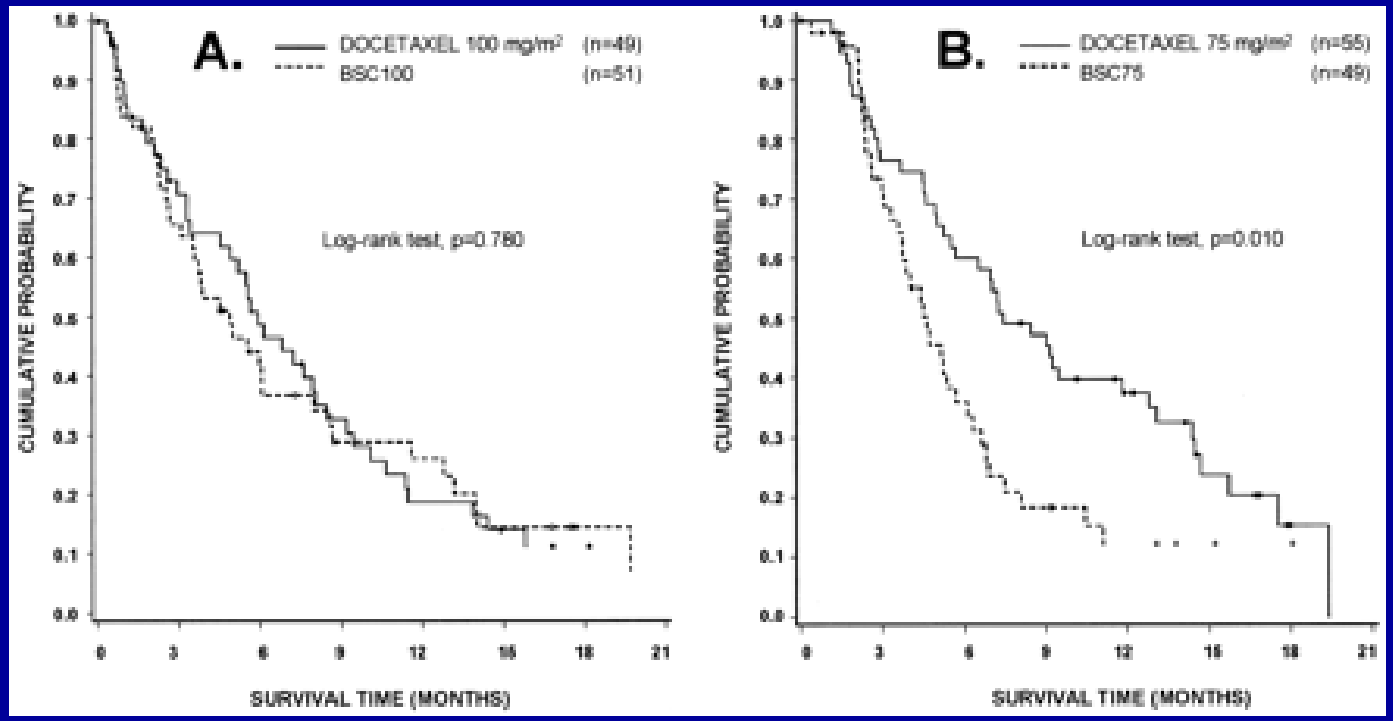
Are We Ready?

Professor Tony Mok
Li Shu Fan Medical Foundation Professor
The Chinese University of Hong Kong

Are We Ready to Integrate Immune Checkpoint Inhibitor (ICI) as a New Standard Therapy for Advanced Stage NSCLC?

Humble standard therapy (Single agent docetaxel vs BSC)

