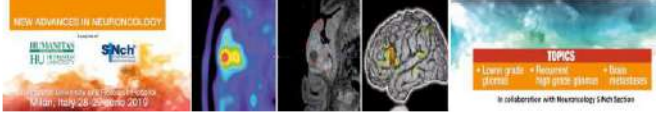
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Bologna
Istituto delle Scienze Neurologiche
Istituto di Ricovero e Cura a Carattere Scientifico

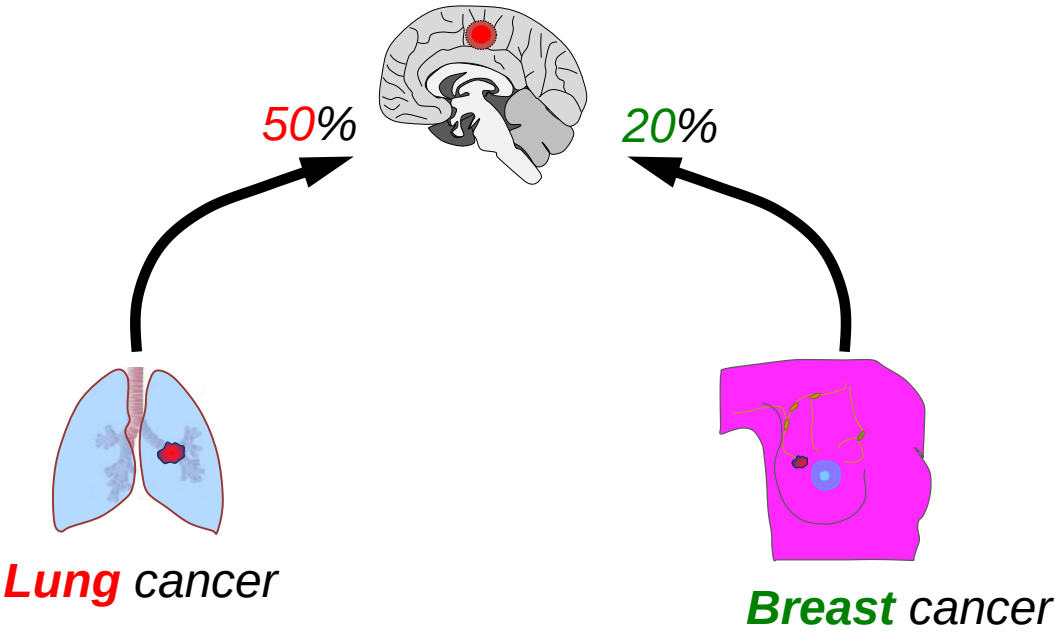


Oncological point of view in breast and lung cancer brain metastases

Enrico Franceschi

Department of Medical Oncology
Azienda USL - IRCCS Institute of Neurological Sciences
Bologna - Italy

Brain metastases



What distinguishes brain metastases from other metastatic sites ?

- No lymphatic vessels, all metastases are hematogenous
- Cerebral blood flow 750-1000 ml/minute
- Symptoms devastating (depending on location)
- Predilection for brain metastases from
  - Melanoma, renal cell cancer, breast cancer, lung cancer
    - Reasons largely unknown or speculative
- Blood-brain barrier

Not all BMs are created equal

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases

Paul W. Sperduto, Norbert Kased, David Roberge, Zhiyuan Xu, Ryan Shanley, Xiangkua Luo, Penny K. Sneed, Samuel T. Chao, Robert J. Weil, John Suh, Amit Bhatt, Ashley W. Jensen, Paul D. Brown, Helen A. Shih, John Kirkpatrick, Laurie E. Gaspar, John B. Fiveash, Veronica Chiang, Jonathan P.S. Knisely, Christina Maria Sperduto, Nancy Lin, and Minesh Mehta

Diagnosis	Survival Time (months) Median	95% CI	No. of Patients
NSCLC	7.00	6.53 to 7.50	1,833
SCLC	4.90	4.30 to 6.20	281
Melanoma	6.74	5.90 to 7.56	481
RCC	9.63	7.66 to 10.91	286
Breast cancer	13.80	11.53 to 15.87	400
GI cancer	5.36	4.30 to 6.30	209
Other	6.37	5.22 to 7.49	450
Total	7.16	6.83 to 7.52	3,940

Heterogeneous Outcomes

Clinical factors affect survival

	GPA Score 0-1.0				GPA Score 3.5-4.0				
	Survival Time (months)		Patients		Survival Time (months)		Patients		*P*
Diagnosis	Median	95% CI	No.	%	Median	95% CI	No.	%	(log-rank)
NSCLC	3.02	2.63 to 3.84	254	14	14.78	11.80 to 18.80	161	9	< .001
SCLC	2.79	1.83 to 3.12	65	23	17.05	4.70 to 27.43	13	5	< .001
Melanoma	3.38	2.53 to 4.27	84	17	13.23	9.13 to 15.64	112	23	< .001
RCC	3.27	2.04 to 5.10	43	15	14.77	9.73 to 19.79	63	22	< .001
Breast cancer	3.35	3.13 to 3.78	23	6	25.30	23.10 to 26.51	133	33	< .001
GI cancer	3.13	2.37 to 4.57	76	36	13.54	9.76 to 27.12	18	9	< .001
Other	—	—	—	—	—	—	—	—	—
Total	3.10	2.83 to 3.45	545	16	16.73	14.65 to 18.80	500	14	< .001

The oncological point of view
When we treat brain metastases:

- Two concomitant diseases: systemic and intracranial

- Competing risks of CNS progression and of extra-CNS progression

The oncological point of view
When we treat brain metastases:

- Intracranial disease more rapidly lethal if untreated

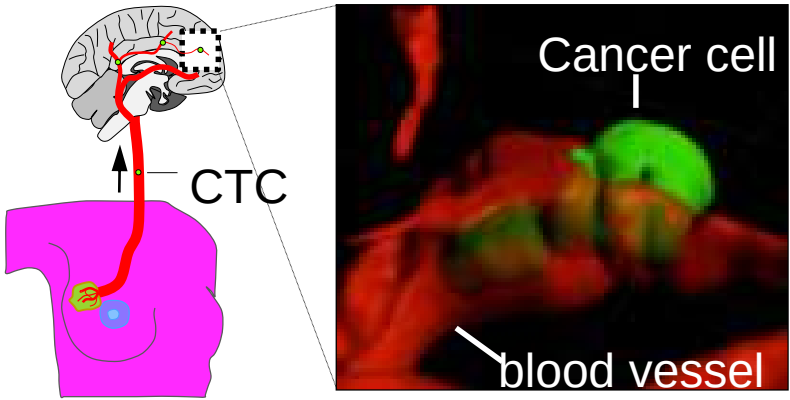
- Presence of intracranial disease is a control limiting event

Potential limitations to the use of target therapies for brain metastases

- Blood brain barrier

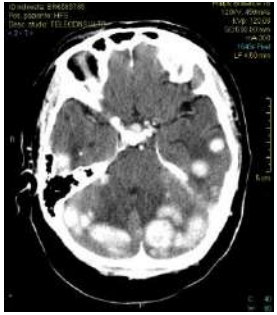
Blood-brain barrier (BBB)

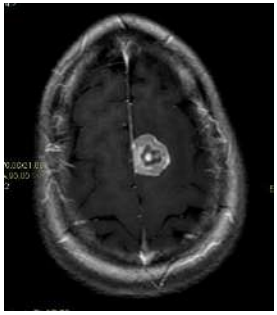
- Covers 600 km of capillaries
- Physical, chemical and metabolic barrier that segregates blood from CNS fluid
- CNS protection against pathogens and toxins
- **Molecules with a molecular weight over 500 D not cross BBB (98% of drugs)**



Potential limitations to the use of target therapies for brain metastases

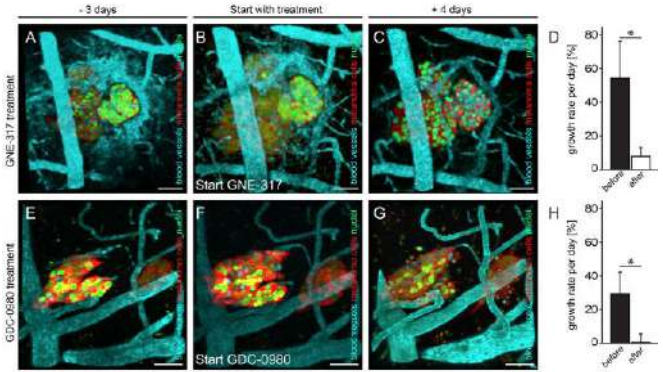
- Blood brain barrier
  - BBB is heterogeneously disrupted in cancer
  - Enhancing lesions on MRI indicate BBB partial disruption





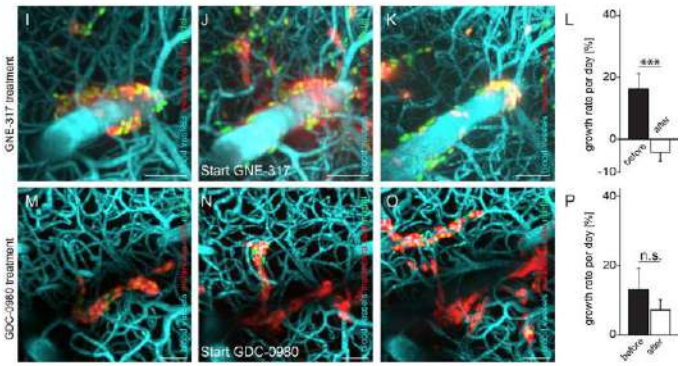
BBB permeability in brain metastases is heterogeneous

