Metastasi cerebrali: Trattamento

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Trattamento delle metastasi cerebrali

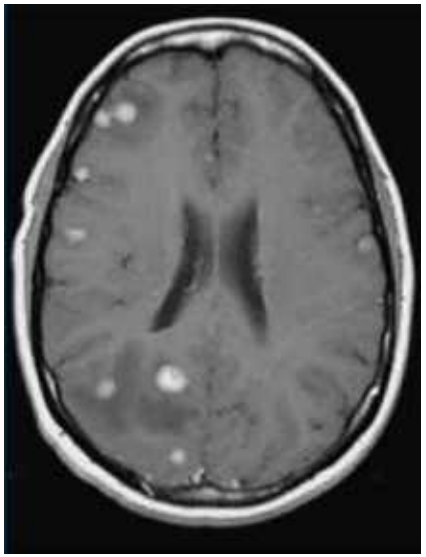
1. Locale
   - Radioterapia panencefalica (WBRT)
   - Chirurgia +/- WBRT
   - Radiochirurgia/radioterapia stereotassica +/- WBRT
2. Sistemico
3. Di supporto

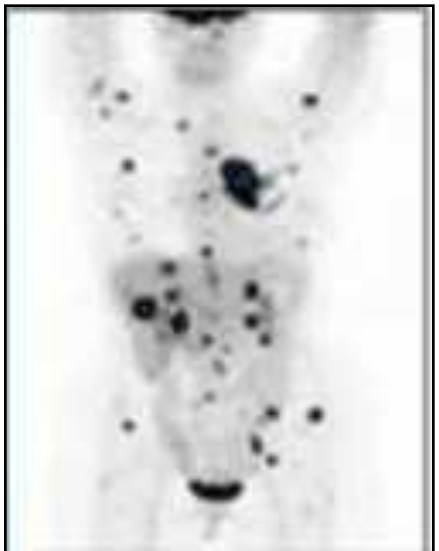
   (t.steroidea e anticomiziale)

- Migliorare la qualità della vita
- Prolungare la sopravvivenza
- Controllare i sintomi neurologici

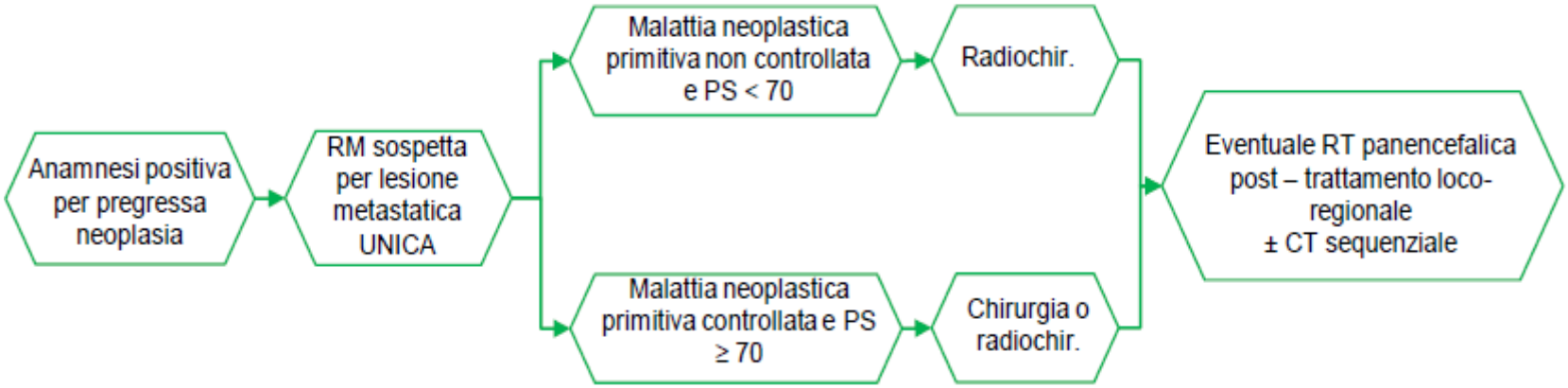
Scelta del trattamento delle metastasi cerebrali

