Raising the bar for targeted therapies
## optimizing management of molecular subsets of NSCLC

Dr Daniel SW Tan

Consultant, Division of Medical Oncology
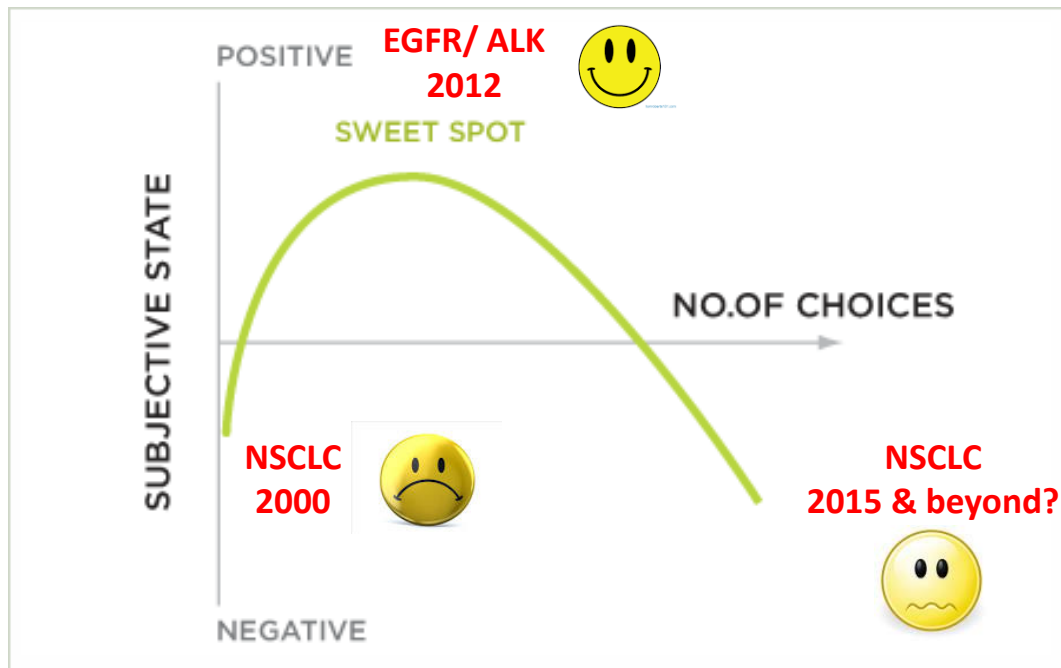
National Cancer Centre Singapore

Disclosures

- Advisory Role and Consultant: Novartis, Bayer, Boehringer Ingelheim
- Research Funding: Novartis

Oncogene-addicted NSCLC

National Cancer
Centre Singapore
SingHealth

- **Transformative potential of clinical genomics**
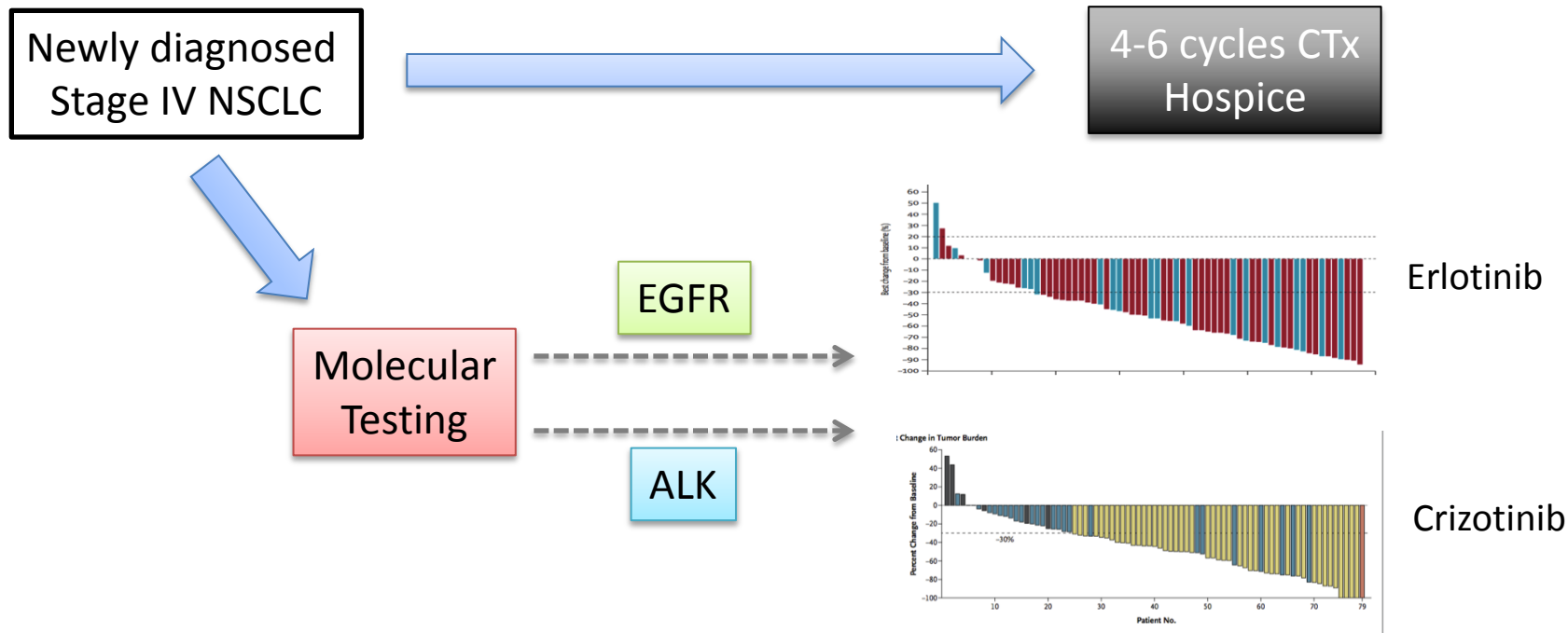
The paradox of choice

Life gets complicated....

