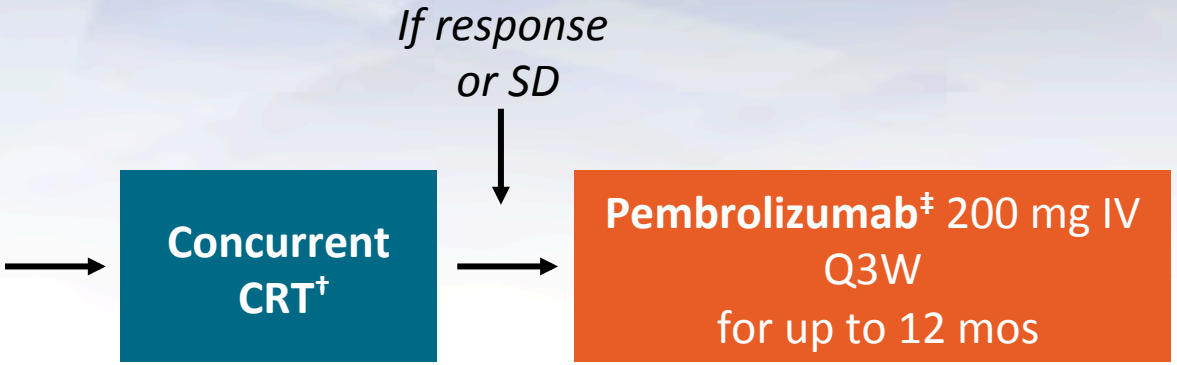
Agent	Phase	Number (*n*)	Primary endpoints	Immunotherapy timing	Register	Sponsor	Dosage
Durvalumab	III	713	OS/PFS	1–42 days after CRT	PACIFIC [ClinicalTrials.gov identifier: NCT 02125461]	AstraZeneca	10 mg/kg IV every 2 weeks for 12 months
Nivolumab	III	660*	OS/PFS	4–12 weeks after CRT	RTOG 3505 [ClinicalTrials.gov identifier: NCT 02768558]	RTOG	240 mg IV every 2 weeks for 12 months
Pembrolizumab	II	93	OS/PFS	4–7 weeks after CRT	[ClinicalTrials.gov identifier: NCT 02343952]	Hoosier Group	200 mg IV every 3 weeks for 12 months
Pembrolizumab	I	30§	Safety	G1: 2–6 weeks after CRT G2: 2 weeks before the end of CRT G3: at start of CRT	[ClinicalTrials.gov identifier: NCT 02621398]	Rutgers	200 mg IV every 3 weeks for 54 weeks
Atezolizumab	II	40§	Safety/timing	4 weeks after CRT (one group receives one dose of atezolizumab in this interval)	[ClinicalTrials.gov identifier: NCT 02525757]	MD Anderson	1200 mg IV every 3 weeks, twice concurrent with two additional cycles of chemotherapy, then atezolizumab alone up to 12 months
Nivolumab	II	78§	Safety	Concurrent from start of RT	NICOLAS [EudraCT 2014-005097-11]	ETOP	360 mg IV every 3 weeks for four cycles then 480 mg IV every 4 weeks, total 12 months

*Trial currently on hold with 13 patients included.
§Trial still recruiting patients.
CRT, concurrent chemoradiotherapy; ETOP, European Thoracic Oncology platform; G1, group/cohort 1; G2, group/cohort 2; G3, group/cohort 3; IV, intravenous; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

LUN 14-179: Study Design

- Multicenter, single-arm phase II trial

Patients with unresectable stage III NSCLC; ECOG PS 0/1; no autoimmune disease or need for immunosuppressive agents/chronic systemic corticosteroids; no history of pneumonitis, interstitial lung disease needing corticosteroids
(N = 93*)



*92 patients evaluable for efficacy. †Cis/etop, carbo/pac, or cis/pemetrexed + radiation at 59.4-66.6 Gy. Consolidation CT up to 2 cycles allowed. ‡Median number of cycles: 13.5 (range: 1-19).

- Primary endpoint: time to metastatic disease or death
- Secondary endpoints: PFS, OS, safety

Durm GA, et al. ASCO 2018. Abstract 8500.

LUN 14-179: Safety

Any-Grade AE in ≥ 10% of Patients,*† n (%)	Patients (N = 93)		
	Any Grade	Grade 2	Grade 3
Fatigue	43 (46.2)	15 (16.1)	4 (4.3)
Cough	24 (25.8)	16 (17.2)	1 (1.1)
Dyspnea	20 (21.5)	10 (10.8)	5 (5.4)
Anorexia	16 (17.2)	3 (3.2)	1 (1.1)
Arthralgia	14 (15.1)	7 (7.5)	1 (1.1)
Diarrhea	14 (15.1)	3 (3.2)	4 (4.3)
Nausea	13 (14.0)	3 (3.2)	1 (1.1)
Rash	12 (12.9)	3 (3.2)	1 (1.1)
Pruritus	10 (10.8)	3 (3.2)	0

*Excluding pneumonitis. †No grade 4 AEs reported.

- 40 (43.5%) patients completed 1 yr of treatment

Durm GA, et al. ASCO 2018. Abstract 8500.

LUN 14-179
Other Key Toxicities, Including Pneumonitis

AE,*† n (%)	Patients (N = 93)	
	Any Grade	Grade 2
Colitis	2 (2.2)	2 (2.2)
Increased creatinine	5 (5.4)	1 (1.1)
Elevated AST	2 (2.2)	0
Hyperthyroidism	7 (7.5)	2 (2.2)
Hypothyroidism	7 (7.5)	6 (6.5)

*Excluding pneumonitis. †No grade 3/4 AEs reported.

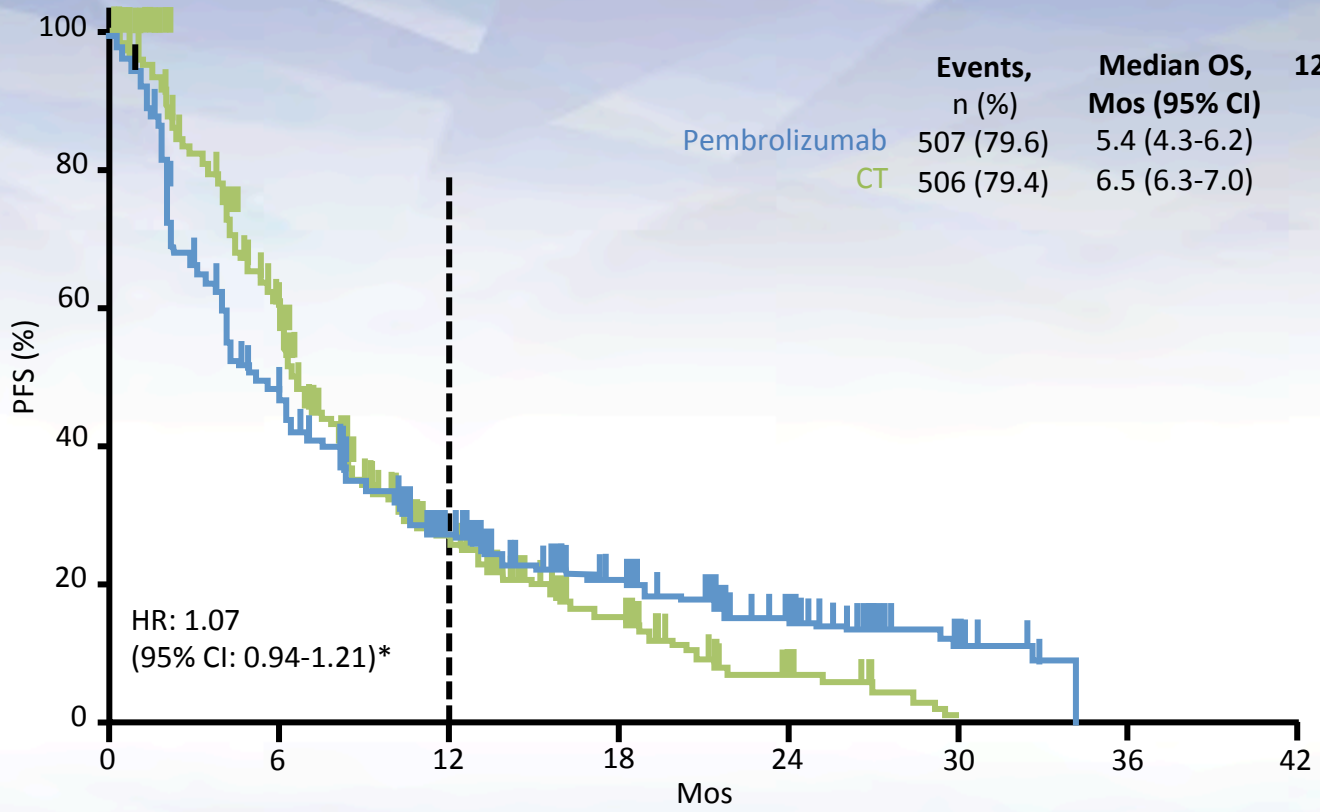
Grade ≥ 2 pneumonitis developed in 16 (17.2%) patients

- Grade 2, n = 10 (10.8%); grade 3, n = 4 (4.3%); grade 4, n = 1 (1.1%); grade 5 leading to death, n = 1 (1.1%)
- Median time to grade ≥ 2 pneumonitis: 8.4 wks (range: 1.1-48.3)
- 75% of grade ≥ 2 pneumonitis cases developed within first 12 wks of pembrolizumab treatment

Durm GA, et al. ASCO 2018. Abstract 8500.

KEYNOTE-042: First-line Pembrolizumab vs Platinum-Based Chemotherapy for Advanced or Metastatic NSCLC With PD-L1 TPS ≥ 1%

KEYNOTE-042: PFS in PD-L1 TPS ≥ 1% Population



	Events, n (%)	Median OS, Mos (95% CI)	12-Mo PFS, %
Pembrolizumab	507 (79.6)	5.4 (4.3-6.2)	28.0
CT	506 (79.4)	6.5 (6.3-7.0)	26.6

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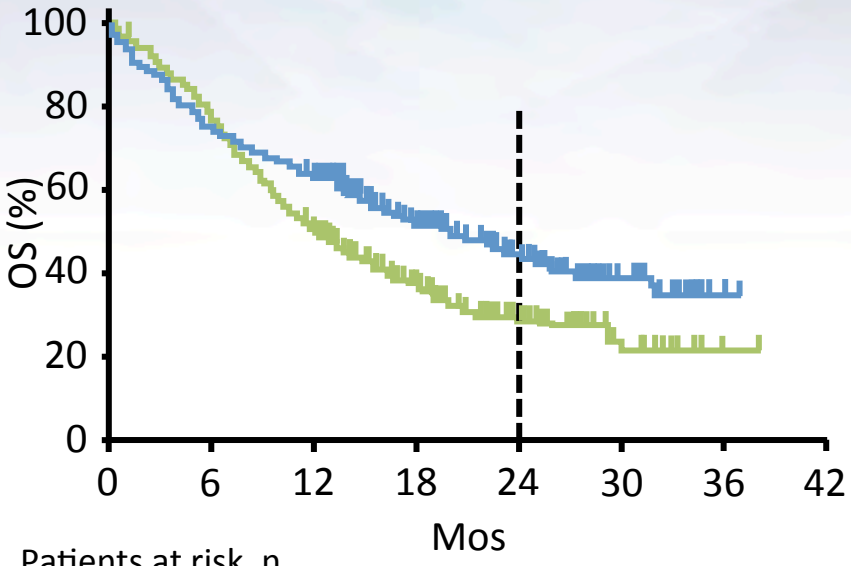
Lopes G, et al. ASCO 2018. Abstract LBA4.

KEYNOTE-042: OS in PD-L1 TPS ≥ 50% and ≥ 20% Populations (Primary Endpoint)

PD-L1 TPS ≥ 50%

	Events, n (%)	Median OS, Mos (95% CI)	24-Mo OS, %
Pembrolizumab	157 (52.5)	20.0 (15.4-24.9)	44.7
CT	199 (66.3)	12.2 (10.4-14.2)	30.1

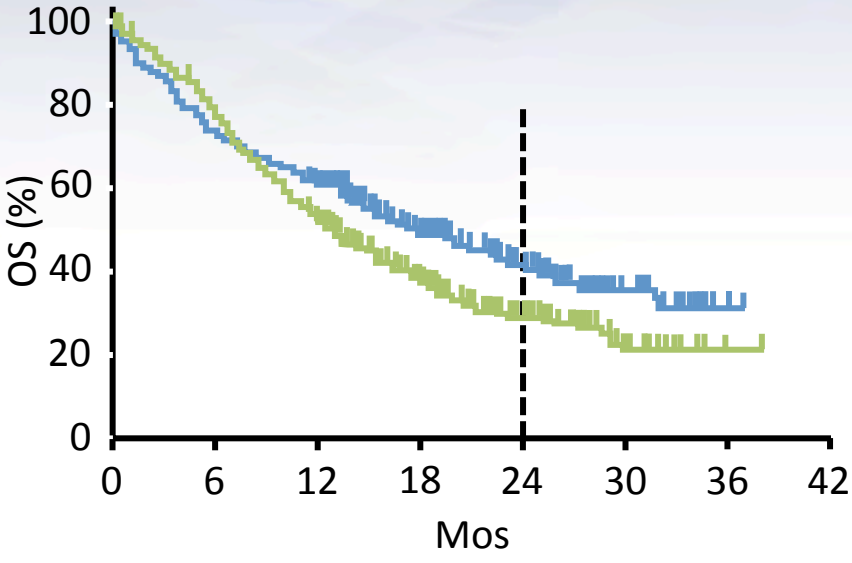


Patients at risk, n

299	224	189	107	59	22	2	0
300	231	149	75	40	11	1	0

PD-L1 TPS ≥ 20%

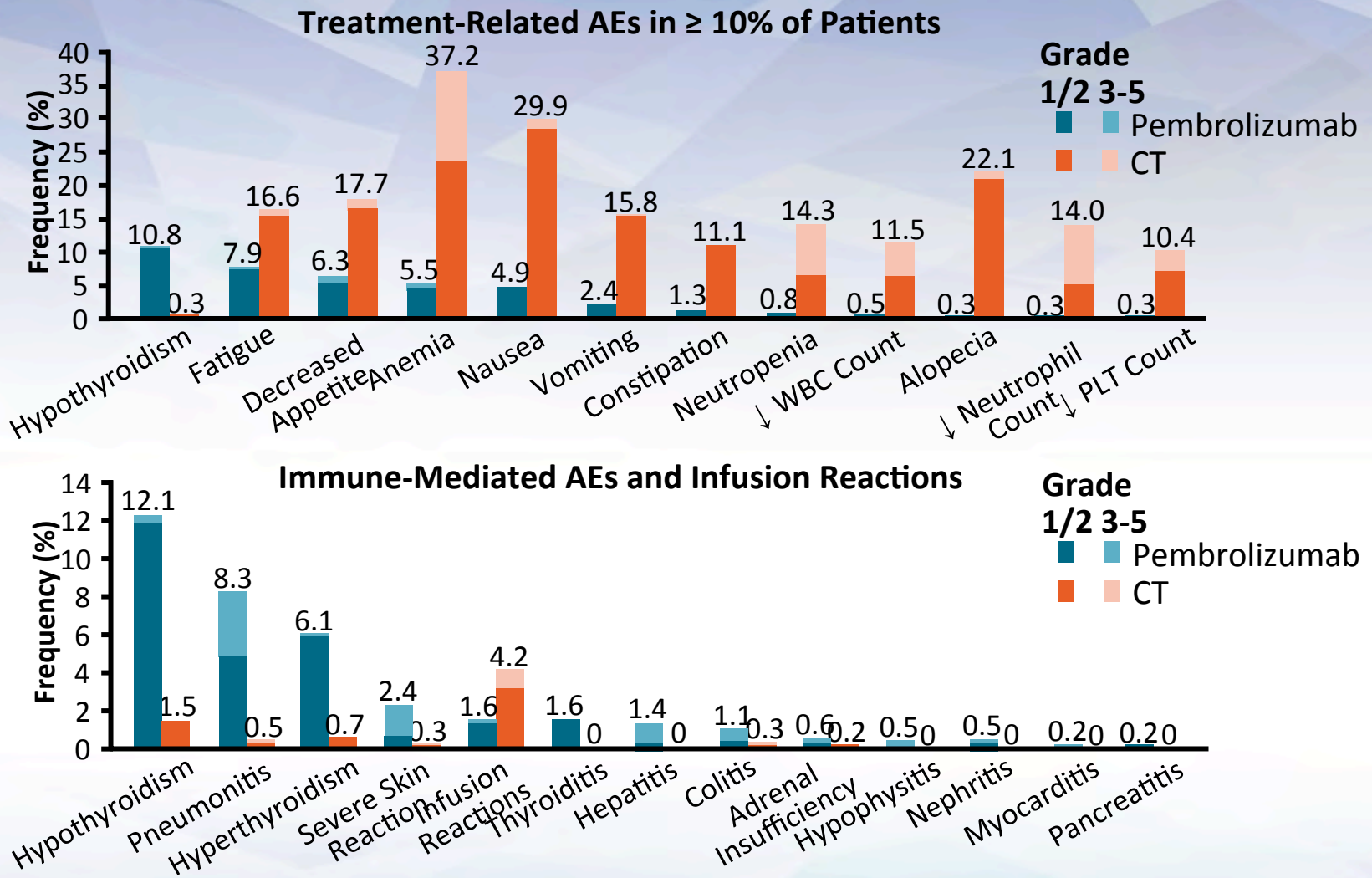
	Events, n (%)	Median OS, Mos (95% CI)	24-Mo OS, %
Pembrolizumab	230 (55.7)	17.7 (15.3-22.1)	40.5
CT	266 (65.7)	13.0 (11.6-15.3)	29.6



413	305	251	144	73	24	2	0
405	313	210	106	53	14	1	0

Lopes G, et al. ASCO 2018. Abstract LBA4. Reproduced with permission.

