Established, emerging and evolving targets in NSCLC

NCIS @ NUH Medical Centre

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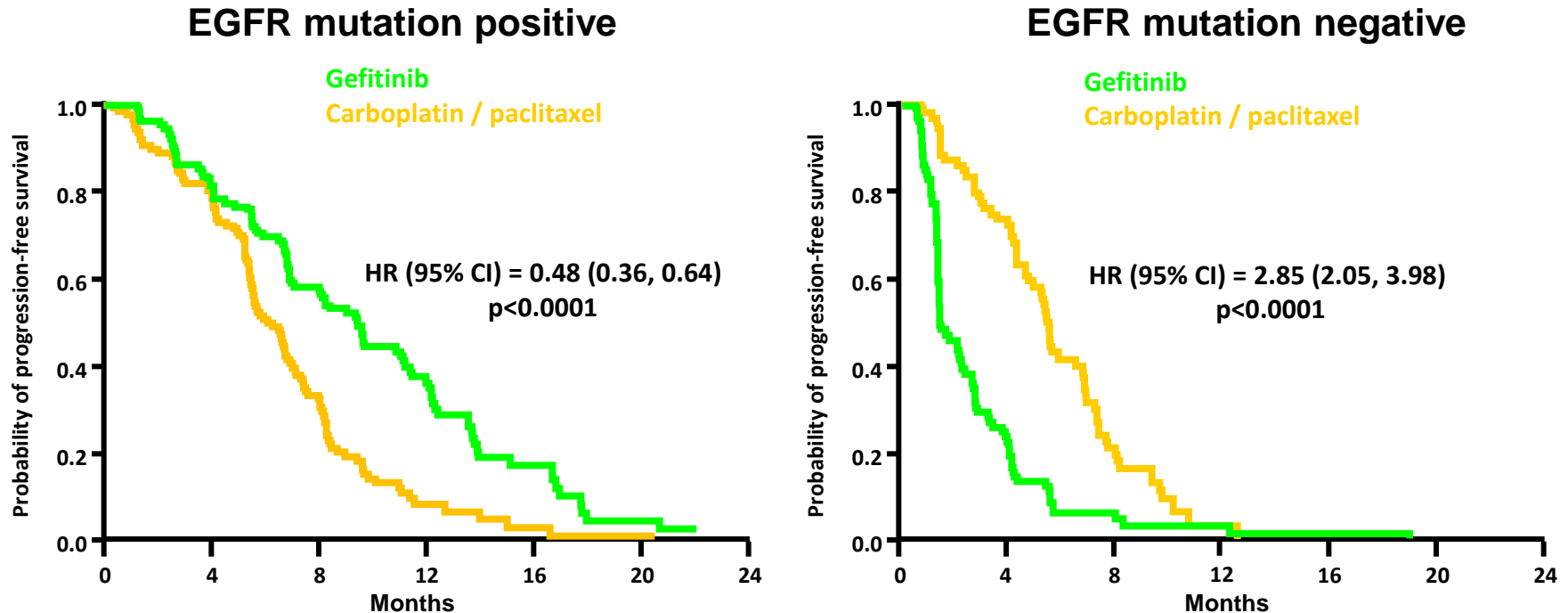National University Health System

Cancer Science Institute, Singapore

Poster discussion abstracts 425PD, 426PD and 427PD, ESMO ASIA 2015, Singapore, 18-21 December 2015

Disclosure slide

- Honorarium/ advisory board: Astra-Zeneca, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche

Author	Title	Abstract
T Mok	**Efficacy by blind independent central review (BICR): Post hoc analyses of the phase III, multicentre, randomised IPASS study of 1st-line gefitinib (G) vs carboplatin/paclitaxel (C/P) in Asian patients (pts) with EGFR mutation-positive advanced NSCLC**	**426PD**
J-S Lee	Clinical activity and safety of the EGFR mutant-specific inhibitor, BI1482694, in patients (pts) with T790M-positive NSCLC	425PD
N Matsuo	Prognostic significance of PD-L1 expression combined with CD8+ TIL density in stage III non-small cell lung cancer patients receiving concurrent chemoradiotherapy	427PD

IPASS: Gefitinib significantly better PFS vs chemotherapy in *EGFR* mutant disease

EGFR mutation positive

Gefitinib
Carboplatin / paclitaxel

HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001

(y-axis: Probability of progression-free survival; 1.0, 0.8, 0.6, 0.4, 0.2, 0.0)
(x-axis: Months; 0, 4, 8, 12, 16, 20, 24)

EGFR mutation negative

Gefitinib
Carboplatin / paclitaxel

HR (95% CI) = 2.85 (2.05, 3.98)
p<0.0001

(y-axis: Probability of progression-free survival; 1.0, 0.8, 0.6, 0.4, 0.2, 0.0)
(x-axis: Months; 0, 4, 8, 12, 16, 20, 24)

- Only 60% of phenotypically selected patients harboured the EGFR mutation

- Patients positive for *EGFR* mutation had substantial benefit
  - HR 0.48; PFS +3.2 months

- Patients negative for mutation did substantially better in control arm
  - HR 2.85 (favoured chemotherapy)

Mok NEJM 2009

Objectives

- Post-hoc analyses of PFS, ORR and DoR data according to blind independent central review (BICR), as performed at the request of the FDA (in 2015), in patients with *EGFR* mutation-positive NSCLC

Results

Table 1: Patient demographics

	Overall IPASS population (n=1217)	EGFR mutation-positive: overall IPASS population (n=261)	EGFR mutation-positive: IPASS BICR population (n=186)
Gender, n/N (%)			
Male	252/1217 (20.7)	50/261 (19.2)	32/186 (17.2)
Female	965/1217 (79.3)	211/261 (80.8)	154/186 (82.8)
WHO PS, n/N (%)			
0,1	1091/1217 (89.6)	241/261 (92.3)	175/186 (94.1)
2	126/1217 (10.4)	20/261 (7.7)	11/186 (5.9)
Smoking history, n/N (%)			
Never-smoker	1140/1217 (93.7)	246/261 (94.3)	178/186 (95.7)
Light ex-smoker	77/1217 (6.3)	15/261 (5.7)	8/186 (4.3)

Never smoker, smoked <100 cigarettes in lifetime; light ex-smoker, stopped smoking ≥15 years previously, and had ≤10 pack-years of smoking
BICR, blind independent central review; EGFR, epidermal growth factor receptor; IPASS, Iressa Pan-ASia Study; PS, performance status; WHO, World Health Organization

71% of patients from EGFR MT population had BICR
Similar patient characteristics compared with overall EGFR+ population

Outcomes according to BICR

	PFS (m)			ORR,%			DoR (m)	
	G	CP	HR	G	CP	OR	G	CP
IPASS overall	5.7	5.8	0.741, p< 0.0001	43	32.2	1.59, p<0.001	NA	NA
IPASS EGFR+	9.5	6.3	0.482, p< 0.0001	71.2	47.3	2.75, p<0.001	8.7	NA
IPASS EGFR+ BICR	10.9	7.4	0.544, p=0.0012	67	40.8	3.0, p=0.0004	9.6	5.5

CP=carboplatin/ paclitaxel; G= gefitinib


Figure 3: Kaplan-Meier curve for PFS by BICR (*EGFR* mutation-positive ITT population)
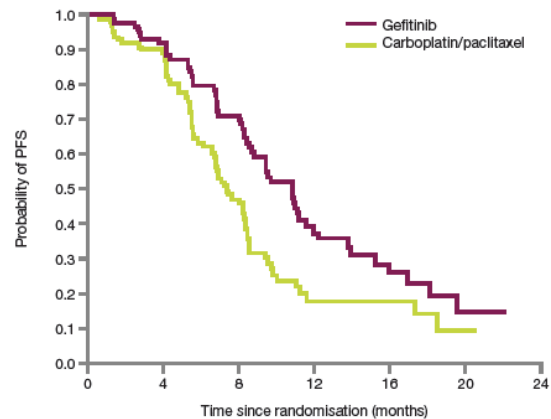
Number of patients at risk
Gefitinib   88   77   56   21   10   2   0
Carboplatin/paclitaxel 98   83   35   8   5   1   0