	EGFR	ALK
1st generation	**Erlotinib, Gefitinib**	**Crizotinib**
Combinations	Erlotinib-bevacizumab	Crizotinib with Dacomitinib, AT13387, Axitinib, pemetrexed
2nd generation	**Afatinib**	**Ceritinib**, Alectinib, Brigatinib
Combinations	Afatinib-cetuximab	Ceritinib-AUY922, Ceritinib-LEE001, Alectinib-Atezolizumab
3rd generation	**Osimertinib**, rocelitinib	**Lorlatinib (PF06463922)**
Combinations	Osimertinib-AZD6244	??

Is there a role for novel therapeutic strategies?

- **Patients are infrequently "cured"**
- **Progression free survival 10-12 months**

Questions

- How do we identify patients most likely to benefit to a specific agent/ combination?
- How can we optimize sequence of therapy?
- How to integrate emerging trial data into clinical practice, so that we select the best treatment for an individual patient?

Abstracts

Efficacy and Safety of Ceritinib in Patients With ALK-Rearranged Non-Small Cell Lung Cancer and Baseline Brain Metastases – results from ASCEND-2 and ASCEND-3

Keunchil Park, Daniel Tan, MyungJu Ahn, Chong-Jen Yu, Chun-Ming Tsai, Toyoaki Hida, Makoto Nishio, Fabrice Branle, Chetachi Emeremni, Santosh Sutradhar, Tony Mok

Erlotinib plus bevacizumab versus erlotinib alone as first-line treatment for advanced non-squamous non-small-cell lung cancer with activating EGFR mutation:JO25567 exploratory subgroup analysis

Yukio Hosomi, Takashi Seto, Makoto Nishio, Koichi Goto, Noboru Yamamoto, Isamu Okamoto, Kosei Tajima, Naohito Inagaki, and Nobuyuki Yamamoto
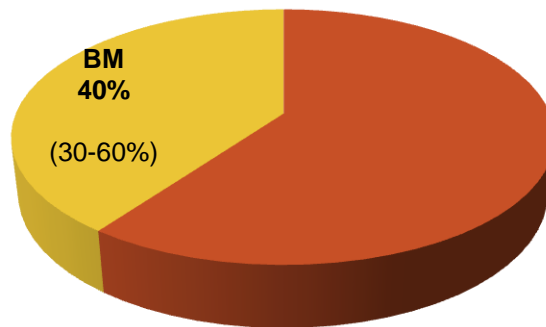
CNS involvement in NSCLC

All comers incidence of BM

BM 40%

(40-50%)
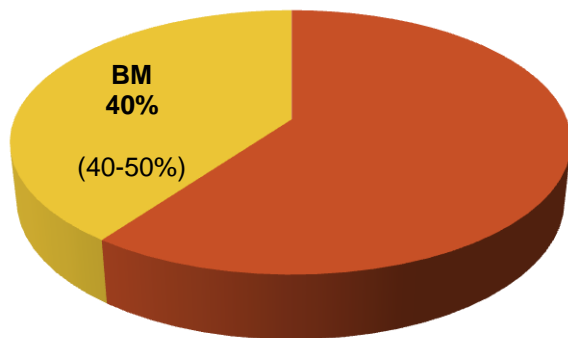
Sorensen JB et al, J Clin Oncol.1988;6: 1474
Langer CJ et al, J Clin Oncol 2005, 23:6207

EGFR + patients treated with 1st generation TKI

BM 40%

(30-60%)

Homuro et al , Cancer.2005: 3, 2344
Hoen S et al, Clin Cancer Res 2010: 16, 5873
Lee YJ et al, Cancer 2010: 116, 1336

ALK+ patients treated with crizotinib

BM 50%
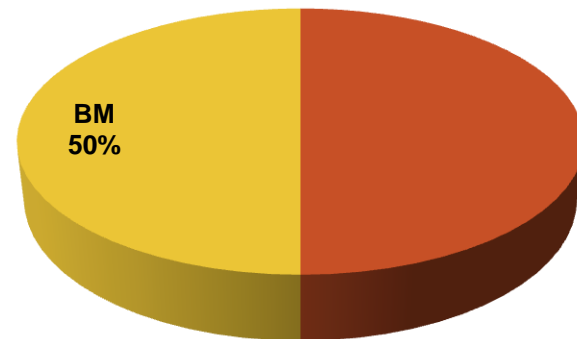
Shaw AT et al, Lancet Oncol 2011: 12, 1004
Camidge R et al, Nat Rev Clin Oncol 2014: 11, 473