KEYNOTE-042: Adverse Events



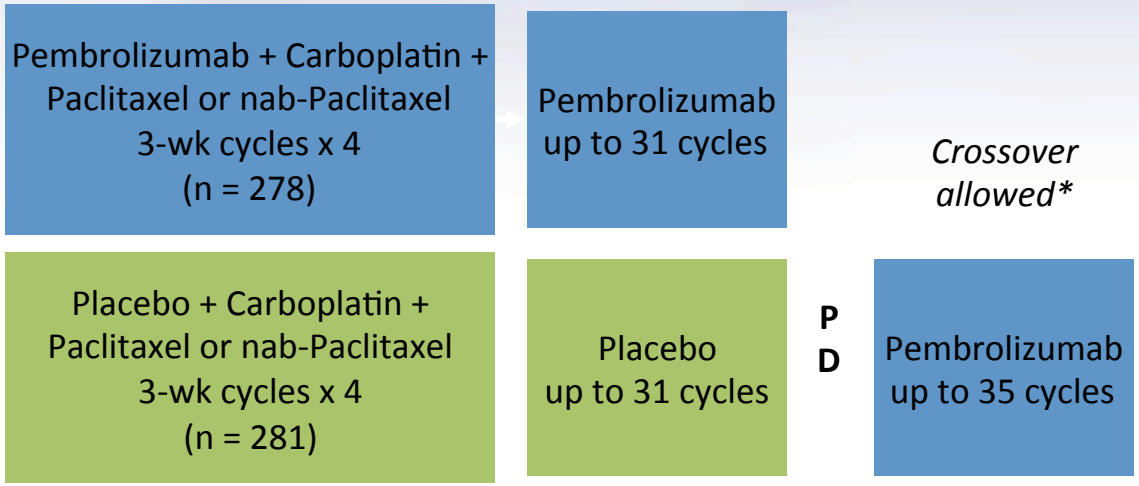
Lopes G, et al. ASCO 2018. Abstract LBA4.

KEYNOTE-407: Study Design

- Randomized, double-blind phase III trial

Stratified by PD-L1 TPS (< 1% vs ≥ 1%), taxane (paclitaxel vs nab-paclitaxel), region (east Asia vs other)

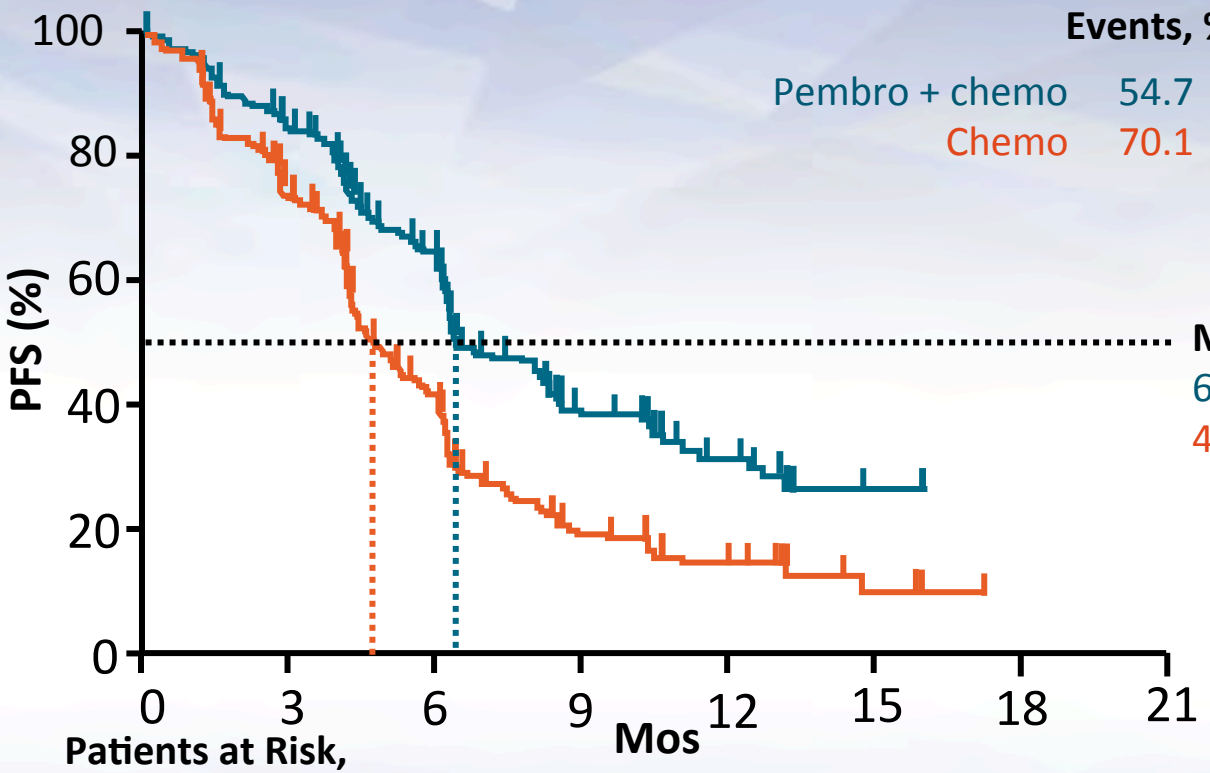
Patients with untreated stage IV squamous NSCLC, ECOG PS 0/1, available tumor biopsy for PD-L1 assessment, no brain mets, and no pneumonitis requiring systemic steroids (N = 559)



Primary endpoint: PFS by RECIST v1.1 (BICR), OS

Paz-Ares LG, et al. ASCO 2018. Abstract 105..

KEYNOTE-407: PFS by RECIST v1.1 (BICR) in ITT Population



	Events, %	HR (95% CI)	*P* Value
Pembro + chemo	54.7	0.56	< .0001
Chemo	70.1	(0.45-0.70)	

Median PFS, Mos (95% CI)

6.4 (6.2-8.3)

4.8 (4.3-5.7)

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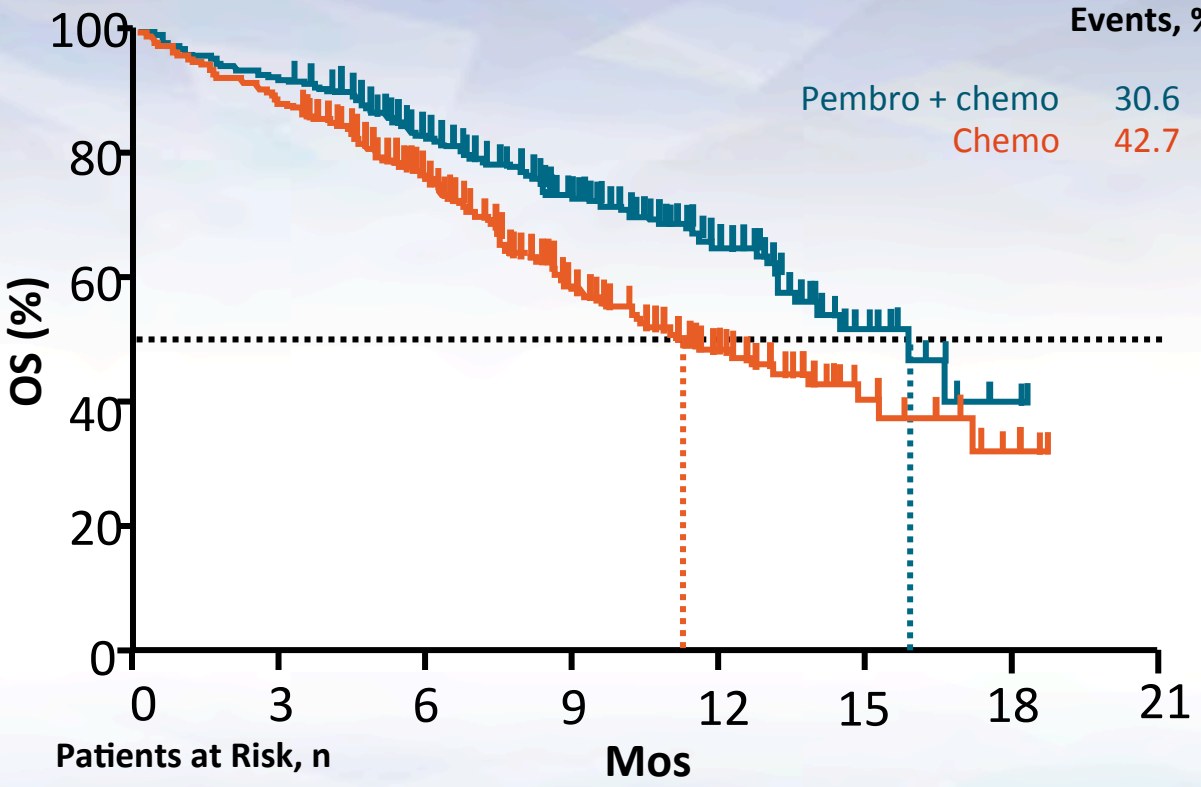
Paz-Ares LG, et al. ASCO 2018. Abstract 105..

KEYNOTE-407: OS in ITT Population



	Events, %	HR (95% CI)	*P* Value
Pembro + chemo	30.6	0.64	0.0008
Chemo	42.7	(0.49-0.85)	

Median OS, Mos (95% CI)
15.9 (13.2-NE)
11.3 (9.5-14.8)

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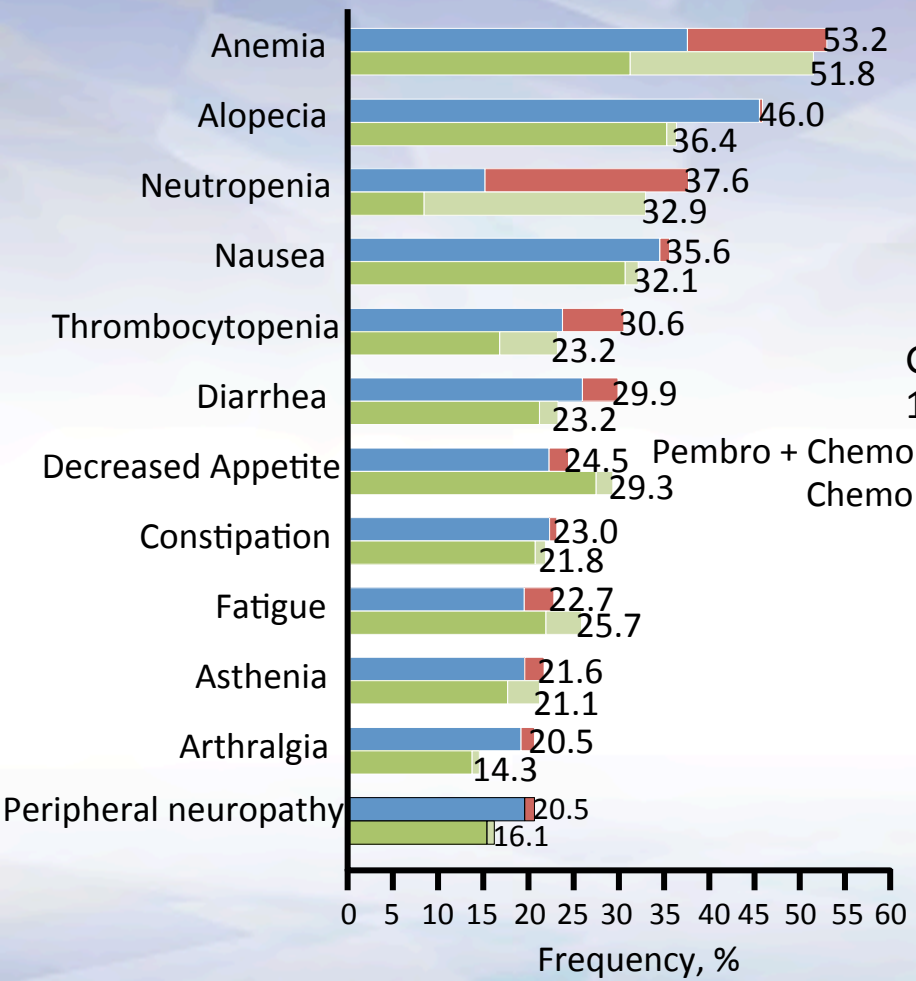
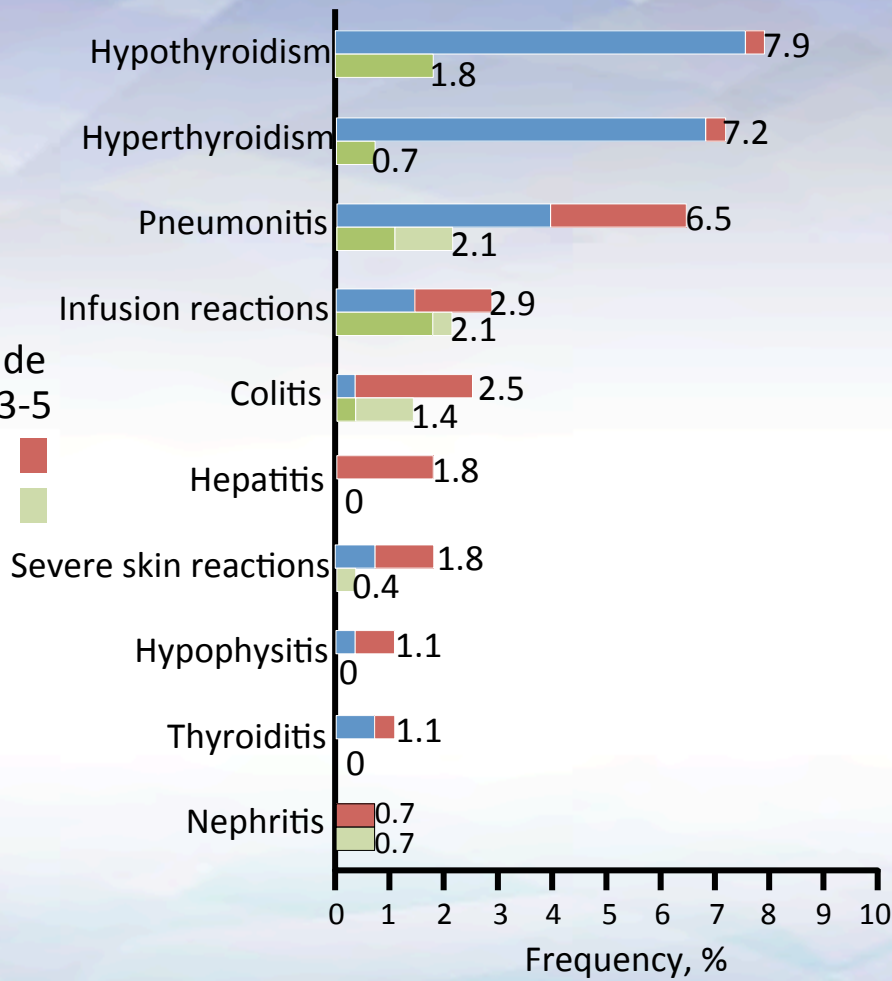
Paz-Ares LG, et al. ASCO 2018. Abstract 105..

KEYNOTE-407: AEs

All-Cause AEs Occurring in ≥ 20% of Patients



Immune-Mediated AEs and Infusion Reactions



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Paz-Ares LG, et al. ASCO 2018. Abstract 105.

IMmotion151
Patient-Reported Outcomes With First-line Atezolizumab + Bevacizumab vs Sunitinib in Treatment-Naive Metastatic RCC

IMmotion 151: Study Design

Stratified by MSKCC risk score, liver mets, PD-L1 status (< 1% vs ≥ 1%)

Treatment-naive patients with advanced or metastatic RCC; clear cell and/or sarcomatoid histology, KPS ≥ 70 and tissue available for PD-L1 staining (N = 915)

Atezolizumab 1200 mg IV Q3W + Bevacizumab 15 mg/kg IV Q3W (n = 454)

Sunitinib 50 mg/day PO 4 wks on, 2 wks off (n = 461)

Primary endpoints: PFS by PD-L1 status, OS in ITT

Motzer R, et al. ASCO GU 2018. Abstract 578. Escudier B, et al. ASCO 2018. Abstract 4511.

IMmotion 151: Atezolizumab + Bevacizumab vs Sunitinib in Untreated mRCC: Background

- IMmotion 151: atezolizumab + bevacizumab vs sunitinib in treatment-naive patients with mRCC[1]
  - Met coprimary endpoint of improved PFS in PD-L1–positive patients: median 11.2 mos with atezolizumab + bevacizumab vs 7.7 mos with sunitinib (*P* = .02)
  - Median OS not yet reached in either treatment group in ITT population
  - Most treatment-related AEs less frequent with atezolizumab + bevacizumab than sunitinib except proteinuria
- Current analysis evaluated patient-reported outcomes as secondary and exploratory endpoints in ITT population[2]

1.Motzer R, et al. ASCO GU 2018. Abstract 578.
2. Escudier B, et al. ASCO 2018. Abstract 4511.