Patients who had not progressed at the data cut-off (14 April 2008) were censored at the BICR data cut-off
BICR, blind independent central review; EGFR, epidermal growth factor receptor; ITT, intent-to-treat; PFS, progression-free survival

EGFR mutation positive

Gefitinib
Carboplatin / paclitaxel

HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001
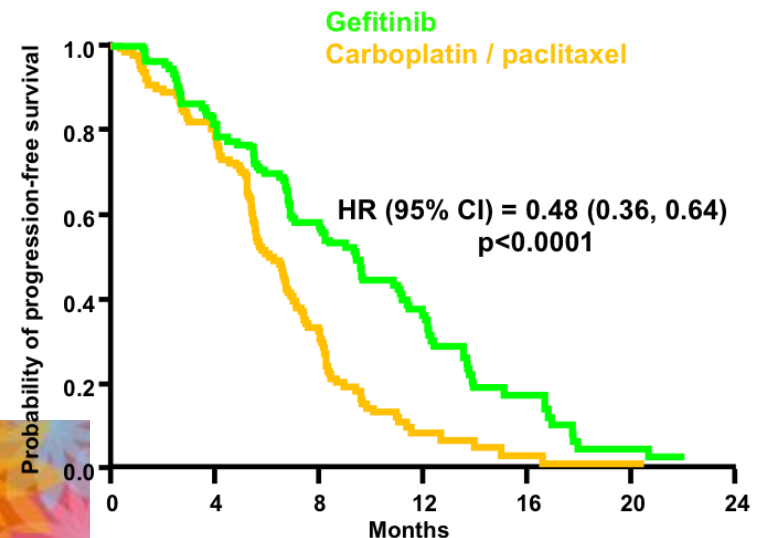
Progression free survival

- PFS: "the date of randomization to the earliest sign of disease progression, as determined by means of RECIST or death from any cause."

- Assessment of PFS:
  - reliable and **unbiased**

Sources of bias
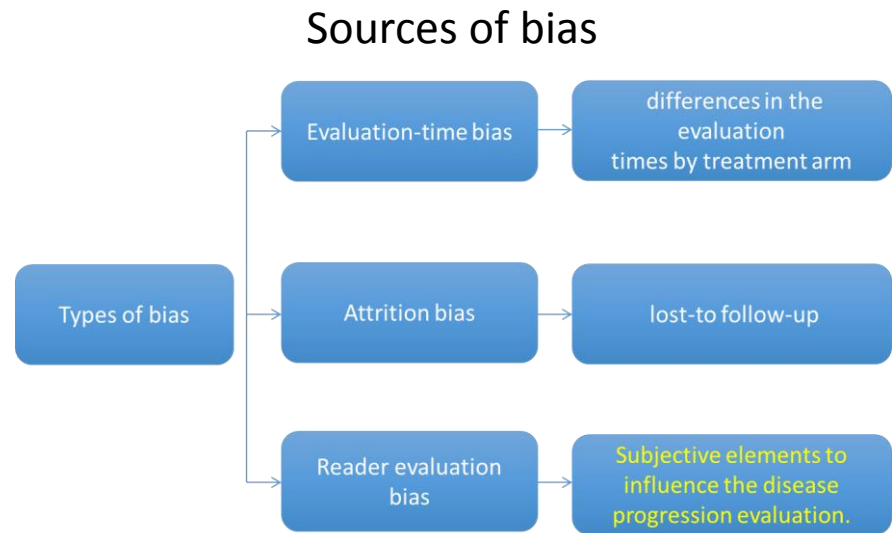
"Unbiased" assessment of PFS

- Often verified through the use of a blinded independent central review (BICR)
- BICR
  - Reduce bias & measurement variability
  - recommended in regulatory guidance documents for unblinded phase III clinical trials
  - Limitations:
    - adds substantial cost & complexity to clinical trials
    - informative censoring (imaging assessment of subjects may cease due to unconfirmed locally determined progression).
    - Unable to detect symptomatic progression

Incorporating BICR in clinical trials

Types of BICR	Comments	Challenges
Real time	central review: basis for any treatment decision	Technical hurdles, ethical & legal issues
Retrospective	reduces measurement variation Use when local evaluations indicate +ve trial	Prospective collection Informative censoring
Extra scans after local progression	more reliable PD (central review)	Required per protocol
Central Review–Directed Follow-Up	Reduce informative censoring	Ability to perform real-time central review
Blinded local review	Reduce biased end point evaluation	Informative censoring if investigator calls PD

