BRAIN METS IN 2018: ANY CLOSER TO THE END OF A LONG AND WINDING ROAD?

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Molecular targets in primary cancers with prospensity for brain metastasis allow better treatment of BM

Several tumors with known brain metastasizing potential have targets that allow targeted treatment

- Melanoma: BRAF mutations (50%)
- NSCLC: EGFR, ALK, ROS1 (10-15%)
- Breast cancer: HER2, PR, ER

Major clinical questions:

- Are targeted treatement equally active in brain metastases patients?
- Do brain metastases require different approaches?
- What is the current role of local treatments
  - Whole brain
  - Stereotactic radiosurgery

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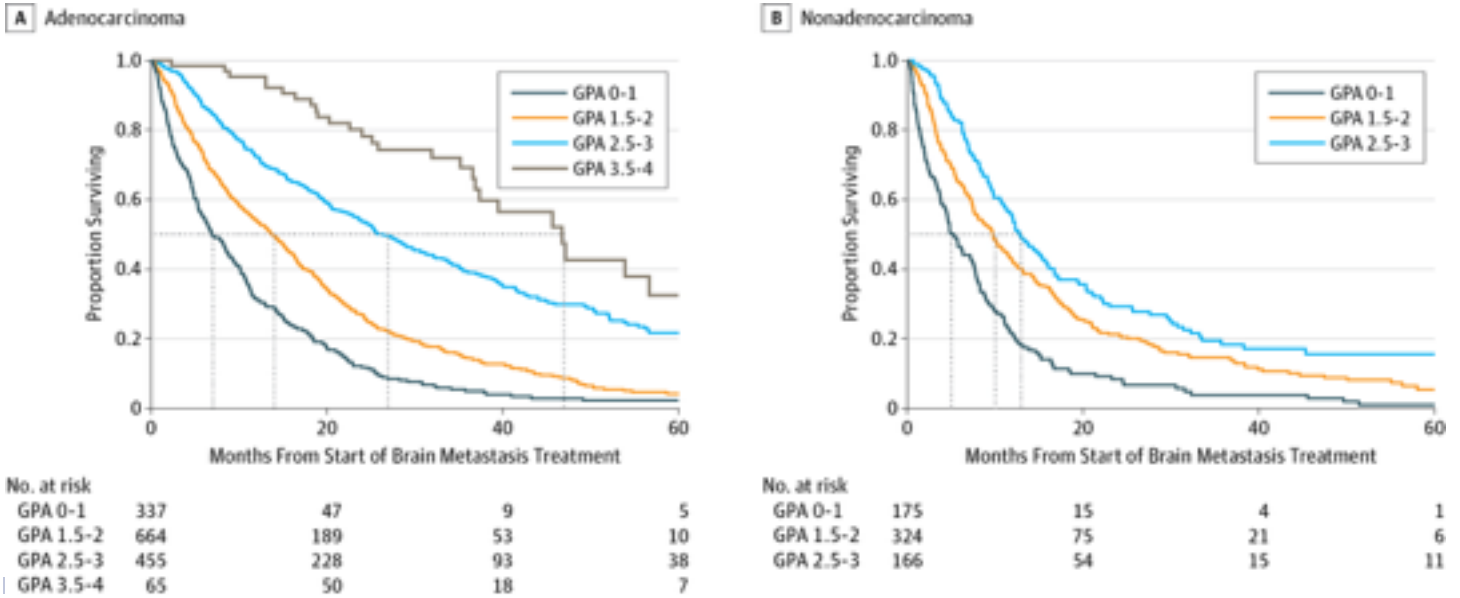
Disease specific graded prognostic : introduction of molecular factors

- The original DS-GPA: 1833 patients, 4 factors identified in 1833 NSCLC / brain metastases patients: age, KPS, extracranial metastases, and number of brain metastases; median OS 7 months.
- Updated Lung-molGPA, 2186 patients with NSCLC and newly diagnosed brain metastases (1521 adenocarcinoma and 665 nonadenocarcinoma).
- Significant prognostic factors: the original 4 factors used in the DS-GPA index plus 2 new factors: ***EGFR* and *ALK* alterations**
- **Median OS 12 months**, NSCLC-adenocarcinoma and Lung-molGPA scores of 3.5 to 4.0: had a median survival of nearly 4 yrs



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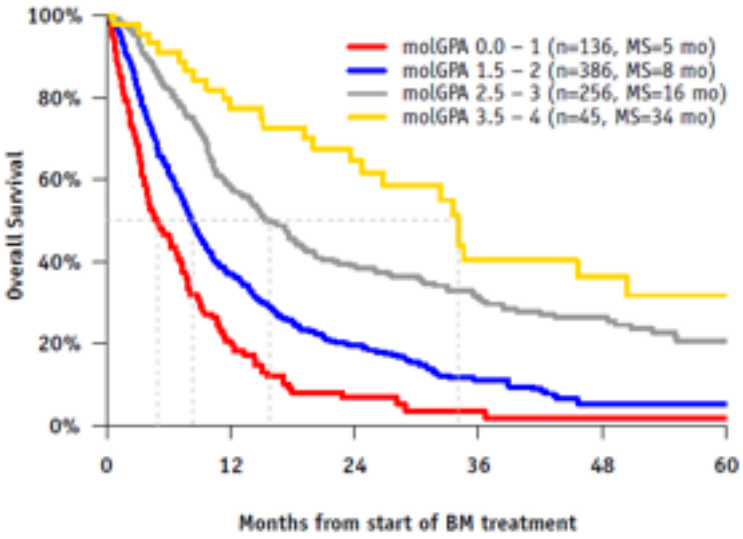
Melanoma brain metastases and molecular GPA

- Original Melanoma-GPA based on 483 patients between 1985 and 2005.
- Updated GPA based on 823 melanoma patients between from 2006 - 2015.
- 5 significant prognostic factors for survival (age, KPS, extracranial metastases, number of brain metastases, and BRAF status),
- In the original: only KPS and number of brain metastases
- **Median survival improved from 6.7 to 9.8 months between the 2 treatment eras**



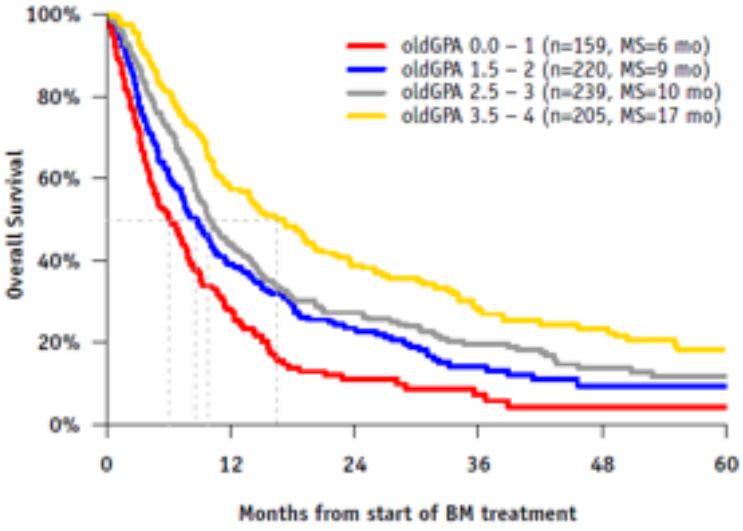


Table 2 Melanoma GPA worksheet

Prognostic factor	GPA scoring criteria 0	0.5	1.0	Patient Score
Age, y	≥70	<0		-
KPS	≤70	80	90-100	-
ECM	Present		Absent	-
No. of BM	>4	2-4	1	-
BRAF gene status	Negative/unknown	Positive		-
			Sum	-

Abbreviations: BM = brain metastases; ECM = extracranial metastases; GPA = Graded Prognostic Assessment; KPS = Karnofsky performance status; MS = median survival in months.

Sperduto et al, Int J Radiat Oncol Biol Phys.