IMmotion 151
Patient-Reported Outcomes

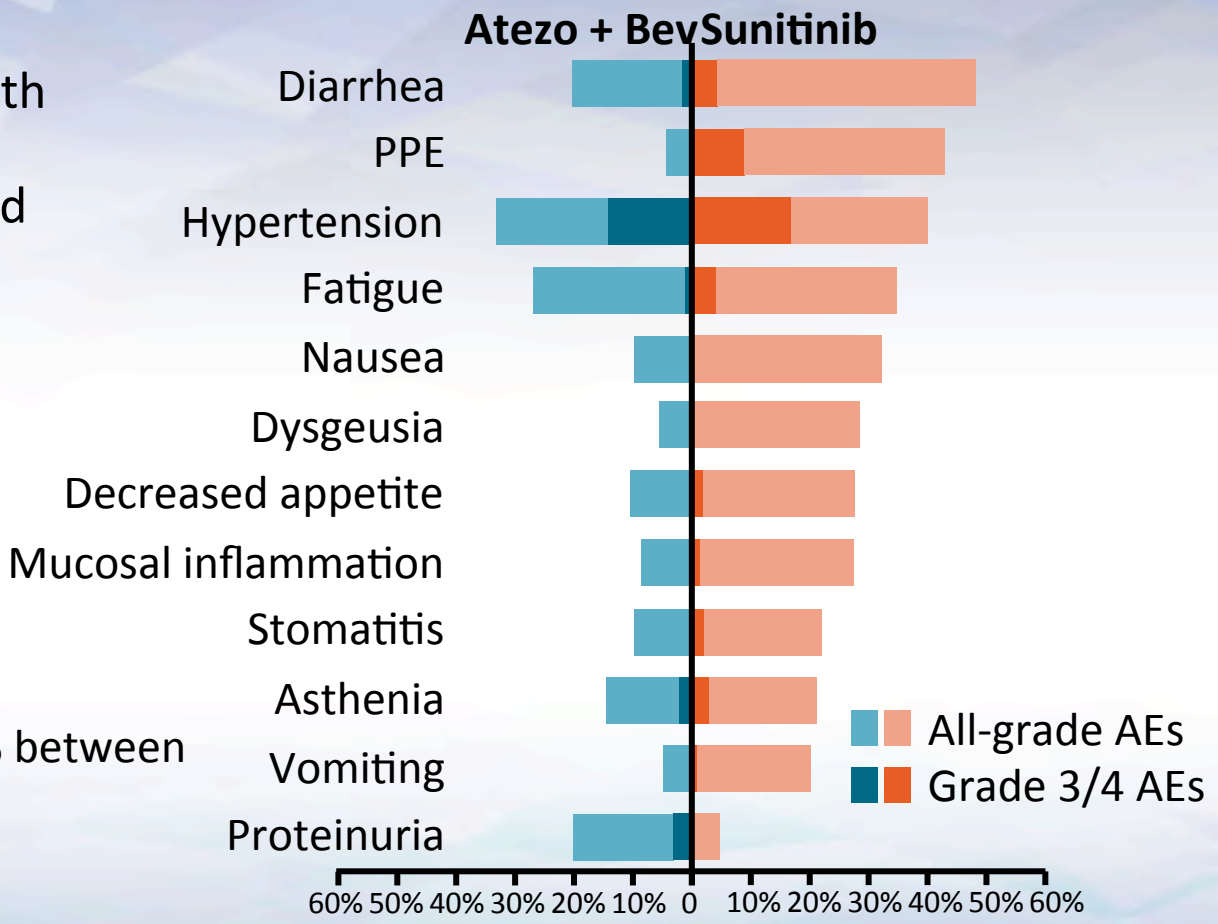
- Patient-reported outcomes assessed via questionnaires on Days 1 and 22 of each 6-wk cycle, at end of treatment, and during follow-up
  - MDASI: symptom severity and interference with daily life
  - FKSI-19: overall AE burden and health-related quality of life
- Questionnaire completion rates > 80% at baseline; both arms maintained ≥ 70% completion through Wk 54

Escudier B, et al. ASCO 2018. Abstract 4511.

IMmotion 151: Treatment-Related AEs*

- Lower severity of 17 assessed symptoms with atezolizumab + bevacizumab compared with sunitinib during treatment
  - Most severe: rash, fatigue, mouth/ throat sores, dry mouth, lack of appetite

*≥ 20% in either arm and > 5% between arms.



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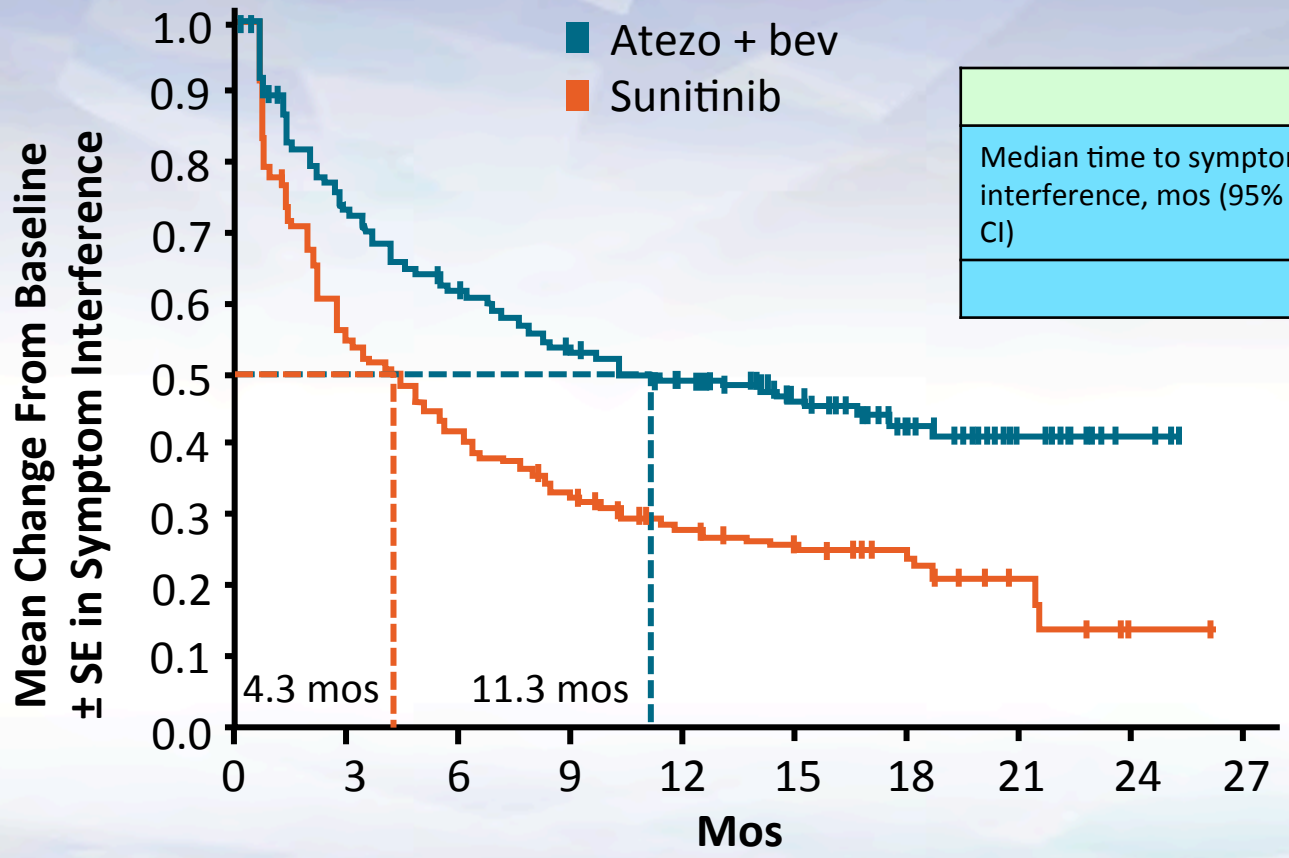
Motzer R, et al. ASCO GU 2018. Abstract 578.
Escudier B, et al. ASCO 2018. Abstract 4511.

IMmotion 151: Time to Deterioration of Patient Daily Functioning by Symptom Interference (MDASI)



	Atezo + Bev	Sunitinib
Median time to symptom interference, mos (95% CI)	11.3 (8.3-17.5)	4.3 (3.1-5.6)
	HR: 0.56 (95% CI: 0.46-0.68)	

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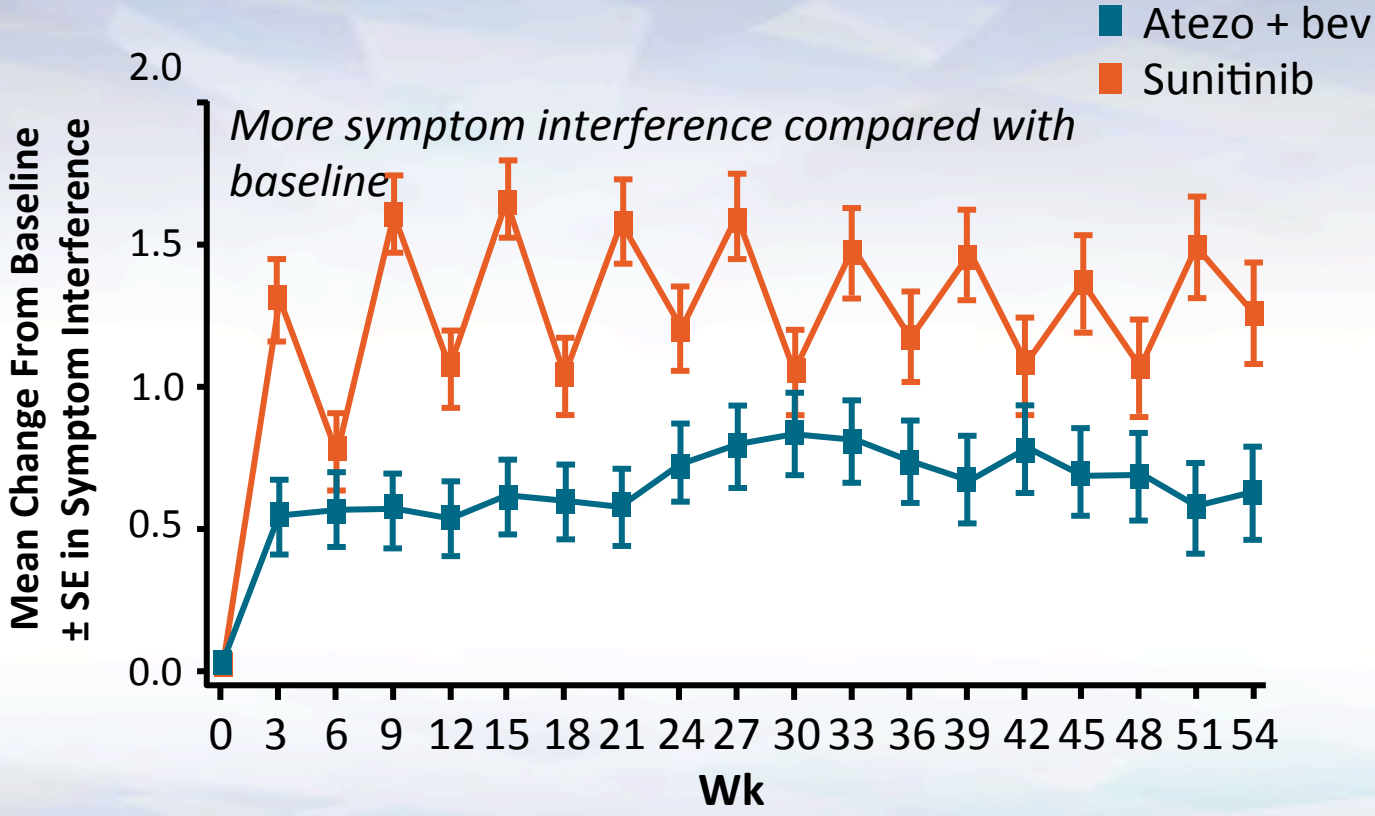
Escudier B, et al. ASCO 2018. Abstract 4511.

IMmotion 151
Patient-Reported Symptom Interference With Daily Living Over Time (MDASI)



- Baseline scores similar between arms indicating no or mild symptom interference
- Patients receiving atezolizumab + bevacizumab had less interference of symptoms with daily life vs sunitinib

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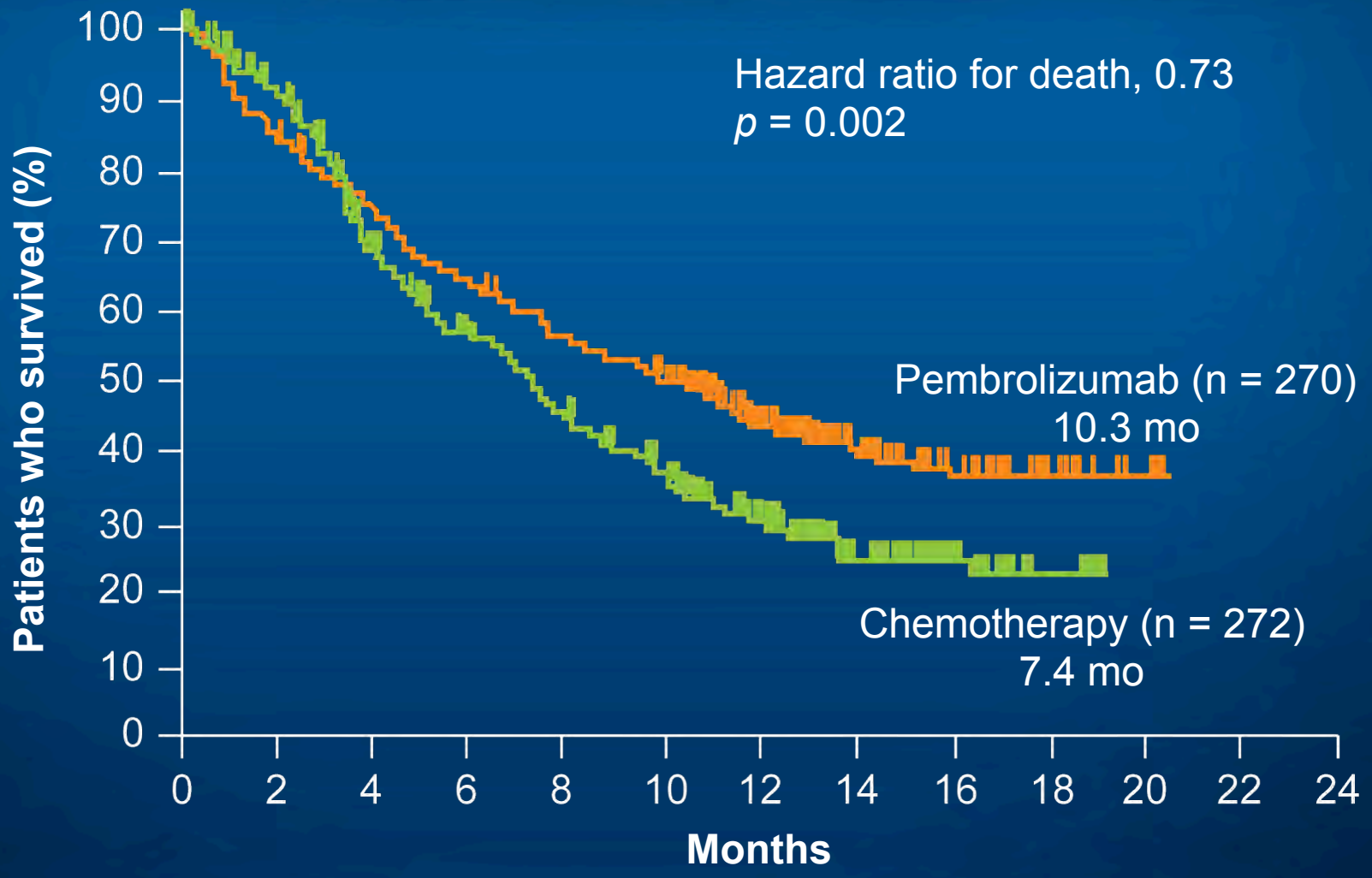
Escudier B, et al. ASCO 2018. Abstract 4511.

IMmotion 151

- All assessed patient-reported outcomes favored atezolizumab + bevacizumab over sunitinib
  - Milder symptoms
  - Lower degree of functional impairment
  - Less bothersome treatment AEs
  - Less negative impact on health-related quality of life
- Investigators suggest better patient-reported outcomes combined with promising efficacy results support atezolizumab + bevacizumab over sunitinib as first-line treatment for metastatic RCC

Escudier B, et al. ASCO 2018. Abstract 4511.

KEYNOTE-045: Phase III Study of Pembrolizumab versus Investigator's Choice of Chemotherapy for Previously Treated Urothelial Carcinoma

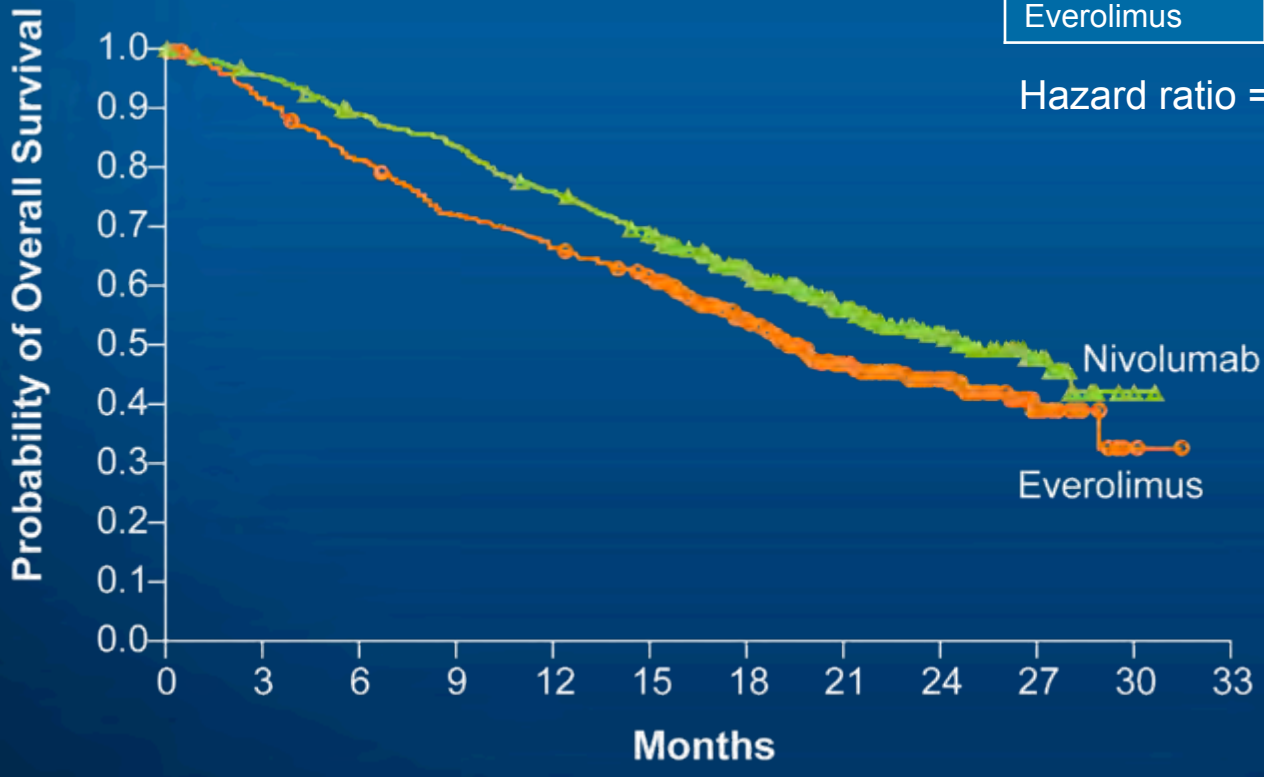


Bellmunt J et al. *N Engl J Med* 2017;376(11):1015-26.