Younger; favourable outcomes

JOURNAL OF CLINICAL ONCOLOGY   ORIGINAL REPORT

Clinical Experience With Crizotinib in Patients With Advanced *ALK*-Rearranged Non–Small-Cell Lung Cancer and Brain Metastases
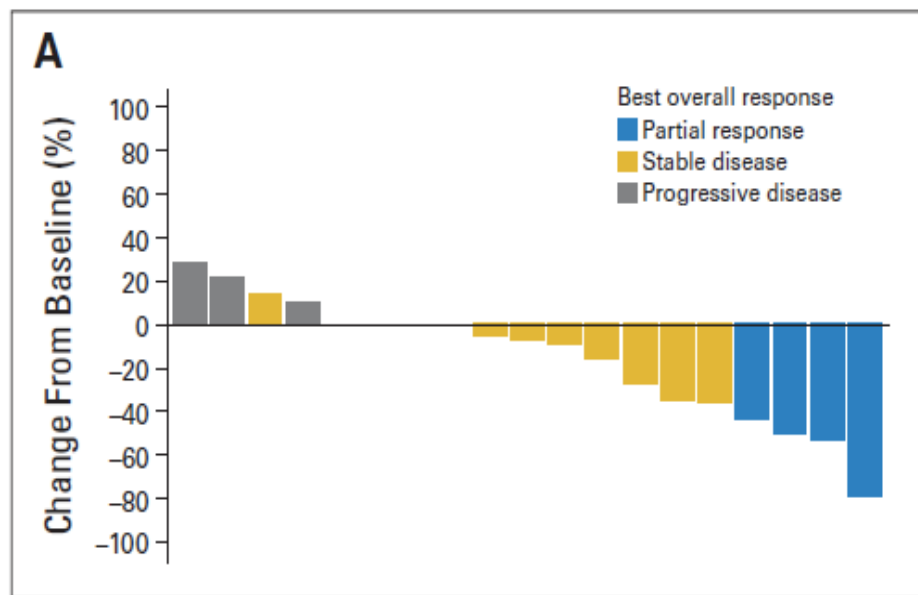
Daniel B. Costa, Alice T. Shaw, Sai-Hong I. Ou, Benjamin J. Solomon, Gregory J. Riely, Myung-Ju Ahn, Caicun Zhou, S. Martin Shreeve, Paulina Selaru, Anna Polli, Patrick Schnell, Keith D. Wilner, Robin Wiltshire, D. Ross Camidge, and Lucio Crinò

Can improve intracranial PFS in patients with baseline CNS mets?

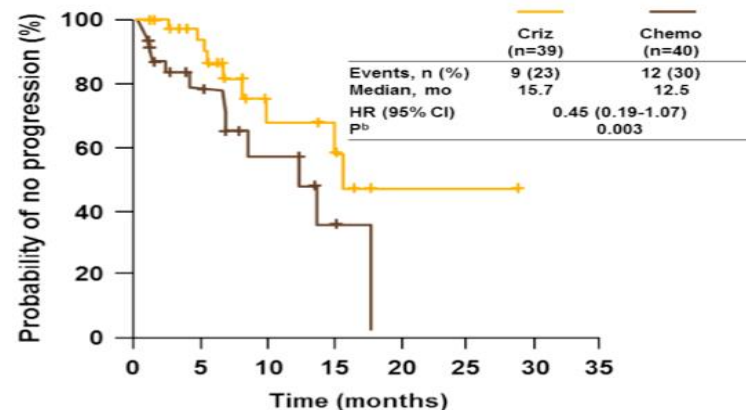**CNS activity (PROFILE 1014)[3]**
23% had brain metastases at baseline

Fig 2. Waterfall plots of best percentage change in intracranial target lesions for p[...] or (B) treated brain metastases.

Costa et al. JCO 2015; Solomon et al. ESMO 2014

Study summary: Park et al.

National Cancer Centre Singapore
SingHealth

ASCEND-2: NCT01685060

Inclusion criteria
- Advanced or metastatic ALK+ NSCLC
- **Progression on standard therapy and crizotinib***
- 1-3 lines of chemotherapy
- WHO PS 0-2

ASCEND-3: NCT01685138

Inclusion criteria
- Advanced or metastatic ALK+ NSCLC
- **ALKi-naïve**
- 0 to 3 lines of chemotherapy
- WHO PS 0-2

	ASCEND-2	ASCEND-3
No of BM at baseline	**100**/140 (71.4%)	**50**/124 (40.3%)
No of prior regimens, n(%)		
1	0	24 (48.0)
2	40 (40.0)	15 (30.0)
≥ 3	60 (60.0)	11 (22.0)
Prior RT	72/100 (72%)	27/50 (54%)
Median (range) months	6.2 (0.5 – 54.0)	2.7 (0.5 – 31.9)
≤ 3 months prior, n (%)	21 (29.2)	14 (51.9)
RR (IC mets)	13/ 33 (39.4) (22.9, 57.9)	10/ 17 (58.8) (32.9, 81.6)
PFS (whole body + IC mets)	**6.8 months (5.4, 7.4)**	**11.0 months (7.2, NA)**
Dose reductions	53 (53%)	27 (54%)

CNS activity observed across 2nd generation ALK TKIs

	Alectinib		Brigatinib*		Ceritinib (Park et al.)	
	Measurable (n=50)	Measurable and non-measurable (n=136)	Measurable (n=15)	Non-measurable (n=31)	Measurable (ASCEND-2) (n=33)	Measurable (ASCEND-3) (n=17)
CNS ORR, %	64.0	42.6	53	35	39.4	58.8
CR	22.0	27.2	7	35	3	5.9
PR	42.0	15.4	47	NA	36.4	52.9
SD	26.0	42.6	20	48	45.5	23.5
PD	6.0	8.8	13	6	0	0
CNS DCR, %	90.0	85.3	87	94	84.8	82.4
CNS mPFS, mths	–	–	(n=46) 15.6 m		At least 6.8 m	At least 11.0 m

*8% patients with CNS mets at baseline were crizotinib-naïve

Gadgeel, et al. WCLC 2015; Camidge, et al. ECC 2015

Does it change my clinical practice?