Korn CCR 2013, Dodd JCO 2008

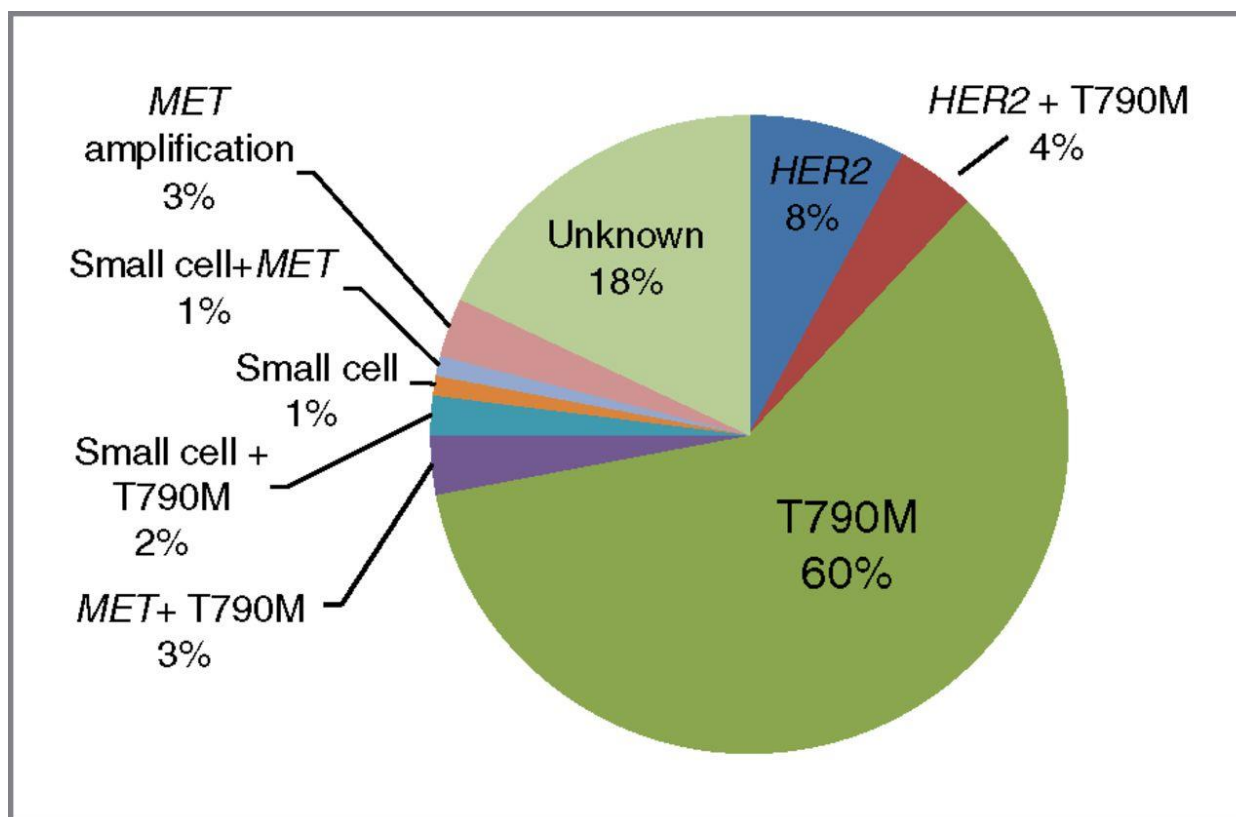# Strong correlation between BICR vs local evaluation to assess PFS
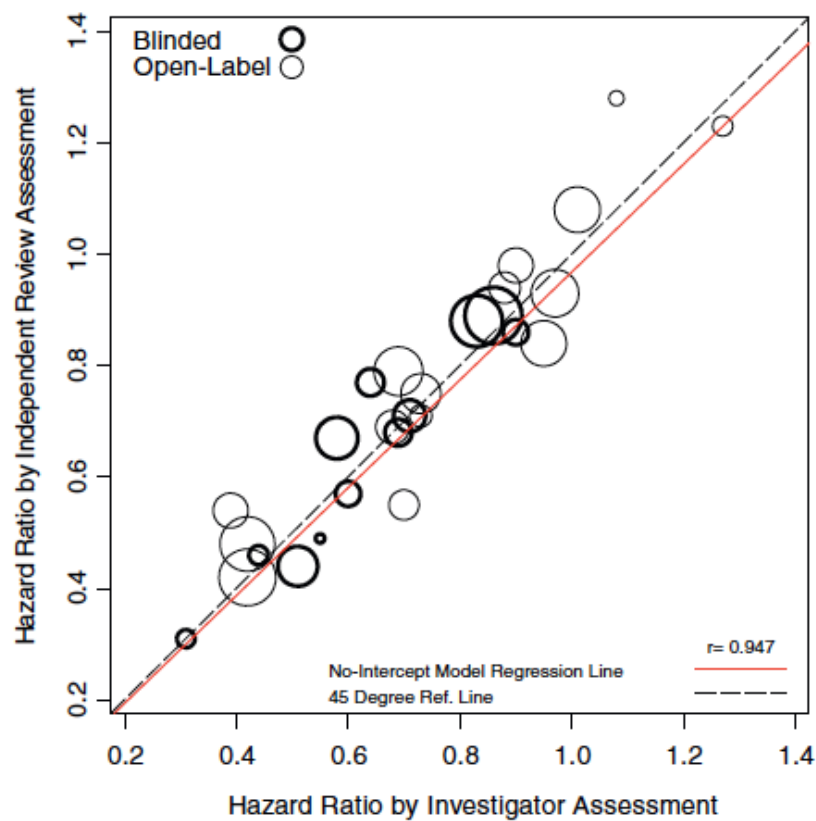
- Can BICR be used more efficiently?
  - Audit tool to detect evaluation bias
  - Full BICR where measurement error likely to be high
  - Better trial design, training, and QA
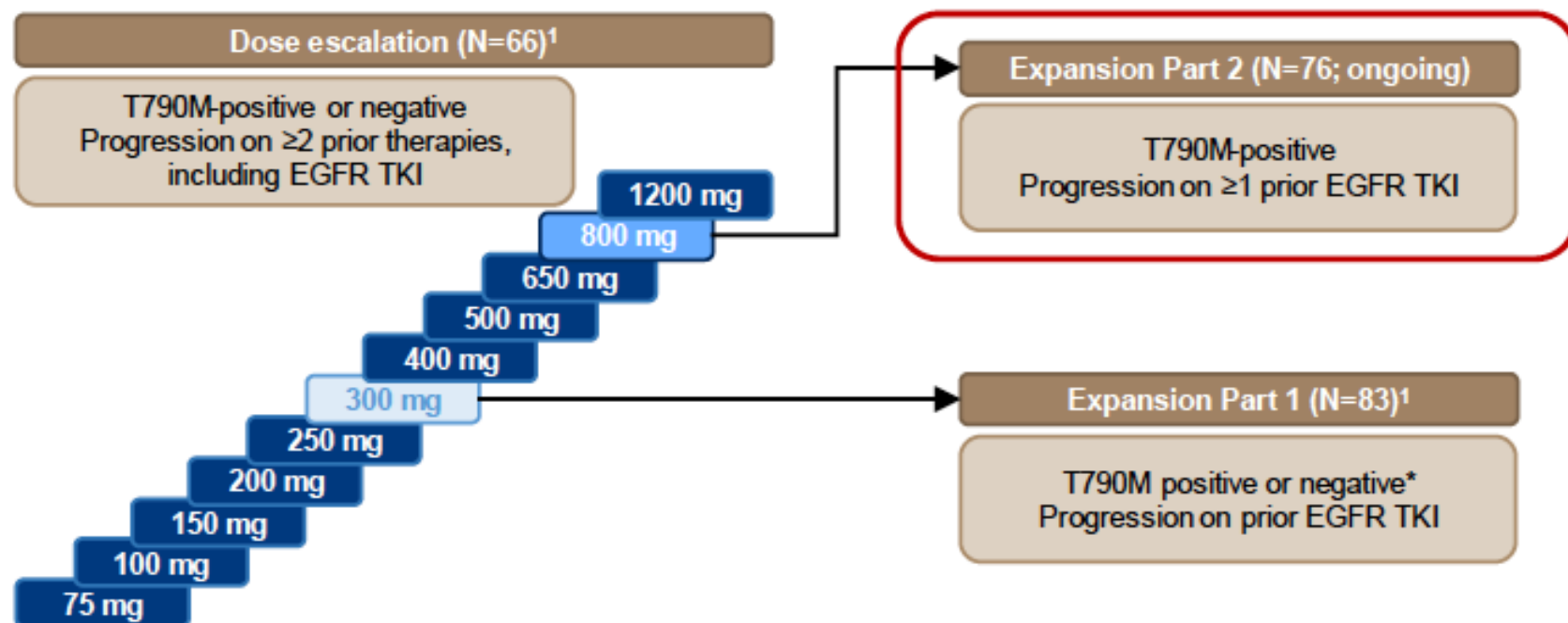
Summary

- BIRC similar to investigator assessment

- Subset of IPASS EGFR+ population (71%)
- Potential for informative censoring

- Challenge: treatment of patients upon progression

Mechanisms of resistance to EGFR TKIs

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T Mok	Efficacy by blind independent central review (BICR): Post hoc analyses of the phase III, multicentre, randomised IPASS study of 1st-line gefitinib (G) vs carboplatin/paclitaxel (C/P) in Asian patients (pts) with EGFR mutation-positive advanced NSCLC	426PD
J-S Lee	**Clinical activity and safety of the EGFR mutant-specific inhibitor, BI1482694, in patients (pts) with T790M-positive NSCLC**	**425PD**
N Matsuo	Prognostic significance of PD-L1 expression combined with CD8+ TIL density in stage III non-small cell lung cancer patients receiving concurrent chemoradiotherapy	**427PD**

Study design and patients

Dose escalation (N=66)[1]

T790M-positive or negative
Progression on ≥2 prior therapies,
including EGFR TKI

1200 mg
800 mg
650 mg
500 mg
400 mg
300 mg
250 mg
200 mg
150 mg
100 mg
75 mg

Expansion Part 2 (N=76; ongoing)

T790M-positive
Progression on ≥1 prior EGFR TKI

Expansion Part 1 (N=83)[1]

T790M positive or negative*
Progression on prior EGFR TKI

- Between August 2014 and April 2015, 76 patients with T790M-positive NSCLC were enrolled
- Of these, 58 (76%) had received prior gefitinib, 21 (28%) prior erlotinib and 11 (14%) prior afatinib
- Most patients (57 [75%]) had received at least two lines of previous systemic treatments

Lee ESMO Asia 2015

18-21 DECEMBER
SINGAPORE

Tumor response with BI1482694/HM61713 800 mg QD (data cut-off 30 June 2015)
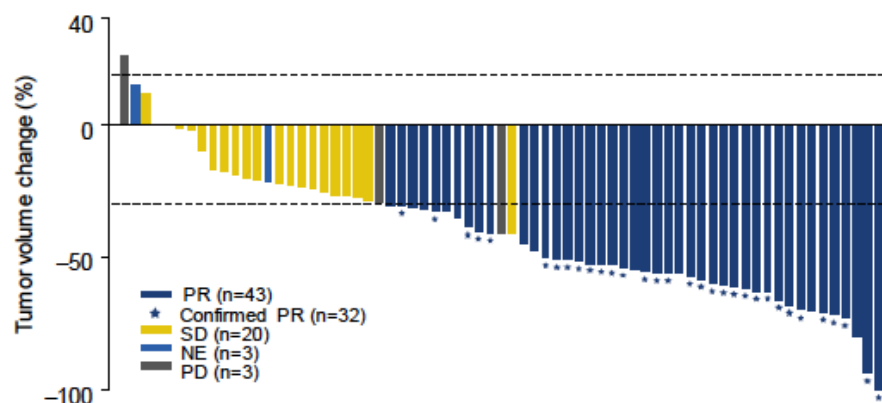
	Evaluable patients (n=69)
OR (confirmed and unconfirmed), n (%)	43 (62)
Disease control, n (%)	63 (91)
Confirmed OR, n (%)	32 (46)
SD, n (%)	31 (45)
PD, n (%)	3 (4)
NE, n (%)	3 (4)