CheckMate 025: Phase III Trial of Nivolumab versus Everolimus in Advanced Renal Cell Carcinoma (RCC)

	No. of patients	Median overall survival	No. of deaths
Nivolumab	410	25.0 mo	183
Everolimus	411	19.6 mo	215

Hazard ratio = 0.73; $p = 0.002$



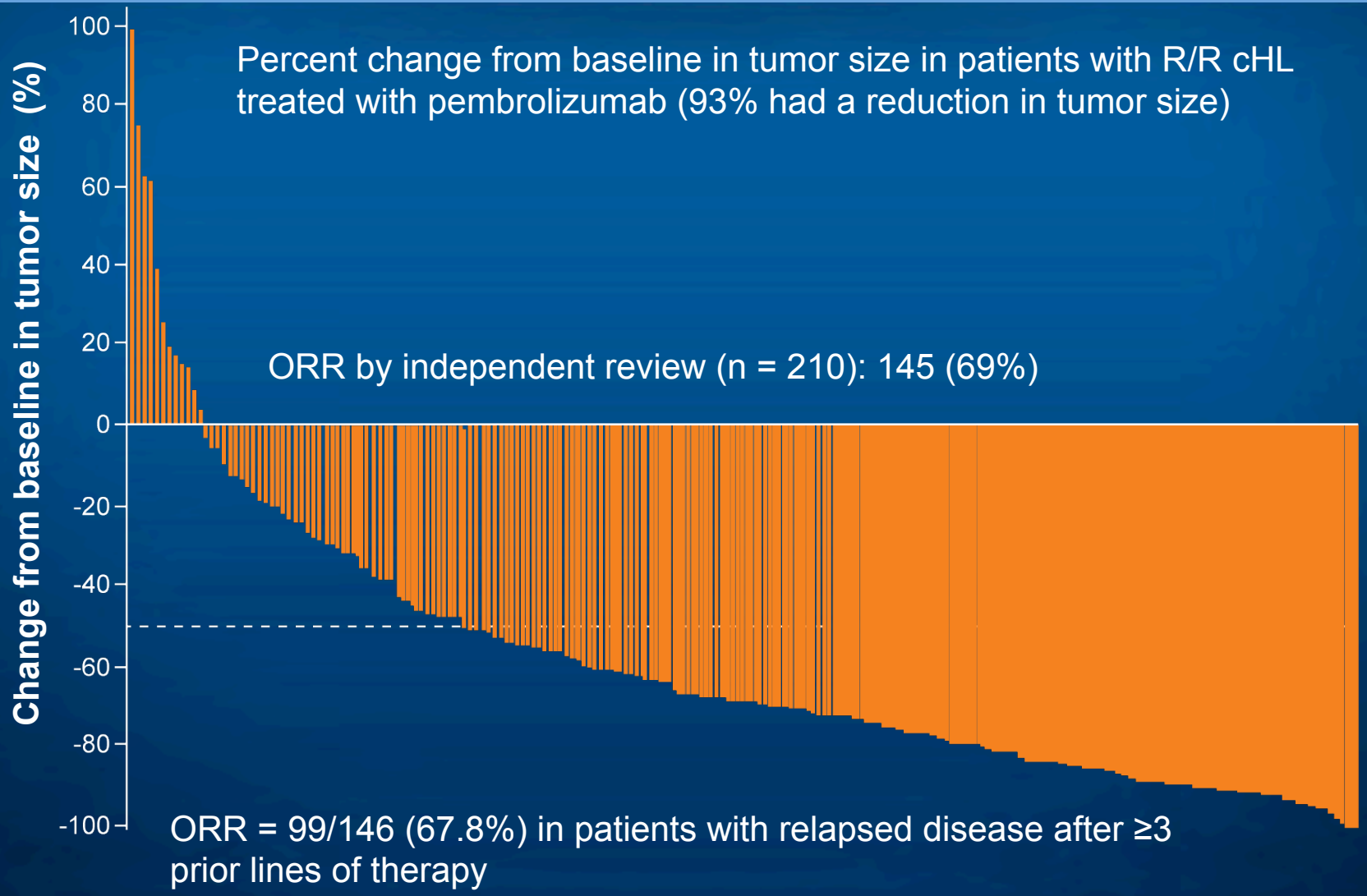
All Grade 3/4 TRAEs
- Nivolumab: 19%
- Everolimus: 37%

Most common Grade 3/4 TRAEs
- Nivolumab: Fatigue (2%)
- Everolimus: Anemia (8%)

TRAE = treatment-related adverse event

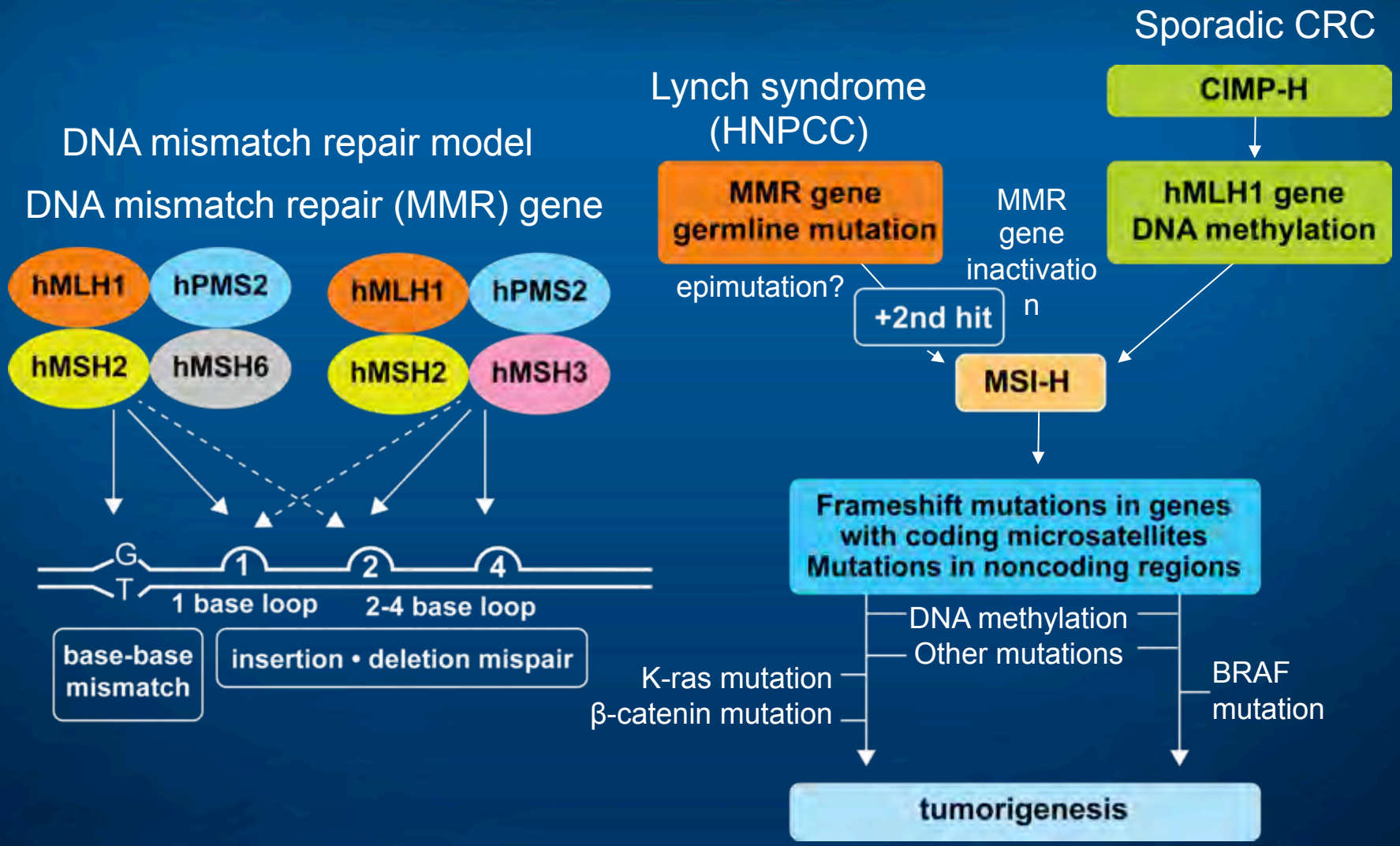
Motzer RJ et al. *N Engl J Med* 2015;373(19):1803-13.

KEYNOTE-087: Phase II Study of Pembrolizumab in Relapsed/Refractory (R/R) Classical HL (cHL)



Moskowitz CH et al. *Proc ASH* 2016;Abstract 1107.

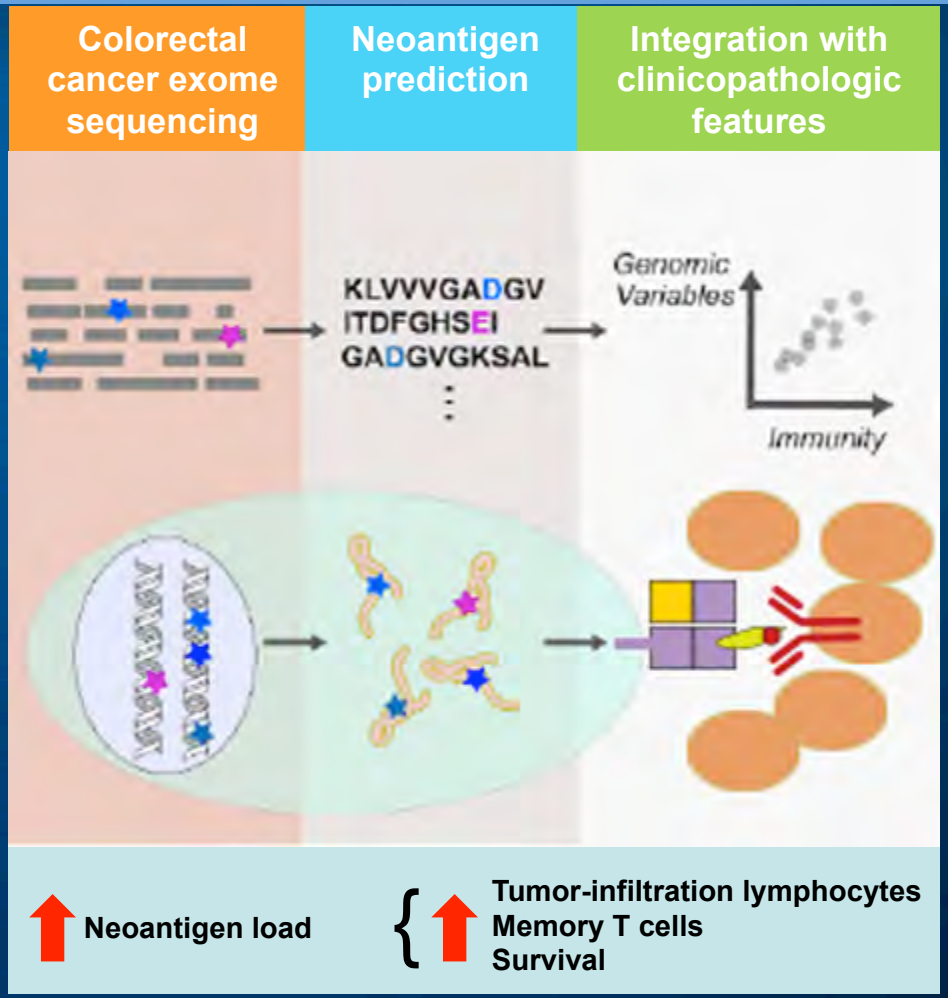
Microsatellite Instability



Imai K, Yamamoto H. *Carcinogenesis* 2008;29(4):673-80.

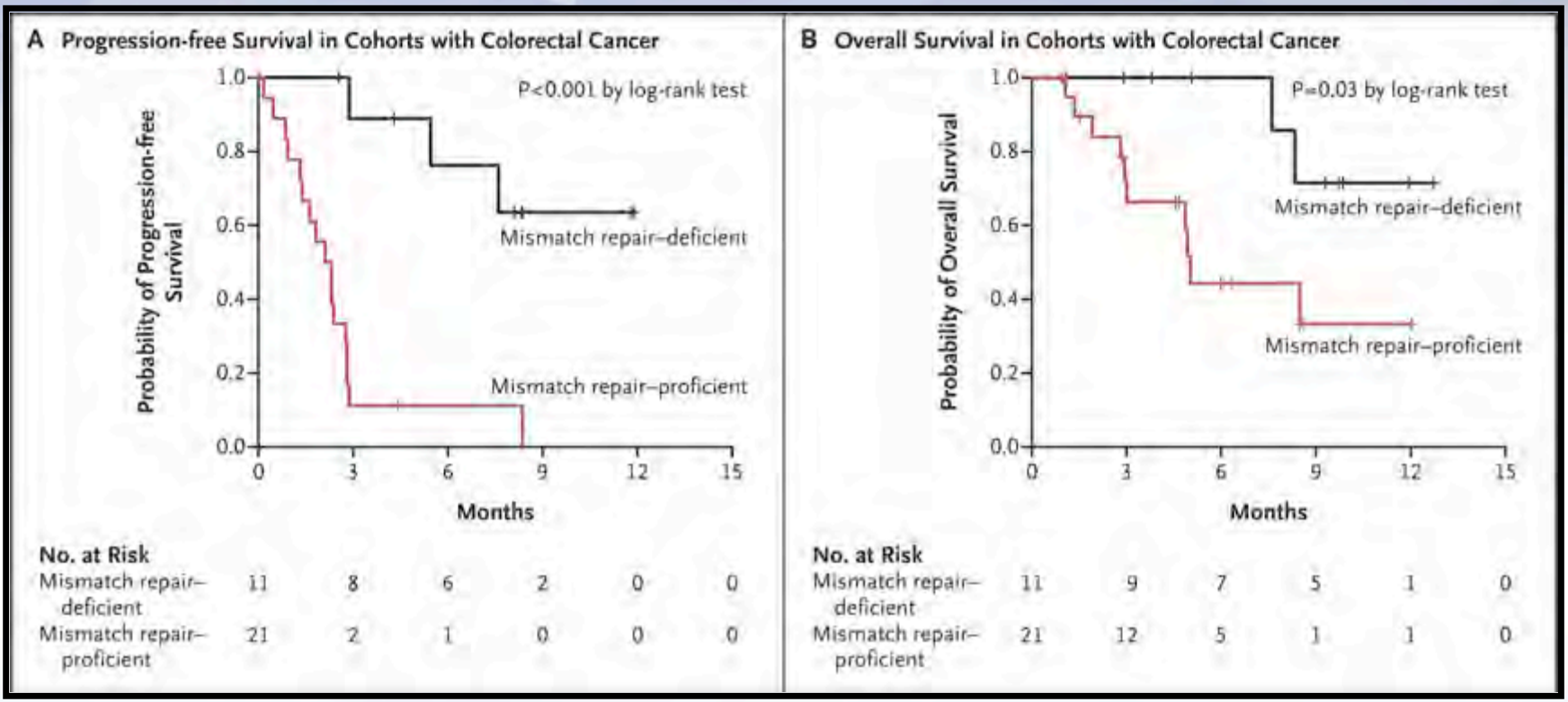
Hypermutation and Immuno-oncology

- In colorectal cancer (CRC), MSI-H is associated with increases in immune infiltration and expression of immune checkpoint regulators[1,2]
- MSI-H is also associated with increased number of mutations per tumor
- Tumor mutations produce tumor-specific neoantigens, which, when expressed on the tumor cell surface, are a target for T cells
  - May improve response to immunotherapy
- Elevated neoantigen load in CRC is associated with improved survival[2]



[1] Llosa NJ et al. *Cancer Discov* 2015;5:43-51;
[2] Giannakis M et al. *Cell Reports* 2016;15:857-65.