National Cancer Centre Singapore
SingHealth

- **Adding to expanding data that 2nd generation ALK TKI are highly efficacious in CNS disease**
  - Better than crizotinib? *Probably*
  - Trials underway to better elucidate CNS activity
    - ASCEND-7 (ceritinib in patients with brain metastasis)
    - ALEX trial (crizotinib vs alectinib) – CNS PFS co-primary endpoint

- **Management of ALK+ NSCLC with brain metastases at diagnosis (26-27%[1])**
  - Crizotinib is still an efficacious upfront option in patients with brain metastasis [15.7 m IC median PFS]
  - Reasonable to consider a 2nd generation in patients: **symptomatic**, **able to tolerate AE**, **accessible within local healthcare system**
  - Less enthusiastic about WBRT

[1]Soloman et al. NEJM 2015

Abstracts

Efficacy and Safety of Ceritinib in Patients With ALK-Rearranged Non-Small Cell Lung Cancer and Baseline Brain Metastases – results from ASCEND-2 and ASCEND-3

Keunchil Park, Daniel Tan, MyungJu Ahn, Chong-Jen Yu, Chun-Ming Tsai, Toyoaki Hida, Makoto Nishio, Fabrice Branle, Chetachi Emeremni, Santosh Sutradhar, <u>Tony Mok</u>

Erlotinib plus bevacizumab versus erlotinib alone as first-line treatment for advanced non-squamous non-small-cell lung cancer with activating EGFR mutation:JO25567 exploratory subgroup analysis

<u>Yukio Hosomi</u>, Takashi Seto, Makoto Nishio, Koichi Goto, Noboru Yamamoto, Isamu Okamoto, Kosei Tajima, Naohito Inagaki, and Nobuyuki Yamamoto

Study Design

Randomized phase II, controlled comparative study

Chemotherapy-naïve

Stage IIIB/IV NSCLC or postoperative recurrence

Non-squamous

Activating *EGFR* mutations*

Age ≥20 years

PS 0–1

No brain metastasis

*T790M excluded

Stratification factors: sex, smoking status, clinical stage, EGFR mutation type

R 1:1

EB combination
Erlotinib 150mg qd +
Bevacizumab 15mg/kg q3w → PD

E monotherapy
Erlotinib 150mg qd → PD
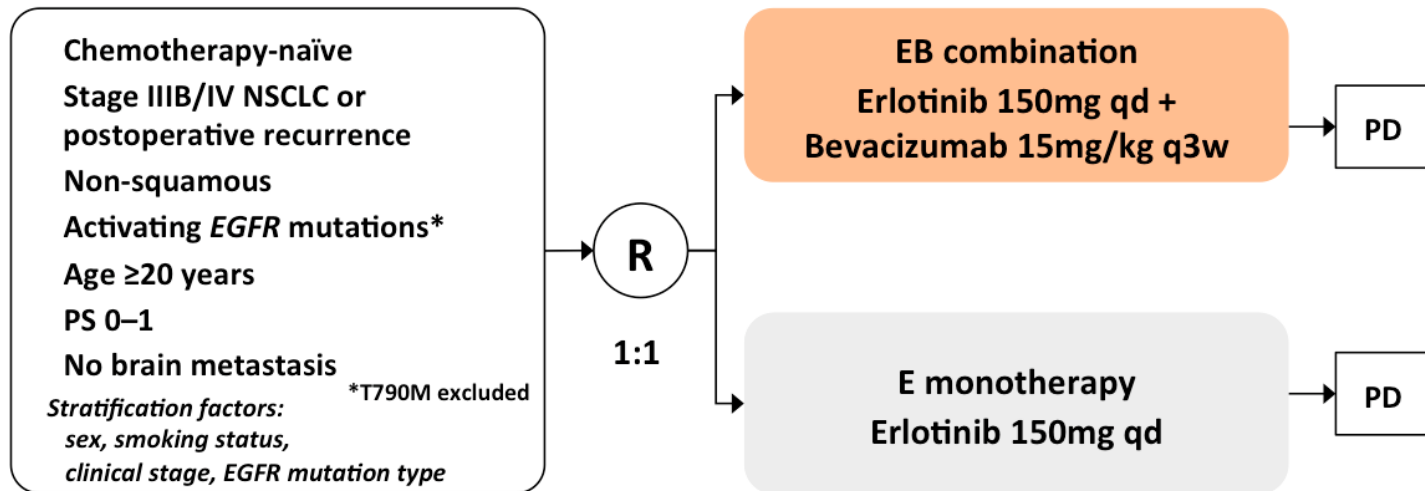
Statistical analysis:
 HR for PFS: 0.7
 One-sided significance level: 0.2
 Power: 0.8
 Planned sample size: 150

Primary endpoint:
 PFS (RECIST v1.1, independent review)