Non-permeable brain metastasis



Only penetrating drug inhibits brain metastasis growth

Permeable brain metastases

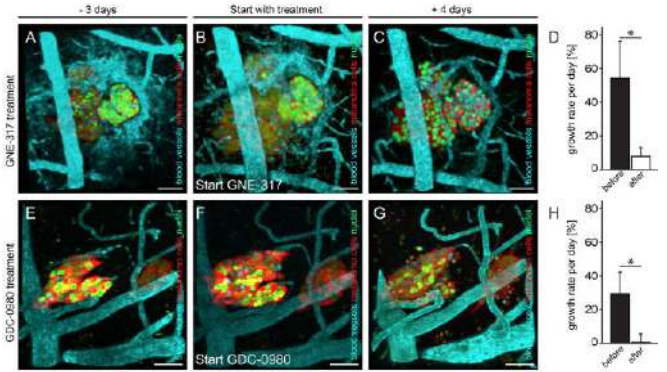


Penetrating AND non-penetrating drug inhibit brain metastasis growth

Osswald, Clin Cancer Res 2016

BBB permeability in brain metastases is heterogeneous

Non-permeable brain metastasis



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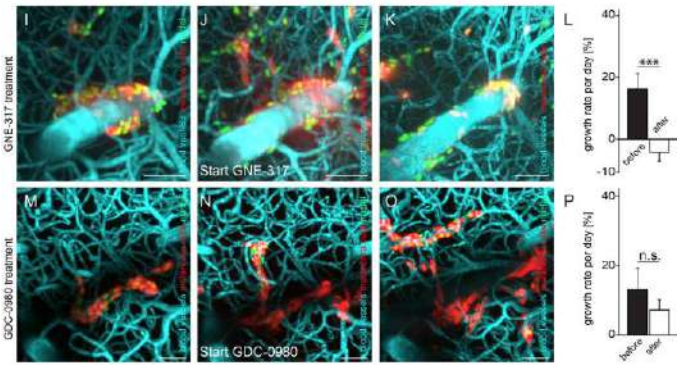

Penetrating AND non-penetrating drug inhibit brain metastasis growth

It is crucial to have agents that penetrate in brain metastases

Osswald, Clin Cancer Res 2016

What do you consider as success in the treatment of brain metastases?

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A) responses in 30% & survival similar to pts wthout BMs

What do you consider as success in the treatment of brain metastases?

A) responses in 30% & survival similar to pts wthout BMs

b) responses in 50% & survival similar to pts wthout BMs

What do you consider as success in the treatment of brain metastases?

A) responses in 30% & survival similar to pts wthout BMs

b) responses in 50% & survival similar to pts wthout BMs

c) responses in >50% & survival increased (2x)

Hit the molecular target and not the site of the disease

Antoine de Saint-Exupéry
The Little Prince

The essential is invisible to the eye

Anti HER-2 therapies in breast cancer revolutionized also the vision of BMs

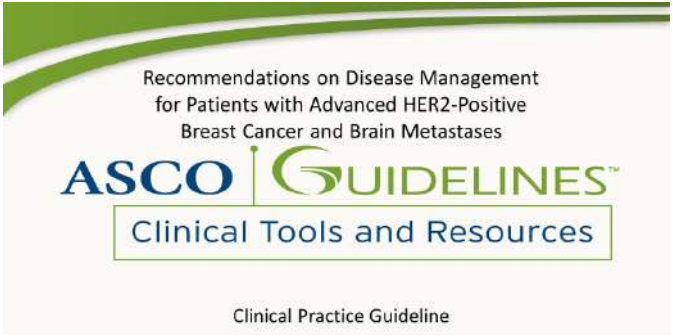
Just when you think you know something, you have to look at in another way

From Dead Poets Society

CNS metastases in breast cancer

Risk factors

- Younger age (<50 years)
- ER-negative status
- HER2-positive disease
  - 2–4 times increased risk
  - Significant risk factor for CNS relapse



- Up to 50% of patients with HER2-positive metastatic breast cancer develop brain metastases over time
- Paucity of guidance for patients in this setting

Survival of brain metastases of HER2+ breast cancer depends on:

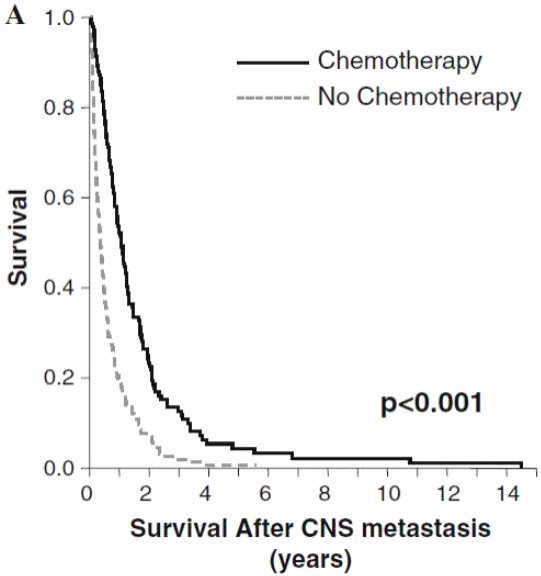
Table 3. Multivariable proportional hazards analysis of survival after CNS metastases ($n = 377$)

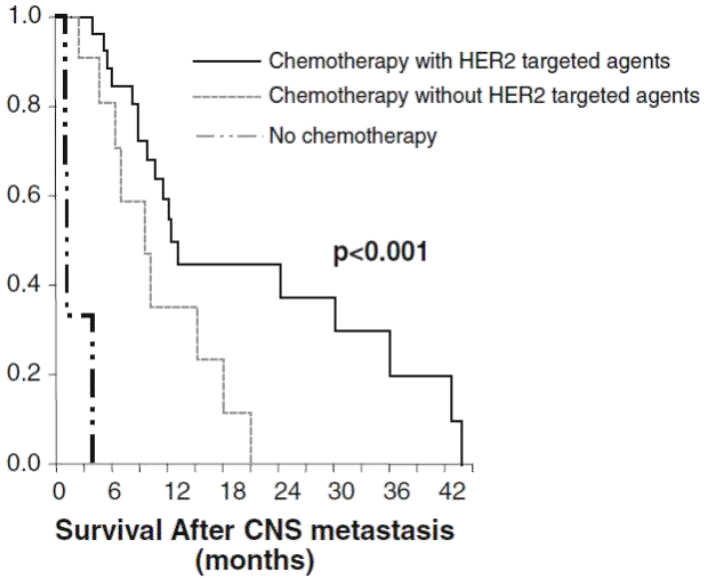
	HR (95% CI)	*P*
Treatment received after first CNS event[a]		
Trastuzumab[b] ($n = 258$)	0.33 (0.25–0.46)	<0.001
Chemotherapy ($n = 262$)	0.64 (0.48–0.85)	0.002
Surgery ($n = 29$)	0.63 (0.39–1.02)	0.062
Radiation therapy ($n = 269$)	0.98 (0.75–1.30)	0.898
Cancer stage at initial dx		
Stage I–III (MBC dx ≤12 mo after initial dx) vs. stage IV	1.41 (0.95–2.10)	0.091
Stage I–III (MBC dx ≥12 mo after initial dx) vs. stage IV	0.96 (0.72–1.27)	0.767
ECOG PS at MBC diagnosis		
≥2 vs. 0 or 1	1.83 (1.14–2.96)	0.013
Unknown or missing vs. 0 or 1	1.12 (0.86–1.46)	0.405
Age, y	1.01 (1.00–1.02)	0.162
Hormone receptor status		
Positive vs. negative	0.80 (0.63–1.03)	0.088
Unknown vs. negative	1.04 (0.61–1.76)	0.888
CNS disease at MBC dx (yes vs. no)	0.50 (0.36–0.71)	<0.001

Role of effective treatments in HER2+ BMs

Brufsky , *Clin Cancer Res* 2011.

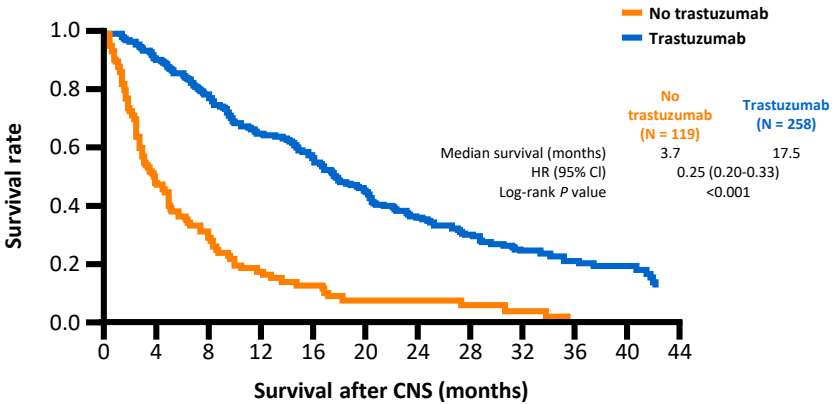
Anti-HER2 treatments work





Kim JNO 2012

Anti-HER2 treatments work



- **Trastuzumab after diagnosis of CNS metastases improved OS**

Brufsky , *Clin Cancer Res* 2011.