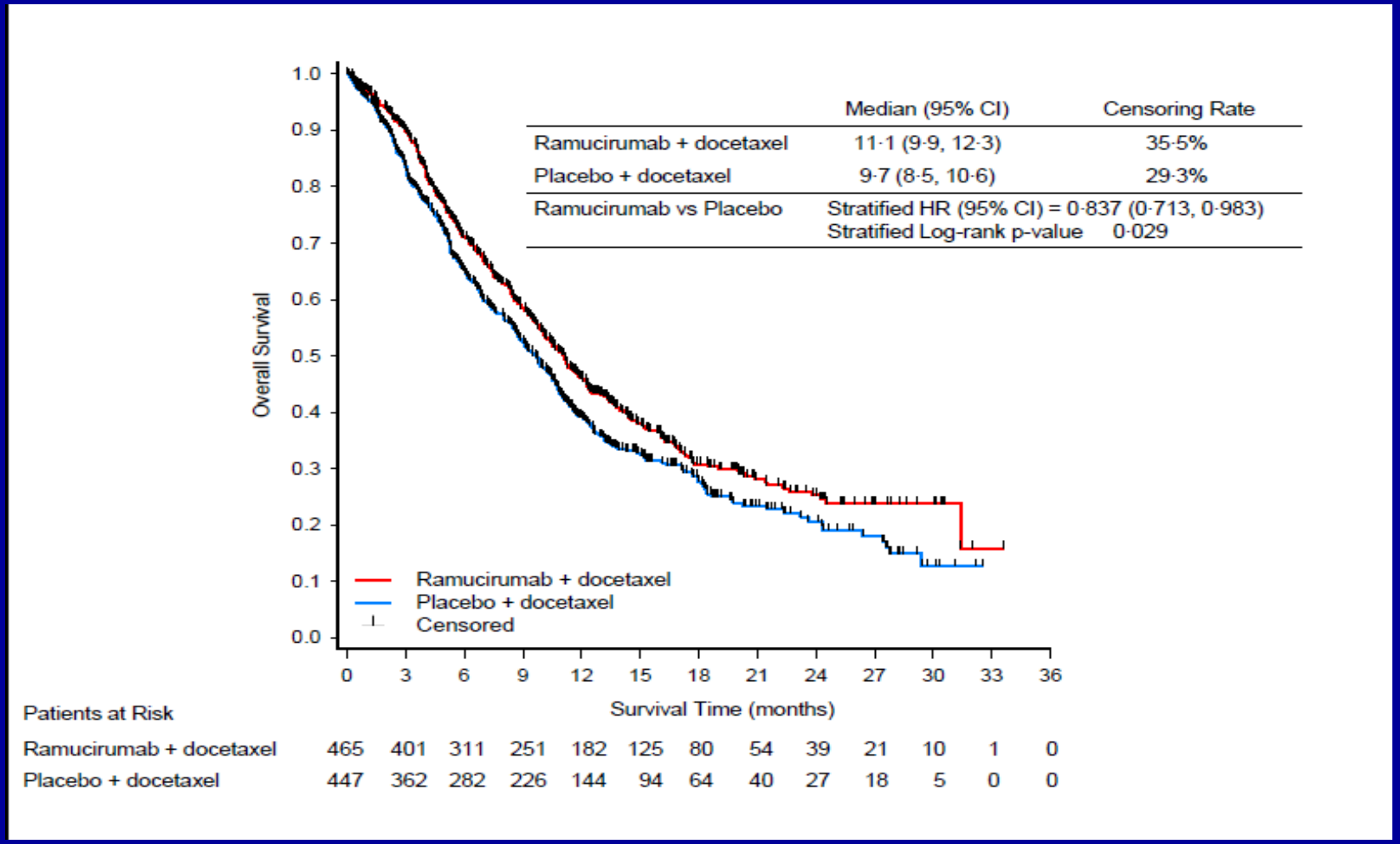


Tumor response rate: 7.1%

Median OS: 7.5 vs 4.6 months p=0.01

Shepherd et al JCO 2000

Ramucirumab/docetaxel is better than docetaxel



Garon et al Lancet 2014

Nivolumab is better than docetaxel

Checkmate 017

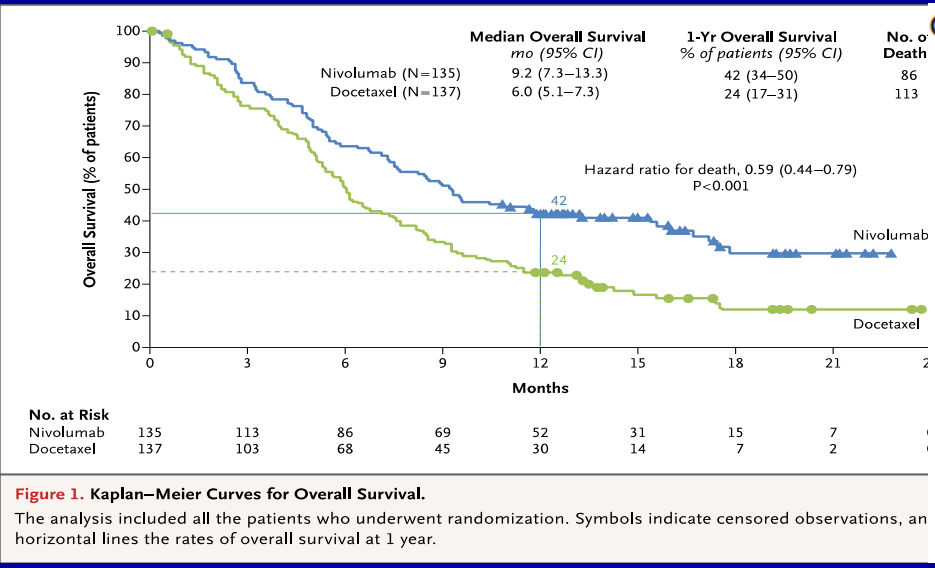
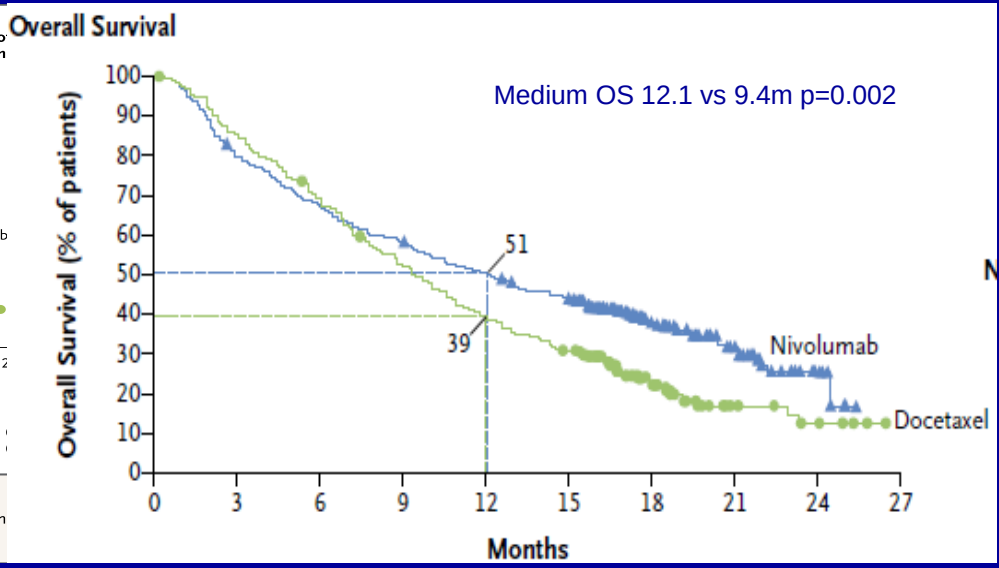


Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, an horizontal lines the rates of overall survival at 1 year.

Squamous cell carcinoma

Checkmate 057

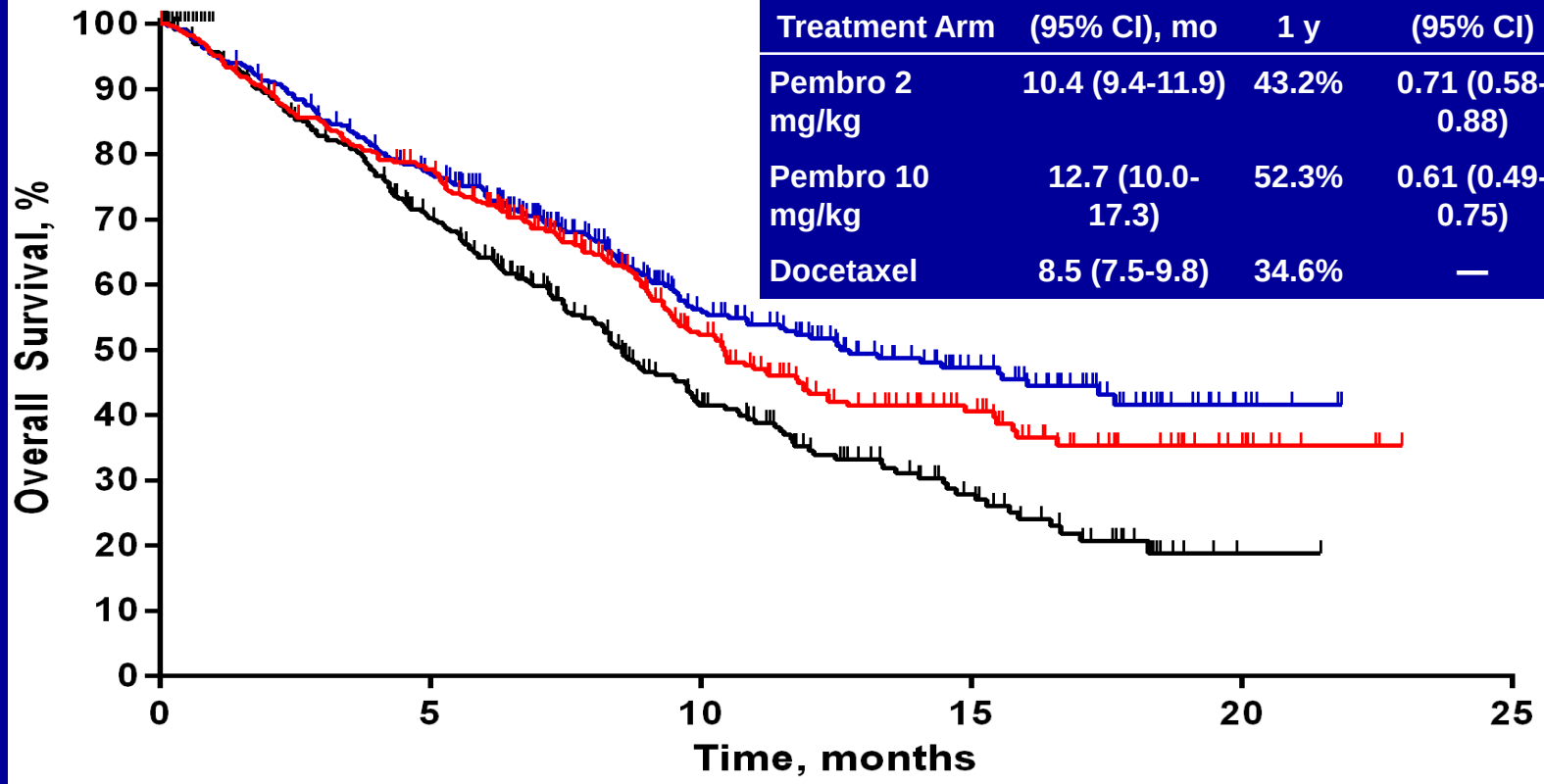


Non-squamous cell carcinoma

Brahmer et al NEJM 2014; Borghaei et al NEJM 2015

Pembrolizumab is better than Docetaxel (KEYNOTE 010)

Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.00076
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.00001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—