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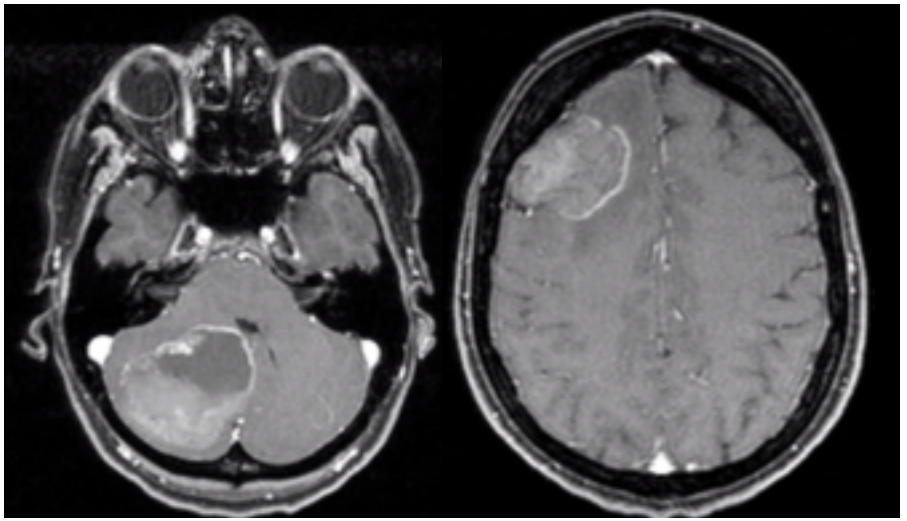
Two CNS lesions with a history of cervical cancer

- Female, 44 years of age
- 2013 RT, chemotherapy for stage IIb cervical cancer
- Aug 2018 vertigo, headache, difficulty walking
- MR scan two lesions, geographically apart
- CT scan: cystic lesion liver?
- Both CNS lesions resected in one session
- Histology: metastases cervical cancer
- Followed with fractionated stereotactic radiotherapy



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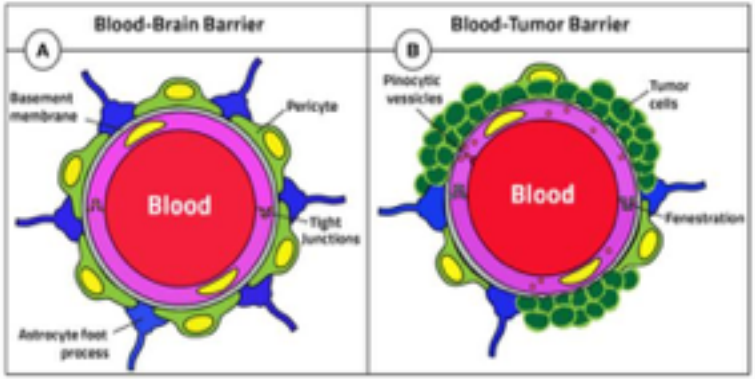
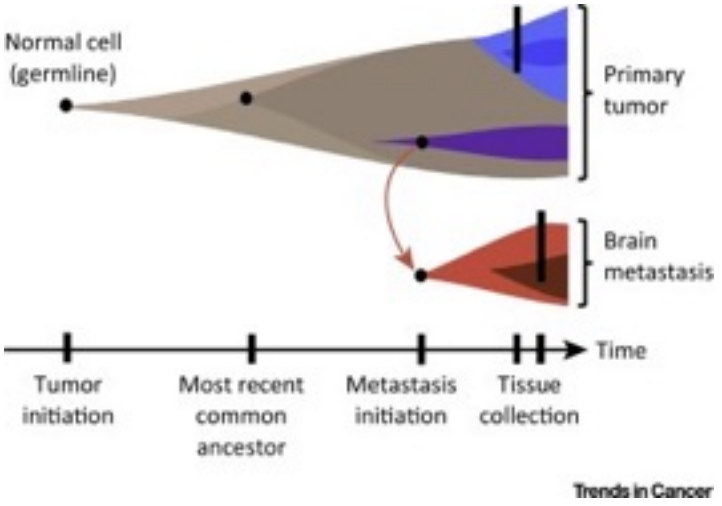
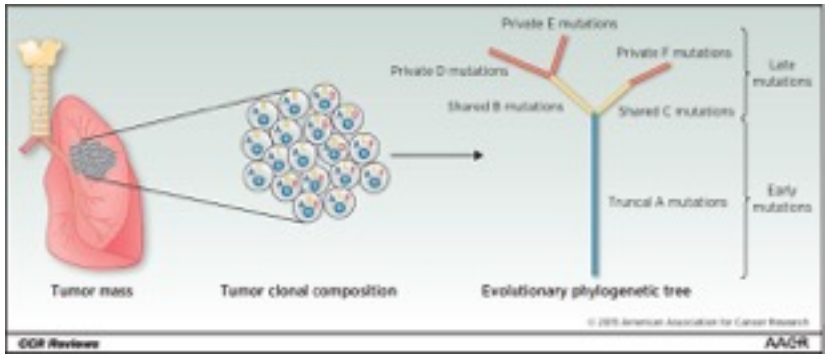
Systemic treatment: are brain mets special?

- Blood brain barrier
  - at least partially disrupted
- Different mutational profile?
  - May impact homing of clones
- Site specific branched evolution?
  - May induce other site specific targets







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Clinical series on systemic treatment of CNS mets

Requirements for the analysis of CNS activity:

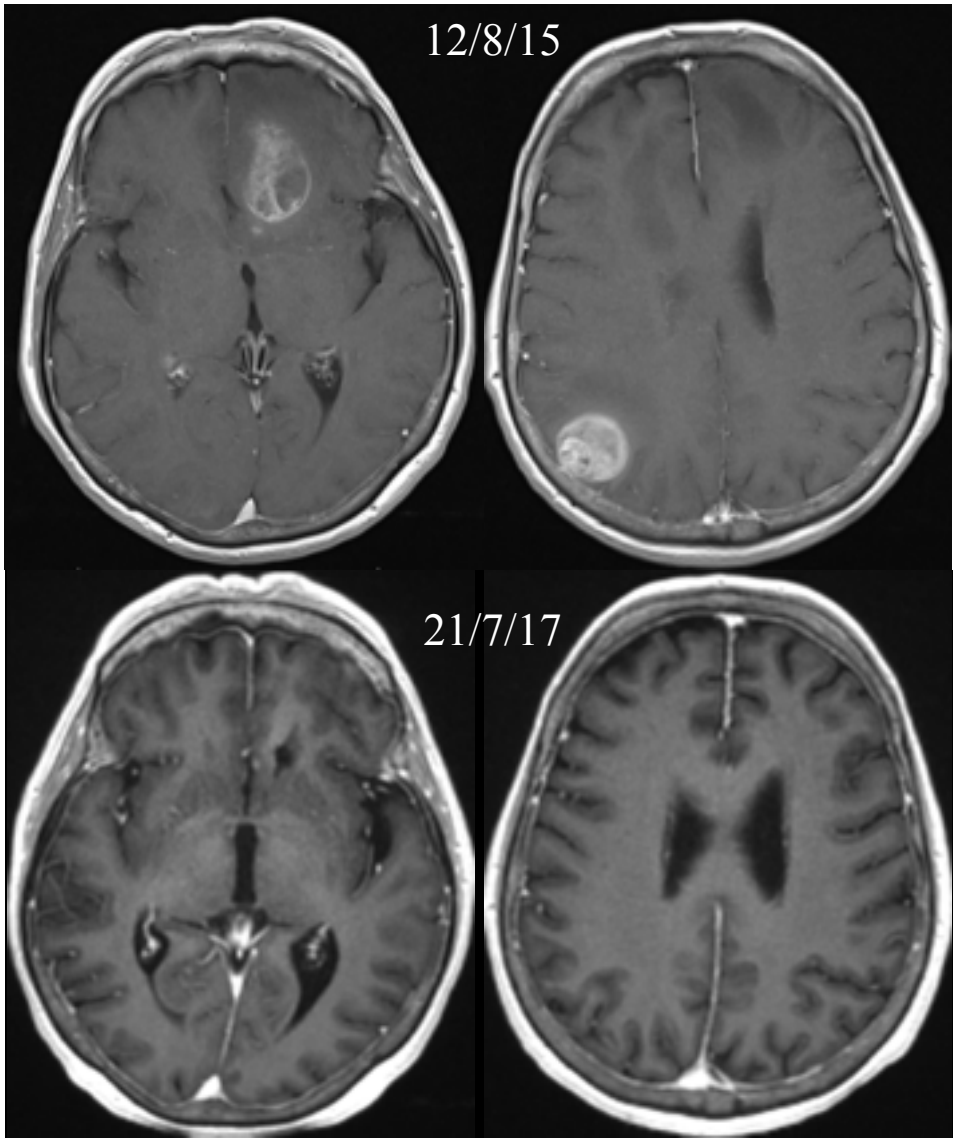
- **Interpretation of new treatments require 'CNS' cohorts in larger studies**
- **With enrollment of patients with active brain metastases**
- **And measurable disease: evaulable for response**
- **With documentation and comparison of systemic and intracranial disease response and progression**

- **Many studies do not meet these requirements**

➢ **Interpretation of CNS activity in studies on novel agents often of a limited scope**