Pembrolizumab in mismatch repair Colon Cancer



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Personalised Cancer Care

Melanoma
Durable Remission
Case Presentation

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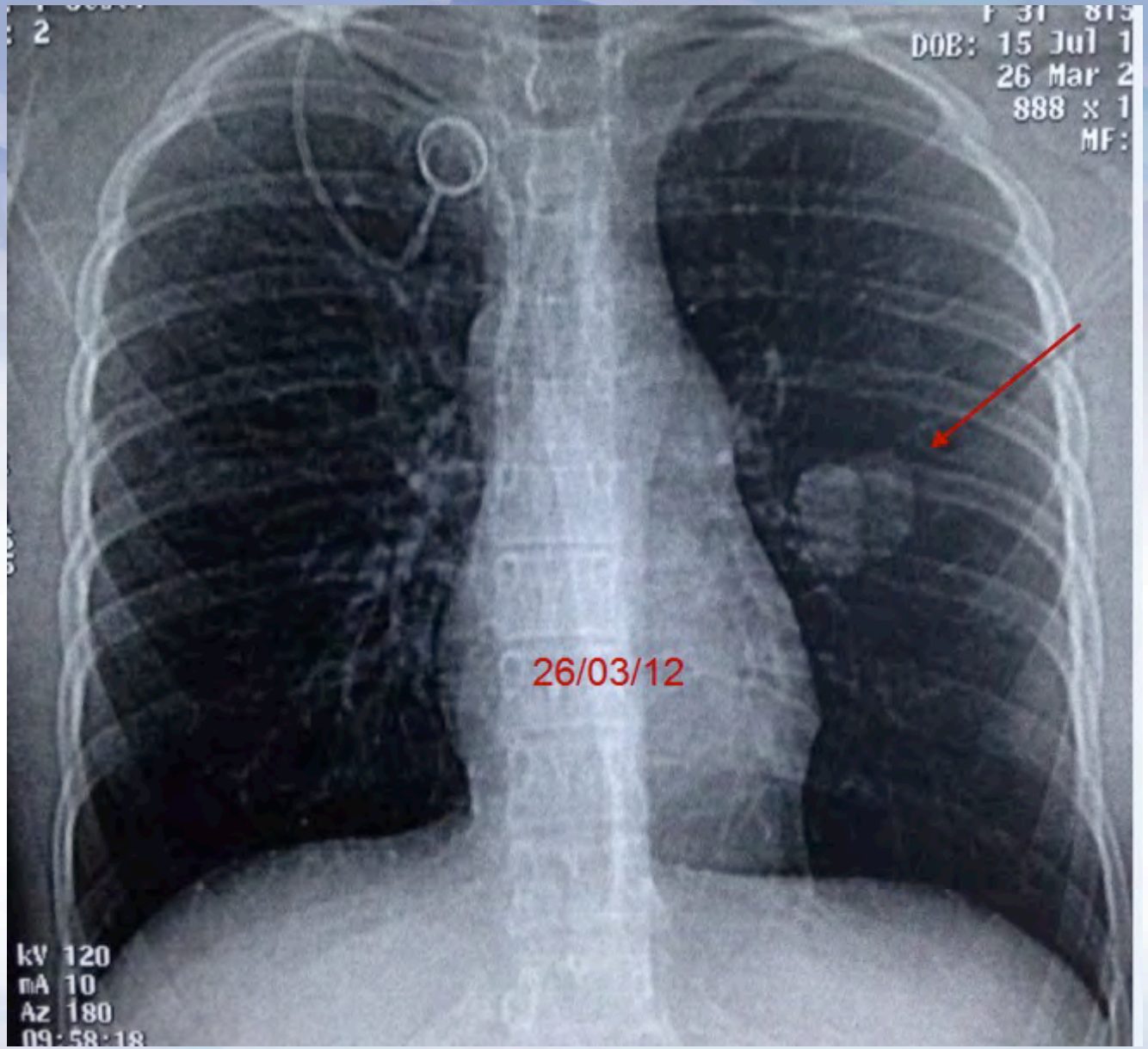
Melanoma

Pre-Ipilimumab



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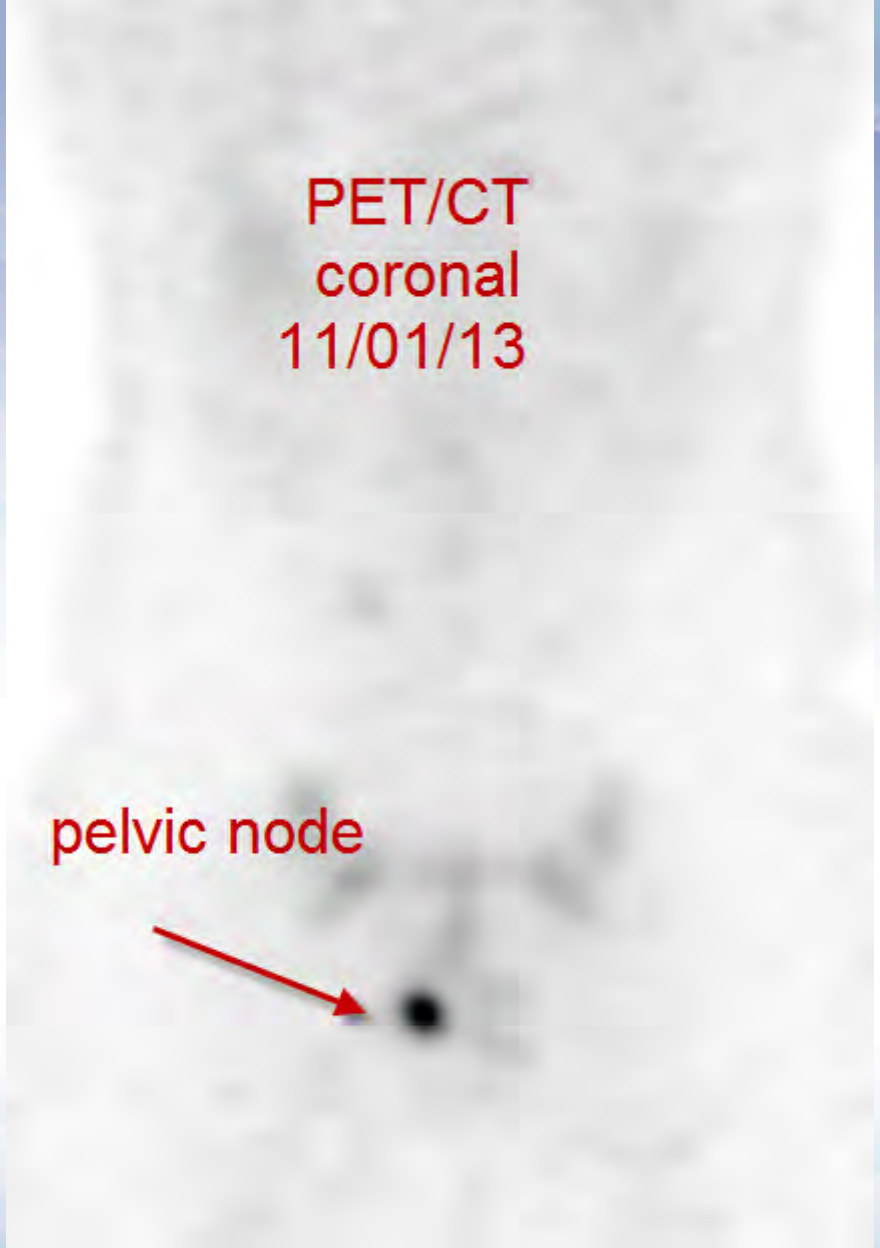
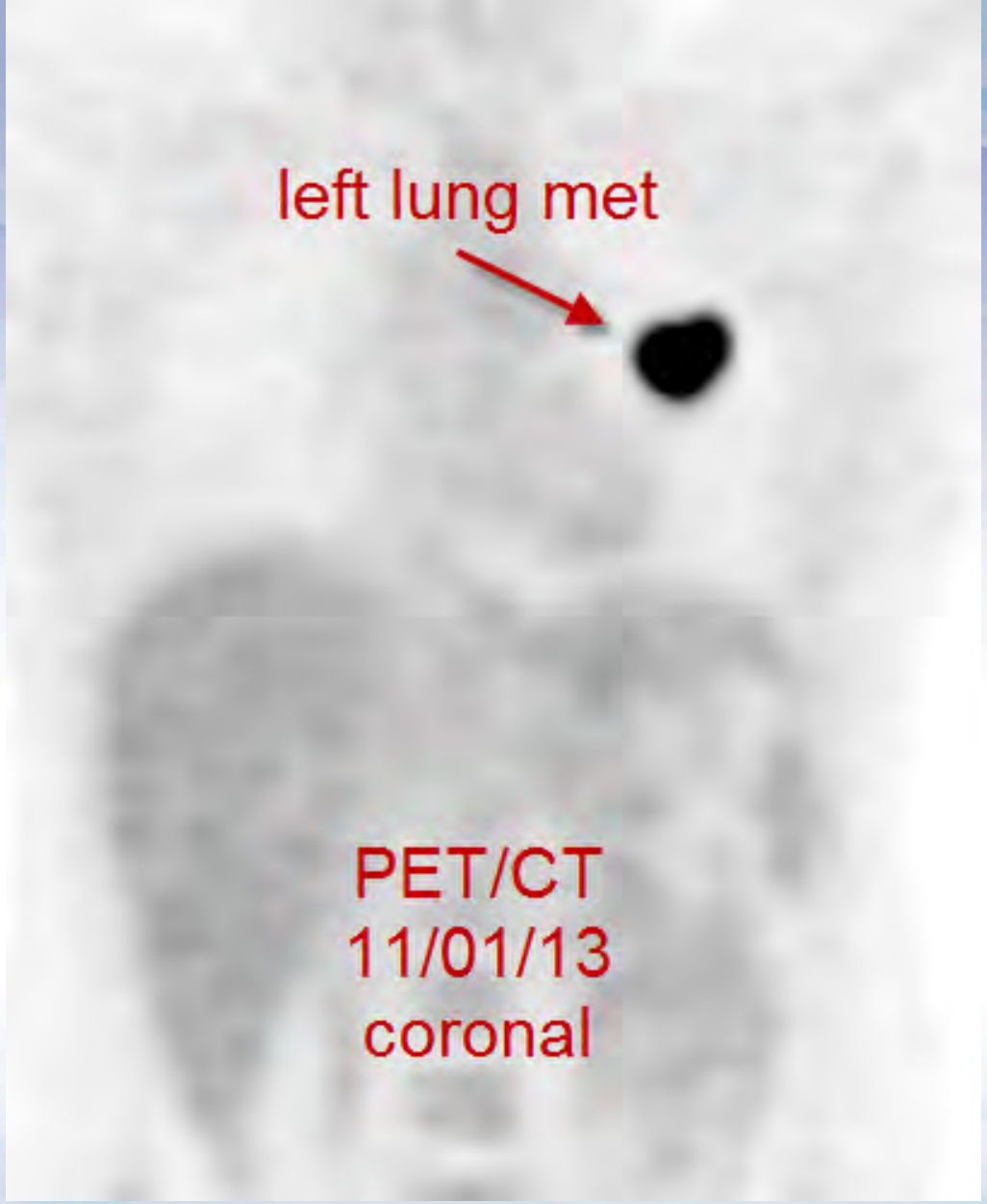
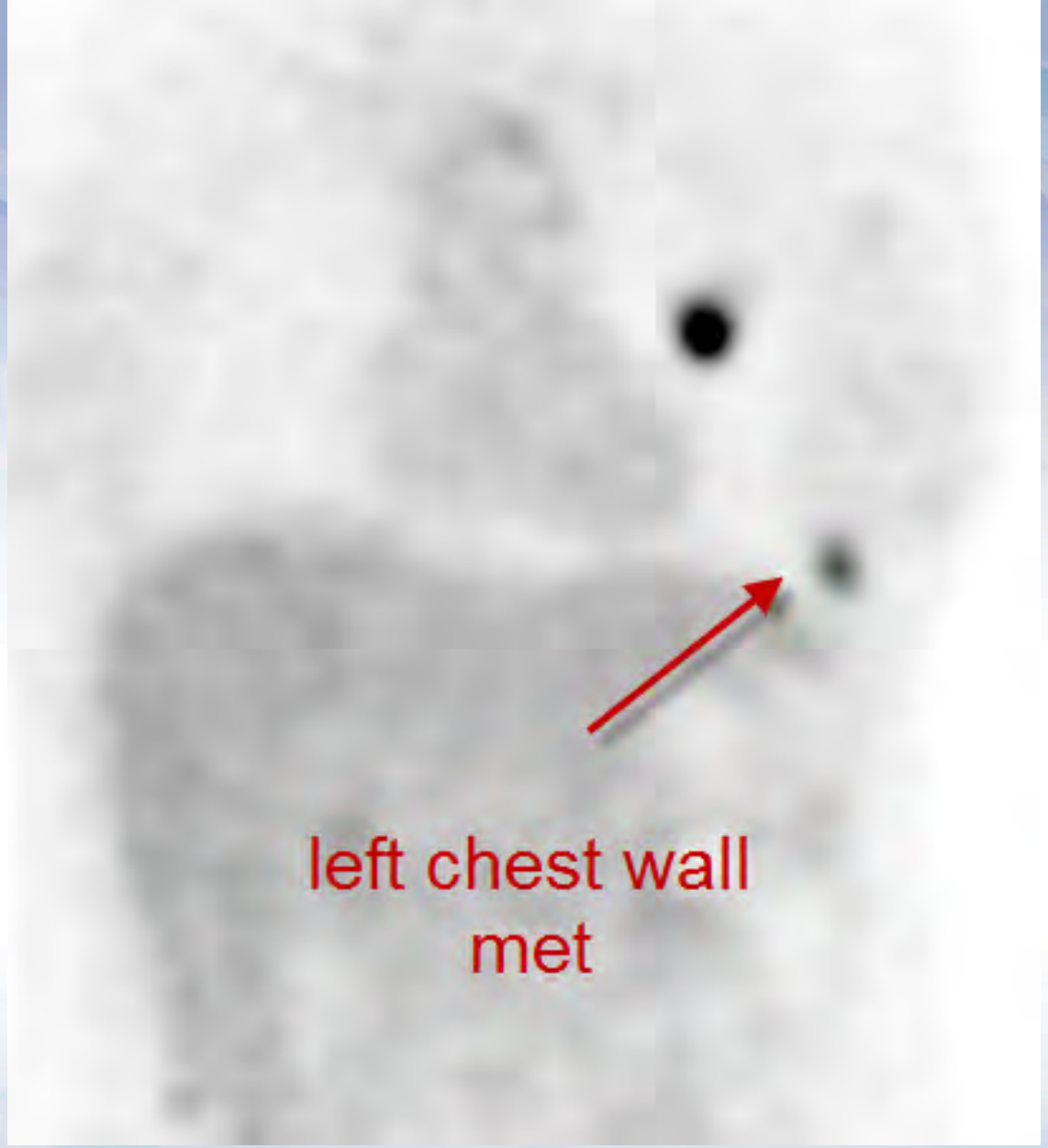
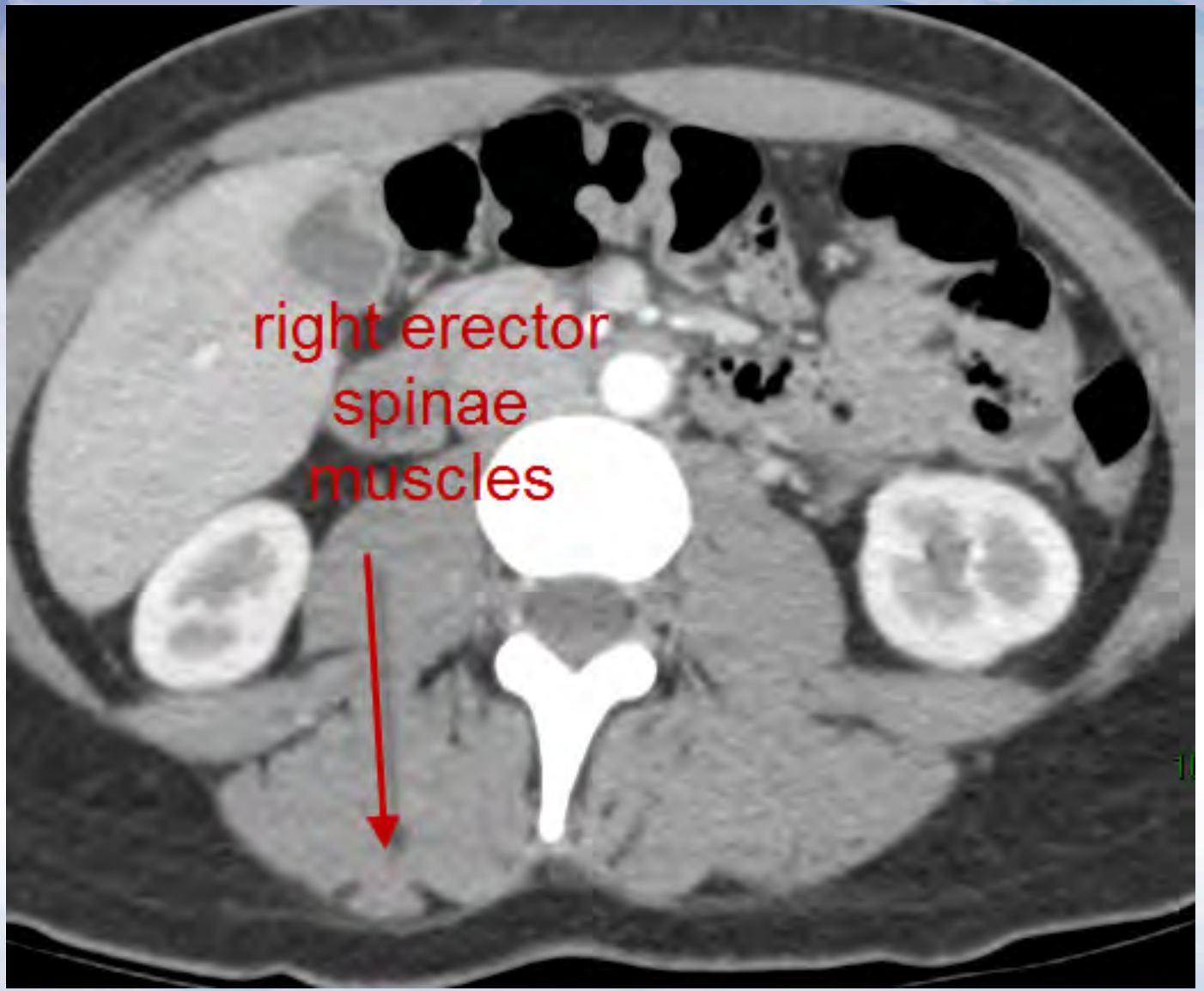