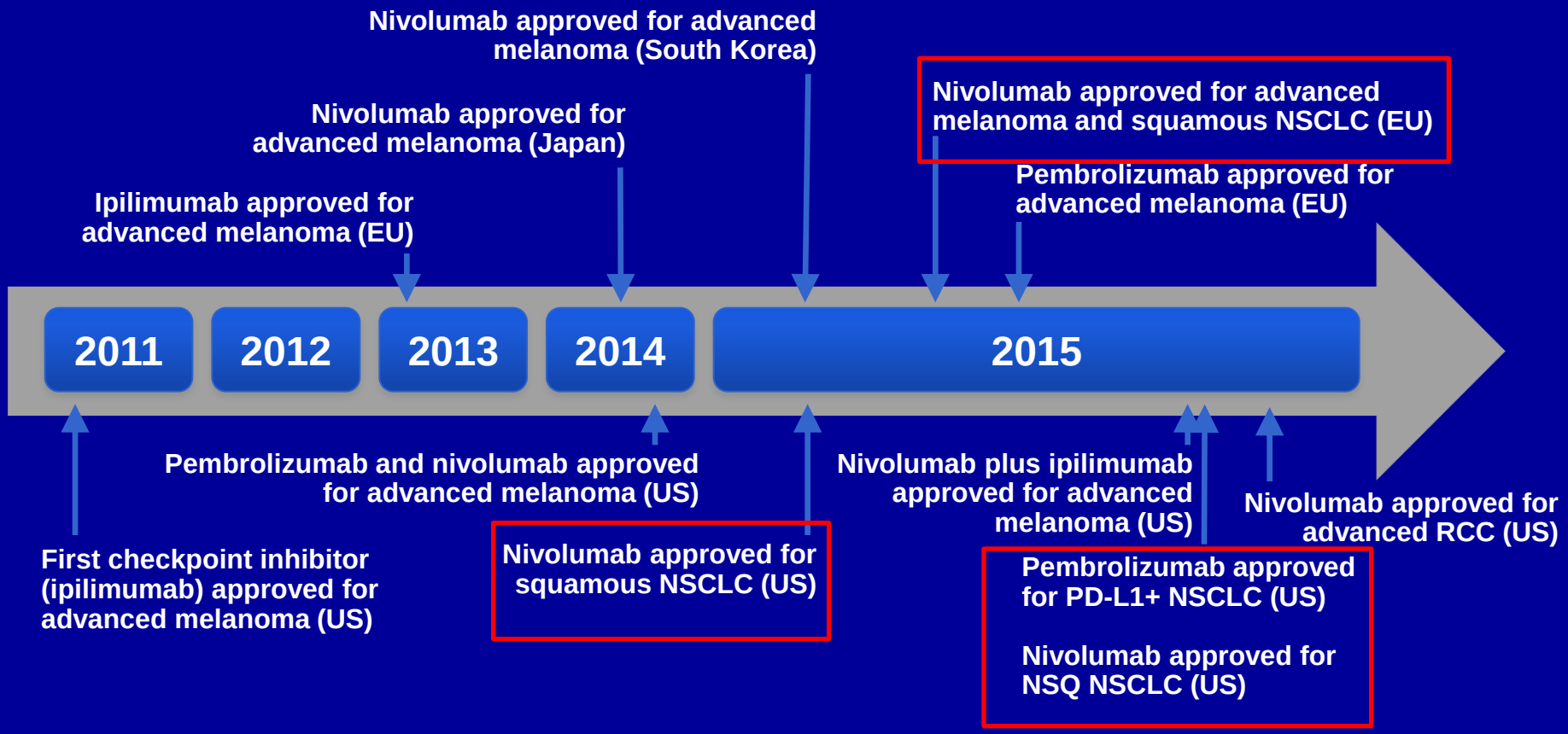
g	344	259	115	49	12	0
kg	346	255	124	56	6	0
	343	212	79	33	1	0

Herbst et al ESMO Asia 2015

“Taller or bigger” represents a new standard

Is ICI taller or bigger than Arnold or just Danny?

Approval of Nivolumab and Pembrolizumab for lung cancer in 2015



Keynote

VERSUS

Checkmate

Key outcomes (total population)

	KEYNOTE 010		Checkmate 057		Checkmate 017	
RR	Pembro 2mg/kg	18%	Nivo	19%	Nivo	20%
	Pembro 10mg/kg	18.5%	Doc	9%	Doc	9%
	Docetaxel	9.3%				
PFS (Total)	Pembro 2mg/kg	3.9m	Nivo	4.2m	Nivo	3.5m
	Pembro 10mg/kg	4.0m	Doc	2.3m	Doc	2.8m
	Docetaxel	4.0m				
OS (Total)	Pembro 2mg/kg	10.4m	Nivo	12.2m	Nivo	9.2m
	Pembro 10mg/kg	12.7m	Doc	9.2m	Doc	6.0m
	Docetaxel	8.5m				

Key distinctive features

	KEYNOTE 010	Checkmate 057	Checkmate 017
Line of chemotherapy	One line or more	One line	One line
Histology	Non-squamous and squamous cell ca	Non-squamous cell ca	Squamous cell ca
Biomarker (PDL1 expression)	Prospective (44% archival, 56% new biopsy)	Retrospective	Retrospective
Drug dose	2mg/kg q3w 10mg/kg q3w	3mg/kg q2w	3mg/kg q2w
Primary Endpoints	PFS/OS Total population PFS/OS >50% stratum	OS Total population	OS Total population

Brahmer et al NEJM 2014; Borghaei et al NEJM 2015; Herbst et al ESMO Asia 2015

Getting ready by addressing some practical questions

- Should ICI be used as second or third line therapy?
- Should all patients be tested for PD-L1 status prior to ICI?
- What is the optimal dose?
- Is ICI cost-effective?

Getting ready by addressing some practical questions

Should ICI be used as second or third line therapy?

Should all patients be tested for PD-L1 status prior to ICI?

What is the optimal dose?

Is ICI cost-effective?

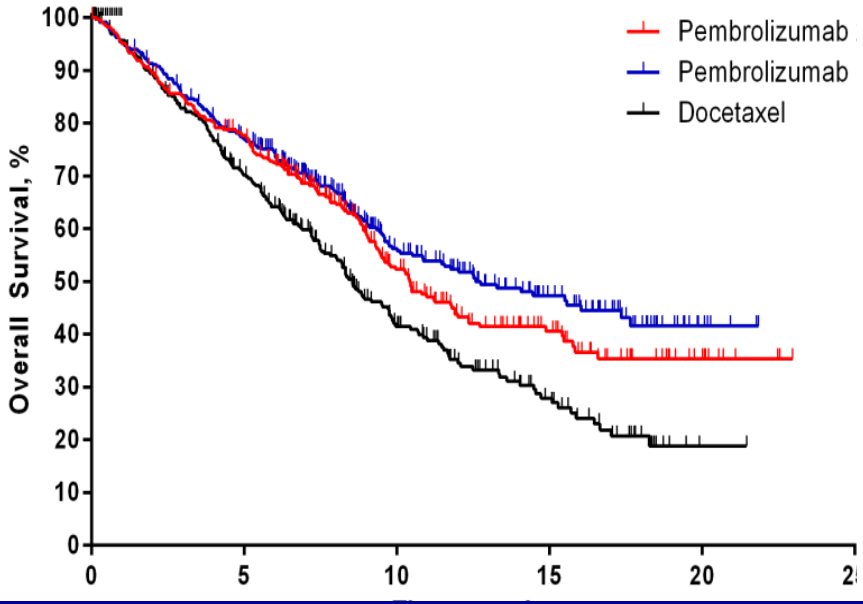
KEYENOTE 010: Baseline Characteristics

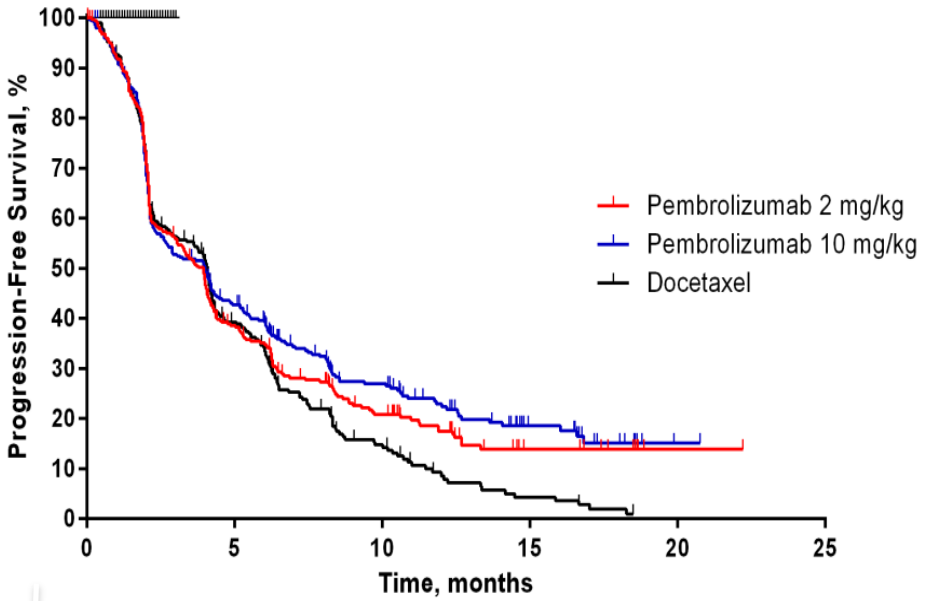
	Pembro 2mg/kg Q3W n = 344	Pembro 10 mg/kg Q3W n = 346	Docetaxel n = 343
Histology, % Squamous Nonsquamous Other/unknown	 22.1 69.8 11.0	 23.1 70.5 6.4	 19.2 70.0 10.8
EGFR mutant, %	8.1	9.2	7.6
ALK translocated, %	0.6	1.2	0.6
Prior adjuvant therapy, %	1.7	2.0	0.9
Prior neoadjuvant therapy, %	0.3	0.3	0
Prior lines of therapy, % 1 2 ≥3 Unknown	 70.6	 67.9	 68.5 21.9 8.5 0.3

300 patients in third line

Analysis cut-off date: September 30, 2015.