Figure 4. Imaging of the target brain lesion in April 2015 (baseline; A), July 2015 (B) and August 2015 (C)
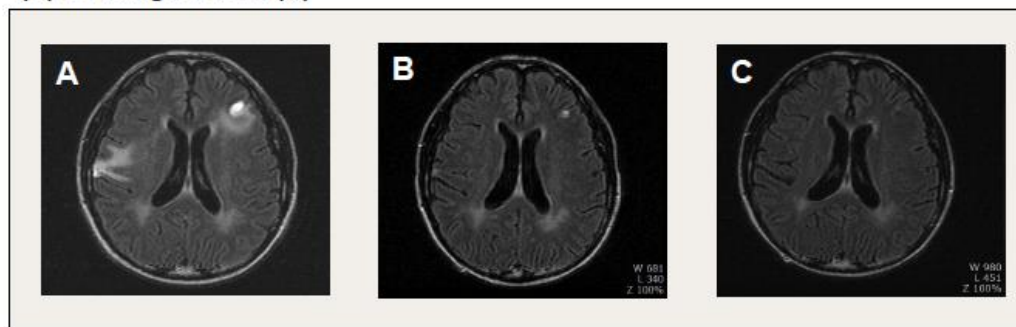
Common treatment-related AEs in patients receiving BI1482694/HM61713 800 mg QD (data cut-off 30 June 2015)

AE, n (%)	BI1482694 (HM61713) 800 mg QD (n=76)	
	All grades	Grade 3
Diarrhea	42 (55)	0
Rash	29 (38)	4 (5)
Nausea	28 (37)	0
Pruritus	27 (36)	1 (1)
Dry skin	22 (29)	1 (1)
Palmar-plantar erythrodysesthesia syndrome	22 (29)	2 (3)
Decreased appetite	20 (26)	0
Skin exfoliation	16 (21)	0
Vomiting	12 (16)	2 (3)
Abdominal pain	11 (14)	0
ALT increased	11 (14)	2 (3)
Abdominal pain upper	10 (13)	0
Constipation	10 (13)	0
Pyrexia	9 (12)	0
AST increased	9 (12)	2 (3)
Platelet count decreased	9 (12)	0
Dyspepsia	8 (11)	0
Fatigue	8 (11)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Lee ESMO Asia 2015

3G EGFR TKIs

Drug	Company	Clinical stage
Tagrisso (Osimertinib AZD9291)	Astra-Zeneca	FDA accelerated approval
Rociletinib (CO-1686)	Clovis	FDA breakthrough
HM61713 (BI1482694)	Hanmi (Boehringer Ingelheim)	Phase III
EGF816	Novartis	Phase I/II
ASP8273	Astellas	Phase III
PF-06747775	Pfizer	Phase I/II
AP26113	Ariad	Phase I/II
Avitinib	ACEA	Phase I

3G EGFR TKIs are mutant specific & WT sparing: less EGFR related AEs

TKI	Drug	IC50 nM		
		WT	Mut	T790M
1st generation	Erlotinib	7	14	>5000
	Gefitinib	61	16	3102
2nd generation	Afatinib	25	0.6	22
	Dacomitinib	26	0.7	40
3rd generation	Osimertinib (AZD9291)	1865	17	15
	Rociletinib (CO-1686)	>2000	59	62
	HM61713 (BI1482694)	2225	9	10
	ASP8273	230	46	26

3G EGFR TKIs are effective in T790M+

Study	Drug	Key criteria	Phase (n)	ORR, %	DCR, %	PFS, months
AURA	AZD9291	EGFR+ or Jackman criteria, PD on prior EGFR tki, chemo	I/II (253)	61	97	9·6
AURA-2	AZD9291	T790M	II (210)	64	90	NR
TIGER-X	Rociletinib (CO-1686	EGFR mt, prior EGFR TKI	I/II (130)	59	93	13.1
JS Lee	**HM61713 (BI1482694)**	**T790M, 2 prior therapies, including EGFR TKI**	**II (76)**	**62**	**91**	**NR**
EGF816X2101	EGF816	T790M	I/II	60	93	NR
	ASP8273	EGFR mt, prior EGFR TKI	I/II	67	NR	NR

3G EGFR TKIs are tolerable

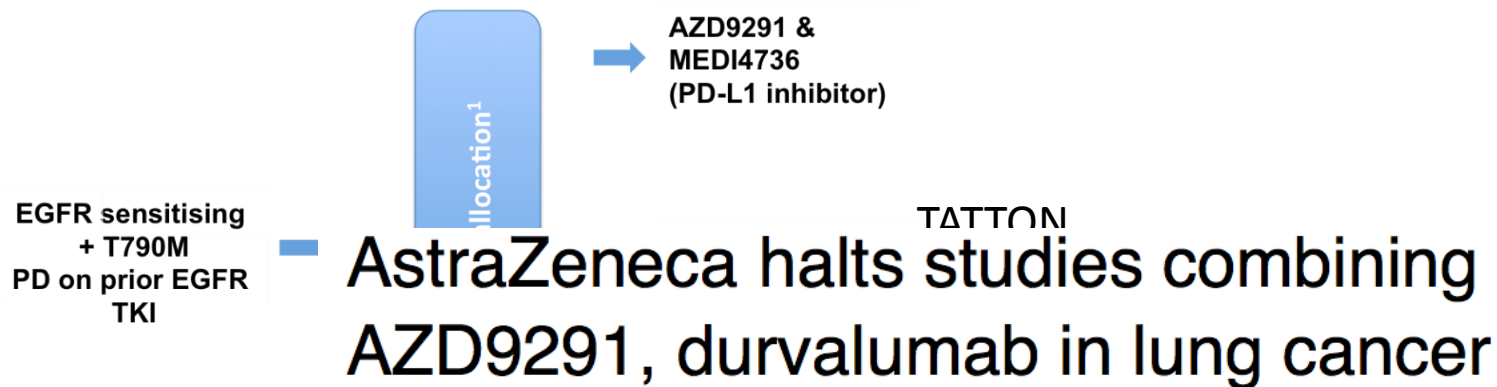| Study	Drug	All grade , %					% G3+ TRAE	% discontinuation due to TRAE
		Diarrhea	Nausea	Rash	Dry skin	Pruritus		
AURA	AZD9291	33	18	32	11	17	11	1
AURA-2	AZD9291	39	16	23	25	15	11	3
TIGER-X	Rociletinib	22	35	<1	NR	NR	NR	2.5
JS Lee	**HM61713**	**55**	**37**	**38**	**29**	**36**	**NR**	**4**
EGF816X2101	EGF816	32	13	43	28	25	21	1.8

Summary

- Activity similar to other 3G EGFR TKIs

- Safe

- Potential CNS activity

Future challenges

- Which is the best 3G EGFR TKI?