Cerebral metastases BRAF V600E mutated melanoma

- 73 year old female, diagnosed in march 2015 with locally metastasized melanoma
- July 2015 confusion, headache,
- MR: multiple cerebral metastases
- Diagnostics: BRAF p.V600E mutation
- Vemurafinib, stop after 6 weeks for skin toxicity
- Continuation therapy with dabrafinib
- MRI scan: complete respons, ongoing in august 2018



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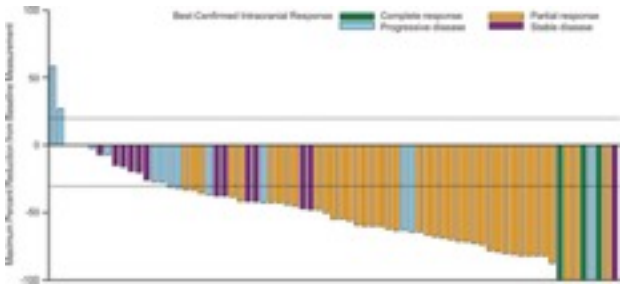
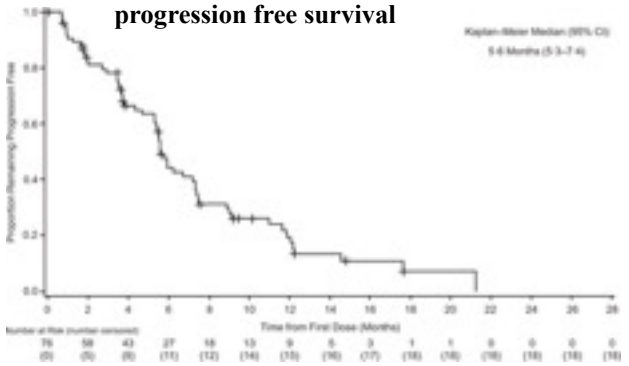
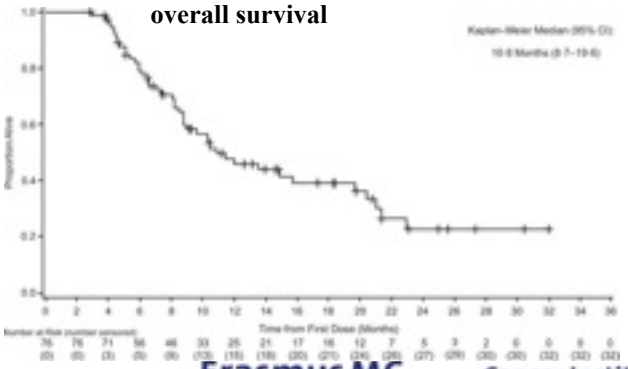
Dabrafinib and trametinib in BRAFv600 mutant melanoma brainmets: COMBI-MB

- Target CNS lesions: 0.5 – 4.0 cm
- Several cohorts:
  - A: V600E mutant, asymptomatic, ***not prior locally treated***: n = 76
  - Median follow-up: 8.5 mo
- Cohort A: 44:76 (58%) ORR; extracranial ORR: 42 (55%); overall: 44 (59%)
  - Most responses by week 4
- Median response duration: 6.5 mo. median PFS: 6.5 mo; median OS 10.8 mo







1Davies et al, Lanc Oncol 2017;;18:863-73, 2Long et al Lancet 2015;386:444-51, 3Schadendorf et al, Eur J Canc 2017;82:45-55

Dabrafinib and trametinib in BRAFv600 mutant melanoma brainmets: COMBI-MB

- In systemic disease (pivotal phase III trial): median response duration 12.0 mo, median PFS 11 mo, median OS 25 mo[2]
- Pooled outcome 3 phase III trials: PFS 11.1 mo, median OS 26.2 mo[3]

➢ **Shorter duration PFS and OS in brain mets patients**

- **6.5 vs 12 mo PFS, 10.8 vs 25 OS**
- No correlation with outcome of systemic disease

➢ Is that due to the blood brain barrier?

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1Davies et al, Lanc Oncol 2017;;18:863-73, 2Long et al Lancet 2015;386:444-51, 3Schadendorf et al, Eur J Canc 2017;82:45-55

Combined Nivolumab and Ipilimumab in melanoma metastastic to the brain

- Report of a phase II study on CNS metastases of melanoma
- Measurable disease (0.5 – 3 cm), non-irradiated targets, not requiring immediate local treatment, **asymptomatic**, **no steroids**
  - Later amendment: 20 symptomatic patients (but not yet reported)
- Nivolumab 1 mg/kg, ipilimumab 3 mg/kg (induction only)
- Endpoints: intracranial clinical benefit
  - CR, PR (RECIST 1.1)
  - Stable disease for ≥ 6 mo
- 94 patients with minimum f-up 6 mo (median: 14 mo)
  - 8 SRS prior to study entry
  - At the time of report: PD 33%, 18% intracranial only

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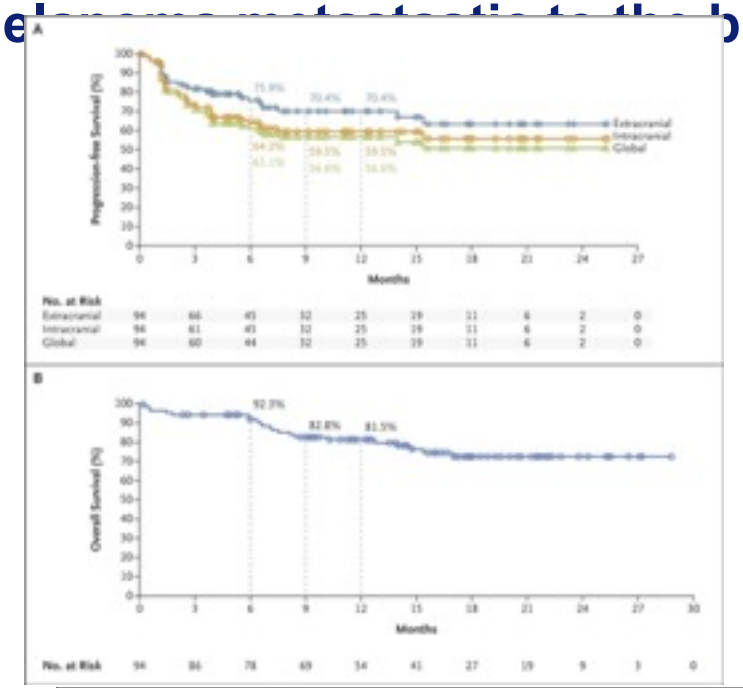
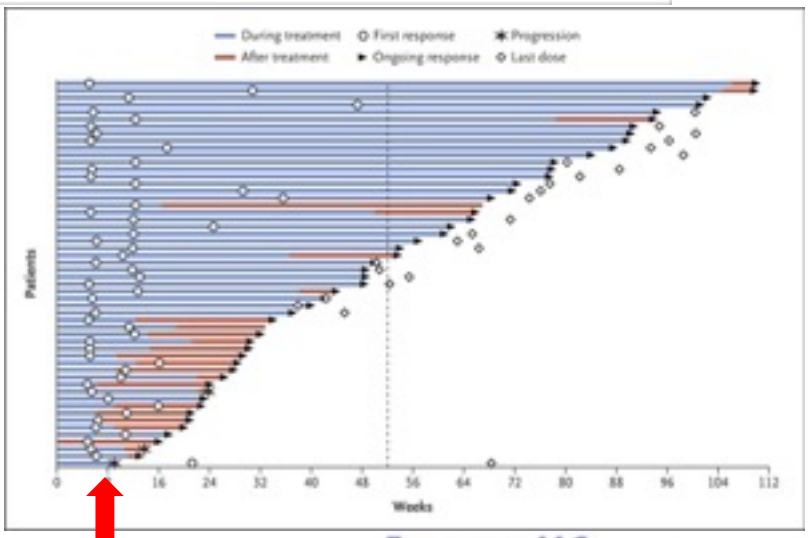
HA Tawbi et al. N Engl J Med 2018;379:722-730

Combined Nivolumab and Ipilimumab in melanoma metastatic to the brain

- Clinical benefit: 55%; CR 26%, PR 30%
  - 6 and 9 mo intracranial PFS: 64.2% and 59.5%
  - 6 and 9 mo global PFS: 61.1% and 56.6%
- Estimated 12 mo OS 81.5%
- Median time to response 2.1 mo
- PD-L1 expression ≥ 5 vs < 5: clinical benefit rate 76% vs 48%





o: first response

HA Tawbi et al. N Engl J Med 2018;379:722-730

11th command:
Thou shalt not compare across trials

treatment	Dabrafinib/trametinib
n, median f-up	76, **8.5 mo**
symptomatic	no
Molecular criteria	BRAF V600E mutant
size	0.5 – 4.0 cm
steroids	Allowed if stable (3%)
Prior systemic treatment	22%
ORR (CR, PR)	58%
Time to response	Most ORR by 4 weeks
PFS median 12 mo	 6.5 mo **19%**
OS Events Median 12 mo	 44 (58%) 10.8 mo **46%**

Adam, Eve, the snake & fruit of knowledge
Cranach the elder

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Do we really need to avoid steroids in brain tumor patients treated with anti-PD1/PD-L1 agents?