Anti-HER2 treatments work

Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study

Thomas Bachelot, Gilles Romieu, Mauro Campone, Véronique Dieras, Claire Cropet, Florence Dalenc, Marta Jimenez, Emilie Le Rhun, Jean-Yves Pierga, Anthony Gonçalves, Marianne Lefeuvre-Plesse, Julien Domont, Maya Gutierrez, Hervé Curé, Jean-Marc Ferrero, Catherine Labbé-Devilles

	Patients (n=44)
≥80% reduction	9 (20%)
50–<80% reduction	20 (45%)
20–<50% reduction	6 (14%)
0–<20% reduction	2 (5%)
Progression*	7 (16%)

*Two patients had progression outside of the CNS.

Table 3: Objective CNS response in assessable patients

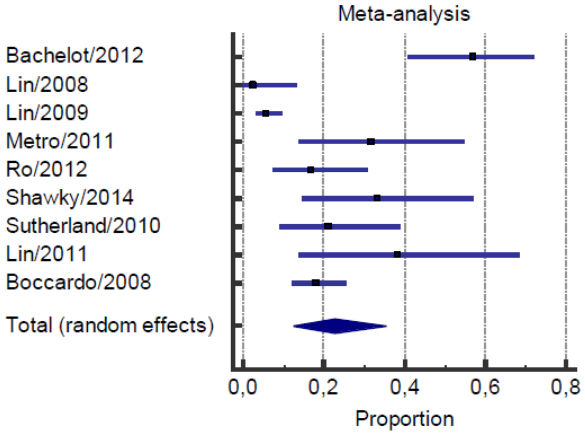
RR=65%
DCR= 79%

Anti-HER2 treatments work

The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: A systematic review and pooled analysis

Fausto Petrelli [a,*], Michele Ghidini [b], Veronica Lonati [a], Gianluca Tomasello [b], Karen Borgonovo [a], Mara Ghilardi [a], Mary Cabiddu [a], Sandro Barni [a]

Large analysis
12 studies , 799 pts



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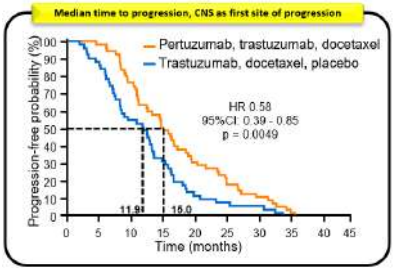
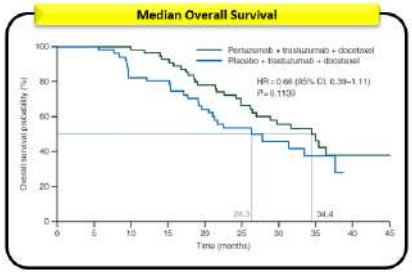
Annals of Oncology 25: 1116–1121, 2014
doi:10.1093/annonc/mdu103
Published online 31 March 2014

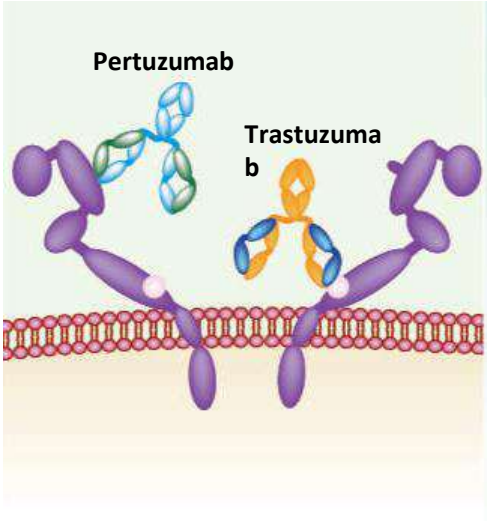
Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA

S. M. Swain[1*], J. Baselga[2], D. Miles[3], Y.-H. Im[4], C. Quah[5], L. F. Lee[5] & J. Cortés[6]





- Total Blockade of HER2 May Provide Greater Antitumor Activity and Overcome Resistance



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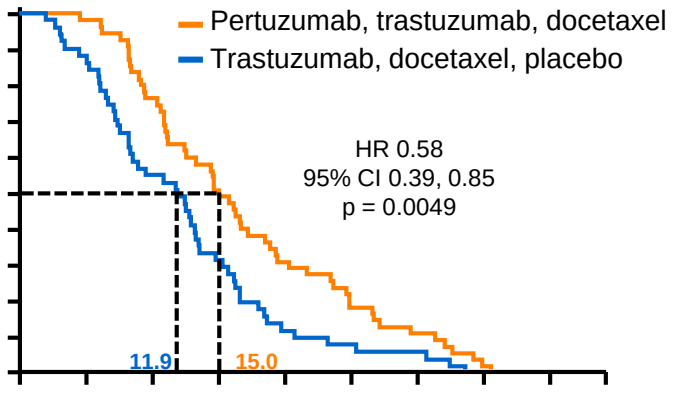
Median time to progression, CNS as first site of progression



PHT	55	54	42	27	17	10	6	1	0	0
HT	51	45	28	16	6	4	3	0	0	0

- **Exploratory, *post hoc* analysis**
- Incidence of CNS metastases as first site of PD was similar between treatment arms
  - Median TTP in the CNS was prolonged with pertuzumab compared with placebo (15.0 vs 11.9 months)

Swain S, *et al*. *Ann Oncol* 2014; **25:**1116–1121.

original articles

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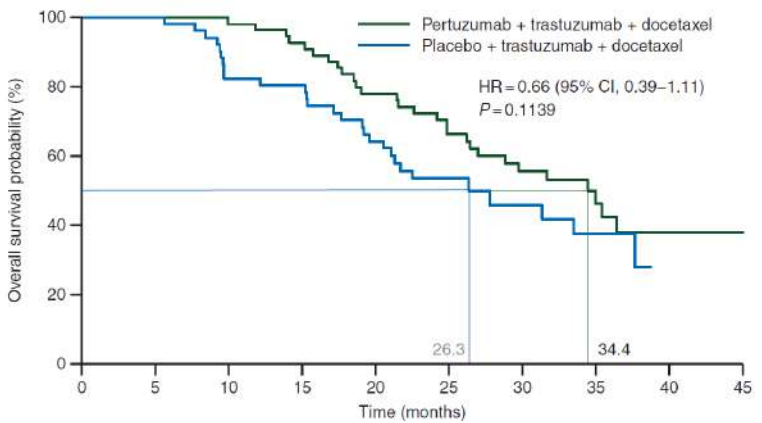
Median Overall Survival



- **Exploratory, *post hoc* analysis**
  - Median OS in patients with CNS progression was numerically higher with pertuzumab treatment compared with placebo (34.4 months vs 26.3 months)
- Supports further investigation of pertuzumab and trastuzumab in patients with CNS metastases

Swain S, *et al*. *Ann Oncol* 2014; **25:**1116–1121

Clinical factors affect survival

	GPA Score 0-1.0				GPA Score 3.5-4.0				
	Survival Time (months)		Patients		Survival Time (months)		Patients		*P*
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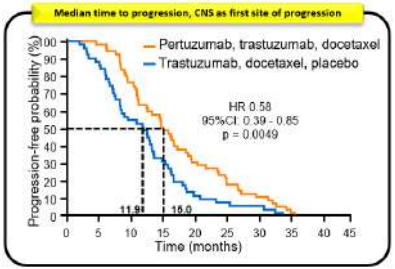
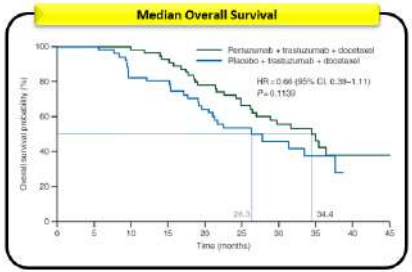
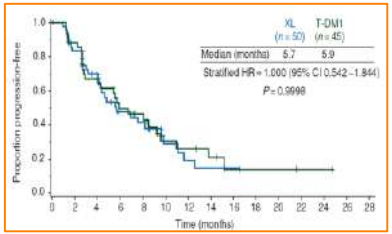
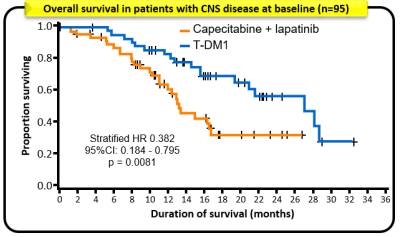




Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA†

I. E. Krop[1*], N. U. Lin[1], K. Blackwell[2], E. Guardino[3], J. Huober[4,†], M. Lu[3], D. Miles[5], M. Samant[6], M. Welslau[7] & V. Diéras[8]