PET/CT
coronal
11/01/13
pelvic node

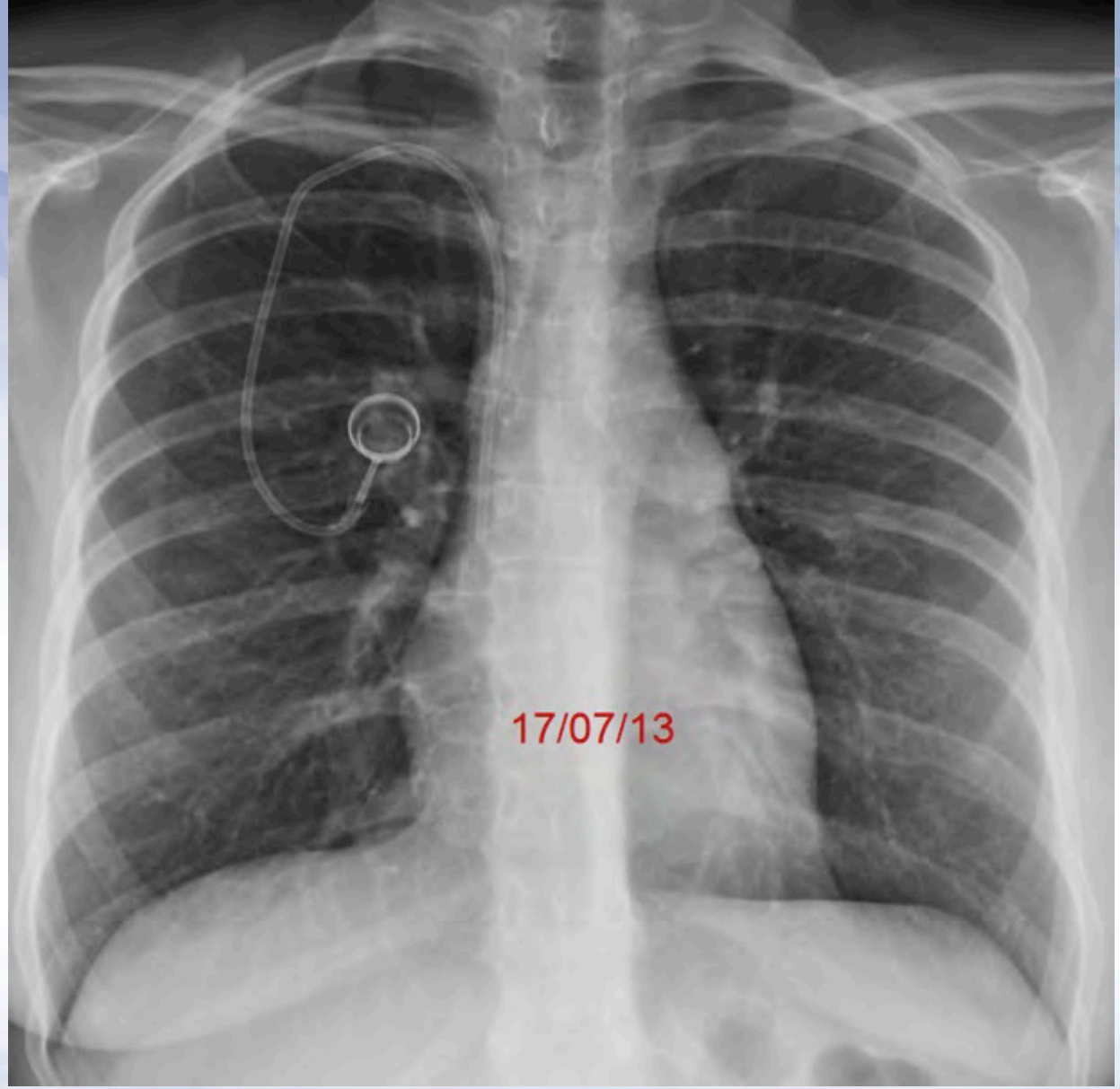

left lung met
PET/CT
11/01/13
coronal


left chest wall
met


right erector
spinae
muscles

Melanoma

Post-Ipilimumab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Melanoma
Durable Remission
Case Presentation 2

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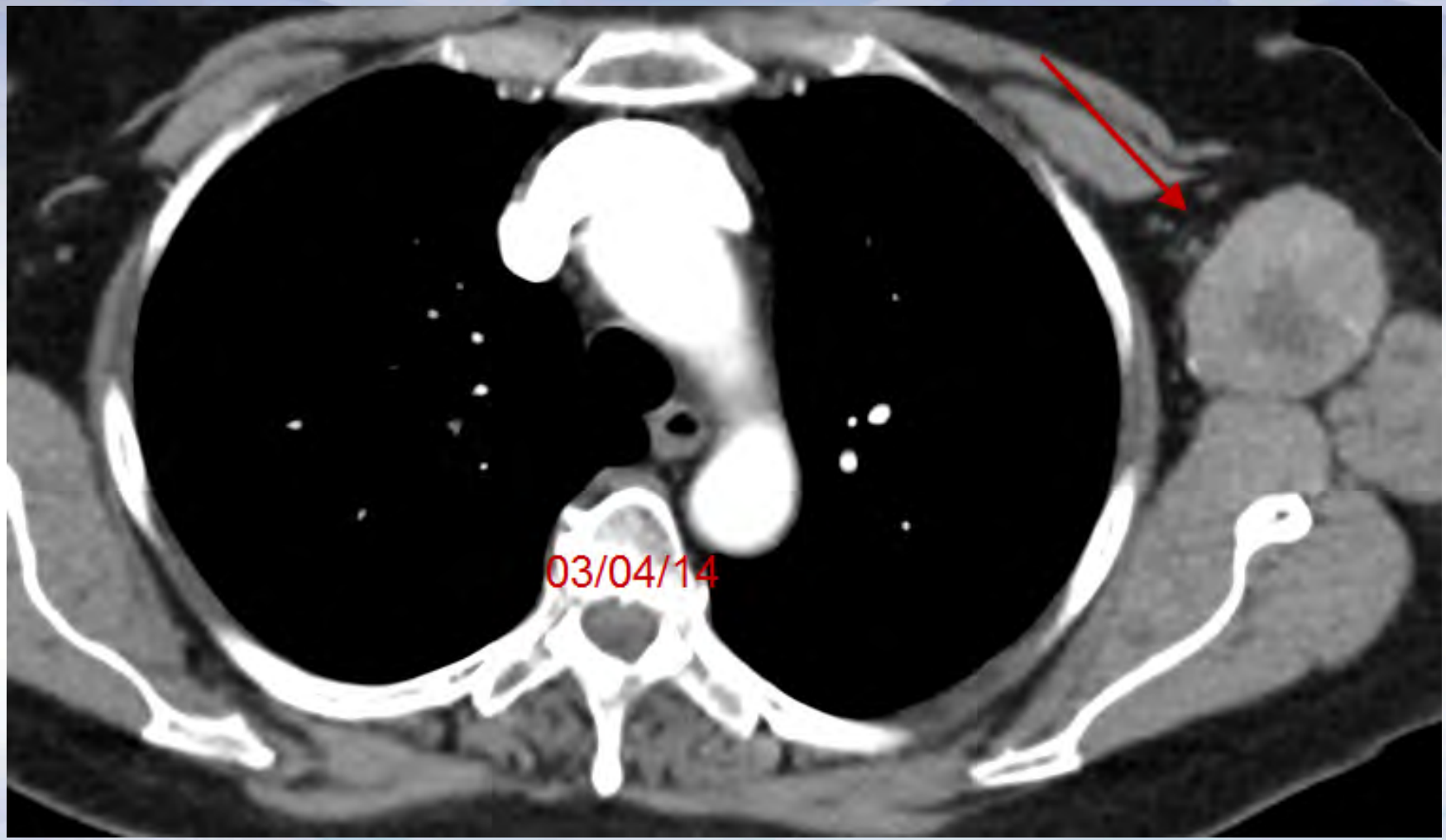
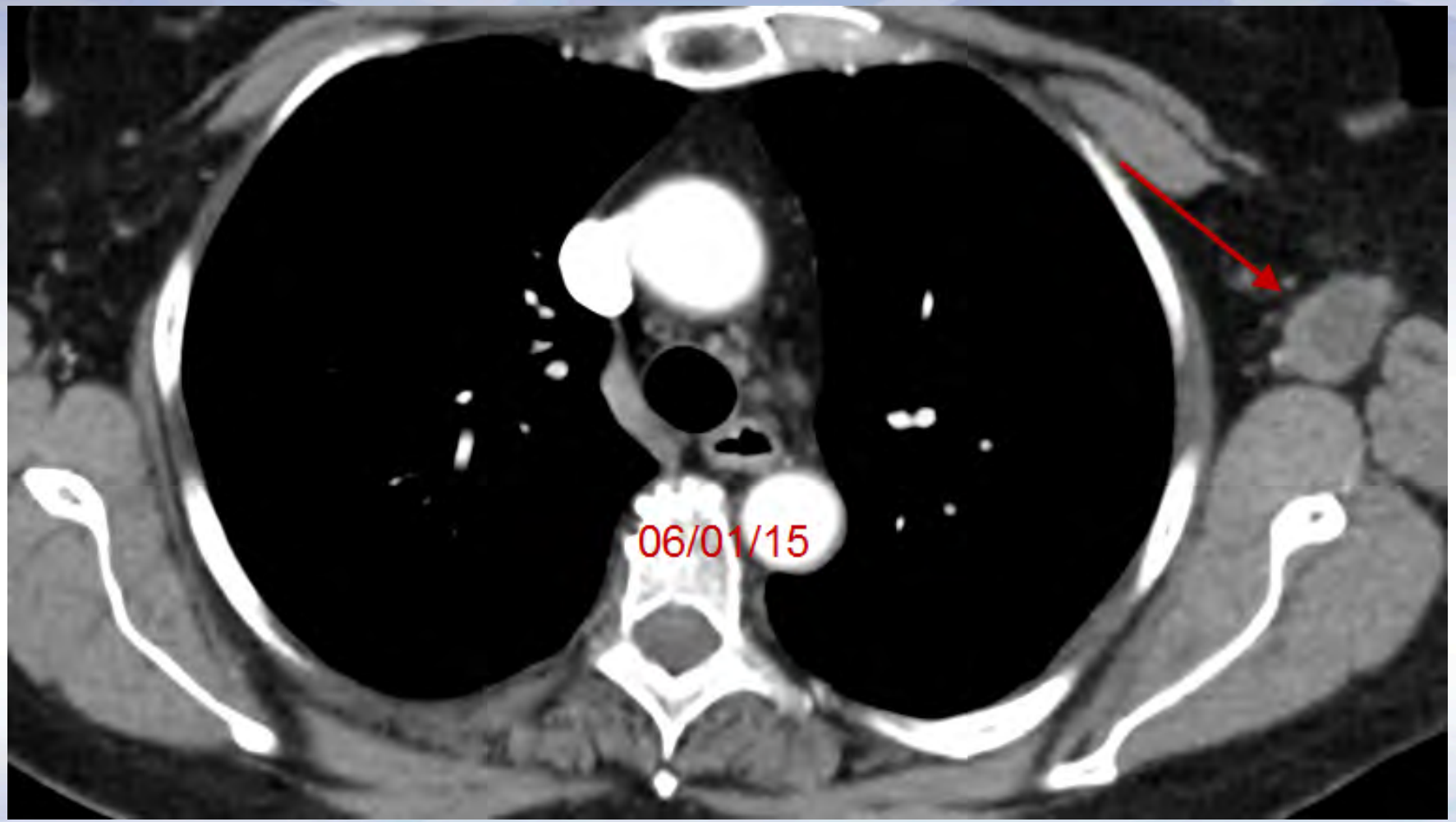
Melanoma
Pre-Ipilimumab



Melanoma
Pre-Ipilimumab



Melanoma
Durable Response
Case Presentation 3

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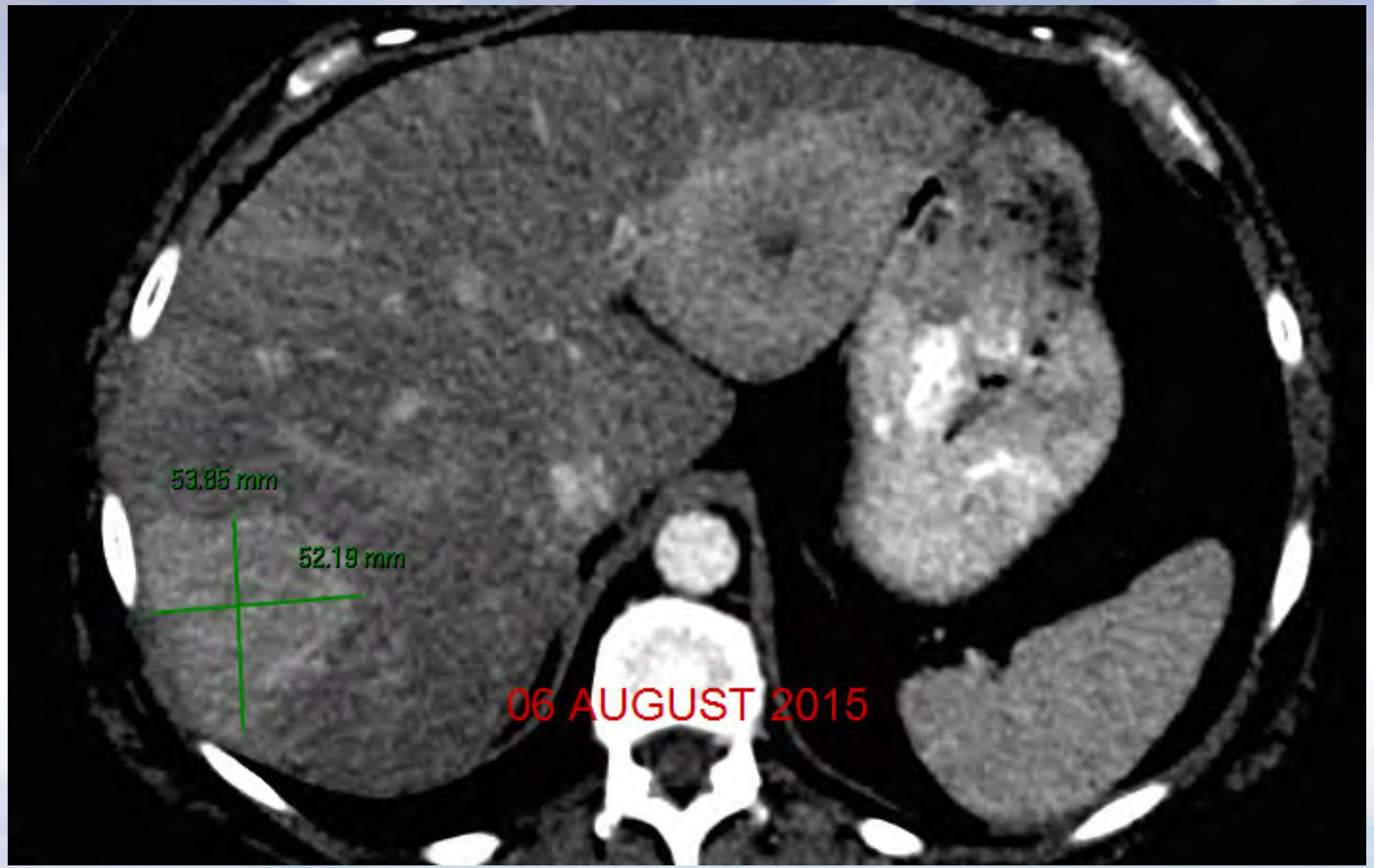
Personalised Cancer Care

Melanoma
Pre-Nivolumab



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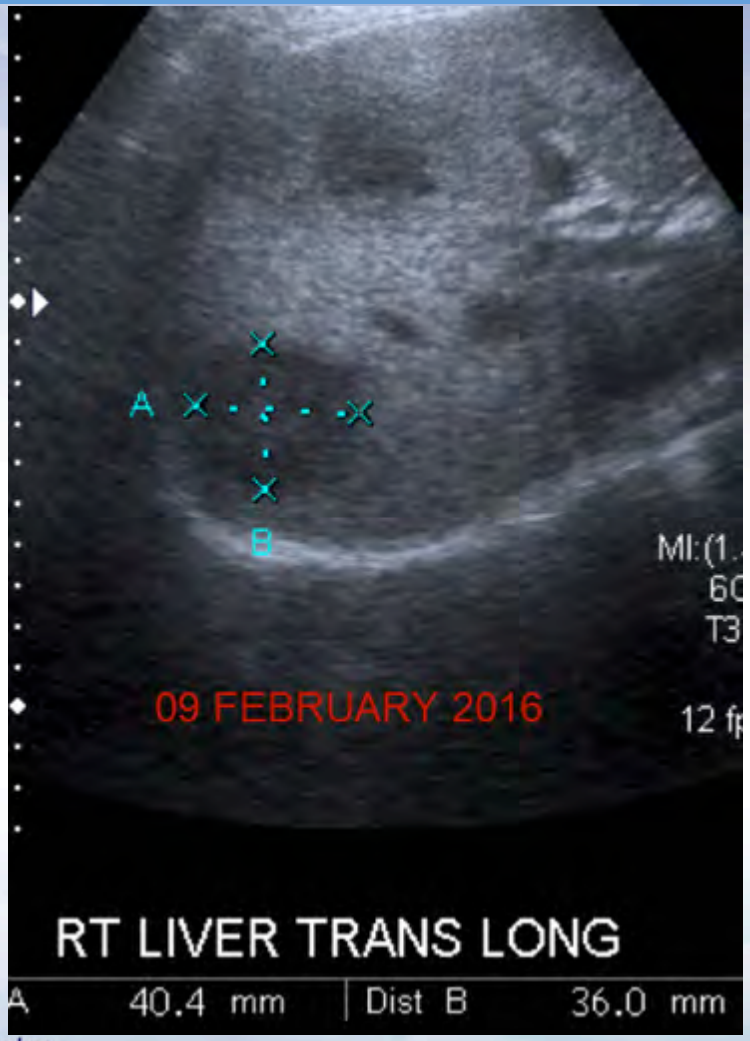
Personalised Cancer Care

Melanoma
Post-Nivolumab



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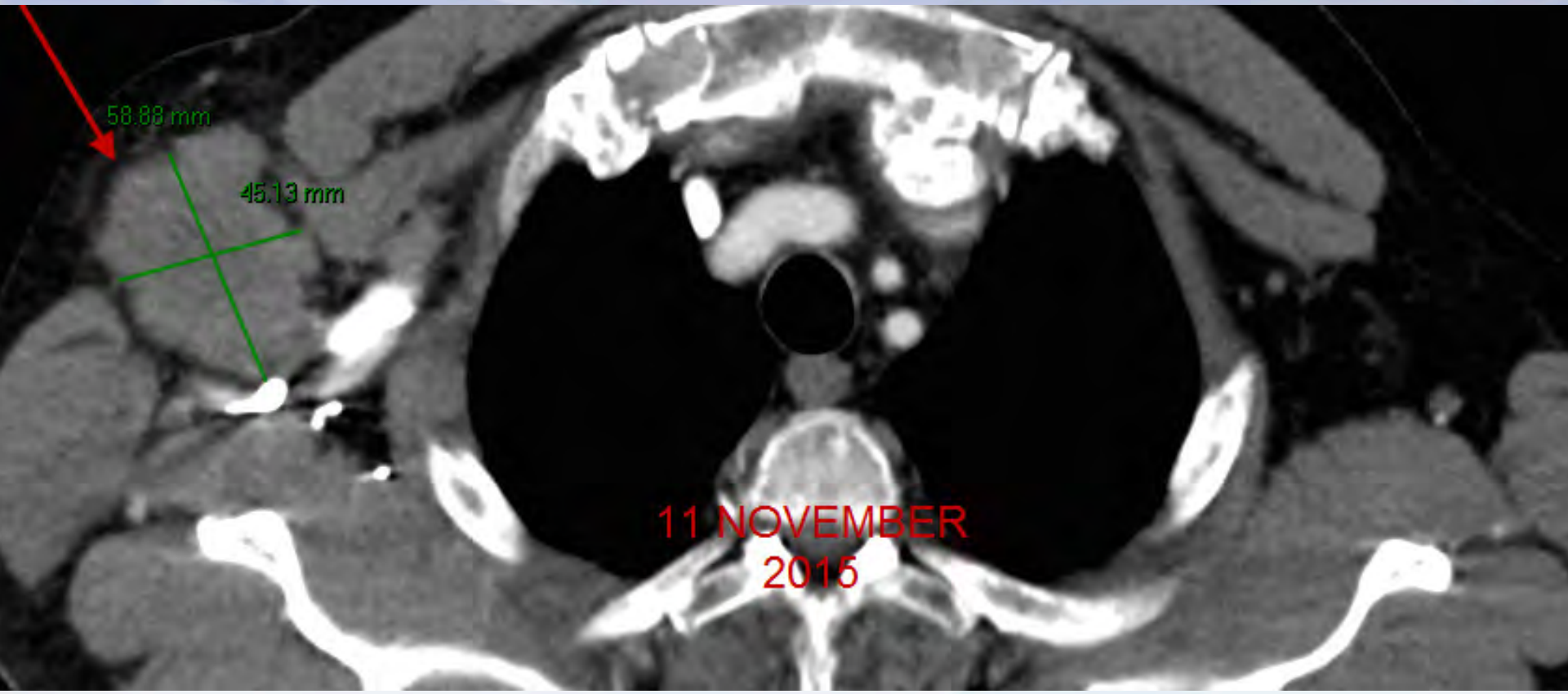
Personalised Cancer Care