KEYNOTE 010: OS and PFS (Total population including 30% of patients with 3rd line therapy)





Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.00076
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0000
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—

Treatment Arm	Median (95% CI), mo	Rate at 9 mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	3.9 (3.1-4.1)	22.9%	0.88 (0.74-1.05)	0.07424
Pembro 10 mg/kg	4.0 (2.7-4.3)	27.5%	0.79 (0.66-0.94)	0.00401
Docetaxel	4.0 (3.1-4.2)	15.9%	—	—

Key outcomes (total population)

	KEYNOTE 010		Checkmate 057		Checkmate 017	
RR	Pembro 2mg/kg Pembro 10mg/kg Docetaxel	18% 18.5% 9.3%	Nivo Doc	19% 9%	Nivo Doc	20% 9%
PFS (Total)	Pembro 2mg/kg Pembro 10mg/kg Docetaxel	3.9m 4.0m 4.0m	Nivo Doc	4.2m 2.3m	Nivo Doc	3.5m 2.8m
OS (Total)	Pembro 2mg/kg Pembro 10mg/kg Docetaxel	10.4m 12.7m 8.5m	Nivo Doc	12.2m 9.2m	Nivo Doc	9.2m 6.0m

Brahmer et al NEJM 2014; Borghaei et al NEJM 2015; Herbst et al ESMO Asia 2015

KEYNOTE 001: Line of prior therapy

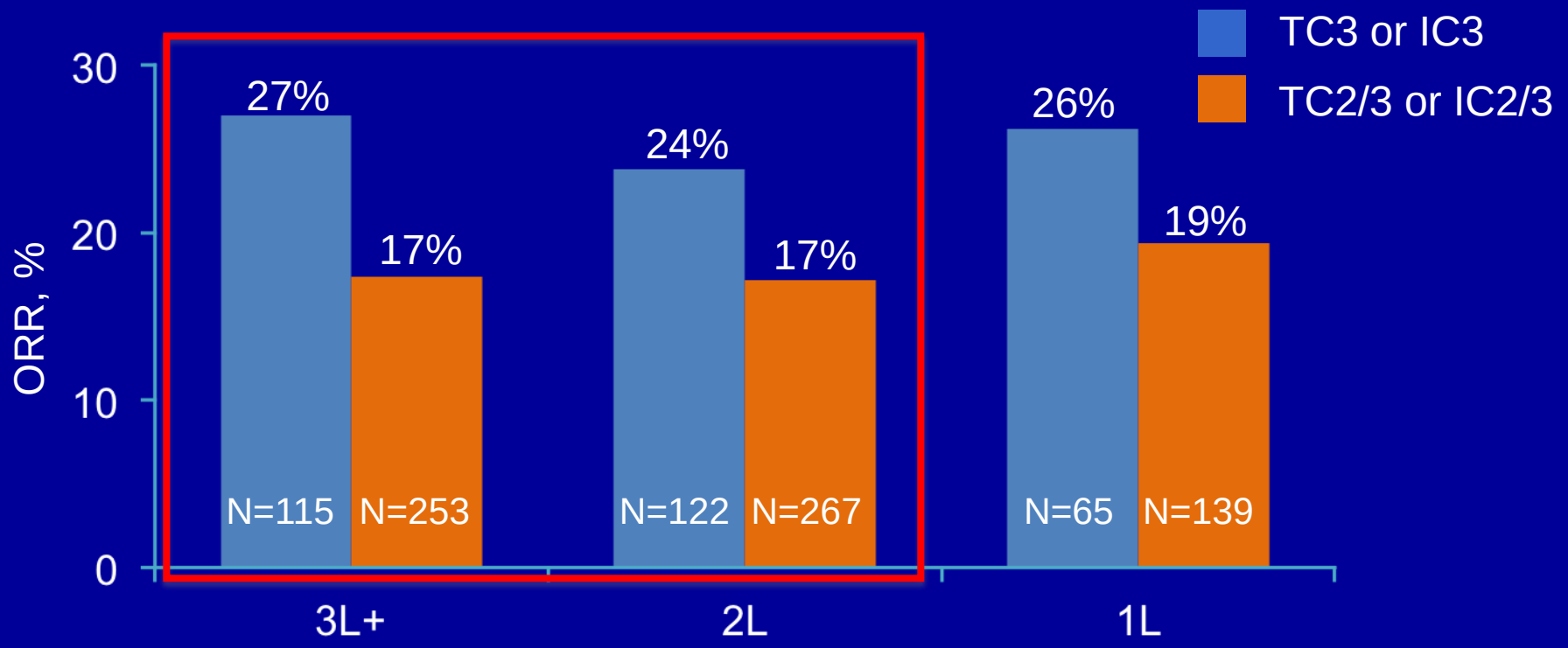
Prior treatment	2mg/kg q3w	10mg/kg q3w	10mg/kg q2w	Total
0	4	45	45	94 (19.0%)
1	2			74(14.9%)
2	0			119(14.9%)
3	0	60	46	106(21.4%)
4 or more	0	59	43	102 (20.6%)

RR 19.4%
PFS 3.7 months
OS 12.0 months

Garon et al NEJM 2015

BIRCH: IRF-assessed ORR by Line of Therapy

TC3 or IC3 and TC2/3 or IC2/3 groups



- BIRCH met its primary endpoint in all predefined subgroups per protocol-specified criteria
- Majority of responses were ongoing (>61% in TC3 or IC3)
  - Median DoR was 7 mo in 3L+, NR in 1L/2L in TC3 or IC3, although follow-up is limited
  - IRF- and INV-assessed ORR (per RECIST v1.1) were similar. In TC3 or IC3, e.g. 27% vs 29% in 3L+; 24% vs 25% in 2L; and 26% vs 31% in 1L, respectively

Data cut-off: May 28, 2015.

Getting ready by addressing some practical questions

Should ICI be used as second or third line therapy?

Should all patients be tested for PD-L1 status prior to ICI?

What is the optimal dose?

Is ICIc 0st-effective?

What did Roy say about PD-L1 biomarker 6 months ago?

However, we still have some work to do on the endgame!