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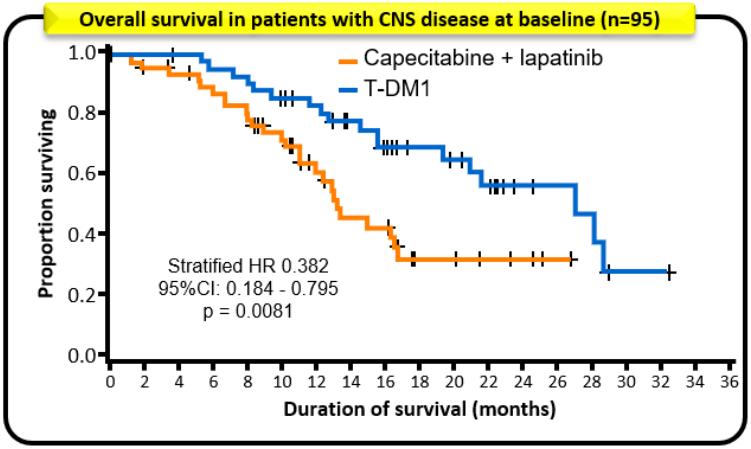

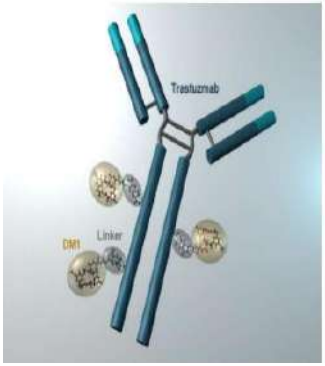

- T-DM1 is an antibody drug-conjugate.
- Trastuzumab linked to a potent chemotherapy (DM1).
- Average of 3.5 DM1 per antibody.

Anti-HER2 treatments work
But pay attention!

Expansive hematoma in delayed cerebral radiation necrosis in patients treated with T-DM1: a report of two cases
Mitsuya K, et al BMC Cancer. 2016 Jul 4;16:391.

A potential enhancement of RN by T-DM1 in the brain may be one of important adverse events associated with the use of T-DM1 for patients after SRS.

Case presentation:
- Two patients with HER2-positive breast cancer had received SRS for single brain metastasis more than 5-years ago.
- They had been heavily treated for HER2-positive metastatic breast cancer (trastuzumab and pacritaxel, lapatinib and capecitabine).
- They initiated T-DM1 therapy for progressive systematic disease 5.5 years after stereotactic irradiation, when a small RN was recognized on brain MR images of each patient.

Pathologically, the lesions represented a mixture of granulation tissue, necrosis and hemorrhage, with telangiectasia and fibrinoid degeneration of the small vessels.
The triggering role of T-DM1 in the induction of these lesions is supported by a chronological relationship between lesion development and T-DM1 exposure.

Okines, A. et al.
Development and responses of brain metastases during treatment with T-DM1 for HER2 positive advanced breast cancer: *A single institution experience.*
Breast J. (2017). doi:10.1111/tbj.12906

55 patients were treated with T-DM1

16 patients with known brain involvement at baseline:
10 patients (62.5%) received WBRT
6 patients (37.5%) received SRT without WBRT

39 patients without known brain involvement at baseline:
7/39 patients (17.9%) developed symptomatic CNS disease

3 of the 23 patients (13.0%) with baseline or new brain disease developed significant intra-cranial hemorrhage associated with parenchymal brain metastases while on T-DM1.

CONCLUSIONS
the development of new brain disease on T-DM1 was more common than previously reported, and survival from diagnosis with symptomatic progression was poor.

Geraud, A., Xu, H. P., Beuzeboc, P. & Kirova, Y. M.
Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer.
J. Neurooncol. 131, 69–72 (2017).

This is preliminary study assessing the efficacy and safety of **concurrent use of radiation therapy (RT) and T-DM1** for the treatment of brain metastases (BM) in patients with HER2-positive metastatic breast cancer (BC).

12 patients treated for BM at the Institut Curie in 2014-2015 with T-DM1 and concurrent (4) or sequential (8) radiosurgery with or without whole brain irradiation.

Radiation necrosis was observed in 50% of patients in the concurrent group and 28.6 % of patients in the sequential group with a similar rate of oedema in the two groups.

The combination of T-DM1 and radiosurgery is feasible but can increase the incidence of radiation necrosis.

Anti-HER2 treatments work
But pay attention!

Expansive hematoma in delayed cerebral radiation necrosis in patients treated with T-DM1: a report of two cases
Mitsuya K, et al BMC Cancer. 2016 Jul 4;16:391.

A potential enhancement of RN by T-DM1 in the brain may be one of important adverse events associated with the use of T-DM1 for patients after SRS.

Case presentation:
- Two patients with HER2-positive breast cancer had received SRS for single brain metastasis more than 5-years ago.
- They had been heavily treated for HER2-positive metastatic breast cancer (trastuzumab and pacritaxel, lapatinib and capecitabine).
- They initiated T-DM1 therapy for progressive systematic disease 5.5 years after stereotactic irradiation, when a small RN was recognized on brain MR images of each patient.

TDM1 - Signals of radionecrosis and hemorrage

Okines, A. et al.
Development and responses of brain metastases during treatment with T-DM1 for HER2 positive advanced breast cancer: *A single institution experience.*
Breast J. (2017). doi:10.1111/tbj.12906

55 patients were treated with T-DM1

16 patients with known brain involvement at baseline:
10 patients (62.5%) received WBRT
6 patients (37.5%) received SRT without WBRT

39 patients without known brain involvement at baseline:
7/39 patients (17.9%) developed symptomatic CNS disease

3 of the 23 patients (13.0%) with baseline or new brain disease developed significant intra-cranial hemorrhage associated with parenchymal brain metastases while on T-DM1.

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Anti-HER2 treatments work

Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study

	Patients (n=44)
≥80% reduction	9 (20%)
50–<80% reduction	20 (45%)
20–<50% reduction	6 (14%)
0–<20% reduction	2 (5%)
Progression*	7 (16%)

*Two patients had progression outside of the CNS.

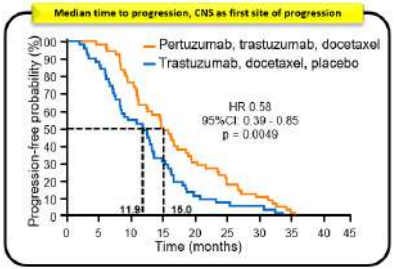
Table 3: Objective CNS response in assessable patients

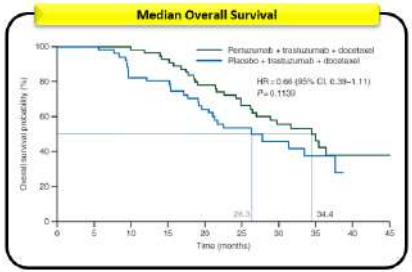
RR=65%
DCR= 79%

original articles

Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA

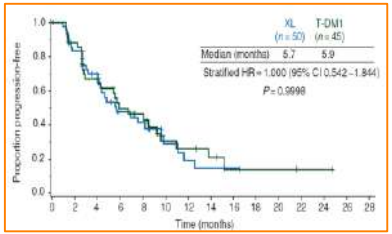
S. M. Swain[1*], J. Baselga[2], D. Miles[3], Y.-H. Im[4], C. Quah[5], L. F. Lee[5] & J. Cortés[6]

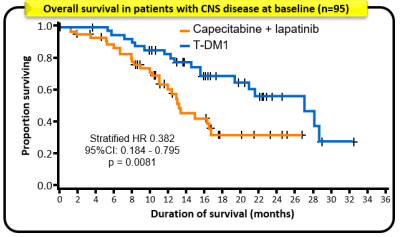




Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA†

I. E. Krop[1*], N. U. Lin[1], K. Blackwell[2], E. Guardino[3], J. Huober[4,†], M. Lu[3], D. Miles[5], M. Samant[6], M. Welslau[7] & V. Diéras[8]

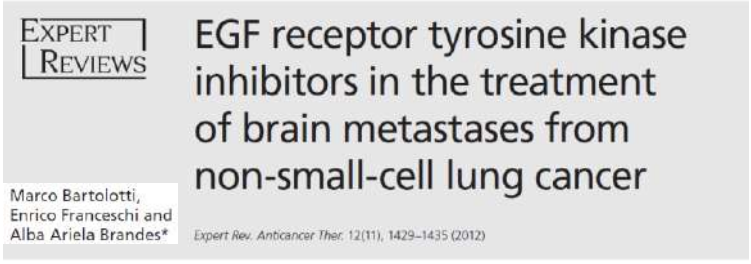




Chemotherapy in brain metastases - NSCLC

Author	Primary tumor	RR brain	RR extrabrain
Moscetti, Cancer 2007	NSCLC	29%	37%
Lee, Cancer 2008	NSCLC	28%	28%
Scagliotti, JCO 2002	NSCLC	25-52%	30-32%
Alberola, JCO 2003	NSCLC	29%	37%
Crinò, JCO 1999	NSCLC	38%	41%

EGFR TKIs in brain metastases - NSCLC



Author	n	RR brain	RR extrabrain
Ceresoli, Ann Onc 2003	41	10%	10%
Namba, Clin Lung Cancer 2004	15	60%	60%
Hotta, Lung Cancer 2004	14	43%	50%
Chiu, Lung Cancer 2005	21	50%	56%
Lee, CCR 2005	10 (never smokers)	70%	80%

Modern Management of Central Nervous System Metastases in the Era of Targeted Therapy and Immune Oncology

Priscilla Brastianos, MD[1]; Michael A. Davies, MD, PhD[2]; Kim Margolin, MD[3]; and Helena A. Yu, MD[4]

PRECISION MEDICINE IN LUNG CANCER BRAIN METASTASES: ARE WE THERE YET?