Secondary endpoints:
 OS, tumor response, QoL, safety

Erlotinib-bevacizumab prolongs PFS compared to erlotinib

	EB	E
Median (months)	16.0	9.7
HR	0.54 (95% CI: 0.36–0.79)	
P value*	0.0015	

*log-rank test, two-sided

Number at risk														
EB	75	72	69	64	60	53	49	38	30	20	13	8	4	4	0
E	77	66	57	44	39	29	24	21	18	12	10	5	2	1	0
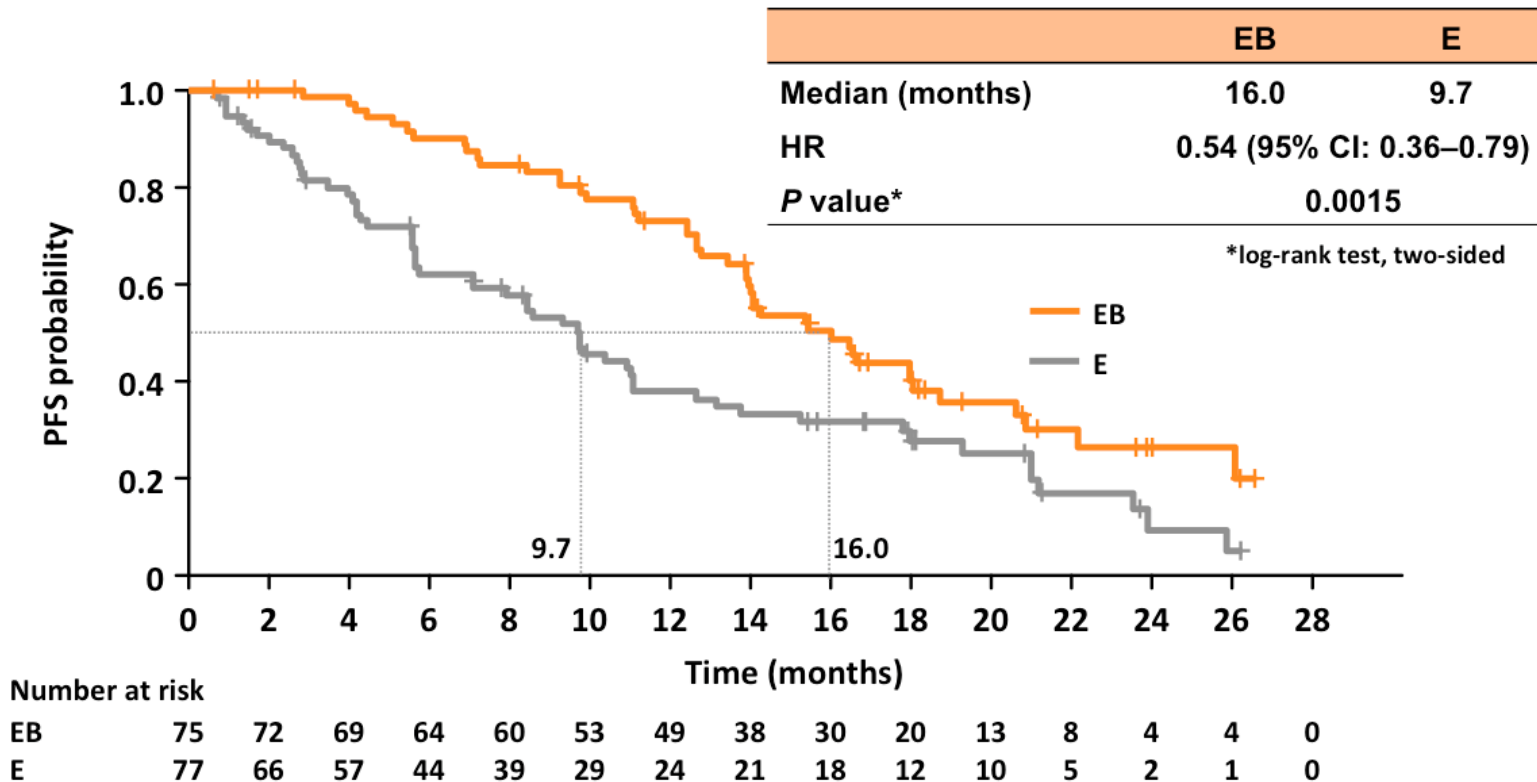
All subgroups seem to benefit

		EB		E		Hazard Ratio (95% CI)
		Median*	(*n*)	Median*	(*n*)	
Age	<75 years	15.4	(63)	9.7	(62)	0.60 (0.39-0.92)
	≥75 years	-	(12)	9.7	(15)	0.23 (0.07-0.81)
Sex	Male	18.0	(30)	9.7	(26)	0.35 (0.19-0.67)
	Female	15.4	(45)	9.7	(51)	0.71 (0.43-1.17)
Smoking status	Non smoker	12.8	(42)	8.4	(45)	0.66 (0.39-1.11)
	Other	18.0	(33)	9.8	(32)	0.41 (0.22-0.74)
PS	0	16.5	(43)	9.7	(41)	0.54 (0.31-0.92)
	1	13.9	(32)	8.4	(36)	0.62 (0.35-1.12)
Clinical stage	IIIB or IV	14.0	(61)	9.7	(62)	0.63 (0.41-0.96)
	Recurrent	20.6	(14)	13.8	(15)	0.25 (0.08-0.73)
EGFR mutation type	Exon19 deletion	18.0	(40)	10.3	(40)	0.41 (0.24-0.72)
	L858R	13.9	(35)	7.1	(37)	0.67 (0.38-1.18)
The SLD of target lesions	<Median: 37.5	16.4	(36)	9.3	(40)	0.61 (0.34-1.08)
	≥Median: 37.5	14.0	(39)	9.7	(37)	**0.49 (0.29-0.84)**
The number of affected organs	<Median: 3	18.0	(34)	15.2	(32)	0.65 (0.34-1.23)
	≥Median: 3	14.1	(41)	8.4	(45)	**0.46 (0.28-0.77)**
PCE	Yes	15.4	(30)	5.7	(36)	**0.45 (0.25-0.82)**
	No	16.4	(45)	11.1	(41)	0.62 (0.37-1.04)

Safety profile of bevacizumab-erlotinib

**68 (91%) patients in the erlotinib plus bevacizumab group and
41 (53%) patients in the erlotinib group had G 3 or 4 AE**

G 3/4 toxicities	EB (n=75)	E (n=77)
Diarrhoea	19 (25%)	15 (19%)
Paronychia	2 (3%)	3 (4%)
Dry skin	2 (3%)	0
Stomatitis	1 (1%)	2 (3%)
Liver function disorder	6 (8%)	14 (18%)
Hypertension	**45 (60%)**	**8 (10%)**
Proteinuria	6 (8%)	0
Haemorrhagic event	2 (3%)	0