2. Should this PD-L1 biomarker assay be used for patient selection?

No- Not Yet

- It is intriguing but for now only hypothesis generating
- Not prospectively stratified and incomplete (22 percent have no measurement))
- While it does improve OR, PFS and OS - even the group <1% appears to have at least equal activity to docetaxel with less toxicity
- Issues with archival tissue, heterogeneity and scoring
- Future markers must be developed to enable safe and effective combinations

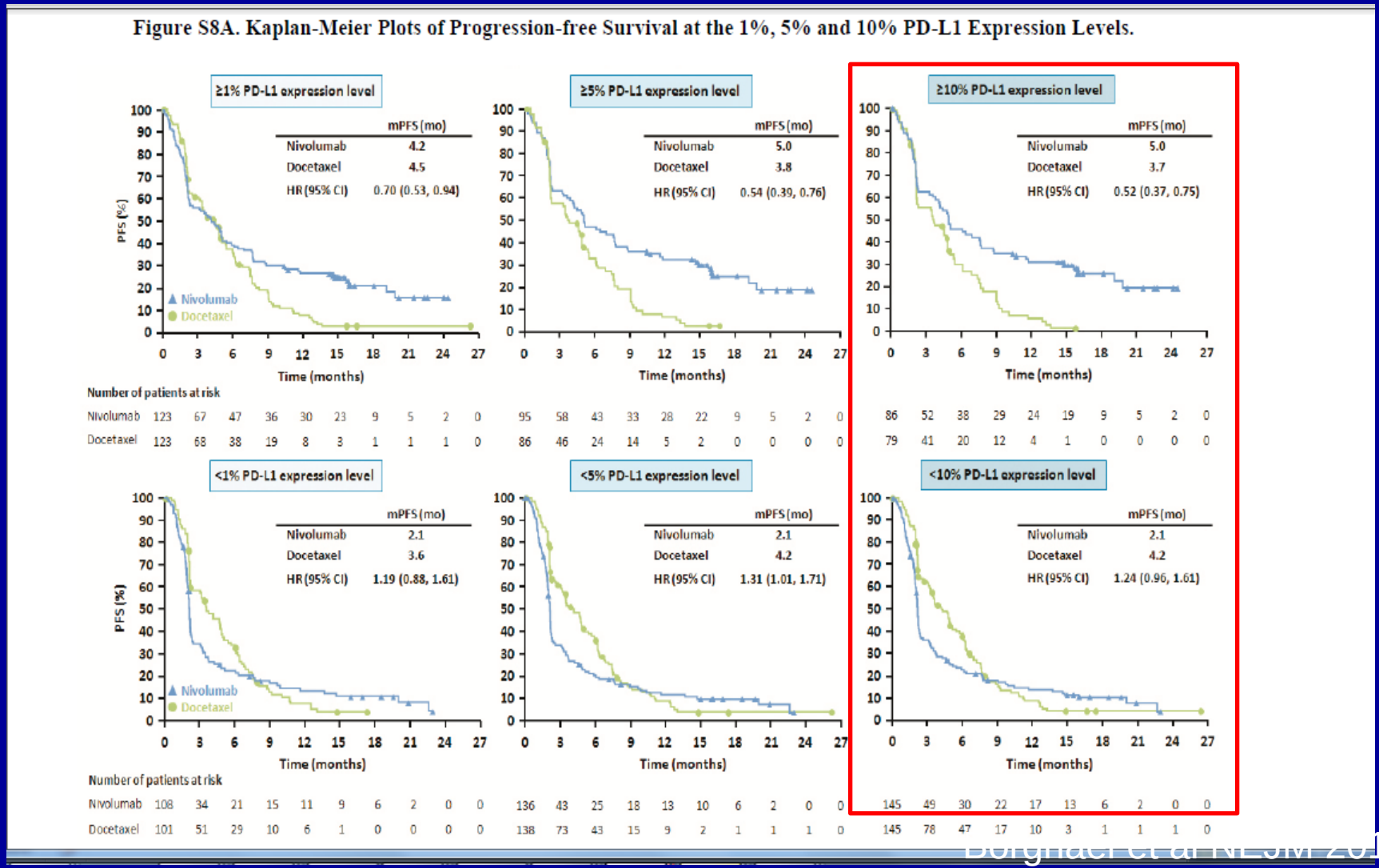
PD-L1 expression as biomarker

	Atezolizumab	Nivolumab	Pembrolizumab
Detection antibody[1]	SP142	28-8	22C3
IHC platform[1]	Ventana	Dako	Dako
Tested cells	NSCLC (IC and TC) UBC (IC)	Lung (TC)	NSCLC (TC) UBC (TC and stroma)
Estimated PD-L1 prevalence in NSCLC	16%*[2] TC3 IC3 37%*[2] TC2/3 IC2/3 68%*[2] TC1/2/3 IC1/2/3	*PD-L1+ as ≥5% of TCs* ~46%[1]	*PD-L1+ as ≥50% of TCs* ~25%[1]

*TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+, respectively
UC = urothelial carcinoma

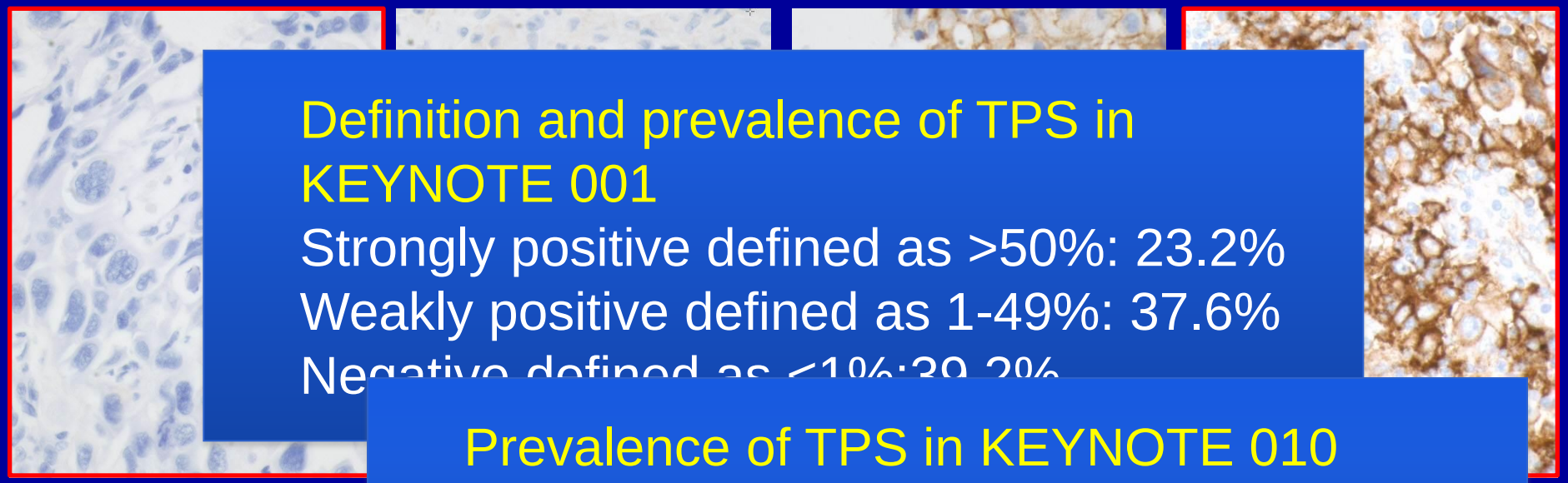
1. Kerr, et al. J Thorac Oncol 2015
2. Spira, et al. ASCO 2015

Checkmate 057 PFS by PD-L1 status



Borghaei et al NEJM 2015

Tumor Proportion Score (TPS) Immunohistochemical Staining by 22C3 antibody



Staining intensity: 0+
PD-L1 = 0% positive

PD-L1-Negative

Definition and prevalence of TPS in KEYNOTE 001

Strongly positive defined as >50%: 23.2%

Weakly positive defined as 1-49%: 37.6%

Negative defined as <1%:39.2%

Prevalence of TPS in KEYNOTE 010 (n=2222)