Using comprehensive genotyping panels at diagnosis, we now routinely identify mutations in *EGFR*, *BRAF*, *MET*, *KRAS*, and *HER2*, rearrangements in *ALK*, *ROS1*, *RET*, *NTRK*, and *NRG1*, and amplifications in *HER2* and *MET* in lung cancers.

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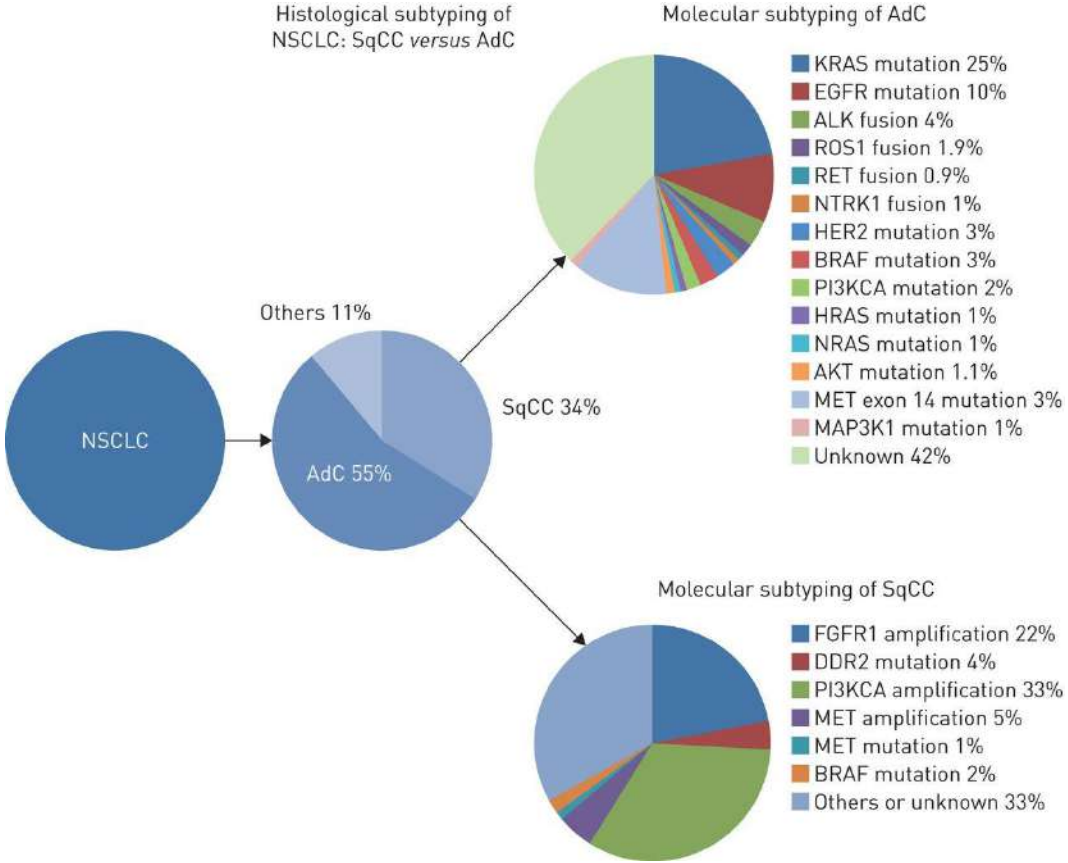

Histological subtyping of NSCLC: SqCC *versus* AdC
Molecular subtyping of AdC
KRAS mutation 25%
EGFR mutation 10%
ALK fusion 4%
ROS1 fusion 1.9%
RET fusion 0.9%
NTRK1 fusion 1%
HER2 mutation 3%
BRAF mutation 3%
PI3KCA mutation 2%
HRAS mutation 1%
NRAS mutation 1%
AKT mutation 1.1%
MET exon 14 mutation 3%
MAP3K1 mutation 1%
Unknown 42%
Others 11%
NSCLC
AdC 55%
SqCC 34%
Molecular subtyping of SqCC
FGFR1 amplification 22%
DDR2 mutation 4%
PI3KCA amplification 33%
MET amplification 5%
MET mutation 1%
BRAF mutation 2%
Others or unknown 33%

Clinical factors affect survival

	GPA Score 0-1.0				GPA Score 3.5-4.0				
	Survival Time (months)		Patients		Survival Time (months)		Patients		*P*
Diagnosis	Median	95% CI	No.	%	Median	95% CI	No.	%	(log-rank)
NSCLC	3.02	2.63 to 3.84	254	14	14.78	11.80 to 18.80	161	9	< .001
SCLC	2.79	1.83 to 3.12	65	23	17.05	4.70 to 27.43	13	5	< .001
Melanoma	3.38	2.53 to 4.27	84	17	13.23	9.13 to 15.64	112	23	< .001
RCC	3.27	2.04 to 5.10	43	15	14.77	9.73 to 19.79	63	22	< .001
Breast cancer	3.35	3.13 to 3.78	23	6	25.30	23.10 to 26.51	133	33	< .001
GI cancer	3.13	2.37 to 4.57	76	36	13.54	9.76 to 27.12	18	9	< .001
Other	—	—	—	—	—	—	—	—	—
Total	3.10	2.83 to 3.45	545	16	16.73	14.65 to 18.80	500	14	< .001

The NEW ENGLAND JOURNAL of MEDICINE

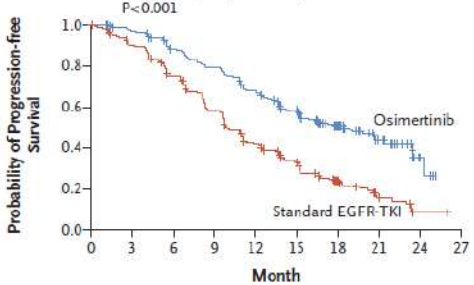
ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

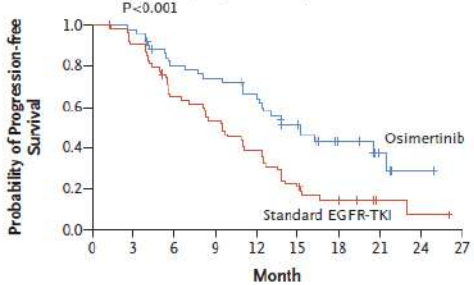
Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

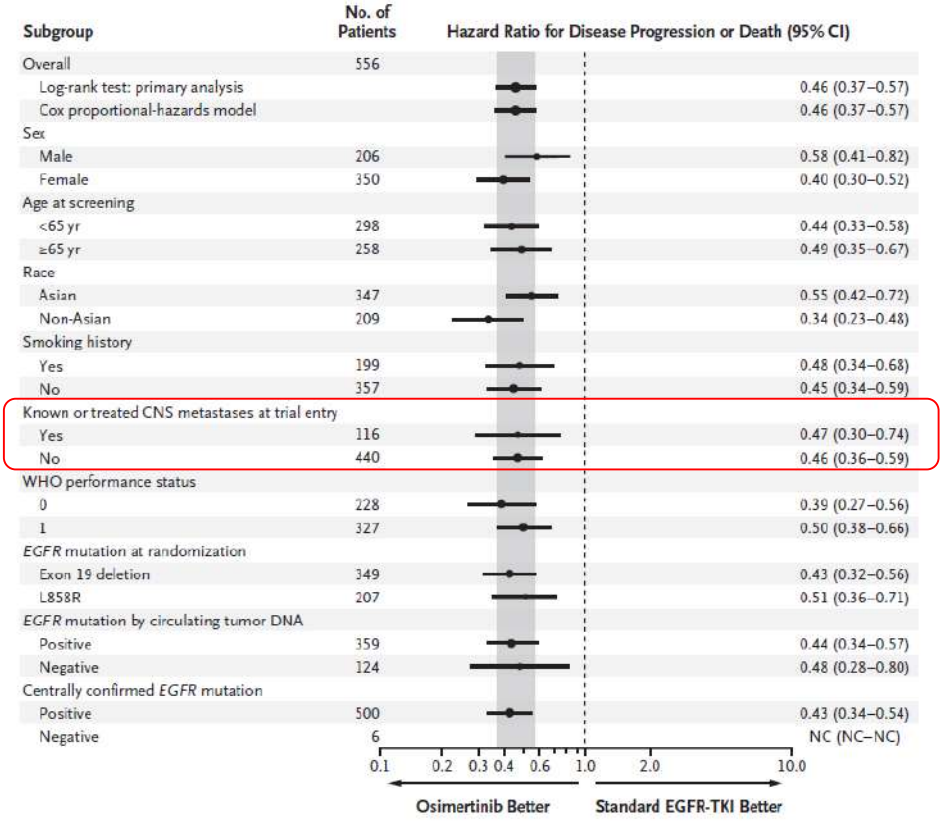


B Progression-free Survival in Patients with CNS Metastases

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	53	15.2 (12.1–21.4)
Standard EGFR-TKI	63	9.6 (7.0–12.4)