- All trials on checkpoint inhibitors try to avoid steroid use
- Steroids block CD-8 positive T-cells, suppress IL-2 mediated activation of effector T-cells and increase immunesuppresive T-reg's
- Often needed for symptom management in brain tumors: to be avoided at all costs?

- Retrospective survey 640 patients treated with single agent PD-(L)1 blockade for advanced NSCLC (2 cohorts: MSKCC, GRCC)
- 90 received steroids at baseline equivalent ≥ 10 mg
  - 19% for brain mets

Arbour et al, J Clin Oncol 2018;36:doi 10.1200/JCO.2018.79.0006

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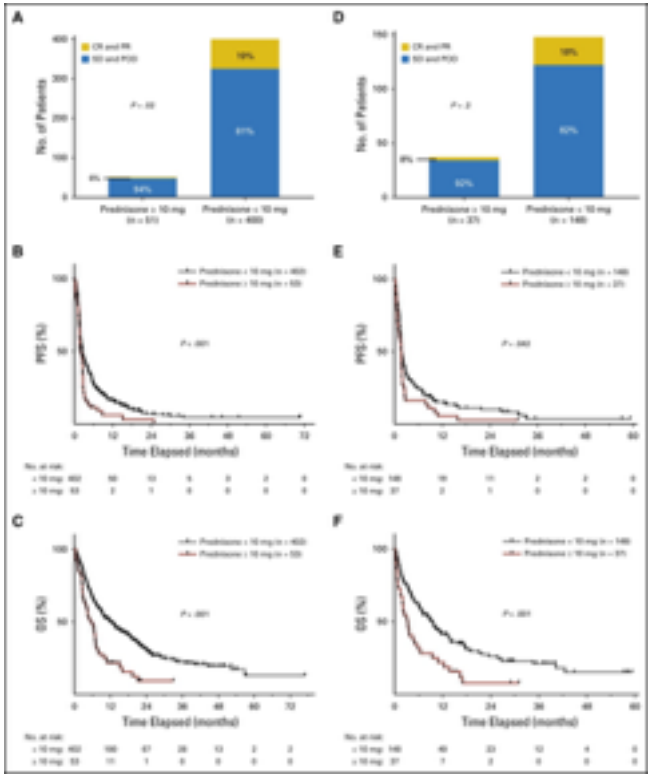
Do we really need to avoid steroids in brain tumor patients treated with anti-PD1/PD-L1 agents?

- Steroid use associated with (MSKCC cohort)
  - decreased ORR (6% vs 19%)
  - Decreased median PFS (1.9 mo vs 2.6 mo)
  - Decreased OS (5.4 mo vs 12.1 mo)
- Similar trend if prednison dosage ≥ 20 mg
- Multivariate analysis incl smoking, PS, brain mets: steroids associated with
  - decreased ORR (HR 0.42)
  - significantly shorter PFS and OS (HR 1.31 and 1.66 respectively)
- Intermediate effect of steroids discontinued 1 – 30 days prior to starting treatment
- Steroids seem less deleterious if used for management of side-effects



Arbour et al, J Clin Oncol 2018;36:doi 10.1200/JCO.2018.79.0006

Next generation ALK, EGFR inhibitors in NSCLC

- Ceritinib
  - ALK and ROS1 inhibitor, 20 x more potent compared to crizotinib
  - Brain penetrant
  - Active in crizotibib failures
  - Similar CNS and systemic ORR
- Alectinib
  - ALK inhibitor
  - More effective compared to crizotinib
  - Reduced developement of new brain metastases
- Osimertinib
  - EGFR inhibitor, incl of mutation T790M induced by classical EGFR inhibitors
  - Brain penetrant
  - Reduced develoment of brain metastases

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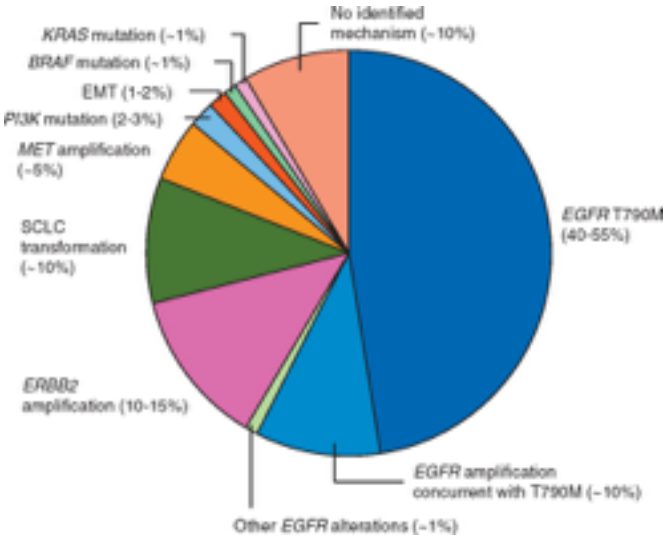
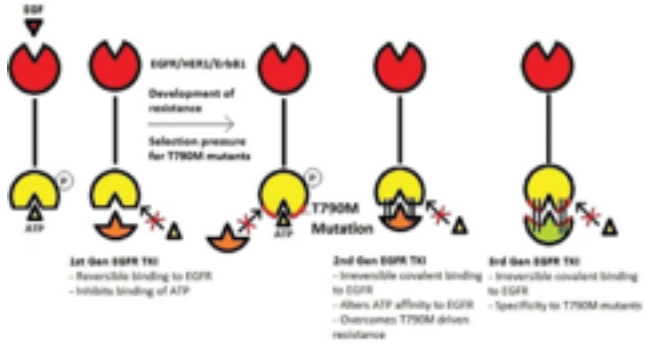
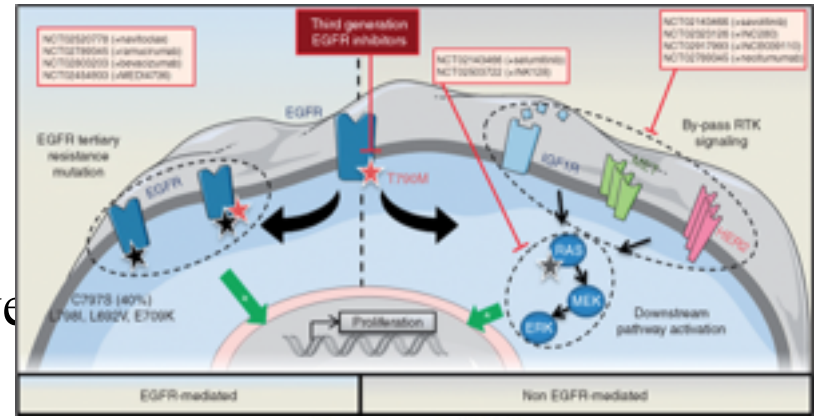
Resistance to EGFR TKI's

- Typically developes 9-15 mo after start 1st/ 2nd generation EGFR TKI's
  - 50% T790M mutation: reduces binding in the tyrosine kinase pocket
  - < 50% non–EGFR-centric adaptations
  - ➢ 'bypass' resistance mechanisms: pathways that activate the same downstream effectors of tumor cell growth and survival as EGFR: ERK1/2, AKT1
  - Eg, amplification of *ERBB2, MET*
- With 3rd generation TKI's, inter and intra patient heterogeneity in mechanisms of resistance
  - Eg, C797S: prevents binding to EGFR active site
- ➢ Longitudinal ctDNA monitoring (tumor, liquid)