Seto et al. TLO 2015

Safety profile of bevacizumab-erlotinib

	Erlotinib plus bevacizumab group (n=75)					Erlotinib alone group (n=77)				
	All	Grade 1–2	Grade 3	Grade 4	Grade 5	All	Grade 1–2	Grade 3	Grade 4	Grade 5
Rash	74 (99%)	55 (73%)	19 (25%)	0	0	76 (99%)	61 (79%)	15 (19%)	0	0
Diarrhoea	61 (81%)	60 (80%)	1 (1%)	0	0	60 (78%)	59 (77%)	1 (1%)	0	0
Paronychia	57 (76%)	55 (73%)	2 (3%)	0	0	50 (65%)	47 (61%)	3 (4%)	0	0
Dry skin	56 (75%)	54 (72%)	2 (3%)	0	0	45 (58%)	45 (58%)	0	0	0
Stomatitis	47 (63%)	46 (61%)	1 (1%)	0	0	46 (60%)	44 (57%)	2 (3%)	0	0
Haemorrhagic event	54 (72%)	52 (69%)	2 (3%)	0	0	22 (29%)	22 (29%)	0	0	0
Liver function disorder or abnormal hepatic function	33 (44%)	27 (36%)	5 (7%)	1 (1%)	0	39 (51%)	25 (32%)	7 (9%)	7 (9%)	0
Hypertension	57 (76%)	12 (16%)	45 (60%)	0	0	10 (13%)	2 (3%)	8 (10%)	0	0
Pruritus	34 (45%)	33 (44%)	1 (1%)	0	0	32 (42%)	32 (42%)	0	0	0
Weight decreased	33 (44%)	33 (44%)	0	0	0	19 (25%)	19 (25%)	0	0	0
Decreased appetite	26 (35%)	25 (33%)	1 (1%)	0	0	26 (34%)	25 (32%)	1 (1%)	0	0
Proteinuria	39 (52%)	33 (44%)	6 (8%)	0	0	3 (4%)	3 (4%)	0	0	0
Dysgeusia	20 (27%)	20 (27%)	0	0	0	17 (22%)	17 (22%)	0	0	0
Nasopharyngitis	20 (27%)	20 (27%)	0	0	0	15 (19%)	15 (19%)	0	0	0
Constipation	17 (23%)	17 (23%)	0	0	0	15 (19%)	14 (18%)	1 (1%)	0	0
Alopecia	13 (17%)	13 (17%)	0	0	0	14 (18%)	14 (18%)	0	0	0
Nausea	12 (16%)	12 (16%)	0	0	0	15 (19%)	15 (19%)	0	0	0
Vomiting	14 (19%)	14 (19%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Malaise	10 (13%)	10 (13%)	0	0	0	10 (13%)	10 (13%)	0	0	0
Insomnia	8 (11%)	8 (11%)	0	0	0	8 (10%)	8 (10%)	0	0	0
Pyrexia	7 (9%)	7 (9%)	0	0	0	9 (12%)	9 (12%)	0	0	0
Upper respiratory tract infection	9 (12%)	9 (12%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Conjunctivitis	8 (11%)	8 (11%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Peripheral oedema	8 (11%)	8 (11%)	0	0	0	6 (8%)	6 (8%)	0	0	0
Fatigue	10 (13%)	9 (12%)	1 (1%)	0	0	3 (4%)	3 (4%)	0	0	0

Seto et al. TLO 2015

Cost-benefit considerations

Identify patients most likely to benefit
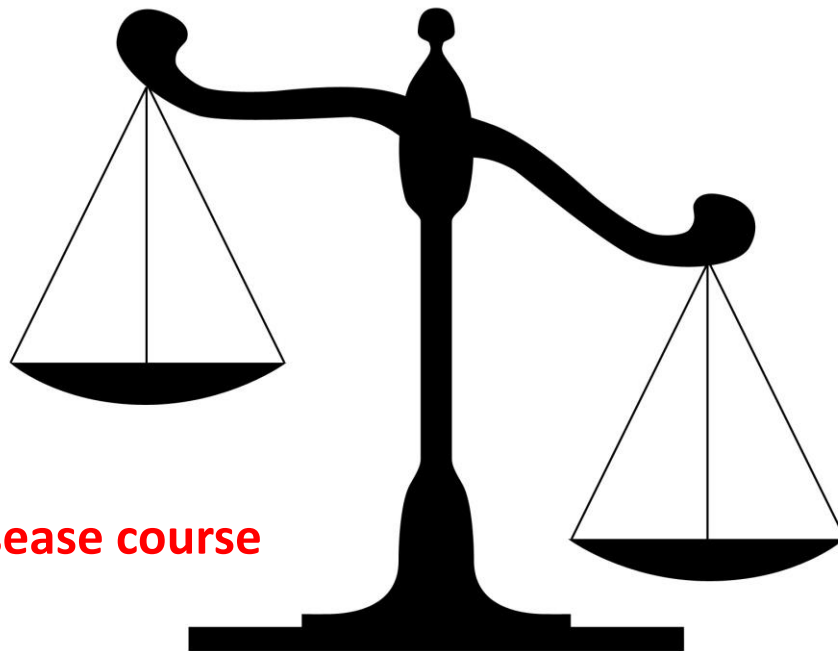
**Side effects
Cost
Inconvenience
Implications on disease course**

Predictive markers for bevacizumab

Table 2: Studies as...