1. Lesioni cerebrali → numero, dimensioni e sede
2. Status della malattia extracranica
3. Performance Status





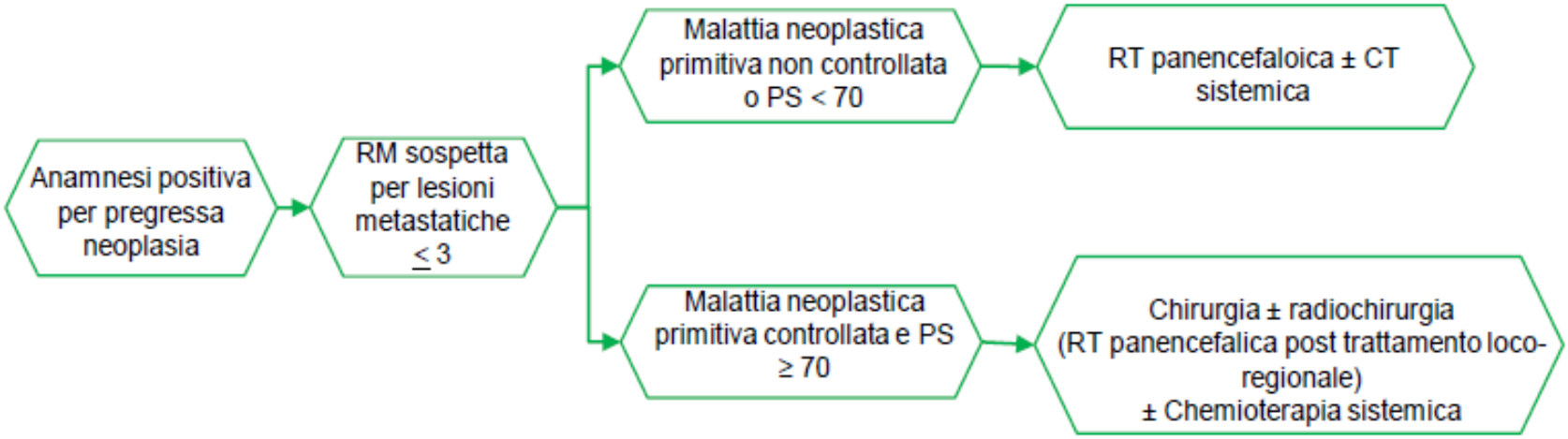
Linee guida AIOM 2012: metastasi cerebrale unica



- **Due studi randomizzati[1,2] hanno dimostrato un beneficio in sopravvivenza della chirurgia rispetto alla radioterapia (9-10 mesi vs 3-6 mesi) e in riduzione delle recidive locali (dal 52% al 20%)**
- **Non ci sono studi di fase III di confronto tra chirurgia e radiochirurgia stereotassica**