Ricordel et al, Ann Oncol 2018 doi:10.1093/1nnonc/mdx705

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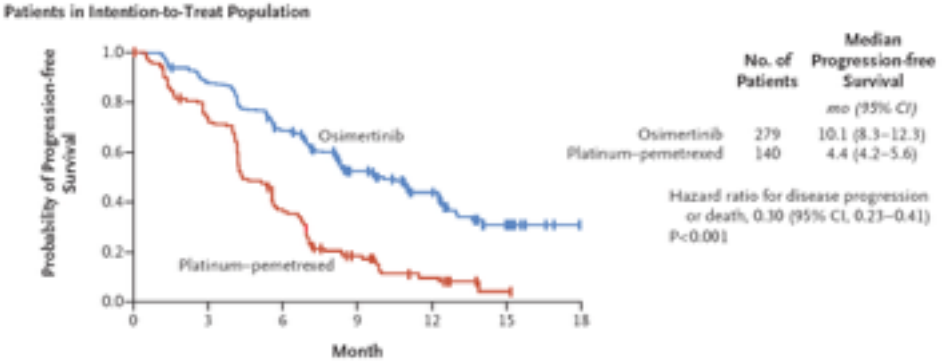
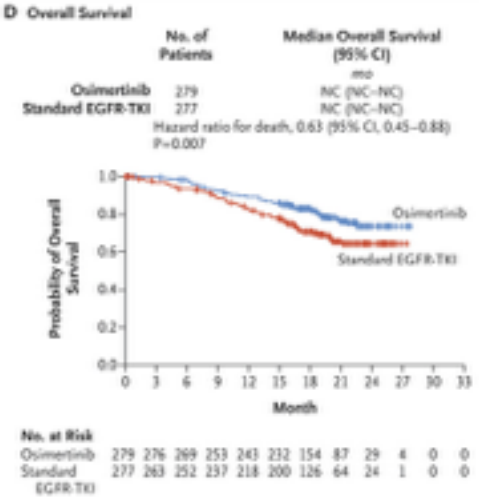
Osimertinib: AURA and FLAURA phase 3 trials

- Many patients sensitive to TKI EGFR inhibitor develop resistance after 9-13 months
  - in 60% with novel mutation T790M
- Osimertinib: oral 3rd generation EGFR-TKI, **brain penetrant**
- inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations





- AURA trial in resistant disease: efficacy osimertinib against platium-pemetrexed
- FLAURA trial efficacy osimertinib against standard EGFR-TKI

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Mok et al, Engl J Med 2017; 376:629-640; Soria et al, N Engl J Med 2018; 378:113-125

AURA trial: CNS Response to Osimertinib Versus Standard EGFR Tyrosine Kinase Inhibitors

- Report from the AURA3 study (n = 419) 2:1 osimertinib vs platinum-premetrexed in NCSLC, **T790M positive with PD after prior TKI**
- Asymptomatic or stable CNS metastases allowed
  - Measurable (> 10 mm) and non-measurable
- Preplanned analysis CNS efficacy
- 200 patients with available brain scans at baseline, 116 (osimertinib, n = 75; standard EGFR-TKIs, n = 41) had measurable and/or non-measurable CNS lesions,
  - ≥ one measurable CNS lesion: 46 patients (osimertinib, n = 30; standard EGFR-TKIs, n = 16)
- Median follow-up 15 mo osimertinib arm, 9.7 mo standard EGFR-TKI

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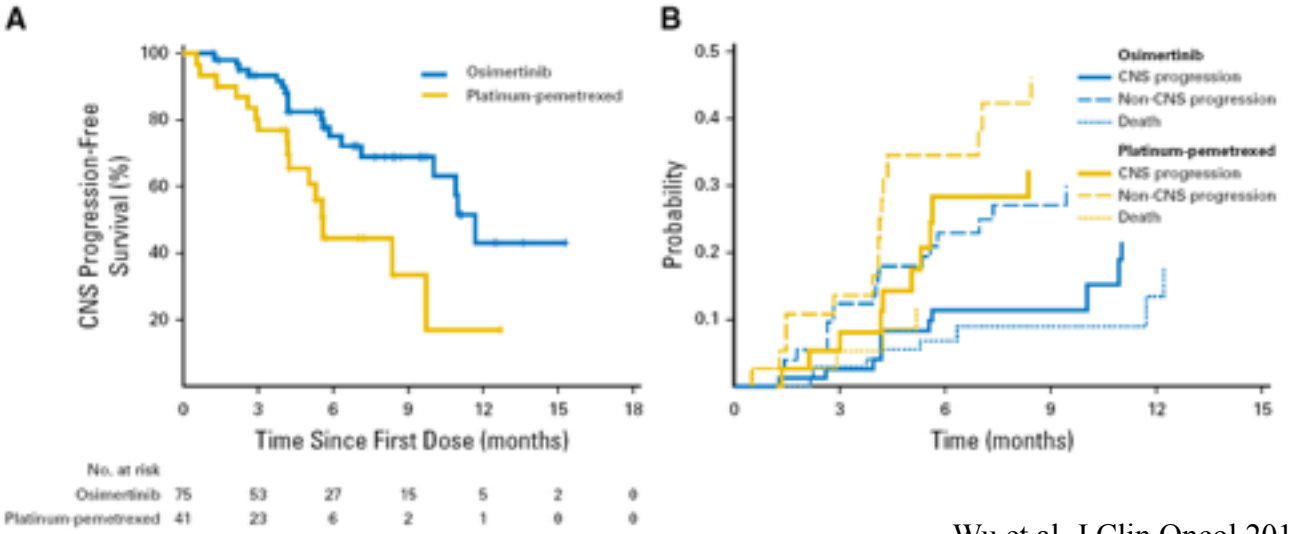
Wu et al, J Clin Oncol 2018;36 doi 10.1200/JCO.2018.77.9363

AURA trial: patients with measurable and/or nonmeasurable CNS lesions

- **Median CNS PFS survival: HR 0.48**; 95% CI, 0.26 to 0.86; P = .014)
  - **osimertinib** 11.7 mo (95% CI, 10 mo to not reached)
  - **platinum-pemetrexed** : 5.6 mo (95% CI, 4.2 mo to 9.7 mo)
- CNS ORR osimertinib vs platinum-pemetrexed 70% vs 31% in patients with measurable CNS lesion (odds ratio, 5.2; 95% CI, 1.44 to 20.64; P = .015)
- Lower probability of CNS progression with osimertinib versus standard EGFR-TKIs (16% vs 32%
- 61 % concordance between systemic and CNS response



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Wu et al, J Clin Oncol 2018;36 doi 10.1200/JCO.2018.77.9363

FLAURA trial: CNS Response to Osimertinib Versus Standard EGFR TKI in Untreated EGFR-Mutated Advanced NSCLC

- EGFRmt advanced NSCLC patients 1:1 randomized to **osimertinib** or standard EGFR-TKIs (**gefitinib or erlotinib**), n = 556
- Patients with asymptomatic or stable CNS metastases were included
  - Preplaned CNS subgroup analyses
- RECICST 1.1 response criteria
- 200 patients with available brain scans at baseline, 128 (osimertinib, n = 61; standard EGFR-TKIs, n = 67) had measurable and/or nonmeasurable CNS lesions
- Measurable: 41 (22 osimertinib, 19 standard EGFR-TKI)

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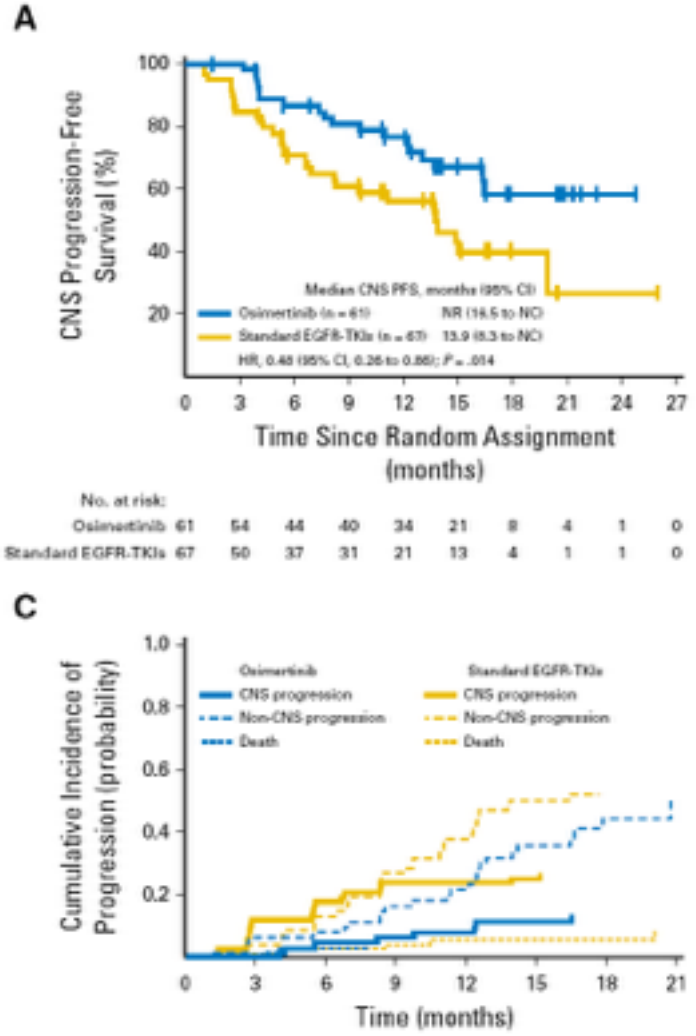
Rengwetwattana et al, J Clin Oncol 2018;36 doi 10.1200/JCO.2018.78.3118