	Setting	Study design	Fluid	Markers	Concentration changed after treatment started	Positively associated with clinical endpoints
Baar et al[28]	Neoadjuvant locally advanced breast carcinoma	Randomised, phase 2	Plasma	VEGF, VCAM-1, ICAM-1, E-selectin	All	Baseline VCAM-1 and E-selectin associated with tumour regression
Bernaards et al[59]*	First-line colorectal, lung, and renal carcinoma	Analysis of AVF2107g, E4599, AVAiL, and	Plasma	VEGF	NR	Not associated with PFS or OS benefit

	Setting	Trial	Markers	Concentration changed with therapy	Positive associations with clinical endpoints
Baar et al[28]	Neoadjuvant locally advanced breast carcinoma	Randomised, phase 2	MVD	None	NR
Cohen et al[67]	Previously treated metastatic squamous cell carcinoma of the head and neck	Single arm, phase 1/2 (including erlotinib)	Phosphorylated AKT, AKT, phosphorylated EGFR, EGFR, phosphorylated MAPK, MAPK, phosphorylated VEGFR2 and VEGFR2*	NR	Tumour cell phosphorylated VEGFR2/VEGFR2* and phosphorylated EGFR/EGFR associated with response
Foernzler et al[60]†	First-line metastatic colorectal cancer	Phase 3 (NO16966)	VEGF-A, VEGFR2†, VEGFR1, HER2, EGFR, and NRP1	NR	Not predictive of PFS benefit
Ince et al[81]	First-line metastatic colorectal cancer	Phase 3 (AVF2107g)	P53	NR	No association with OS benefit
Jubb et al[82]	First line metastatic colorectal cancer	Phase 3 (AVF2107g)	VEGF, MVD, and THBS2	NR	No association with OS benefit
Sathornsumetee et al[83]	Malignant astrocytoma	Single arm, phase 2	VEGF, CD31, VEGRF2, CA9, and HIF2α	NR	CA9 associated with OS
Schneider et al[44]	First-line advanced breast carcinoma	Phase 3 (E2100)	VEGF and VEGFR2	NR	Outcomes not defined
Wedam et al[56]	Neoadjuvant locally advanced and inflammatory breast carcinoma	Single arm, phase 2	VEGF, MVD, antigen KI67, phosphorylated VEGFR2*, VEGFR2*, and TUNEL assay	Ki67, phosphorylated VEGFR2*, VEGFR2*, and TUNEL	VEGF associated with response
Willett et al[7]	Neoadjuvant rectal cancer	Single arm, phase 1/2 (NCI5642)	MVD and vascular maturation	MVD and vascular maturation	NR
Xu et al[73]	Neoadjuvant rectal cancer	Single arm, phase 1/2 (NCI5642)	SDF1α, CXCR4, CXCL6, DLL4, GM-CSF, ANG1, ANG2, HIF1α, PIGF, NRP1, CXCL5, IL8, bFGF, TGF-β-1, TNFAIP2, MIF, NRP2, VEGF, VEGFR1, VEGFR2*, VEGFC, and VEGFR3	SDF1α, and CXCR4	NR
Yang et al[84]	Neoadjuvant locally advanced and inflammatory breast carcinoma	Single arm, phase 2	CD31, PDGFRβ, VEGF, phosphorylated VEGFR2*, MVD, antigen KI67, TUNEL, ER, HER2, and P53	CD31	CD31, PDGFRβ, and VEGF associated with response

Adherence to REMARK criteria could not be assessed in all cited articles. MVD=diphosphomevalonate decarboxylase. NR=not reported. AKT=Ser-Thr protein-kinase B. EGFR=endothelial growth factor receptor. MAPK=mitogen-activated protein kinase. VEGFR=vascular endothelial growth factor receptor. HER2=receptor tyrosine-protein kinase erbB-2. NRP1=neuropilin-1. P53= cellular tumour antigen p53. VEGF=vascular endothelial growth factor. HIF=hypoxia-inducible factor. TUNEL=terminal deoxynucleotidyl transferase dUTP nick end labelling. SDF-1α=stromal-cell-derived factor 1α. CXCR4=chemokine receptor 4. CXCL6=chemokine ligand 6. DLL4=δ-like protein 4. GM-CSF=granulocty-macrophage-colony-stimulating factor. ANG=angiopoietin. PIGF= phosphatidylinositol-glycan biosynthesis class F protein. IL8=interleukin 8. bFGF=basic fibroblast growth factor. TGF-β-1=transforming growth factor-β-1. MIF=macrophage migration inhibitory factor. VEGFC=vascular endothelial growth factor C. PDGFRβ=platelet-derived growth factor receptor β. ER=oestrogen receptor. REMARK=REporting recommendations for tumour MARker prognostic studies. *The specificity of VEGFR2 antibodies has been called into question.[5] †Presented in abstract form only.

Table 3: Clinical trials assessing in-situ biomarkers in relation to the activity or efficacy of bevacizumab

Hypertension

Circulating biomarkers
E.g. VEGF, E-selectin, IL-8
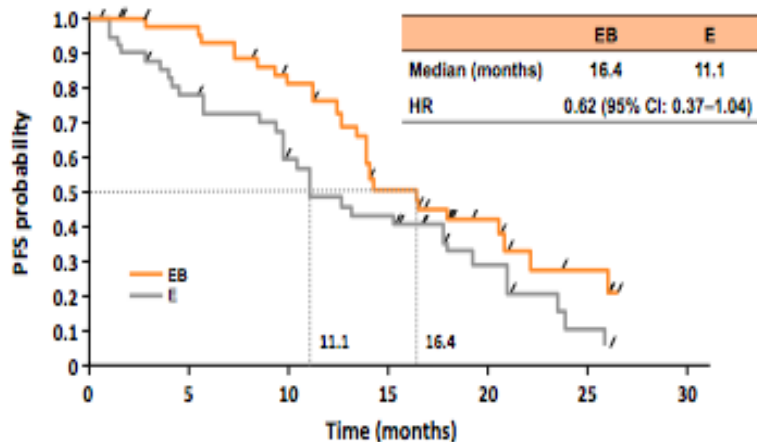
Polymorphisms in
VEGF pathway