- Use in 1st line setting

- Role in T790M-ve patients

- Activity in CNS disease

- Mechanisms of acquired resistance

- Improve efficacy 3G EGFR TKIs

- Combination therapy eg. Immune checkpoint inhibitor

3G EGFR TKI + immune checkpoint inhibition

AZD9291 &
MEDI4736
(PD-L1 inhibitor)

Allocation[1]

EGFR sensitising
+ T790M
PD on prior EGFR
TKI

TATTON

AstraZeneca halts studies combining AZD9291, durvalumab in lung cancer

(Ref: Bloomberg, Yahoo!Finance)

October 9th, 2015

By: Matthew Dennis

AZD9291

RANDOMISATION

CAURAL,
NCT02454933

EGFR sensitising
+ T790M
PD on prior
EGFR TKI

AZD9291 +MEDI473

SINGAPORE 2015 ESMO

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PD-L1 as a target

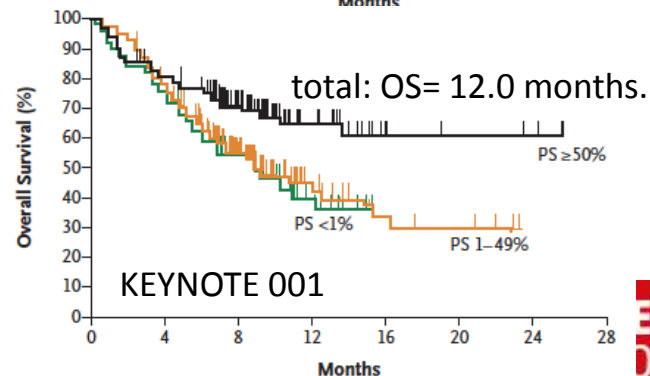| Author	Title	Abstract
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Association btw PD-L1 expression & OS/PFS when treated with immune checkpoint inhibitors

CHECKMATE 017

	Median Overall Survival mo (95% CI)	1-Yr Overall Survival % of patients (95% CI)	No. of Deaths
Nivolumab (N=135)	9.2 (7.3–13.3)	42 (34–50)	86
Docetaxel (N=137)	6.0 (5.1–7.3)	24 (17–31)	113

Hazard ratio for death, 0.59 (0.44–0.79) P<0.001

C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab no. of patients	Docetaxel	Unstratified Hazard Ratio (95% CI)
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)

Nivolumab Better — Docetaxel Better

A Overall Survival

OS: 12.2 months vs 9.4 months (HR 0.73, 95% CI 0.59-0.89)

CHECKMATE 057

PD-L1 expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction P-value
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.06
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	<0.001
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	<0.001
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.02
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	<0.001
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	

● High PD-L1 expression
● Low to no PD-L1 expression
● PD-L1 not quantifiable

Nivolumab — Docetaxel

total: OS= 12.0 months.

PS ≥50%
PS <1%
PS 1–49%

KEYNOTE 001

PS ≥50%
PS <1%
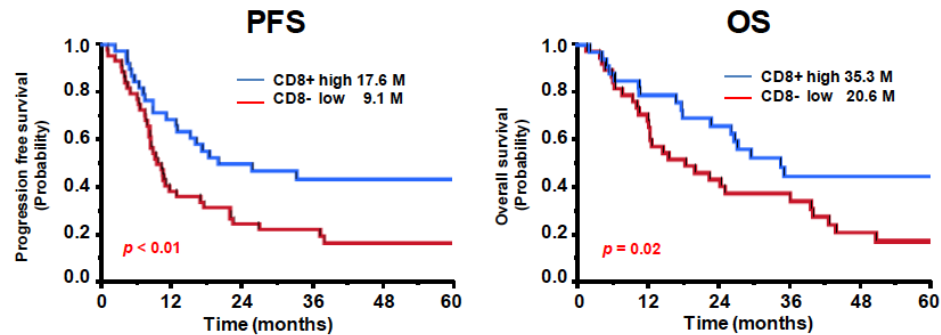PS 1–49%

1. Brahmer NEJM 2015, 2. Garon NEJM 2015, 3. Borghaei NEJM 2015

- Objectives:
  - To investigate the prognostic significance of PD-L1 expression and CD8+ TIL density in patients with locally advanced NSCLC receiving concurrent CT-RT
  - PD-L1 definition: <5% tumor staining of PD-L1
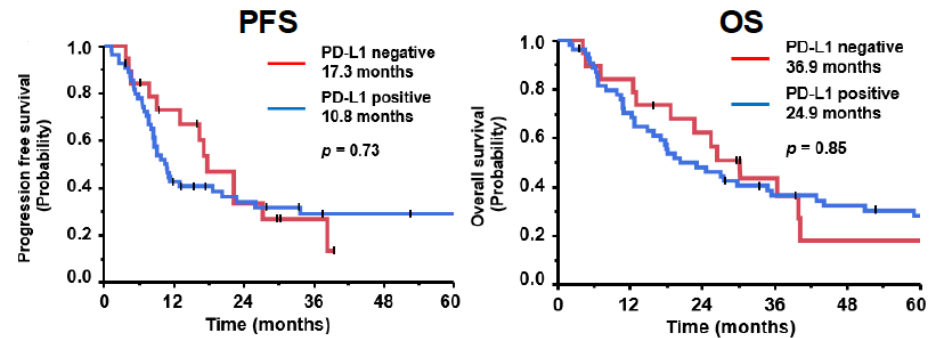- Ab clone:
  - abcam, Cambridge, UK

Results

CD8 group

PFS
CD8+ high 17.6 M
CD8- low 9.1 M
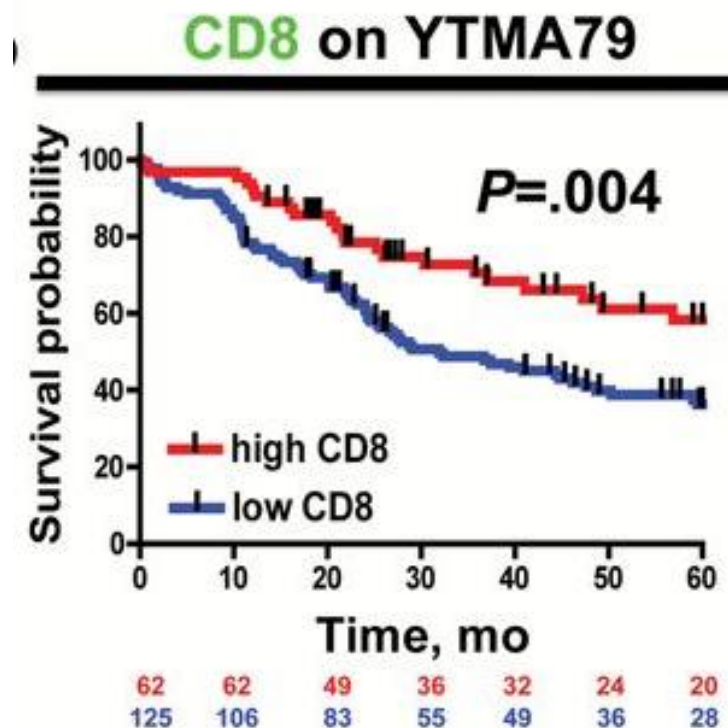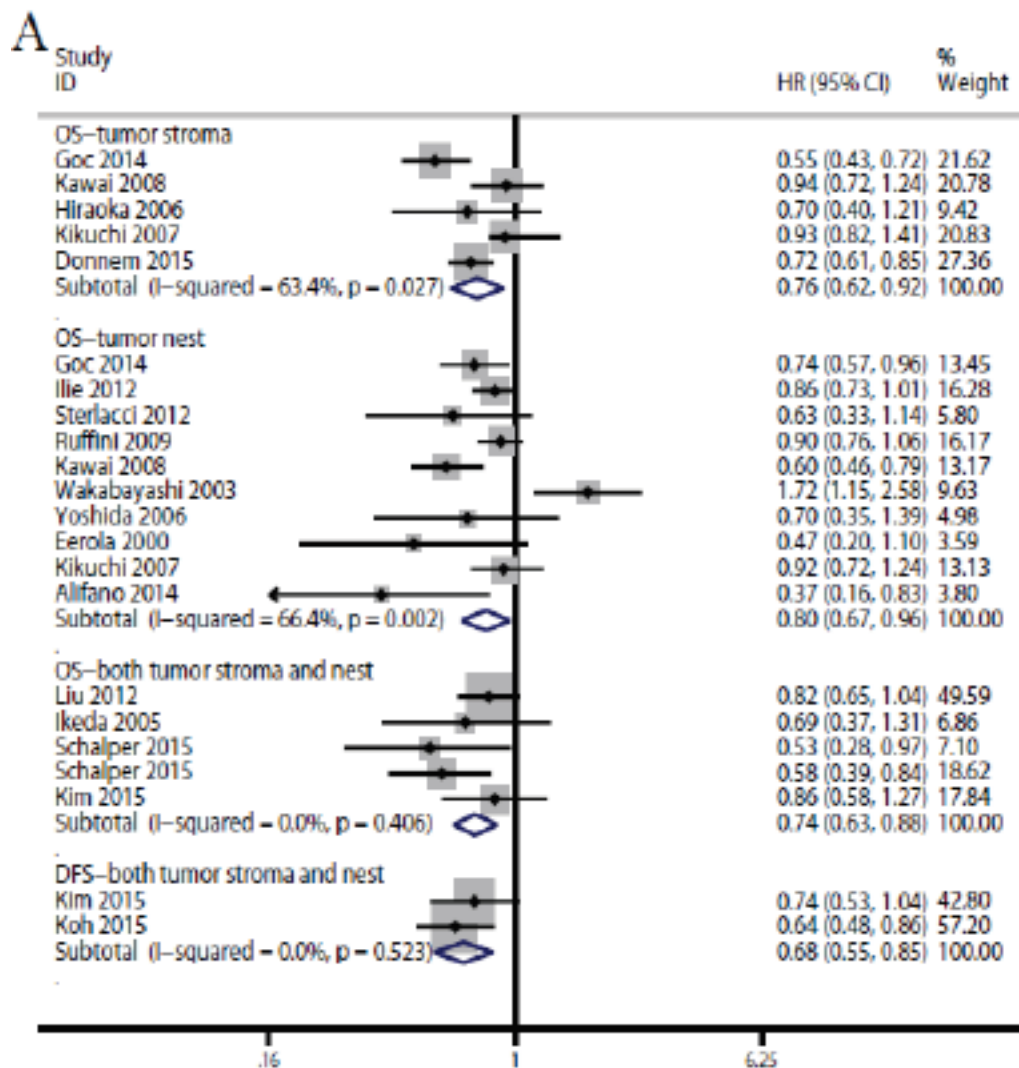p < 0.01