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)
P<0.001

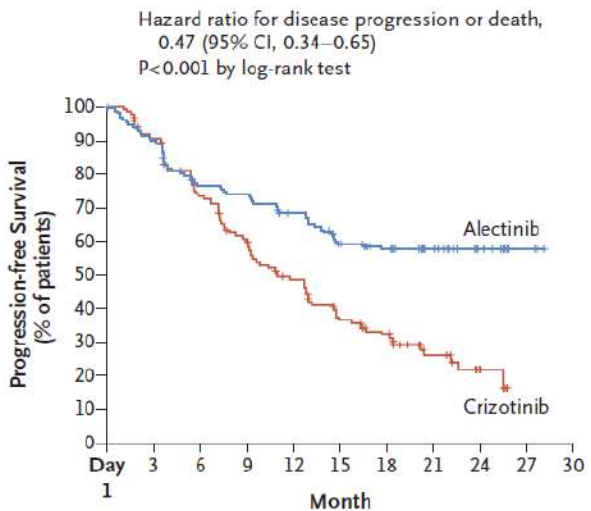


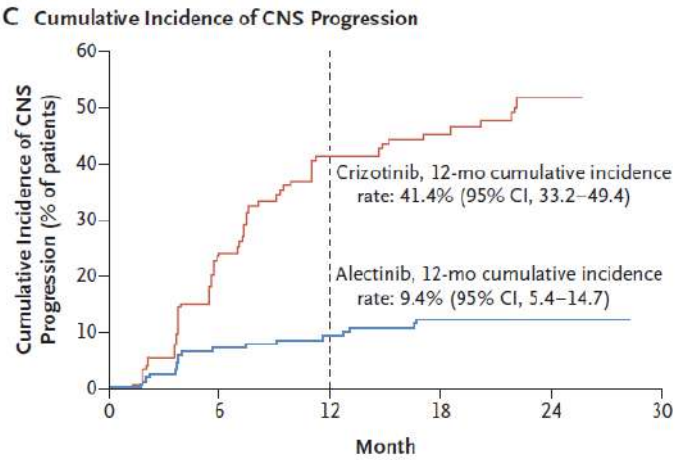

Subgroup
No. of Patients
Hazard Ratio for Disease Progression or Death (95% CI)
Overall 556
Log-rank test: primary analysis 0.46 (0.37–0.57)
Cox proportional-hazards model 0.46 (0.37–0.57)
Sex
Male 206 0.58 (0.41–0.82)
Female 350 0.40 (0.30–0.52)
Age at screening
<65 yr 298 0.44 (0.33–0.58)
≥65 yr 258 0.49 (0.35–0.67)
Race
Asian 347 0.55 (0.42–0.72)
Non-Asian 209 0.34 (0.23–0.48)
Smoking history
Yes 199 0.48 (0.34–0.68)
No 357 0.45 (0.34–0.59)
Known or treated CNS metastases at trial entry
Yes 116 0.47 (0.30–0.74)
No 440 0.46 (0.36–0.59)
WHO performance status
0 228 0.39 (0.27–0.56)
1 327 0.50 (0.38–0.66)
EGFR mutation at randomization
Exon 19 deletion 349 0.43 (0.32–0.56)
L858R 207 0.51 (0.36–0.71)
EGFR mutation by circulating tumor DNA
Positive 359 0.44 (0.34–0.57)
Negative 124 0.48 (0.28–0.80)
Centrally confirmed EGFR mutation
Positive 500 0.43 (0.34–0.54)
Negative 6 NC (NC–NC)
0.1
0.2
0.3
0.4
0.6
1.0
2.0
10.0
Osimertinib Better
Standard EGFR-TKI Better

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

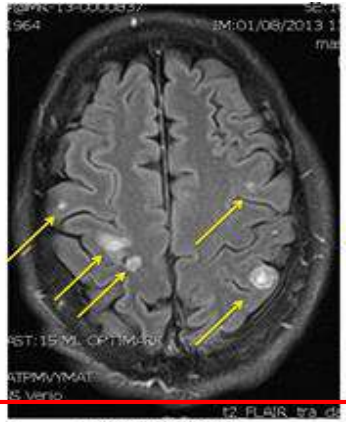
Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer



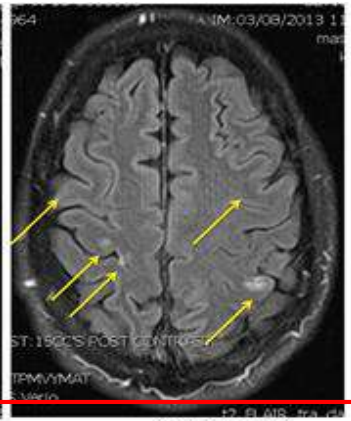


CNS response rate : 81% vs 50%

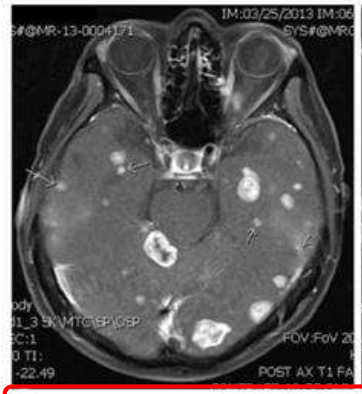
CNS Complete responses: 38% vs 5%



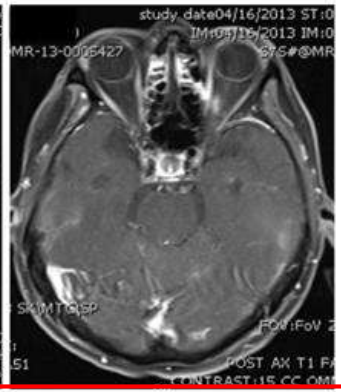
January 8, 2013



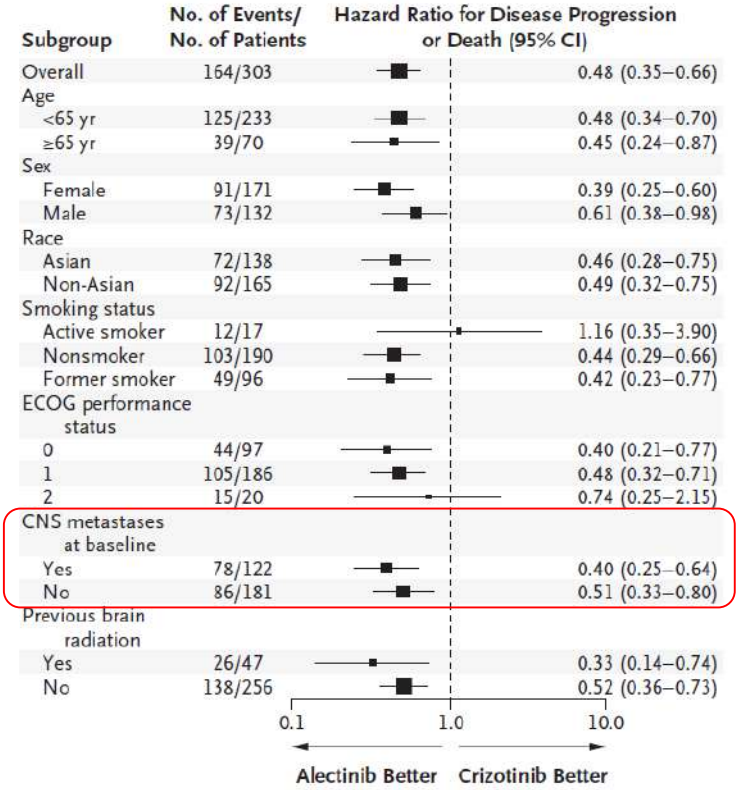
March 8, 2013



Day -4



Day + 18


Subgroup
No. of Events/ No. of Patients
Hazard Ratio for Disease Progression or Death (95% CI)
Overall 164/303 0.48 (0.35–0.66)
Age
<65 yr 125/233 0.48 (0.34–0.70)
≥65 yr 39/70 0.45 (0.24–0.87)
Sex
Female 91/171 0.39 (0.25–0.60)
Male 73/132 0.61 (0.38–0.98)
Race
Asian 72/138 0.46 (0.28–0.75)
Non-Asian 92/165 0.49 (0.32–0.75)
Smoking status
Active smoker 12/17 1.16 (0.35–3.90)
Nonsmoker 103/190 0.44 (0.29–0.66)
Former smoker 49/96 0.42 (0.23–0.77)
ECOG performance status
0 44/97 0.40 (0.21–0.77)
1 105/186 0.48 (0.32–0.71)
2 15/20 0.74 (0.25–2.15)
CNS metastases at baseline
Yes 78/122 0.40 (0.25–0.64)
No 86/181 0.51 (0.33–0.80)
Previous brain radiation
Yes 26/47 0.33 (0.14–0.74)
No 138/256 0.52 (0.36–0.73)
0.1
1.0
10.0
Alectinib Better
Crizotinib Better