FLAURA trial: patients with measurable and/or nonmeasurable CNS lesions

- **Median CNS PFS survival: HR 0.48**; 95% CI, 0.26 to 0.86; P = .014)
  - **osimertinib** not reached (95% CI, 16.5 months to not calculable)
  - **Standard TKI**: 13.9 months (95% CI, 8.3 months to not calculable)
- CNS ORR 91% vs 68% in patients with ≥ 1 measurable CNS lesion (odds ratio, 4.6; 95% CI, 0.9 to 34.9; P = .066) treated with osimertinib vs standard EGFR-TKIs
- Lower probability of CNS progression with osimertinib versus standard EGFR-TKIs
  - 20% vs 39%
- 77% concordance between systemic and CNS response



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Management of PD under first generation TKI's

- Three clinical subtypes of acquired resistance according to the extent anc sites of progressive disease
  - systemic or multi-site progression (60-70%
  - oligo-progression (three or less progressing locations; 20-25%)
  - isolated CNS progression (15%).
- Presence of absence of T790M in plasma or tumor?
  - If +: osimertinib
- Oligo-progression (incl CNS): consider local ablative treatments and continue TKI

Role of liquid biopsies for T790M? CSF? Longitudinal monitoring?

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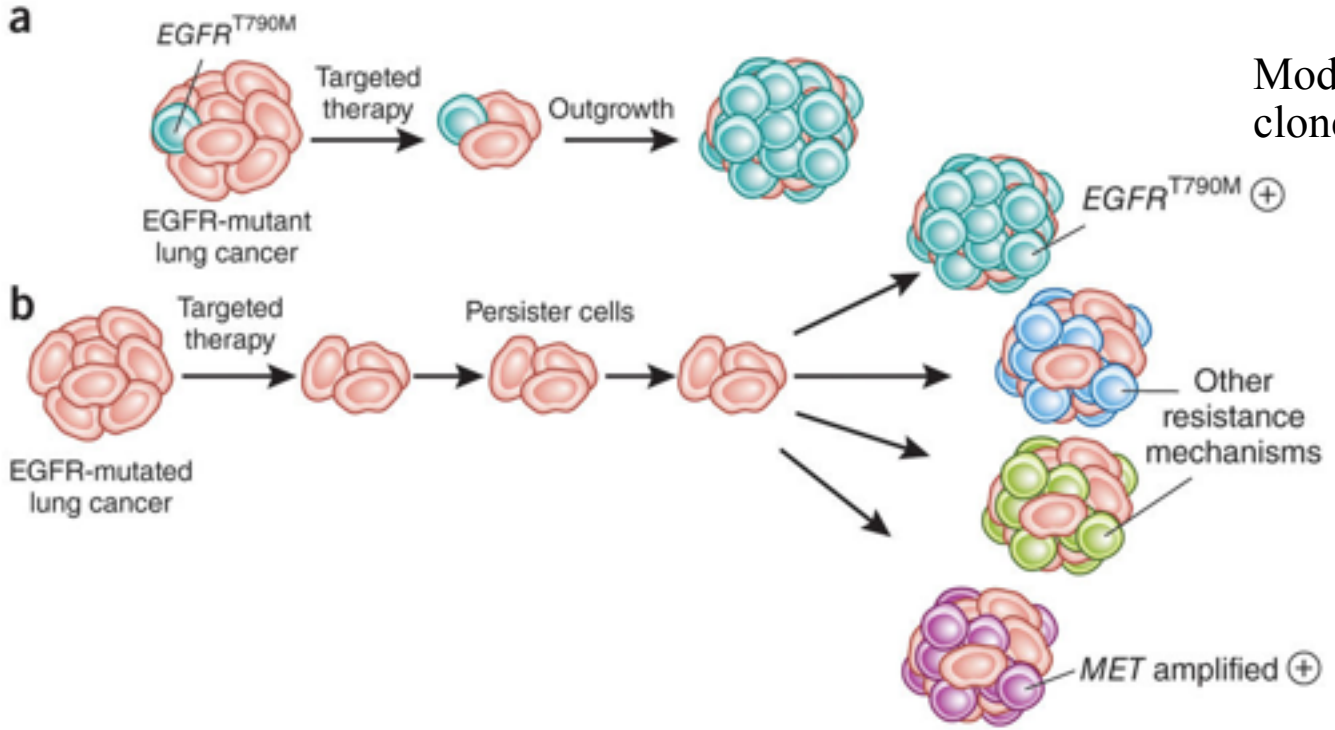
Westover et al, Ann Oncol 2018 doi:10.1093/1nnonc/mdx703

Different biologies of acquired resistance?



Models of the development of resistant clones in EGFRmt NSCLC

- This becomes clinically actionable of this process is
  - Predicatable
  - Diagnosable
  - Druggable
- Unlikely to guide treatment decisions in single brain mets, let alone in multiple CNS mets

Oxnard, Nat Med 2016;22:232-4, Mcdermott oral communication

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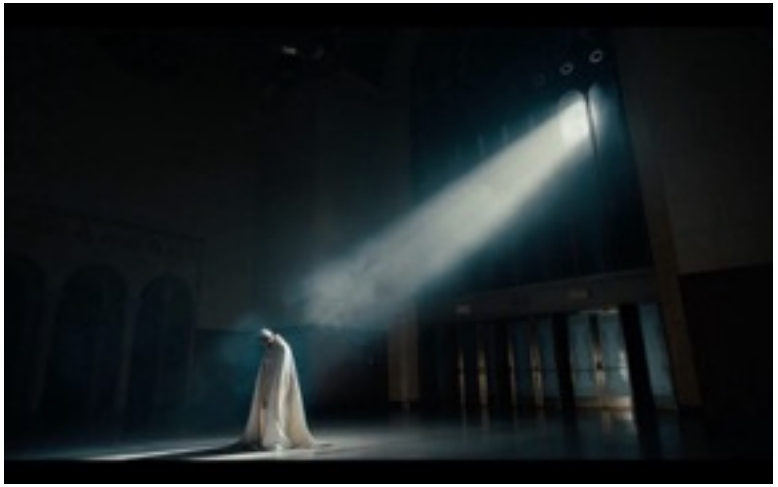
The role of radiotherapy

- For many years mainstay of treatment for CNS metastases
- Many schedules tried, no superiority
  - Keep it short and simple?
- Surgery, SRS more effective local control in patients with few brain metastases
- Outcome determined by systemic disease
- The QUARTZ has raised the fundamental question: is WBRT superior to best palliative care?
  - Adverse effects WBRT



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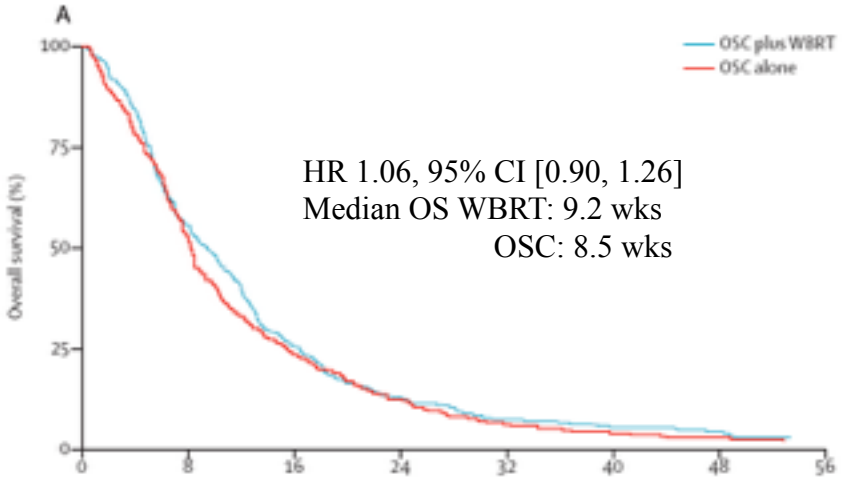
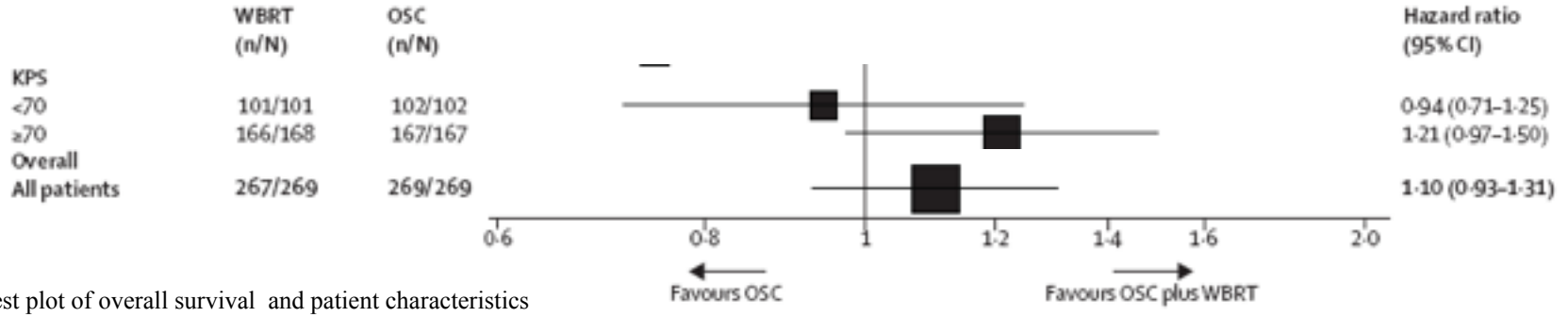
The QUARTZ trial: a new perspective on WBRT in NSCLC