Strongly positive: 28.5%

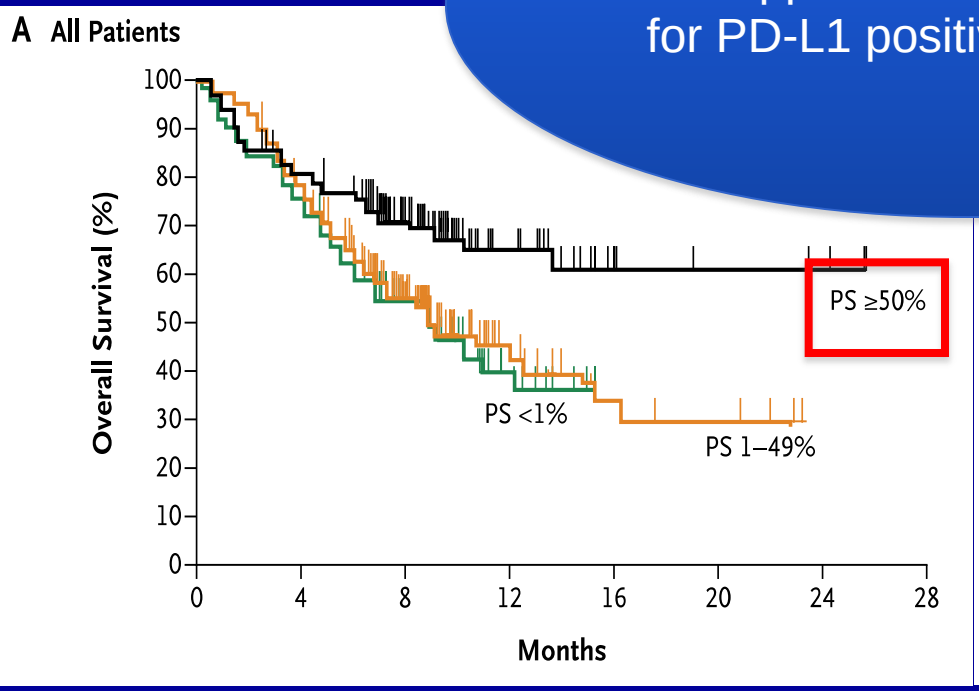
Weakly positive: 33.9%

Negative: 33.6%

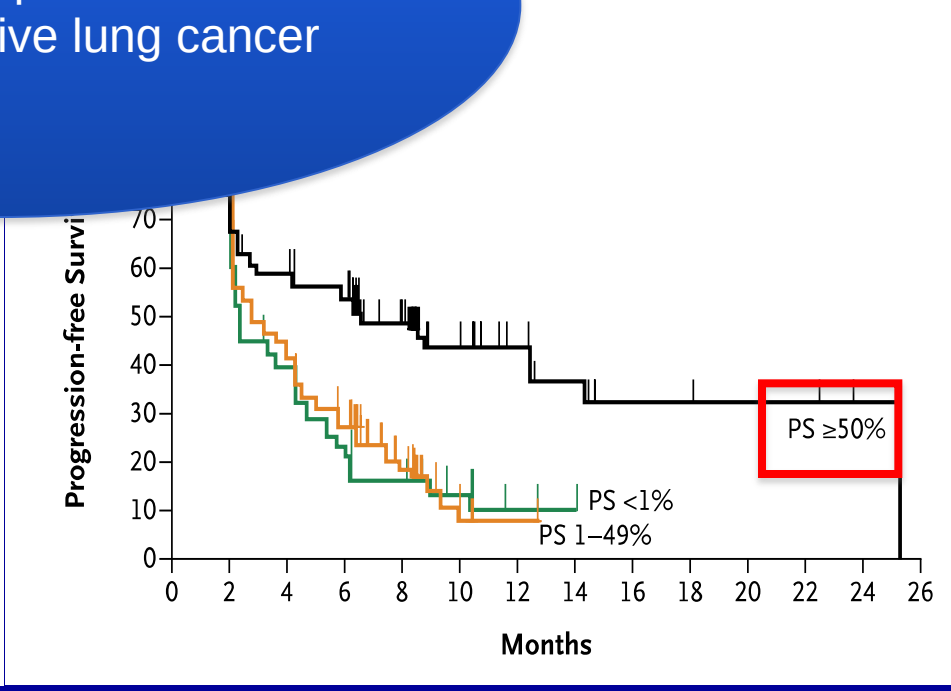
*Clinical trial assay

KEYNOTE 001: PFS and OS

FDA approval of pembrolizumab
for PD-L1 positive lung cancer

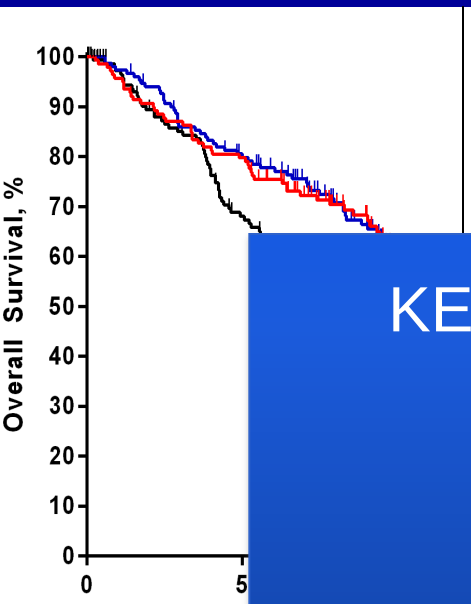


Overall survival



Progression free survival

KEYNOTE 010 (>50% Stratum): PFS and OS



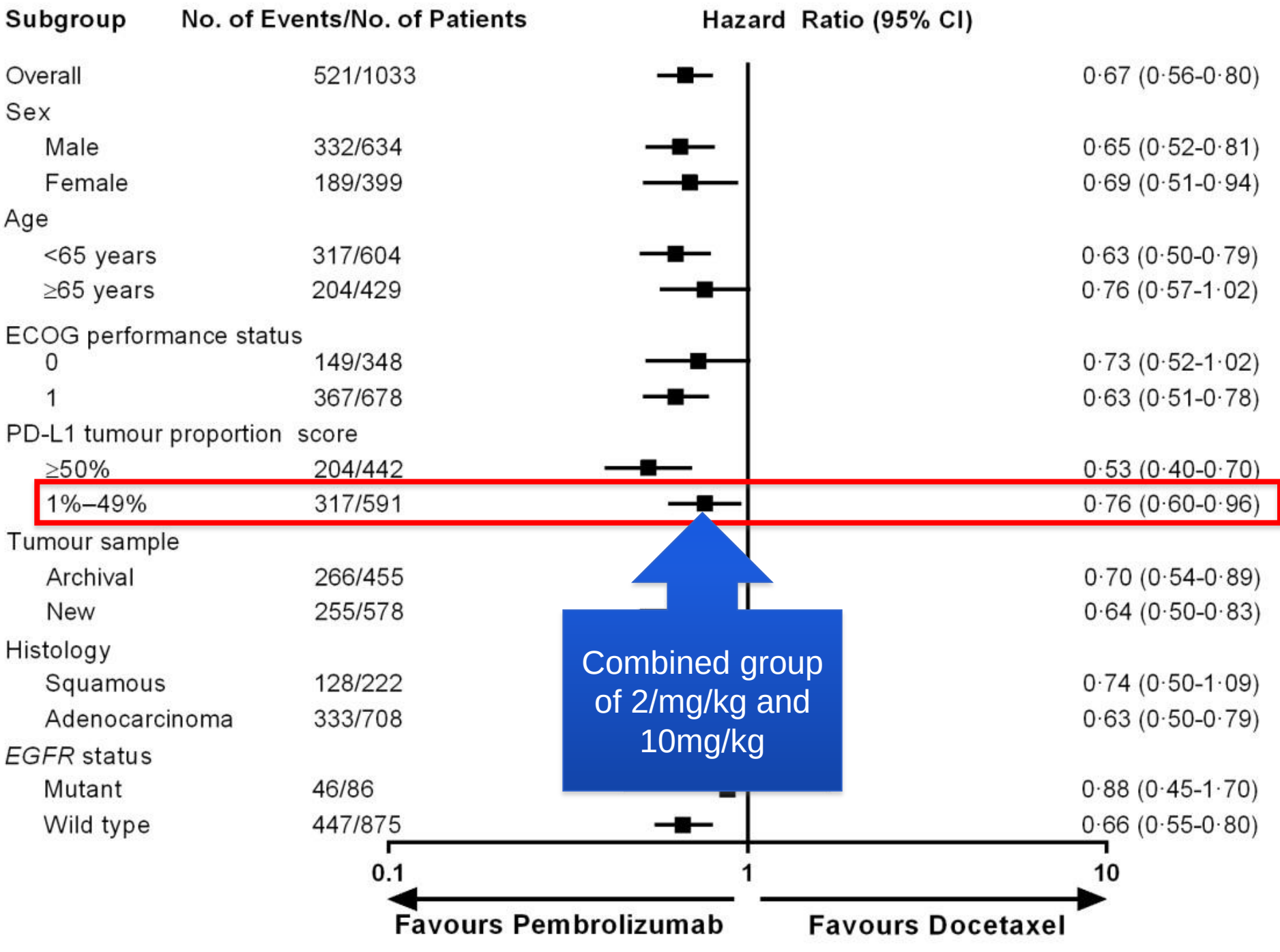
Tumor Proportion Score ≥50% Stratum

Pembrolizumab 2 mg/kg n=139	Pembrolizumab 10 mg/kg n=151	Docetaxel n=152

KEYNOTE 001 (>50% stratum, previously treated)
RR: 43.9%
Median PFS: 6.1 months
Median OS: Not reached

Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR (95% CI)	*P*
Pembro 2 mg/kg	14.9 (10.4-NR)	53.4%	0.54 (0.38-0.77)	0.00024
Pembro 10 mg/kg	17.3 (11.8-NR)	58.1%	0.50 (0.36-0.70)	0.00002
Docetaxel	8.2 (6.4-10.7)	38.0%	—	—

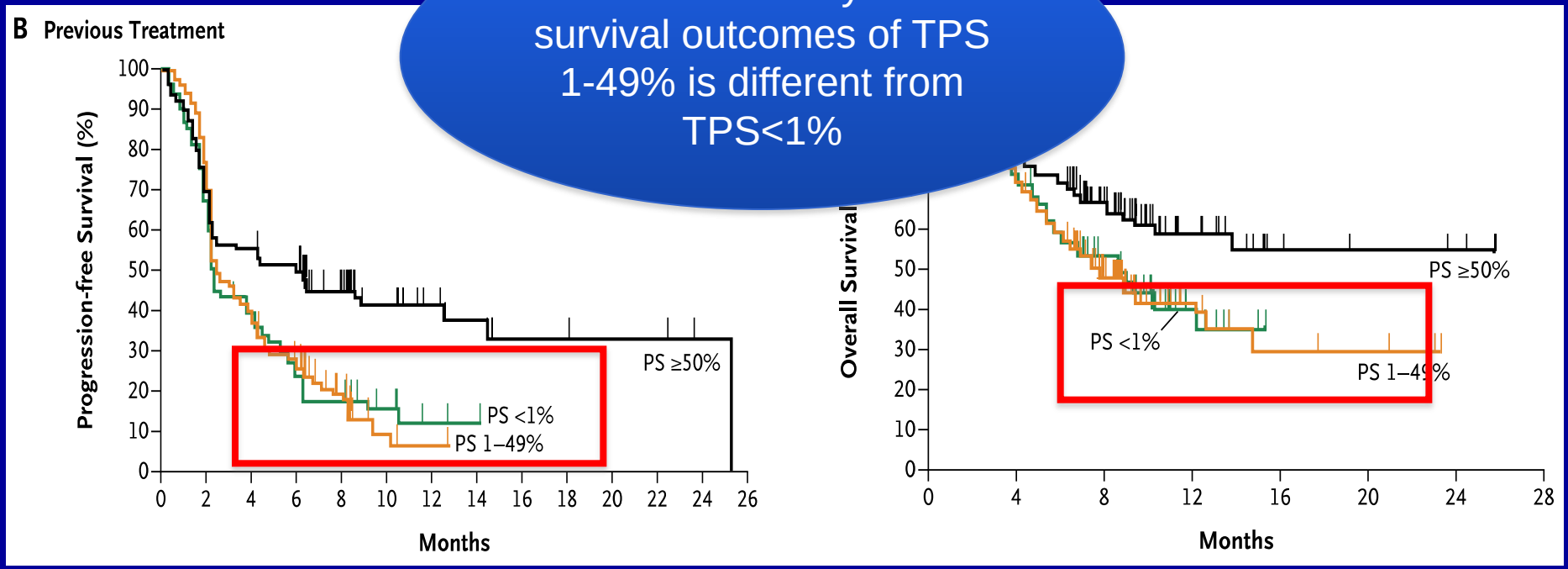
Treatment Arm	Median (95% CI), mo	at 9 mo	(95% CI)	*P*
Pembro 2 mg/kg	5.0 (4.0-6.5)	35.5%	0.59 (0.44-0.78)	0.00012
Pembro 10 mg/kg	5.2 (4.1-8.1)	37.8%	0.59 (0.45-0.78)	0.00007
Docetaxel	4.1 (3.6-4.3)	19.2%	—	—


Subgroup
No. of Events/No. of Patients
Hazard Ratio (95% CI)
Overall 521/1033 0·67 (0·56-0·80)
Sex
Male 332/634 0·65 (0·52-0·81)
Female 189/399 0·69 (0·51-0·94)
Age
<65 years 317/604 0·63 (0·50-0·79)
≥65 years 204/429 0·76 (0·57-1·02)
ECOG performance status
0 149/348 0·73 (0·52-1·02)
1 367/678 0·63 (0·51-0·78)
PD-L1 tumour proportion score
≥50% 204/442 0·53 (0·40-0·70)
1%–49% 317/591 0·76 (0·60-0·96)
Tumour sample
Archival 266/455 0·70 (0·54-0·89)
New 255/578 0·64 (0·50-0·83)
Histology
Squamous 128/222 0·74 (0·50-1·09)
Adenocarcinoma 333/708 0·63 (0·50-0·79)
EGFR status
Mutant 46/86 0·88 (0·45-1·70)
Wild type 447/875 0·66 (0·55-0·80)
Combined group of 2/mg/kg and 10mg/kg
0.1
1
10
Favours Pembrolizumab
Favours Docetaxel

What about patients with <1% tumor proportion score?

KEYNOTE 001: PFS and OS in the previously treated patients

We cannot say the survival outcomes of TPS 1-49% is different from TPS<1%



PFS

OS

Garon et al NEJM 2015

>50% stratum benefit significantly from 2nd/3rd line pembrolizumab (KEYNOTE 010)

1-49% stratum benefit moderately from 2nd/3rd line pembrolizumab (KEYNOTE 010)

<1% stratum is not different from 1-49% (KEYNOTE 001)

Why should we test then?

Getting ready by addressing some practical questions

Should ICI be used as second or third line therapy?

Should all patients be tested for PD-L1 status prior to ICI?

What is the optimal dose?

Is ICI cost-effective?

We didn't know 2mg/kg works in NSCLC

KEYNOTE-001.[24-26] The interpretation of response among patients receiving 2 mg per kilogram is limited by the lack of data for that dose. The 2-mg dose is being evaluated in a recently enrolled cohort of KEYNOTE-001, as well as in the phase

Table 1. Clinical Characteristics of the Total Population (N = 495)

Characteristic	2 mg/kg Q3W	10 mg/kg Q3W	10 mg/kg Q2W	Total
	n = 6	n = 287	n = 202	N = 495

Garon et al NEJM 2015

KEYNOTE 010 helps to define the dose of pembrolizumab at 2mg/kg

	KEYNOTE 010	
RR	Pembro 2mg/kg	18%
	Pembro 10mg/kg	18.5%
	Docetaxel	9.3%
PFS (Total)	Pembro 2mg/kg	3.9m
	Pembro 10mg/kg	4.0m
	Docetaxel	4.0m
OS (Total)	Pembro 2mg/kg	10.4m
	Pembro 10mg/kg	12.7m
	Docetaxel	8.5m

>50% stratum

Treatment Arm	Median (95% CI), mo
Pembro 2 mg/kg	5.0 (4.0-6.5)
Pembro 10 mg/kg	5.2 (4.1-8.1)

Treatment Arm	Median (95% CI), mo
Pembro 2 mg/kg	14.9 (10.4-NR)
Pembro 10 mg/kg	17.3 (11.8-NR)

Similar incidence of immune related toxicity

Pembrolizumab	2mg q3w (all grade)	2mg q3w (grade 3-5)	10mg q3w (all grade)	10mg q3w (grade 3-5)
Hypothyroidism	8.3%	0	8.2%	0
Pneumonitis	4.7%	2.1%	4.4%	2.0%
Hyperthyroidism	3.5%	0	5.8%	0.3%
Colitis	1.2%	0.9%	0.6%	0.3%
Skin reaction	1.2%	0.9%	2.0%	1.7%

Herbst et al ESMO Asia 2015

Can we give lower than 2mg/kg?