OS
CD8+ high 35.3 M
CD8- low 20.6 M
p = 0.02

CD8+ TIL density was associated with PFS/ OS

PD-L1 group

PFS
PD-L1 negative 17.3 months
PD-L1 positive 10.8 months
p = 0.73

OS
PD-L1 negative 36.9 months
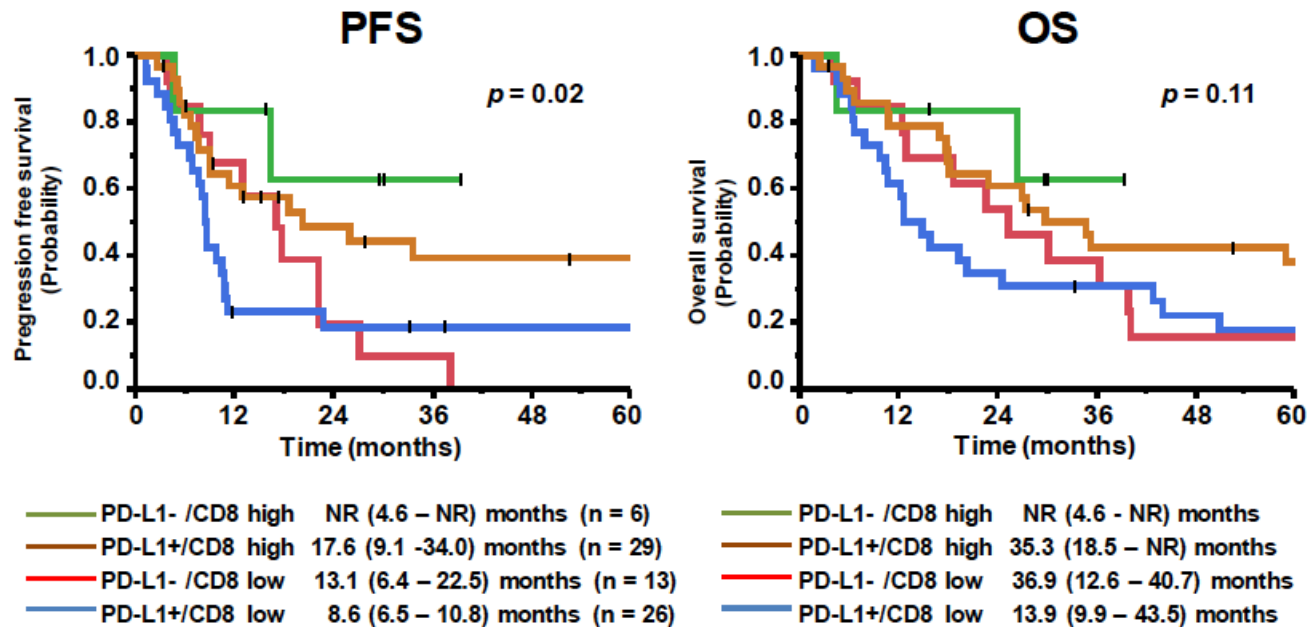PD-L1 positive 24.9 months
p = 0.85

PD-L1 not associated with PFS/ OS
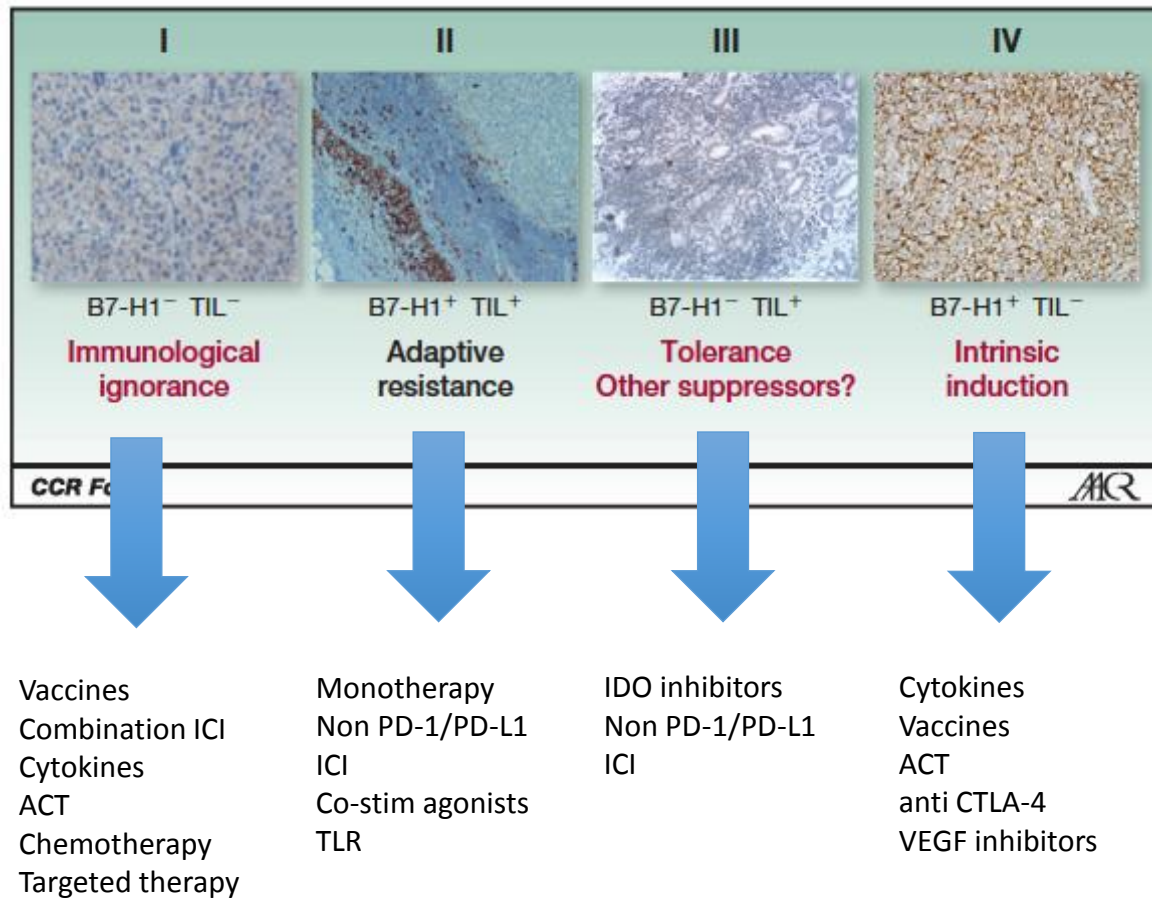
High CD8+ lymphocytes: improved OS, PFS in NSCLC