1 Mintz AH et al. Cancer 1996;78:1470-1476
2 Vecht CJ et al. Ann Neurol 1993;33:583-590

Linee guida AIOM 2012: metastasi cerebrali ≤ 3

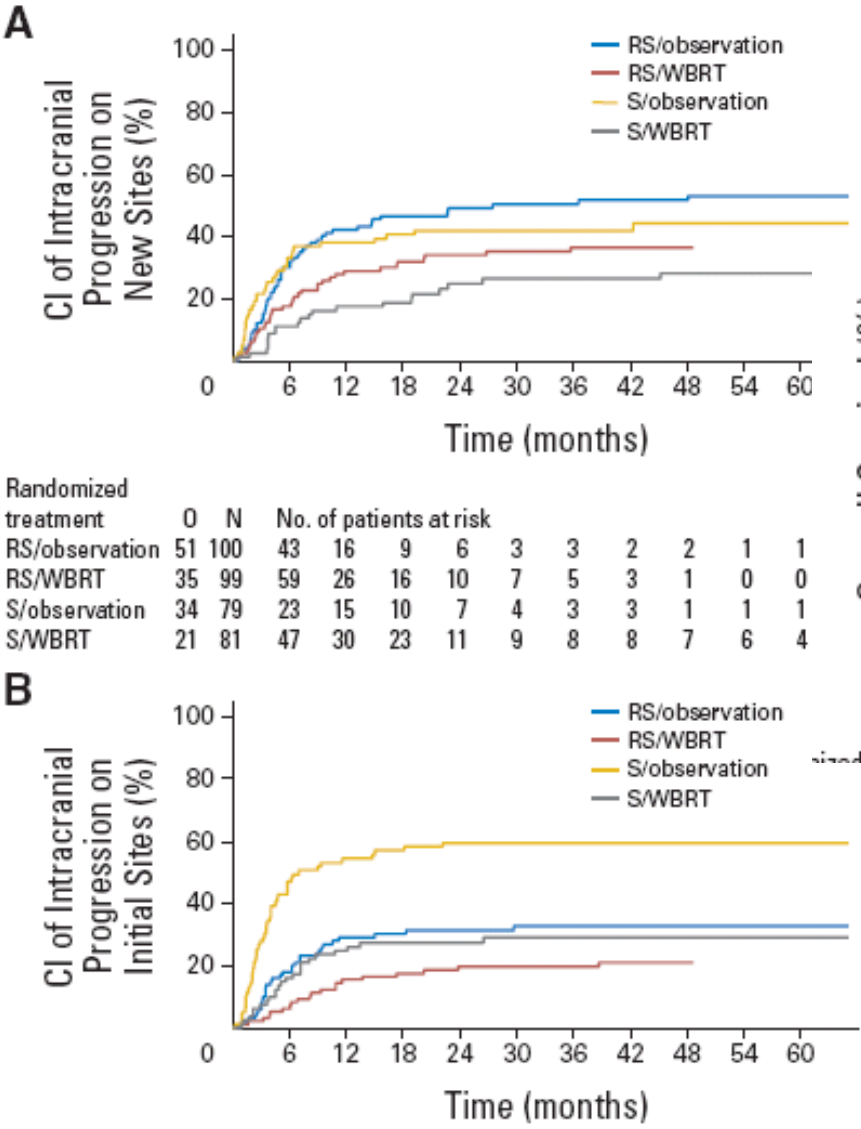


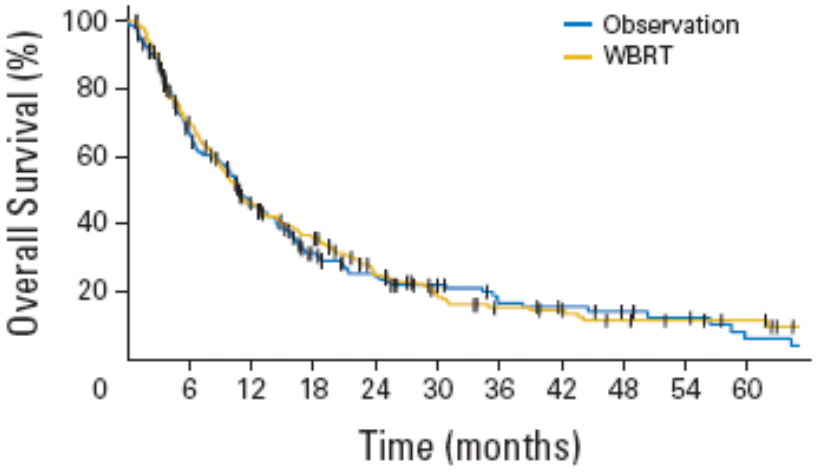
Studi randomizzati di confronto tra chirurgia/radiochirurgia da sola o in combinazione con WBRT

		NO WBRT			WBRT		
Studio	T.locale	Recidiva cerebrale (%)	Recidiva cerebrale locale (%)	Recidiva cerebrale a distanza (%)	Recidiva cerebrale (%)	Recidiva cerebrale locale (%)	Recidiva cerebrale a distanza (%)
Patchell	CHIR	70	68	60	24	21	18
Ayoama	SRS	76	27	64	47	11	42
Chang	SRS	73	33	55	27	0	27
Kocher	CHIR	78	59	42		27	23
	SRS		31	48		19	33
Range		70-78	27-69	42-64	24-47	0-27	18-42

Patchell RA,et al.JAMA 1998;280:1485–1489
Aoyama H,et al.JAMA 2006;295:2483–2491
Chang EL,et al. Lancet Oncol 2009;10:1037–1044
Kocher M, et al. JCO 2011;29:134–141

Progressione intracranica e sopravvivenza globale





N=359

1-3 metastasi cerebrali

Kocher M. et al JCO2011;29:134-141

Chirurgia/radiochirurgia in associazione a RT panencefalica?

- Chirurgia/RTchir + RT panencefalica

↓ recidive intracraniche

- Mancano dati di vantaggio in sopravvivenza
- Peggioramento delle funzioni neurocognitive?