VOLUME 34 · NUMBER 34 · DECEMBER 1, 2016
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With *ALK*-Positive Non–Small-Cell Lung Cancer

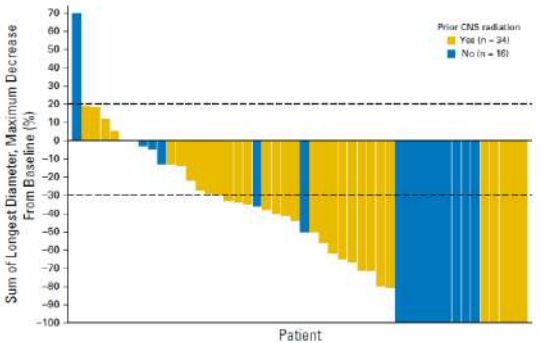


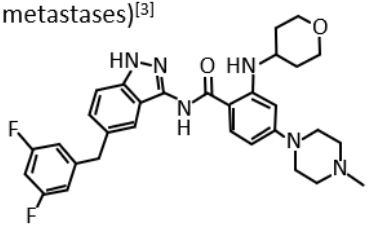
Table 3. IRC CORR by Prior Radiation Therapy

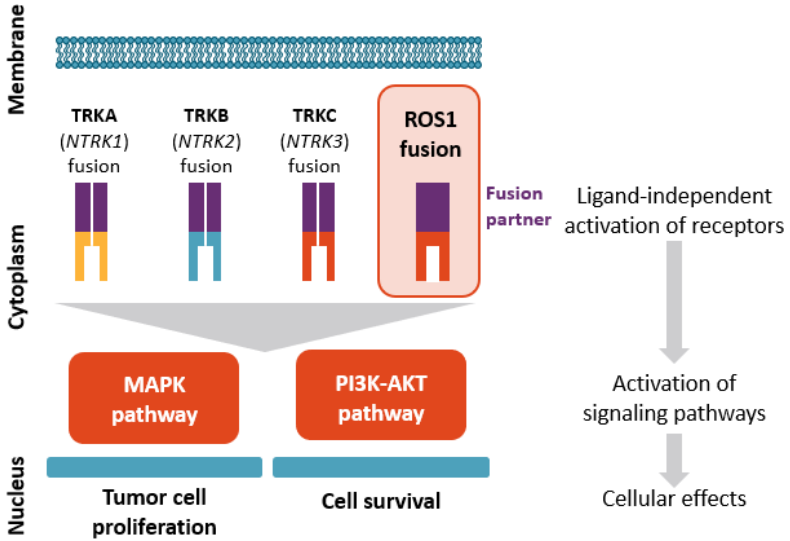
Response	All Patients With CNS Metastases* (n = 136)	
	Prior Radiation (n = 95)	No Prior Radiation (n = 41)
Responders (CORR), %	35.8	58.5
95% CI	26.2 to 46.3	42.1 to 73.7
Complete response, No. (%)	17 (17.9)	20 (48.8)
Partial response, No. (%)	17 (17.9)	4 (9.8)
Stable disease, No. (%)	48 (50.5)	10 (24.4)
Progressive disease, No. (%)	9 (9.5)	3 (7.3)
Missing/unevaluable, No. (%)	4 (4.2)	4 (9.8)
CDCR, No. (%)	82 (86.3)	34 (82.9)
95% CI (%)	77.7 to 92.5	67.9 to 92.9

NOTE. Data cutoff for both NP28673 and NP28761 was April 27, 2015. Responses evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST).
Abbreviations: CDCR, CNS disease control rate; CORR, CNS objective response rate; IRC, independent review committee.
*Patients who had both measurable and/or nonmeasurable disease at baseline.

Entrectinib in *ROS1*-Positive NSCLC: Background

- *ROS1* gene fusions are oncogenic drivers (1% to 2% of NSCLC cases)[1]
- Entrectinib: oral, potent, selective ROS1/NTRK/ALK TKI with CNS activity, can cross blood–brain barrier, remain within CNS[2]
- More potent inhibitor of ROS1 than crizotinib (preclinical data)[2]
- Demonstrated activity in multiple tumor types (eg, primary brain tumors, secondary CNS metastases)[3]





1. Dugay. Oncotarget. 2017;8:53336. 2. Ardini. Mol Cancer Ther. 2016;15:628-639. 3. Drilon. Cancer Discov. 2017;7:963.

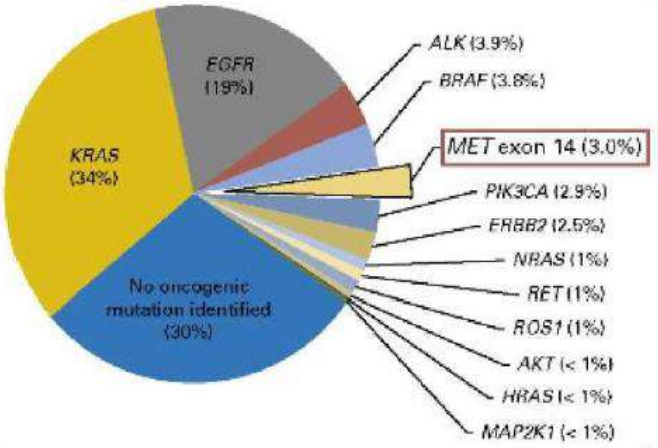
Entrectinib in *ROS1*-Positive NSCLC: Conclusions

- Entrectinib highly active in *ROS1*-positive NSCLC: clinically meaningful, deep and durable systemic responses, with and without CNS metastases

- Clinically meaningful intracranial activity in patients with baseline CNS disease
  - **Intracranial ORR: 55% (CR: 20.0%)**
  - Intracranial median DoR: 12.9 mos

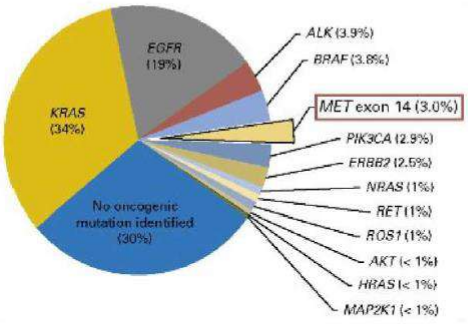
Barlesi. ELCC 2019. Abstr 109O.

New targets: MET



	Capmatinib	Savolitinib	Tepotinib	Cabozantinib	Crizotinib
IC_{50} (nM)	0.6	2.1	3.0	7.8	22.5

New targets: MET



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IC_{50} (nM)	0.6	2.1	3.0	7.8	22.5

Best overall response (treatment naive cohort 5b)

All responses confirmed per RECIST 1.1
Response rates consistent between BIRC and investigator assessment

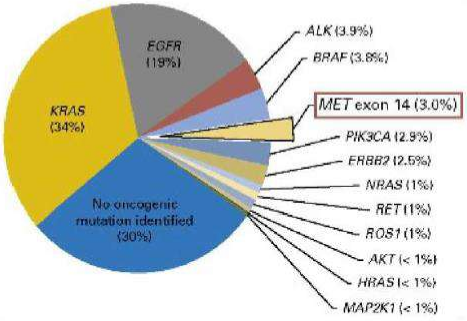
	Cohort 5b (11) N=28	
	BIRC	Investigator
Best overall response, n (%)		
Complete Response	1 (3.6)	0
Partial Response	(64.3)	17 (60.7)
Stable Disease	8 (28.6)	10 (35.7)
Progressive Disease	1 (3.6)	1 (3.6)
Overall response rate (ORR) %, (95% CI)	67.9 (47.6, 84.1)	60.7 (40.6, 78.5)
Disease control rate (DCR) %, (95% CI)	96.4 (81.7, 99.9)	96.4 (81.7, 99.9)

67.9%

mDoR: 11.1 months

Wolf J; Paik PK ASCO 2019

New targets: MET



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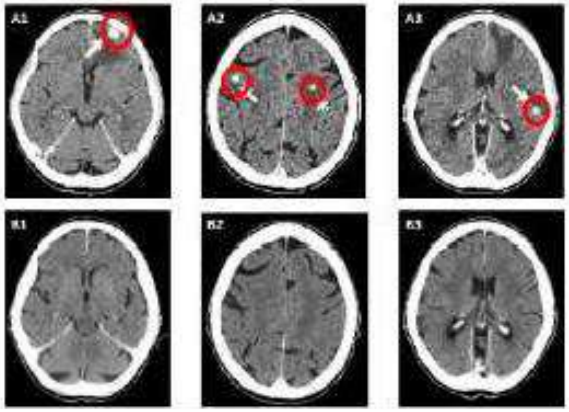
Wolf J; Paik PK ASCO 2019



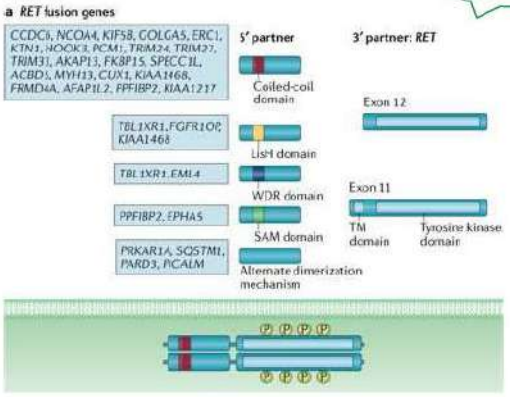
54% (n=7/13) had intracranial response*:

- 4 patients had complete resolution of all brain lesions
- The other 3 responding patients had:
  - complete resolution in 3 lesions, -50% reduction in 1 lesion, stabilization in remaining 4 lesions (total of 7 lesions)
  - Complete resolution in 2 lesions, stabilization in 1 remaining lesion (total of 3 lesions)
  - Complete resolution in 1 lesion, stabilization in 3 remaining lesions (total of 4 lesions)

Wolf J, ASCO 2019

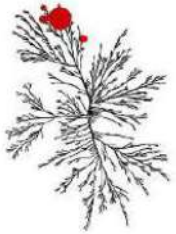
New targets: RET

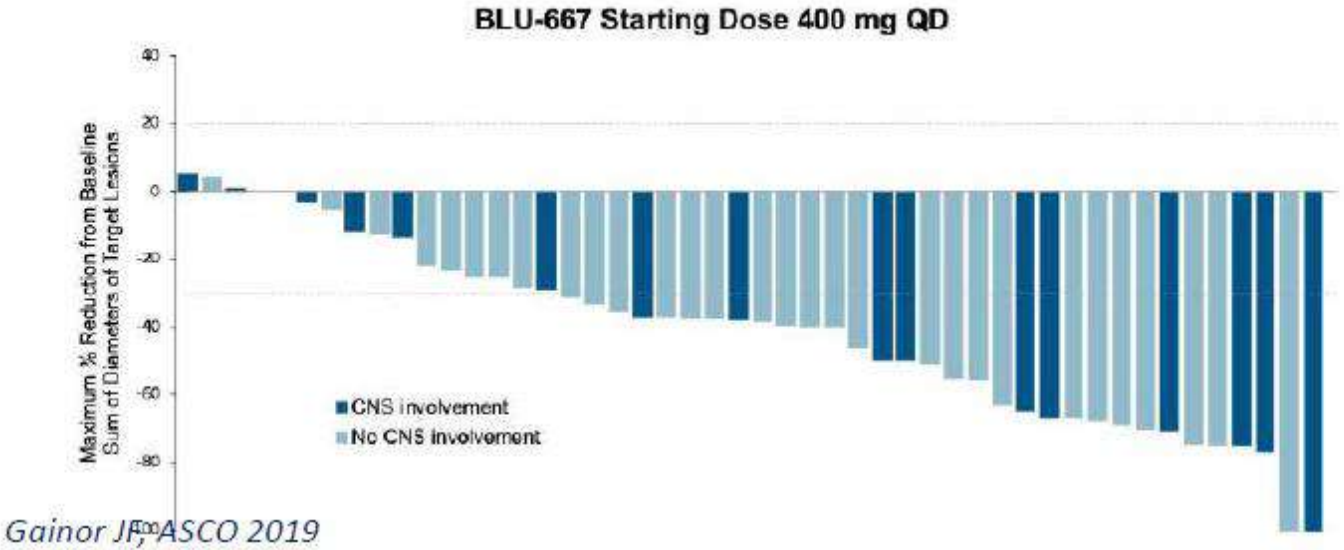
1-2% NSCLC



Nature Reviews | Clinical Oncology

BLU-667: High kinome selectivity for RET[a]

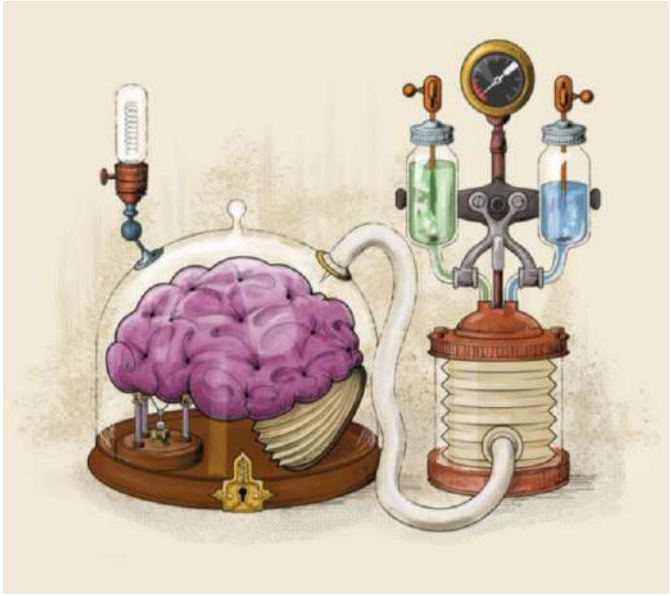




Gainor JF, ASCO 2019

Take away

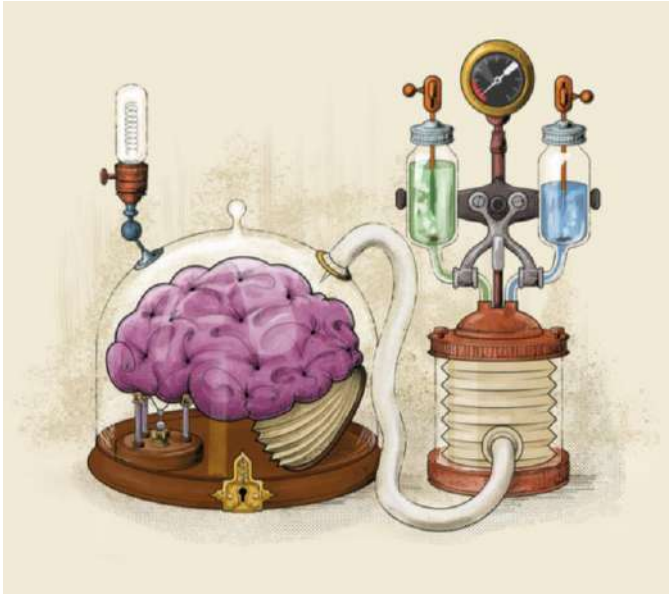
- The brain is not separate from the rest of the body! (the seed is the same)
- We have to consider both intracranial and extracranial disease
- Targeted approaches are effective also for BM (despite of the soil)

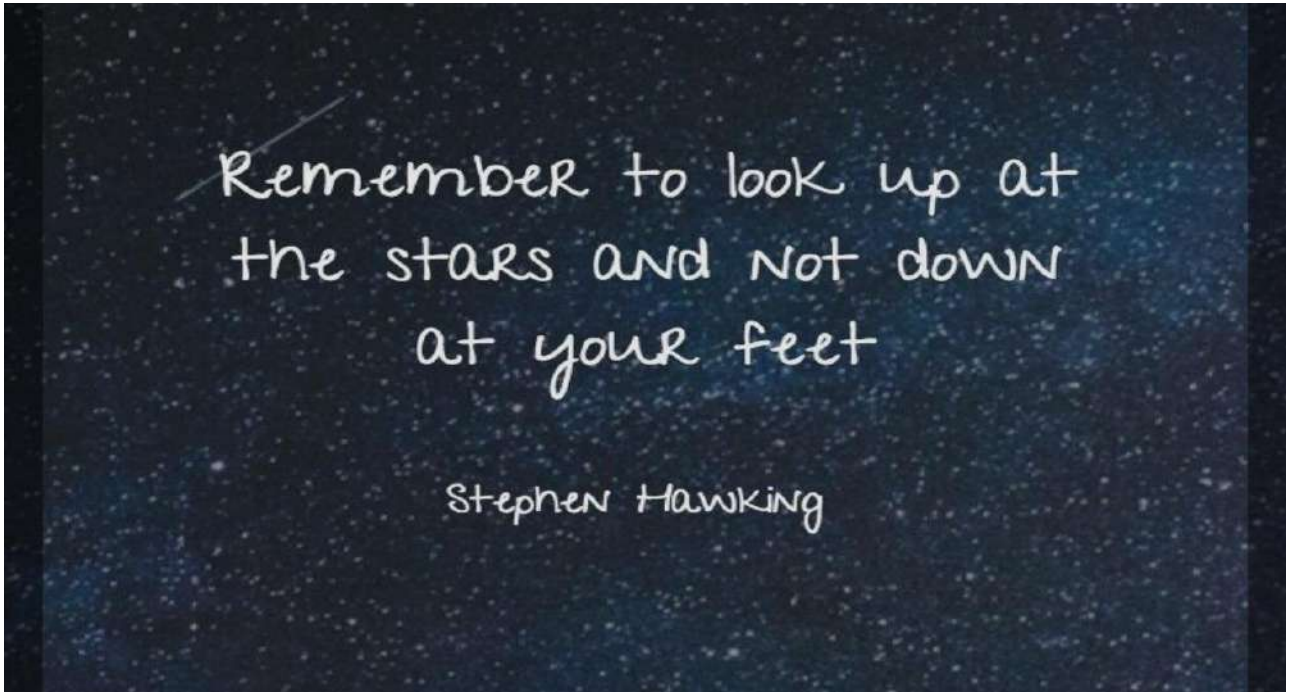


Take away

- Crossing the BBB is important

- Agents that hit the target and cross the BBB provide responses in 50-80% of brain mets




Remember to look up at
the stars and not down
at your feet
Stephen Hawking