PD-L1 tumor expression is associated with worse survival in NSCLC

Asuncion… Soo WCLC 2015, Zhou Transl Lung Cancer Res 2015, Pan J Thorac Dis 2015, Wang Eur J Surg Oncol 2015

PD-L1/CD8 group

PFS

OS
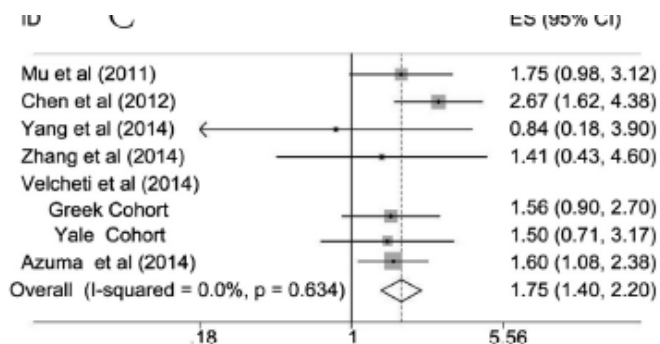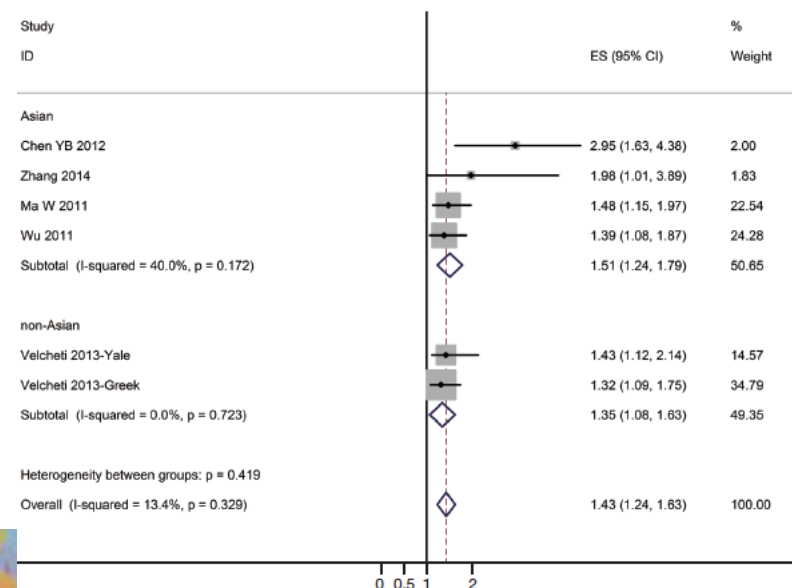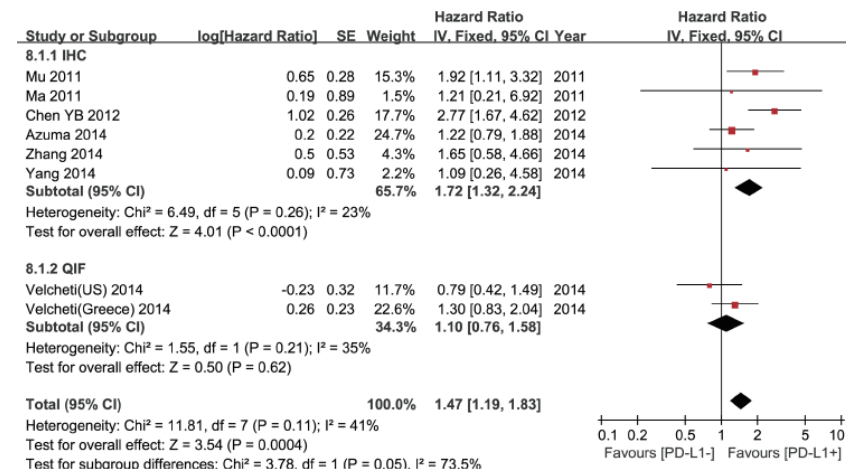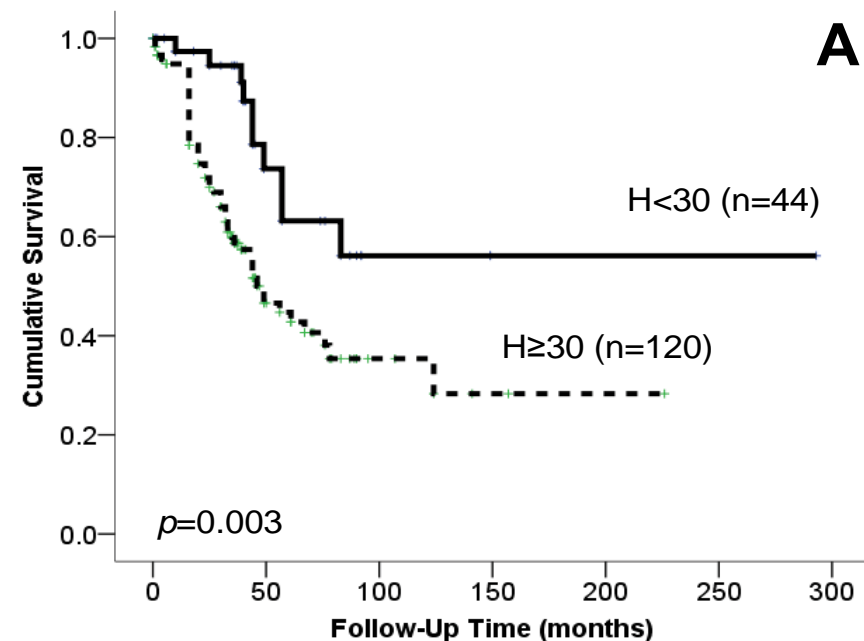
Tailoring treatment based on type of tumor microenvironment

I	**II**	**III**	**IV**
B7-H1⁻ TIL⁻	B7-H1⁺ TIL⁺	B7-H1⁻ TIL⁺	B7-H1⁺ TIL⁻
Immunological ignorance	Adaptive resistance	Tolerance Other suppressors?	Intrinsic induction

Vaccines
Combination ICI
Cytokines
ACT
Chemotherapy
Targeted therapy

Monotherapy
Non PD-1/PD-L1
ICI
Co-stim agonists
TLR

IDO inhibitors
Non PD-1/PD-L1
ICI

Cytokines
Vaccines
ACT
anti CTLA-4
VEGF inhibitors

Sznol CCR 2013

Multiple commercially available PD-L1 IHC assays with different scoring & cutoffs:

Author	Manufacturer	clone	Scoring	Cutoff (+)
Yang	Proteintech Group	NR	% tumor cells	>=5%
Azuma	Lifespan Biosciences	NR	H-score	>=30
D'Incecco	Abcam	ab58810,	H-score	>=75
Mu	NR	NR	H-score	>Median
Chen	Abcam	236A/E7	Immunoreactive score	>=3
Zhang	Sigma-Aldrich	SAB2900365	Quickscore	>Median
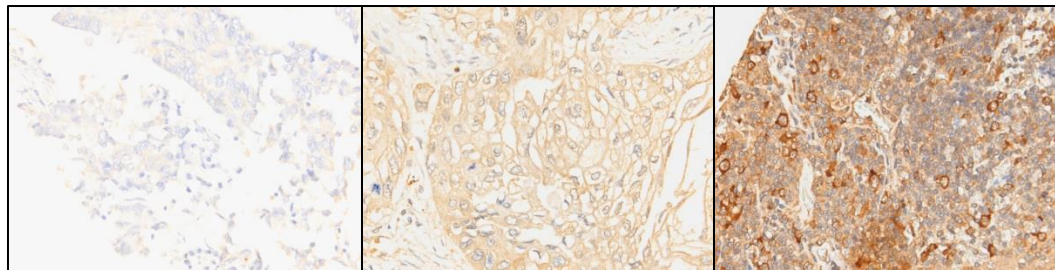
ProSci