- Design: optimal supportive care vs OSC with WBRT 20 Gy in 5 fractions
- Eligible: NSCLC patients with radiologically proven brain mets
  - Not candidate for surgery or SRS
- N = 538
  - KPS < 70 38%, ≥ 70 62%
  - Uncontrolled primary: 64%
- Non-inferiority trial, primary endpoint: QALY

➢ No OS difference in outcome between arms





Forest plot of overall survival and patient characteristics

➢ Still to be considered for good KPS patients

Mulvenna et al, Lancet 2016;388:2004-14

Icotinib versus WBRT in EGFR-mutant NSCLC and multiple brain metastases (BRAIN): a multicentre, phase 3 trial

- Multicentre phase III trial (n = 176) on patients with EGFRmt NSCLC, naive to treatment with EGFR-TKIs or radiotherapy, at least three metastatic brain lesions.
- Randomization (1:1) to icotinib or WBI (10 x 3 Gy) plus concurrent or sequential chemotherapy for 4–6 cycles
- Complex cross over design:
  - patients receiving icotinib who had
    - intracranial progression only were switched to WBI plus either icotinib or chemotherapy until further PD
    - extracranial progression only were switched to icotinib plus chemotherapy.
  - Patients receiving WBI who progressed were **switched to icotinib** until further progression.
- Primary endpoint: intracranial progression-free survival (PFS)
- 18 withdrew from the WBI group before treatment, leaving 73 for assessment
- Median follow-up 16·5 months

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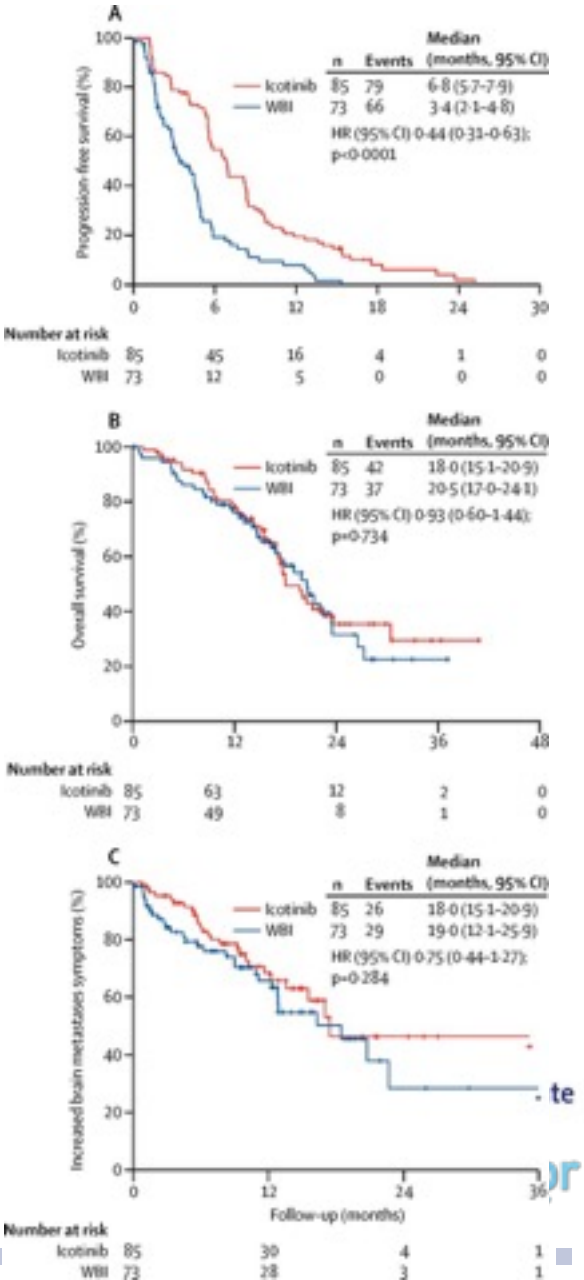
Yang et al, Lanc Resp Med 2017;5:707-716

Icotinib versus WBRT in EGFR-mutant NSCLC and multiple brain metastases (BRAIN): a multicentre, phase 3 trial

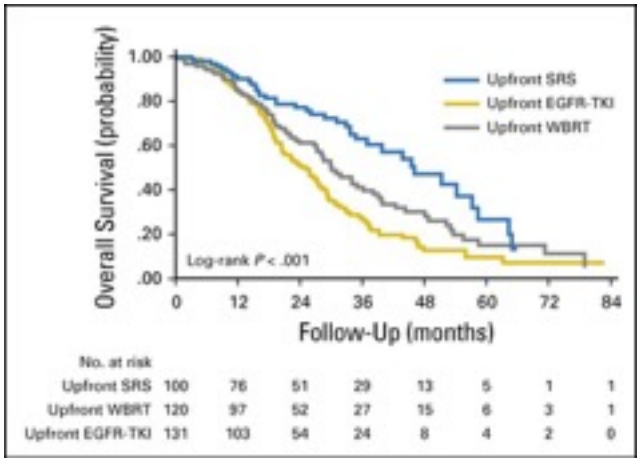
- patients with *EGFR*-mutant NSCLC and multiple brain metastases
- Median intracranial PFS: 10·0 months (95% CI 5·6–14·4) with icotinib versus 4·8 months (2·4–7·2) with WBI (HR 0·56, 95% CI 0·36–0·90; p=0·014).
- No impact on OS (cross over design!)
- icotinib was associated with significantly longer intracranial PFS than WBI plus chemotherapy,
- icotinib better first-line therapeutic option for this patient population?

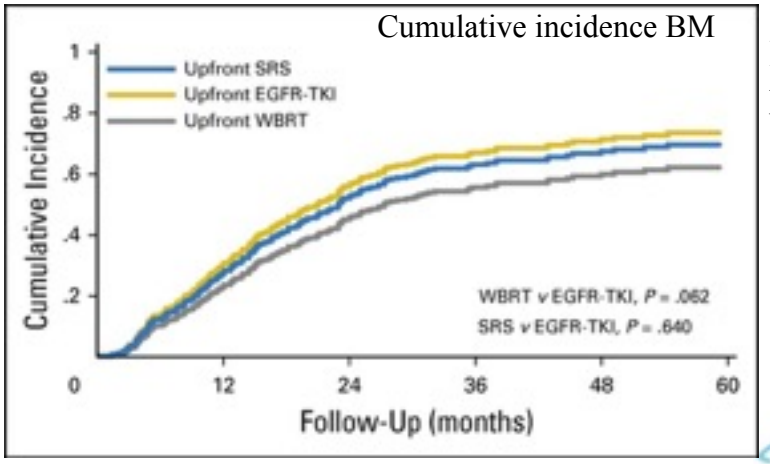


Yang et al, Lanc Resp Med 2017;5:707-716

New brain mets in EGFRmt NSCLC: how to treat?

- Retrospective multicenter survey in 351 patients, EGFR-TKI (98% erlotinib) and RT naive, with newly diagnosed brain metastases
- Treatment: SRS followed by EGFR-TKI, WBRT followed by TKI, or EGFR-TKI followed by SRS or WBRT at intracranial PD
  - EGFR-TKI: more often lesions < 1cm, more often asymptomatic
  - WBRT: worse GPA, more often > 10 lesions
- Deferral of RT associated with worse outcome; OS difference remained in GPA subgroups and after matched comparision
- Should we still avoid WBRT in that situation? Results due to control oligometastatic disease?