Tissue VEGF expression
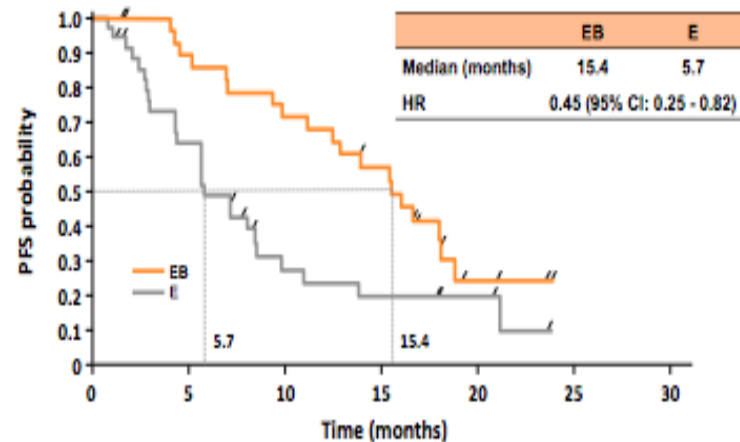
**Majority are
association studies**

Jubb and Harris et al. TLO 2010

How about a clinical biomarker?

No PCE
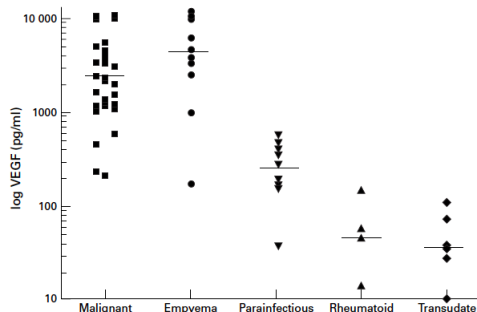
	EB	E
Median (months)	16.4	11.1
HR	0.62 (95% CI: 0.37–1.04)	

PCE

	EB	E
Median (months)	15.4	5.7
HR	0.45 (95% CI: 0.25 - 0.82)	

	Erlotinib	Erlotinib + Bev	
No PCE	11.1 m	16.4 m	HR 0.62 (95% CI 0.37 – 1.04)
PCE	5.7 m	15.4 m	HR 0.45 (95%CI 0.25 – 0.82)

43.4% of patients had pericardial effusion or pleural effusion

Mechanism of action?

Unlikely to be PK failure

Therapeutic synergy?

Case	Erlotinib		OSI-420	
	$C_{PE}0$ (ng/mL)	$C_{PE}0$: $C_{plasma}0$ (%)	$C_{PE}0$ (ng/mL)	$C_{PE}0$: $C_{plasma}0$ (%)
1	855	47	308	77
2	1564	122	170	175
3	657	74	95	83
4	2597	56	489	59
5	917	98	116	113
6	1032	130	318	143
7	848	291	381	349
8	2152	98	292	98
9	2516	94	310	81
Mean ± SD	1459 ± 771	112 ± 72	275 ± 128	131 ± 89

RR 65%

RR 62%

Figure 4: Waterfall plot of best percentage change from baseline in the sum of longest tumour diameters
Responders were confirmed by Response Evaluation Criteria in Solid Tumors. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. NE=non-evaluable. SLD=sum of longest diameters.
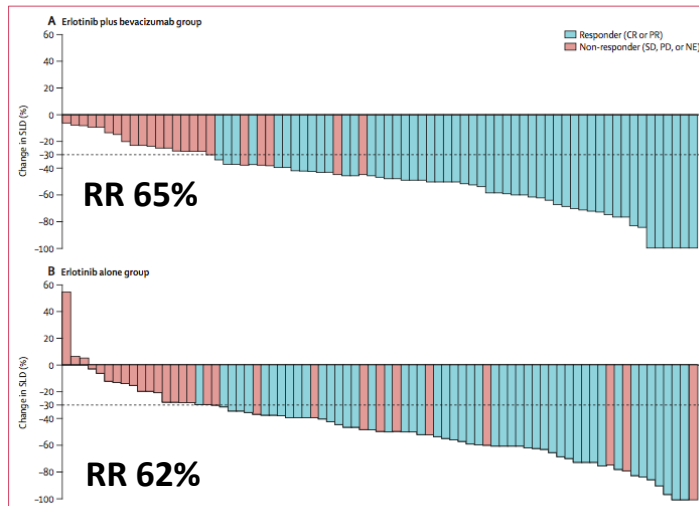
Pleural effusions have high VEGF levels

Response of a Nonmalignant Pleural Effusion to Bevacizumab

TO THE EDITOR: The potential role of vascular endothelial growth factor in malignant as well as nonmalignant pleural effusion[1,2] prompted us to use bevacizumab, a monoclonal antibody against vascular endothelial growth factor, in a 68-year-old man with primary cardiac amyloidosis who had severe dyspnea and underwent repeated thoracenteses for pleural effusions. Cytologic assessments of the

Masago et al. Clin Lung Cancer 2011; Pichelmayer NEJM 2005; Thickett et al. Thorax 1999; Seto et al TLO 2015

Concluding thoughts

- **Both abstracts provide additional data on subsets that may benefit from approved but not necessarily SOC interventions**
    - Ceritinib is efficacious in patients with baseline CNS disease both pre and post crizotinib
    - Erlotinib-bevacizumab is efficacious in patients presenting with PCE

- **Clinical decision making and access to therapies**
    - What is the magnitude of benefit?
    - Is there a clinical trial available?
    - How does this influence subsequent options?

- **Continues to be a "happy" problem**
    - Capitalize on choices available through high quality translational studies