Multiple CDx PD-L1 IHC assays

Drug	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
Pharmaceutical	BMS	Merck	Roche	AZ	Merck Serono/ Pfizer
Ab clone	28-8	22C3	SP142	SP263	NR
Manufacturer	Dako	Dako	Ventana	Ventana	NR
Cells scored	TC	TC	TC, IC	TC	TC
Cutoff	1%, 5%,10%	1-49%, 50%	1%, 5%, 10%	25%, 95%	1%

SP263

SP142

E1L3N

Adapted from Soo Trans Lung Cancer Res 2015
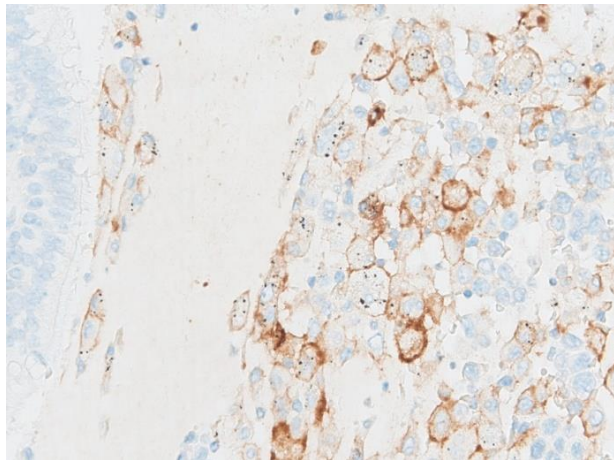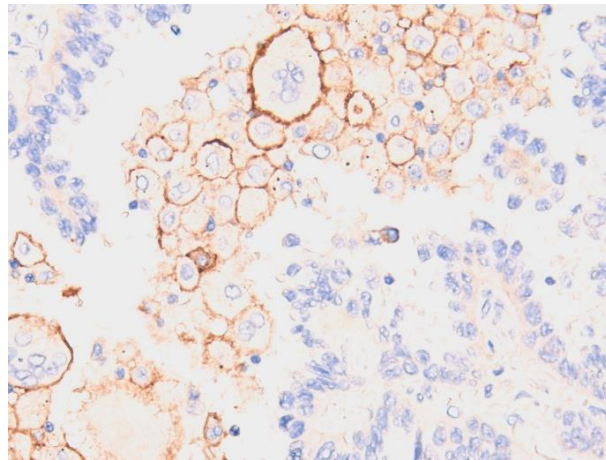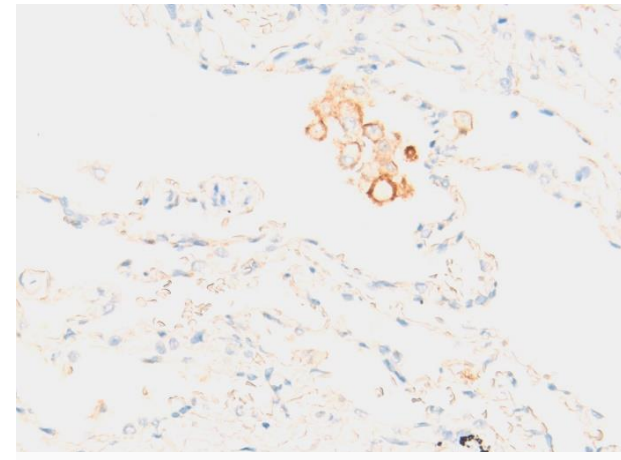
Immune checkpoint inhibition in Stage III NSCLC

Study	Population	Treatment	Phase	NCT
NICOLAS	Stage III NSCLC, Amenable to Concomitant or Sequential CT-RT	Nivolumab after completion CT, RT	II	NCT02434081
PACIFIC	Stage III NSCLC, No PD after platinum based CT/RT x2	MEDI4736 v placebo	III	NCT02125461

Summary

- No association btw PD-L1 expression and clin-path

- Provides data for stage III NSCLC

- CD8 high has better prognosis, c/w literature

- Challenges for PD-L1 as a biomarker
  - Tumor heterogeneity
  - Dynamic expression
  - Primary vs LN/ metastatic disease
  - Multiple IHC Ab and staining conditions
  - Multiple cutoffs & scoring systems:

Mechanisms of EGFR inhibitor resistance and therapeutic strategies: established, emerging and evolving

Established: Mok, gefitinib
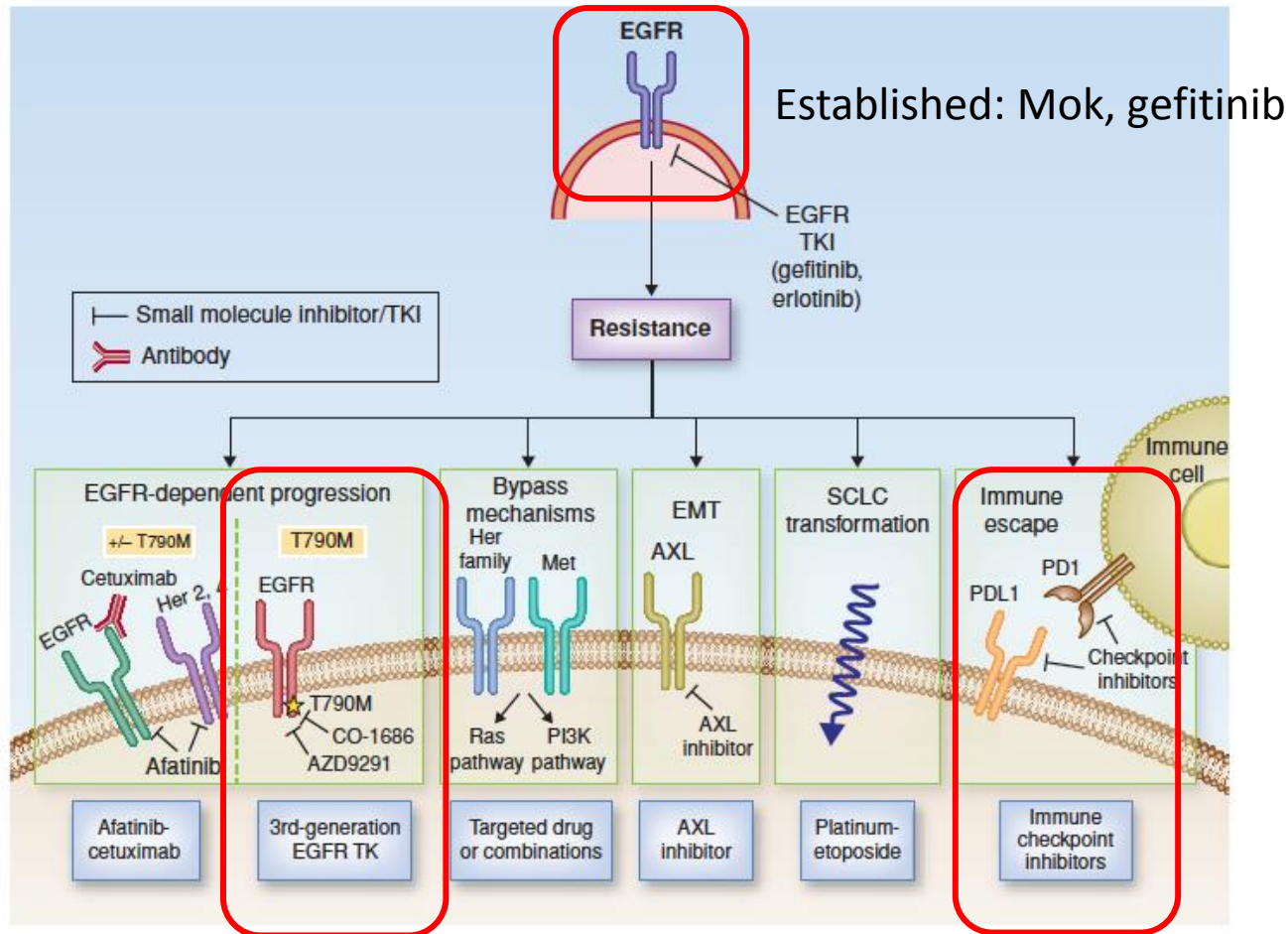
Emerging: JS Lee, BI1482694

Evolving: Matsuo, PD-1/ PD-L1

Gibbons Cancer Discovery 2014

Thank you for your attention