Median time to intracranial progression after TKI: 23 mo

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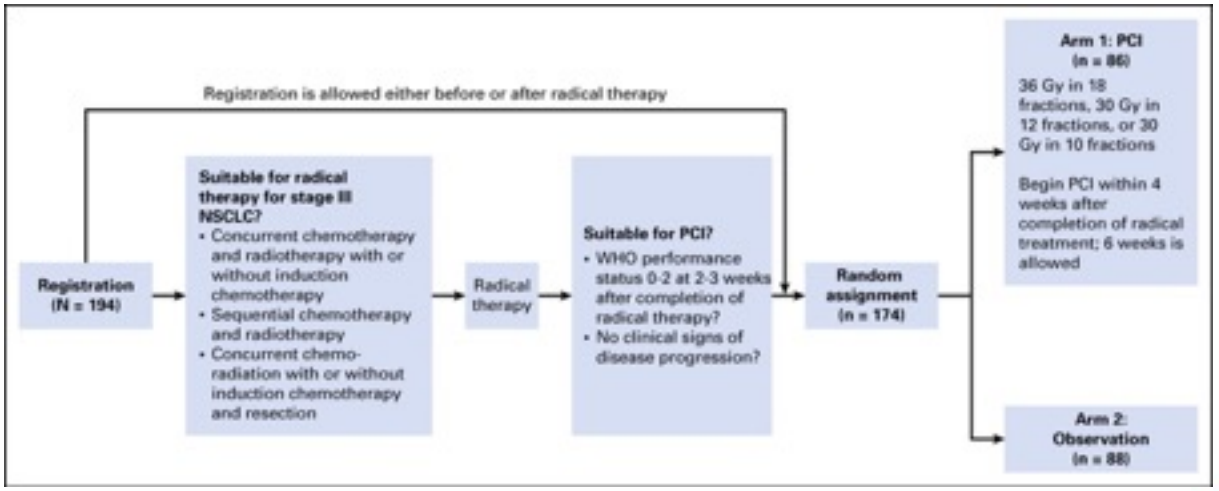
Magnuson et al J Clin Oncol 2017;35:1070-7, Soon et al Radioth Oncol 2015;114:167-172

New trial on PCI for radically treated stage III NSCLC

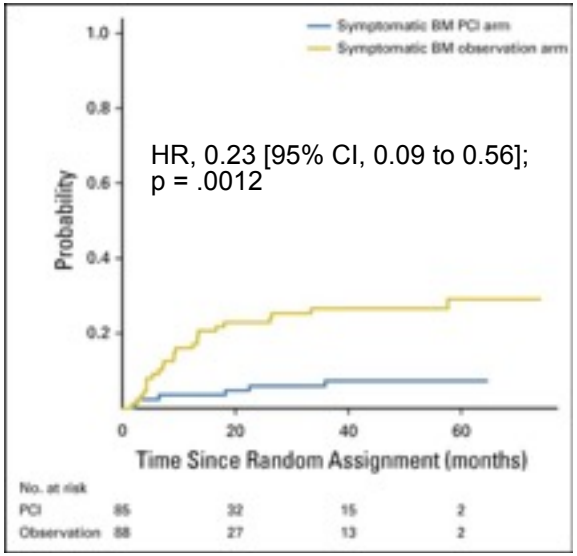
- Primary end point: development of symptomatic brain metastases at 24 mo
  - Key symptoms: one or a combination of signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures, and/or focal neurologic symptoms
  - Mandated imaging
- AE event assessment CTC for adverse events 3.0
- QoL assesssment with QoL C30 and BN20, EuroQol 5D
- n = 172

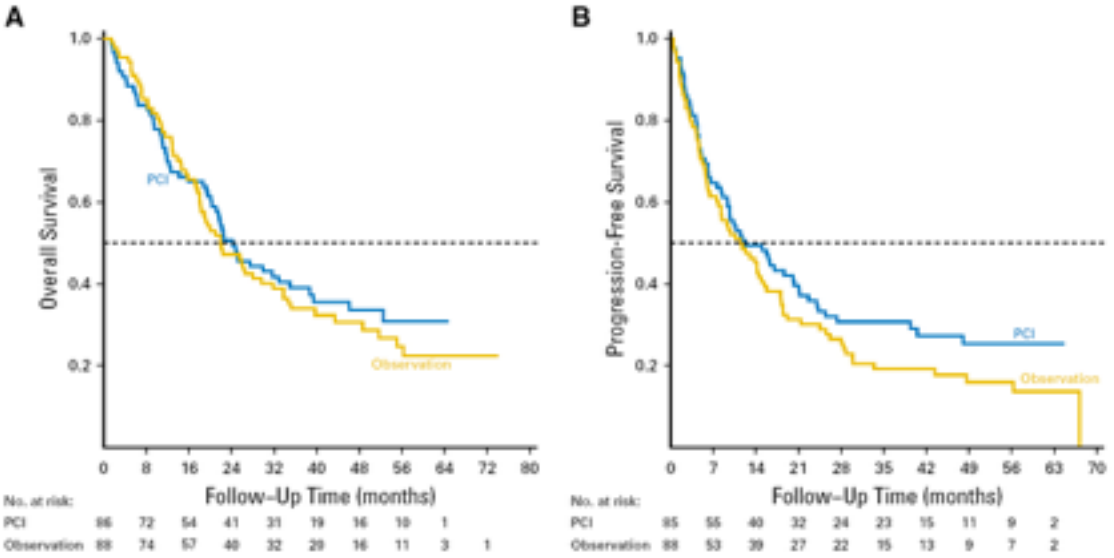


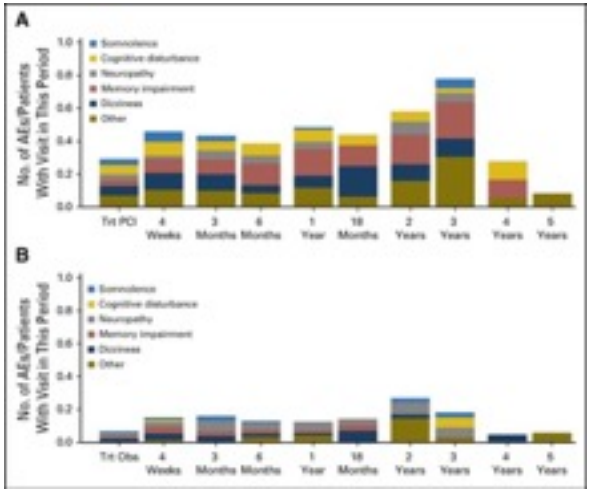
Ruysscher et al, J Clin Oncol Clin Oncol 2018;36:2366-2377

New trial on PCI for radically treated stage III NSCLC

- 6 (7.0%) of 86 patients PCI group vs 24 (27.2%) of 88 patients control group symptomatic brain metastases (p = .001)
- PCI increased time to develop symptomatic brain metastases (hazard ratio, 0.23; [95%CI, 0.09 to 0.56]; p = .0012).
- Less symptomatic brain metastases but no difference in Overall Survival







- After PCI more neurologic AEs, most low grade (grade 1 and 2)

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PCI: quality of survival

- Significantly increased: grade 1 / 2 memory impairment (30% v 8%, respectively) and cognitive disturbance (19% v 3%, respectively
- Virtually all AEs under-reported by physicians compared with patients
  - Fatigue and memory impairment more under-reported by physicians in the observation arm than in the PCI arm.
  - memory impairment was reported by 57% and 54% of patients in the PCI arm and observation arm
- Reflecting bias of physicians? **Requires PRO's…**
- OS and progression-free survival similar in both arms
  - PCI is efficacious in reducing the incidence of brain metastases
  - majority of patients developed extracranial recurrences, thus lowering the potential effect of PCI on OS
  - Effect of treatment of symptomatic (CNS) metastases

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Some clinical conclusions

- If possible and reasonable brain mets should be treated systemically
  - Consider that BBB…
- There is no rational to leave patients with **active** brain mets out of clinical studies on novel agents
  - Hmm… anti-PD-L1? No steroids at baseline?
- Early on, concerted efforts must be made to assess activity in CNS mets in studies on novel agents
- RANO brain mets criteria: assess systematically both intracranial and extracranial response and PFS, and report both separately
- Treatment should be aiming at the driver mutations, clinical significance of late and subclonal events at least unclear
- Consider SRS first in patients that are candidates for local RT, followed by systemic treatment

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Lin et al, Lancet Oncol 2013;14:e396-406, Lin et al Lancet Oncol 2015;16:e270-8

On shipwrecks?

J C Dahl - 1832
Shipwreck on the coast of Norway

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