NSCLC
Durable Remission
Case Presentation

The Medical **Oncology** Centre
of Rosebank
Personalised Cancer Care

NSCLC
Pre-Nivolumab



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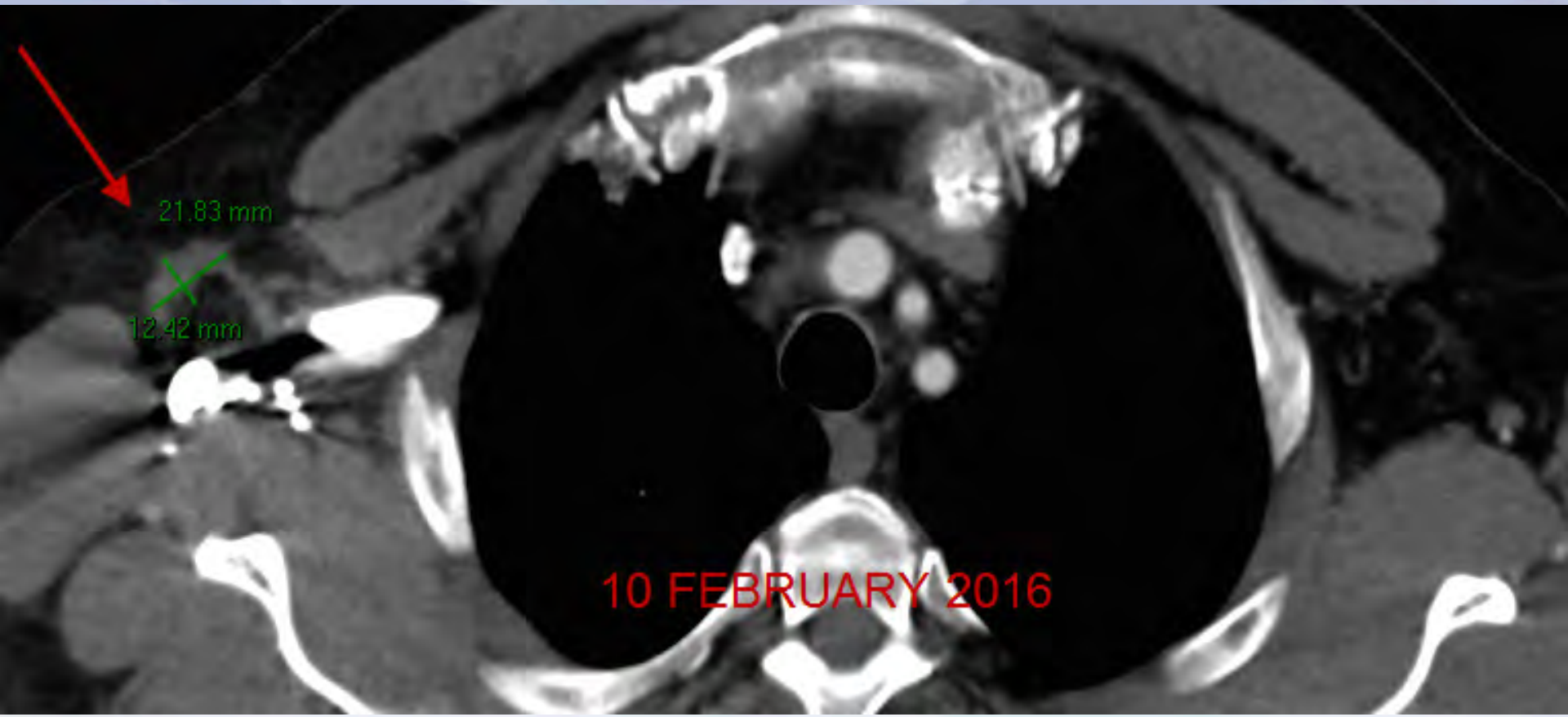
Personalised Cancer Care

NSCLC
Post-Nivolumab



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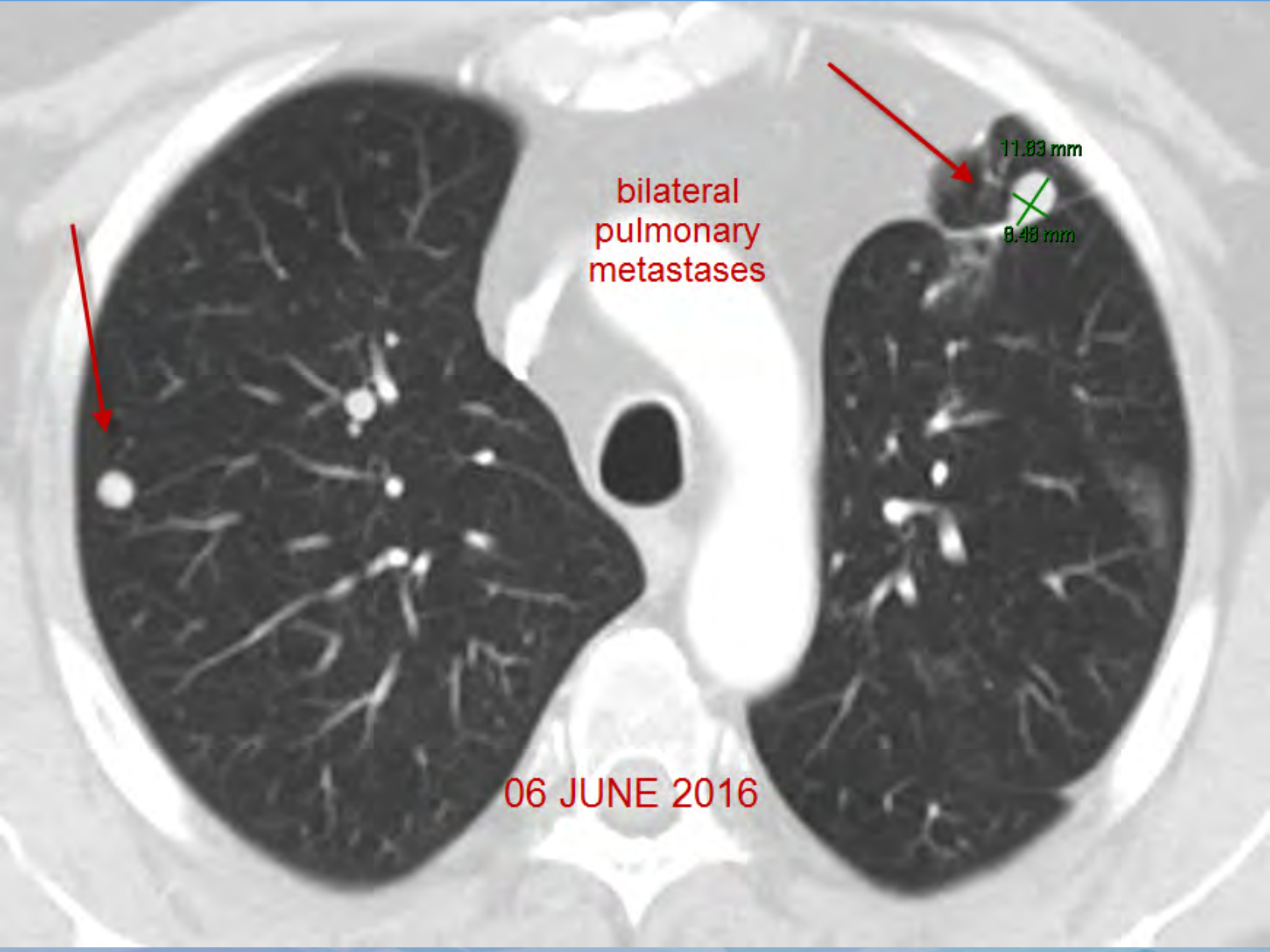
of Rosebank

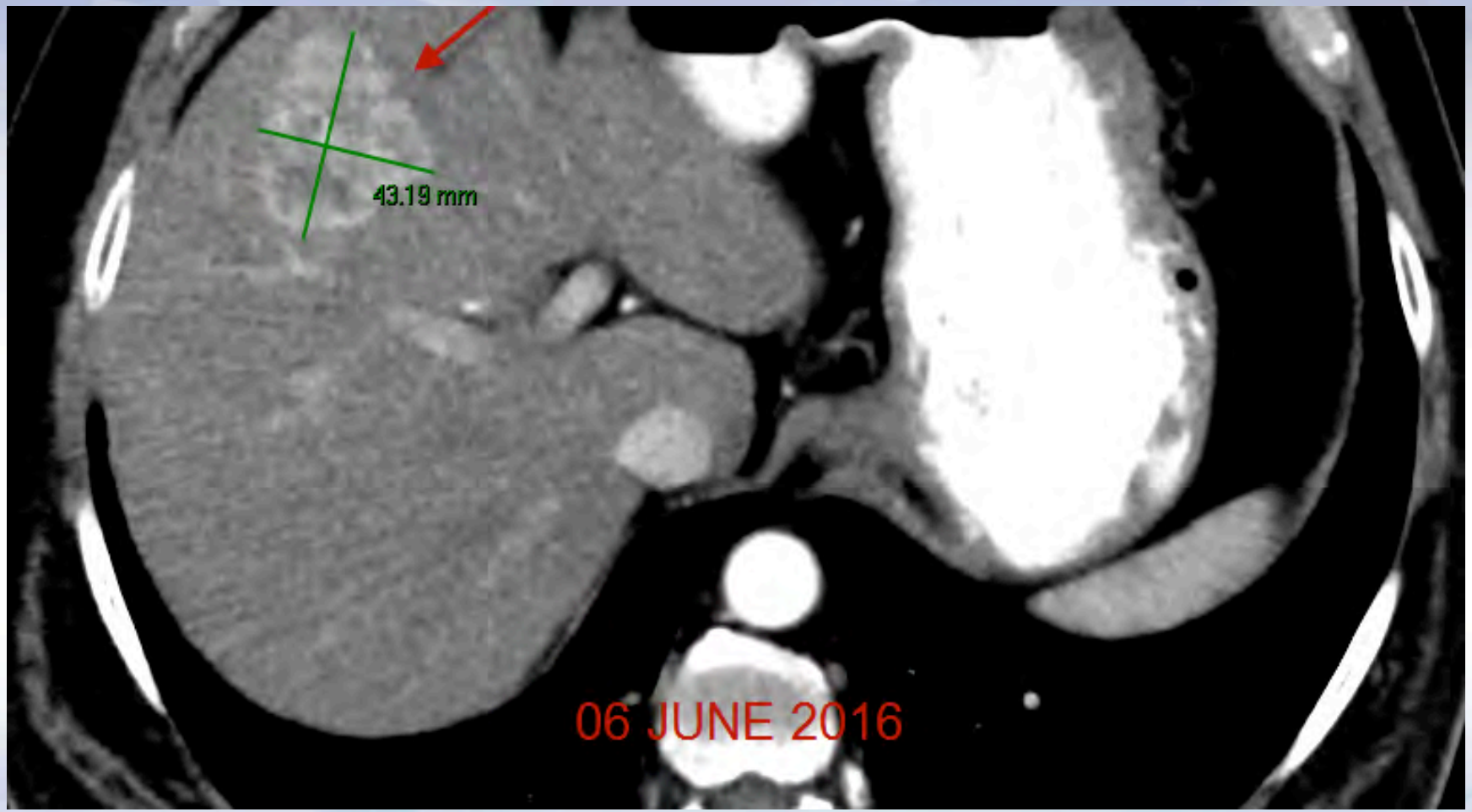
Personalised Cancer Care

RCC
Durable Remission
Case Presentation

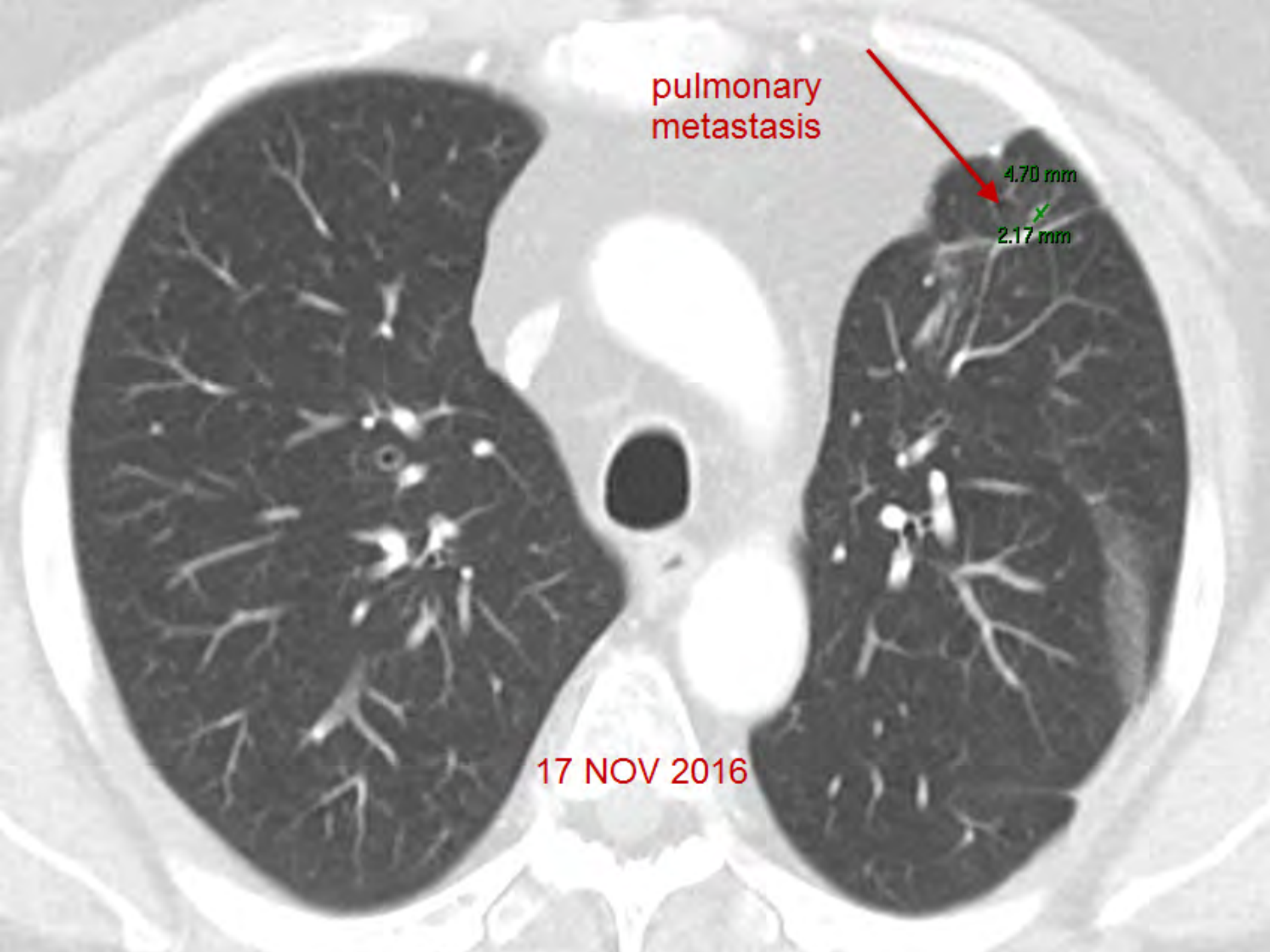
The Medical **Oncology** Centre
of Rosebank
Personalised Cancer Care