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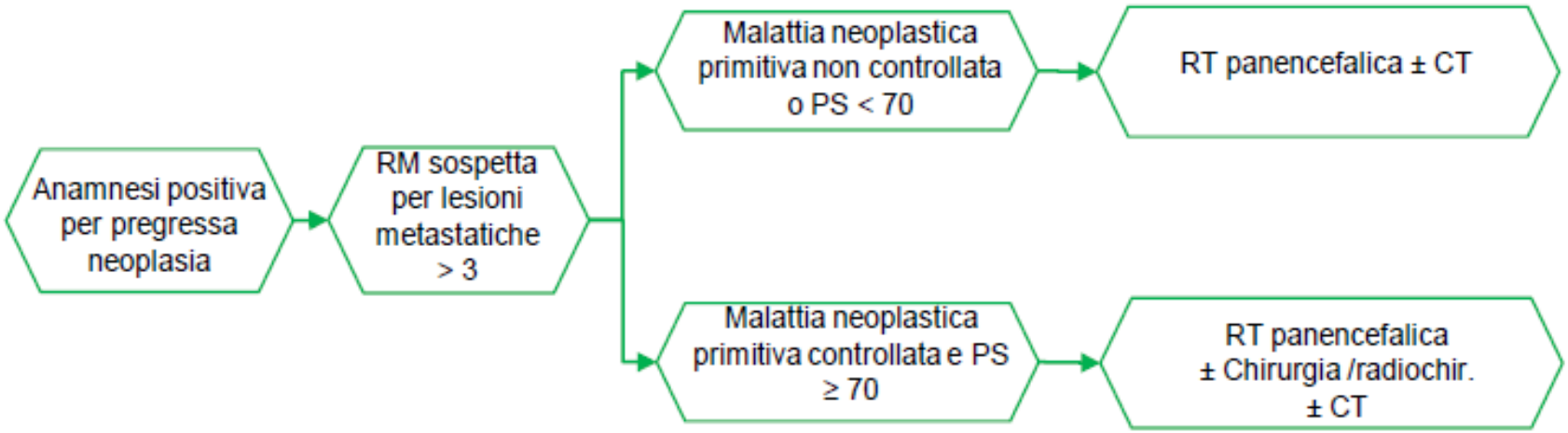
ORIGINAL REPORT

A European Organisation for Research and Treatment of Cancer Phase III Trial of Adjuvant Whole-Brain Radiotherapy Versus Observation in Patients With One to Three Brain Metastases From Solid Tumors After Surgical Resection or Radiosurgery: Quality-of-Life Results

Riccardo Soffietti, Martin Kocher, Ufuk M. Abacioglu, Salvador Villa, François Fauchon, Brigitta G. Baumert,

Riccardo Soffietti, University of Torino and San Giovanni Battista Hospital, Turin; Laura Fariselli, Fondazione Istituto Neurologico

Linee guida AIOM 2012: metastasi cerebrali > 3



RT panencefalica: dose totale 30-40 Gy in 10-15 frazioni

TERAPIA SISTEMICA DELLE METASTASI CEREBRALI

1. Quale trattamento?
2. Quando iniziare?

1- Quale trattamento?