Lower than standard dose (nivolumab)

Dose of Anti–PD-1 Antibody	Objective Response†	Objective-Response Rate‡	Duration of Response§	Stable Disease ≥24 wk		Progression-free Survival Rate at 24 wk¶
	no. of patients/ total no. of patients	*% (95% CI)*	*mo*	*no. of patients/ total no. of patients*	*% (95% CI)*	*% (95% CI)*
Non–small-cell lung cancer						
Squamous						
1.0 mg/kg	0/5	0		0/5	0	0
3.0 mg/kg	3/6	50 (12–88)	ND	0/6	0	50 (10–90)
10.0 mg/kg	3/7	43 (10–82)	ND	0/7	0	43 (6–80)
All doses	6/18	33 (13–59)	ND	0/18	0	33 (12–55)
Nonsquamous						
1.0 mg/kg	0/12	0		1/12	8 (0.2–39)	14 (0–37)
3.0 mg/kg	3/13	23 (5–54)	ND	2/13	15 (2–45)	37 (10–64)
10.0 mg/kg	4/31	13 (4–30)	ND	2/31	6 (0.8–21)	21 (6–36)
All doses	7/56	12 (5–24)	ND	5/56	9 (3–20)	22 (11–34)

Topalian et al NEJM 2012

Past practice of defining dose by MTD (maximum tolerated dose)

Pembrolizumab 2mg/kg = 10 mg/kg
(in efficacy and toxicity)

Dose is defined by minimal effective dose (MED)

This is not the MTD

Getting ready by addressing some practical questions

Should ICI be used as second or third line therapy?

Should all patients be tested for PD-L1 status prior to ICI?

What is the optimal dose?

Is ICI cost-effective?

Cost-Effectiveness of Epidermal Growth Factor Receptor Mutation Testing and First-Line Treatment With Gefitinib for Patients With Advanced Adenocarcinoma of the Lung

Gilberto de Lima Lopes Jr, MD, MBA, FAMS[1,2]; Joel E. Segel[3]; Daniel S. W. Tan, MBBS[4]; Young K. Do, MD, MPH, PhD[3]; Tony Mok, MD[5]; and Eric A. Finkelstein, PhD, MHA[3]

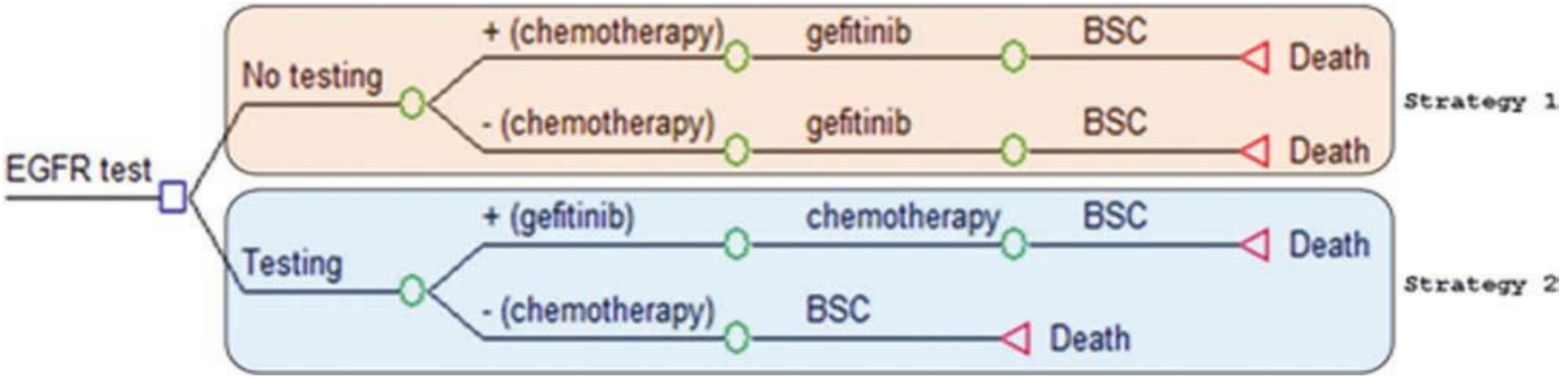


Table 2. Costs and QALYs Associated With Each Treatment Arm

Arm	Cost	Incremental Cost	QALYs	Incremental QALYs
Standard treatment (no EGFR testing followed by first-line chemotherapy and gefitinib in the second line)	$47,100	—	0.87	—
EGFR testing followed by first-line gefitinib for EGFR$^+$ and second-line chemotherapy	$44,700	−$2,400	0.91	0.04

This model may not be applicable to ICI

- Lack of a clear-cut biomarker for patient selection
- Monthly cost of ICI is at least three times more than Gefitinib

Cost USD$4500 in Hong Kong

If only 100mg vial is available

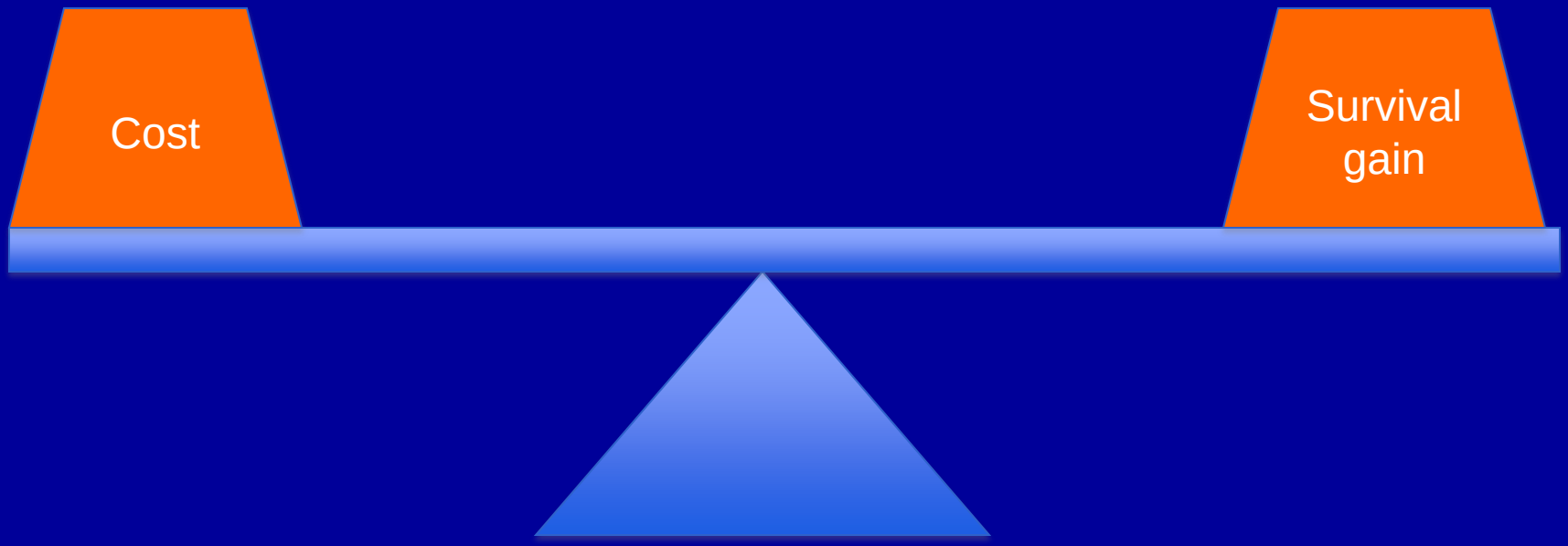
60kg
Asian Male

= 1.7mg/kg
= USD$4500 every 3 weeks

Availability of 20mg vials may improve cost-effectiveness

= 3.3mg/kg or
= 2mg/kg (wasted 80mg)
= USD$9000 every 3 weeks

Cost and survival gain



Cost and survival gain

What KEYNOTE 010 teaches us?

ICI can be given either as second or third line therapy

Patients with TPS >50% benefit most from ICI but the study design preclude the use of TPS <1% as negative predictor.

Optimal dose for pembrolizumab should be 2mg/kg but not sure if we can go lower

Cost-effectiveness is a highly debatable

Comment

THELANCET-D-15-08840

[PII_REPLACE]

Embargo: December 19, 2015—15:55 (GMT)

Are we ready for immune checkpoint inhibitors for advanced non-small-cell lung cancer?

Mok and Loong Lancet ePub Dec 19 2015

Are We Ready?

Yes, we are ready!

Almost

But I am surely ready for this !!!!