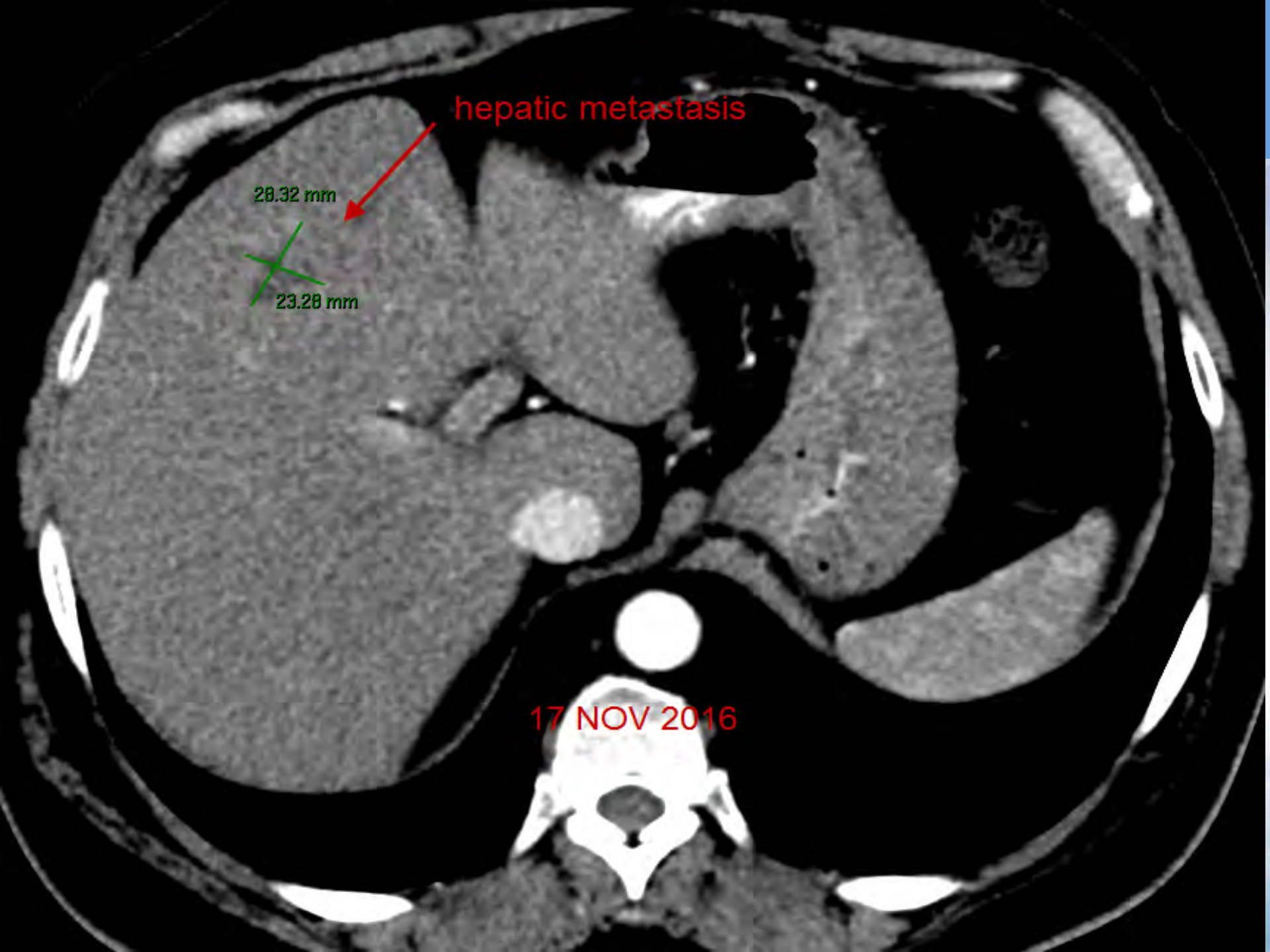
RCC
Pre-Nivolumab


bilateral
pulmonary
metastases
11.83 mm
8.48 mm
06 JUNE 2016


43.19 mm
06 JUNE 2016

RCC
Post-Nivolumab


pulmonary
metastasis
4.70 mm
2.17 mm
17 NOV 2016


hepatic metastasis
28.32 mm
23.28 mm
17 NOV 2016

Hodgkin's Disease
Pre-Nivolumab

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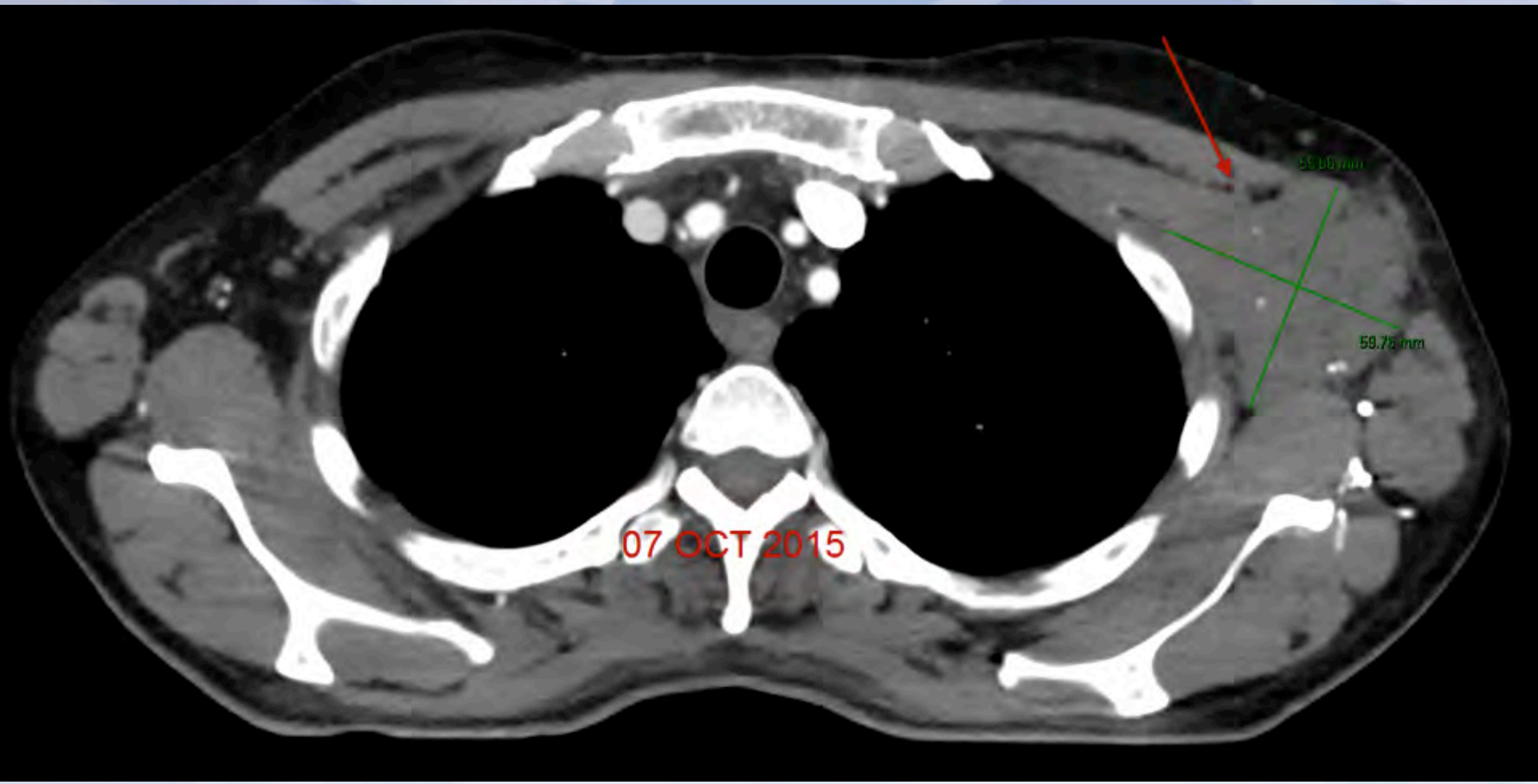

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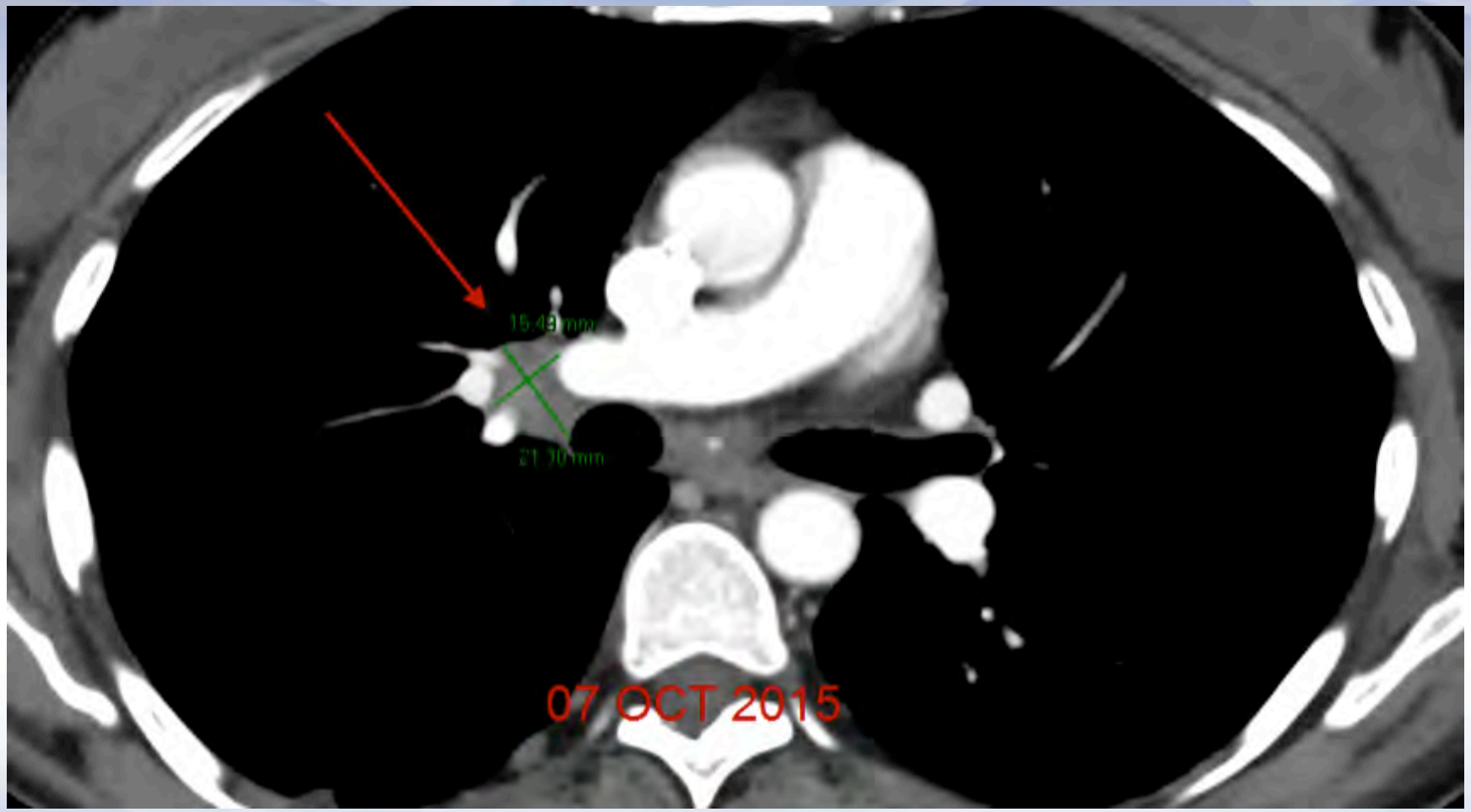
Personalised Cancer Care



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Hodgkin's Disease
Post-Nivolumab

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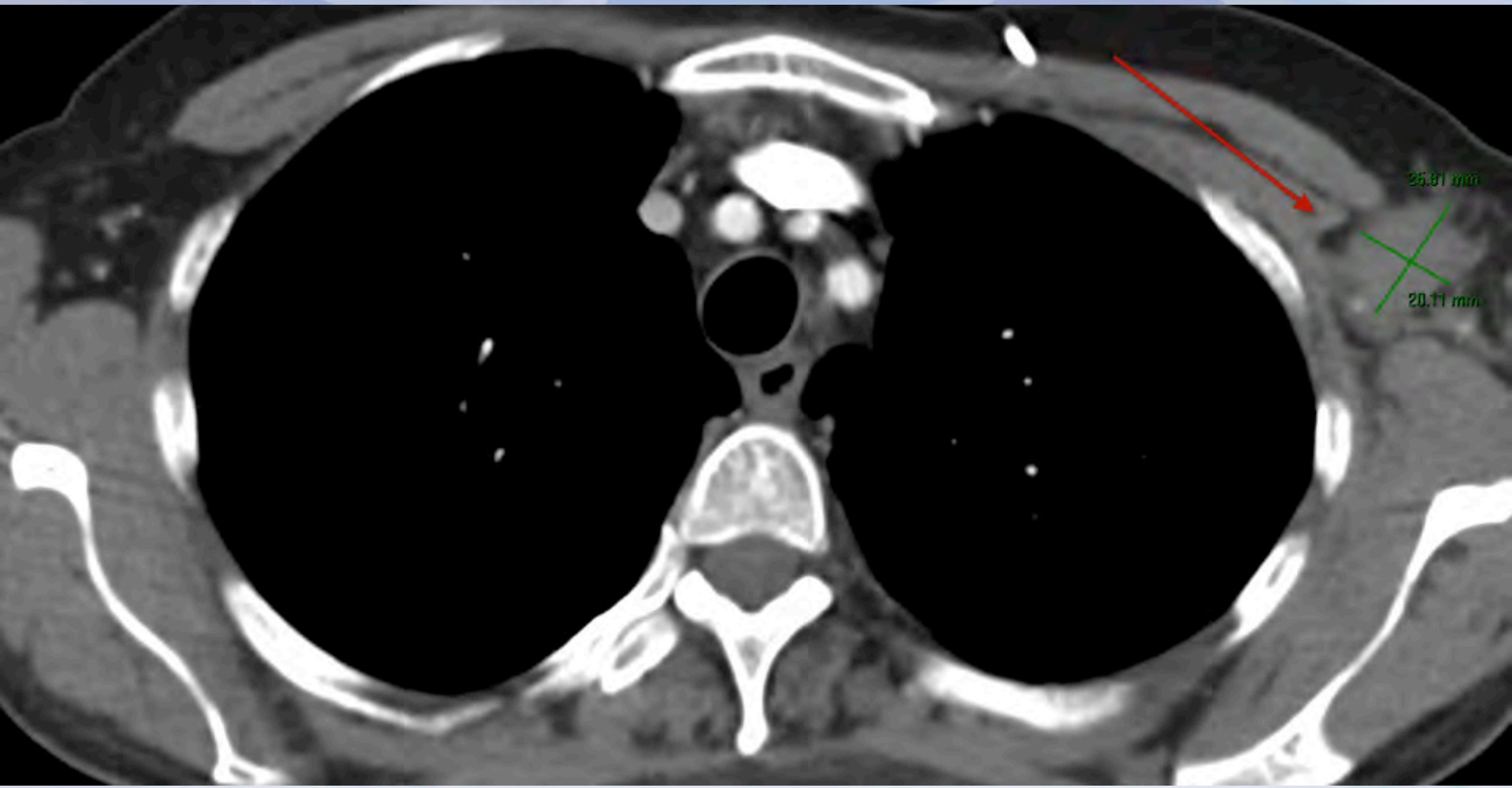
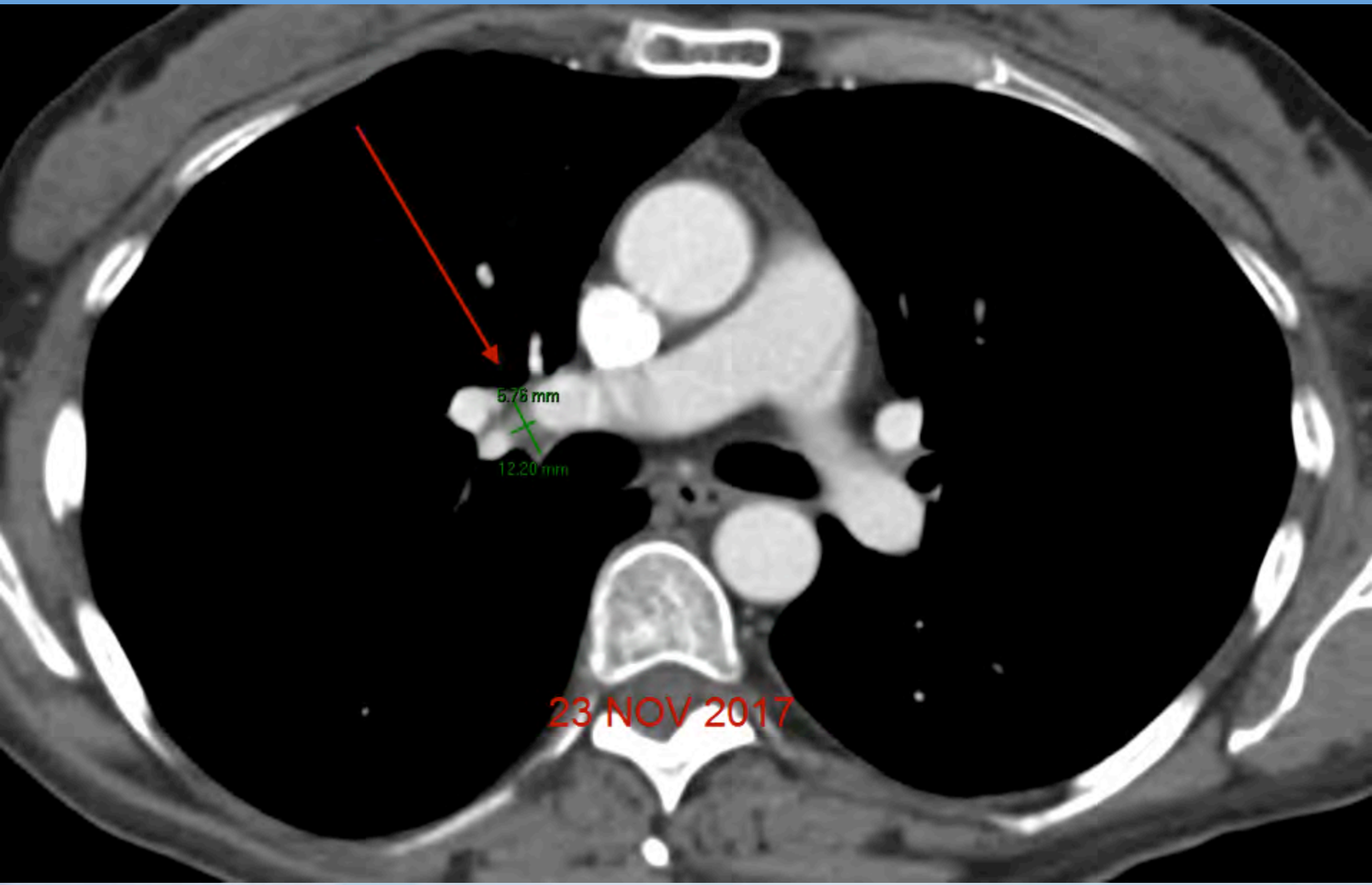

25.81 mm
20.11 mm


5.76 mm
12.20 mm
23 NOV 2017

Conclusions

- **Anti-PD1 and anti-CTLA4 antibody treatment is associated with durable remissions in patients with a variety of solid tumors**
- **Possible cures**
- **Different toxicity profiles**