HER-2+

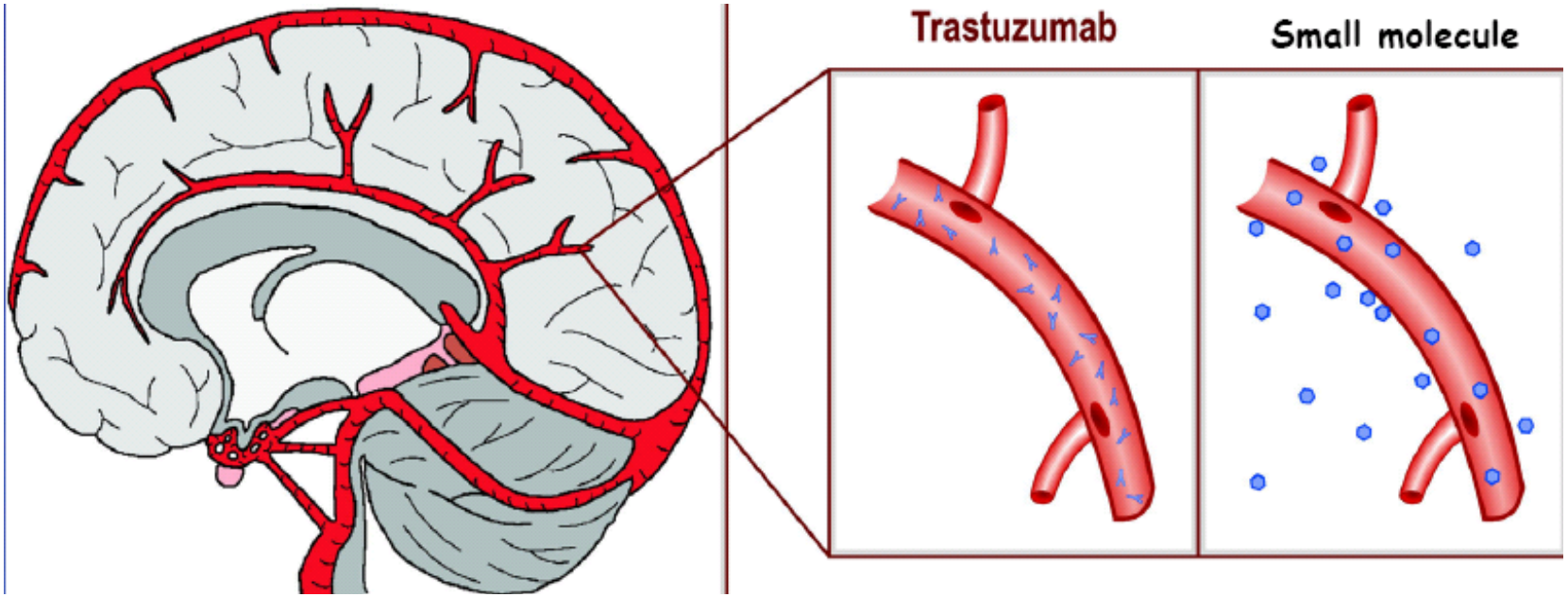
1. **Chemioterapia + trastuzumab**
2. **Lapatinib + capecitabina**
3. **Chemioterapia da sola**
4. **Nuovi farmaci?**

HER-2 -

1. **Chemioterapia da sola**
2. **Nuovi farmaci?**

- Valutare PS e precedenti trattamenti effettuati

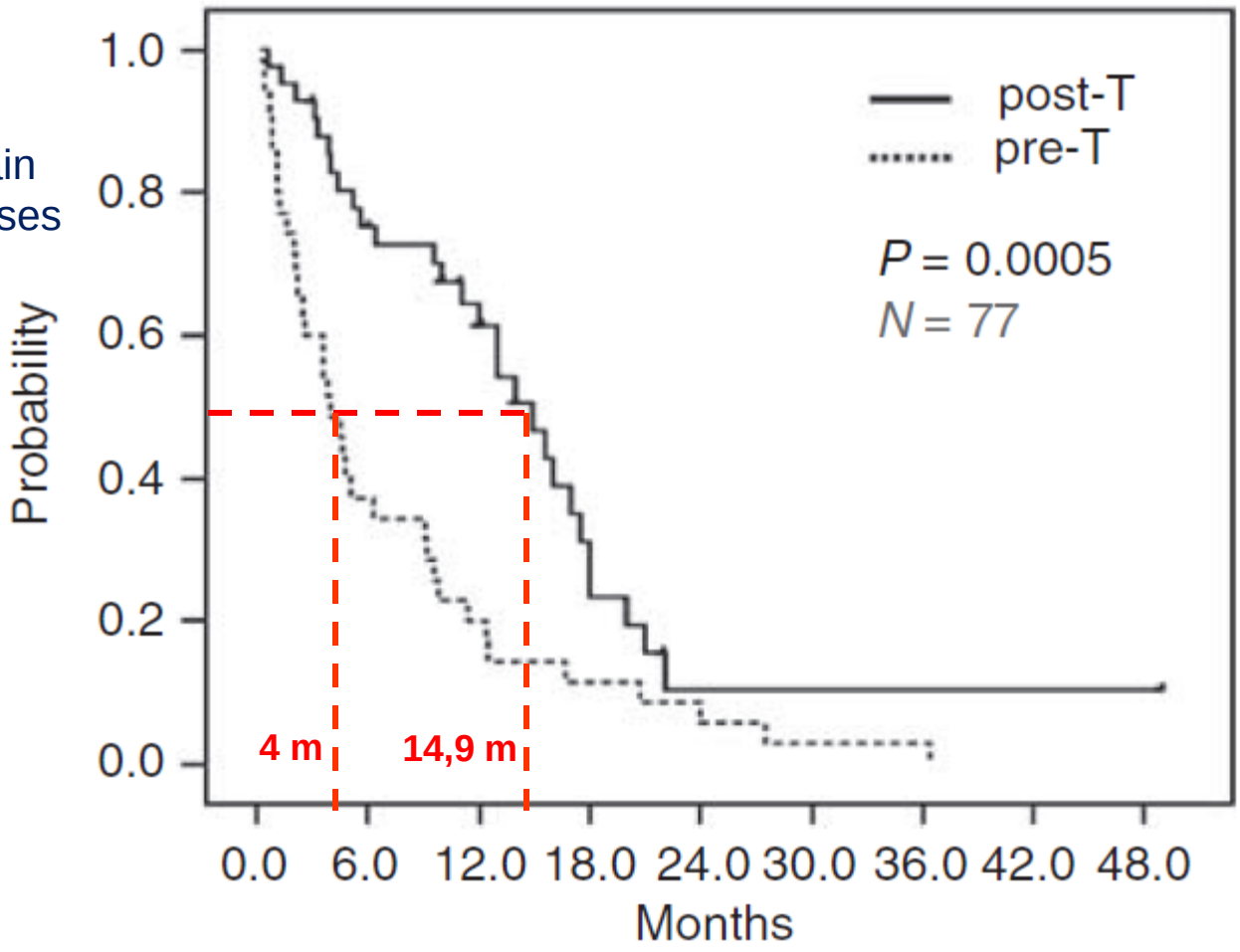
Capacità degli anticorpi monoclonali e delle piccole molecole di attraversare la barriera emato-encefalica



Contessa JN et al. Mol Pharmacology 2008;73:271-273

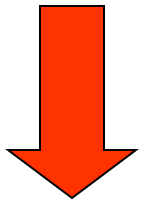
Continuare trastuzumab dopo l'insorgenza di metastasi cerebrali migliora la prognosi

Time to Death (TTD) from brain metastases



Park YH, et al. BJC 2009;100:894-900

Tuttavia circa metà delle pazienti con carcinoma mammario HER2+ muore per progressione cerebrale[1,2]



Necessità di altre terapie efficaci oltre trastuzumab

1 Lin NU, et al. Clin Cancer Res 2007;13:1648-1655

2 Bendell JC, et al. Cancer 2003;97:2972-2977

Lapatinib: efficacia nel trattamento delle metastasi cerebrali

	STUDIO	N	Precedente RT encefalo	Precedente trastuzumab	Precedente Cape	Criterio Risposta	ORR SNC	TTP-PFS (mesi)	OS (mesi)
	Boccardo F, ASCO 2008 **Capri G,** Ann Oncol 2010	138	NR	SI	SI (42%)	Investigator -assessed	**18%**	2,8	NR
	Sutherland S BJC 2010	34	SI (94%)	SI	SI (35%)	RECIST	**21%**	5,1	NR
	Huang C ASCO 2010	26	SI (100%)	SI	NO	RECIST	**34%**	8,4	NR
	Metro G Ann Oncol 2011	22	SI (87%)	SI	NO	WHO	**32%**	5,1	27.9
Prosp. Fase II	**Lin NU,** CCR 2009	50*	SI (100%)	SI	NO	Compositi (↓vol ≥50%)	**20%**	3,6	NR
Prosp. Fase II	**Lin NU,** J Neurooncol 2011	13	SI (100%)	SI	NO	Compositi (↓vol ≥50%)	**38%**	NR	NR
Prosp. Fase II	**Bachelot T,** Lancet 2013	45	**NO**	SI (93%)	NO	Compositi (↓vol ≥50%)	**65,9%**	5,5	17

Courtesy of S. Gori

2- Quando iniziare la terapia sistemica?

1-3 lesioni cerebrali

Trattamento locale

Terapia sistemica

Metastasi cerebrali multiple (>3)

WBRT

Terapia sistemica

Terapia sistemica

WBRT

Studio LANDSCAPE: terapia sistemica up-front

- Studio di fase II, in aperto, multicentrico
- Almeno una metastasi cerebrale misurabile ≥ 1cm (no metastasi cerebrale singola)
- NO precedente trattamento radioterapico panencefalico o stereotassico
- Lapatinib 1250 mg/os/die + capecitabina 2000 mg/mq/os gg.1-14 (cicli ogni 21 gg) fino a progressione o tossicità inaccettabile
- End-point principale: risposte obiettive SNC definite come ↓≥50%

Bachelot T et al, Lancet Oncol 2013;14:1-8

Studio LANDSCAPE:

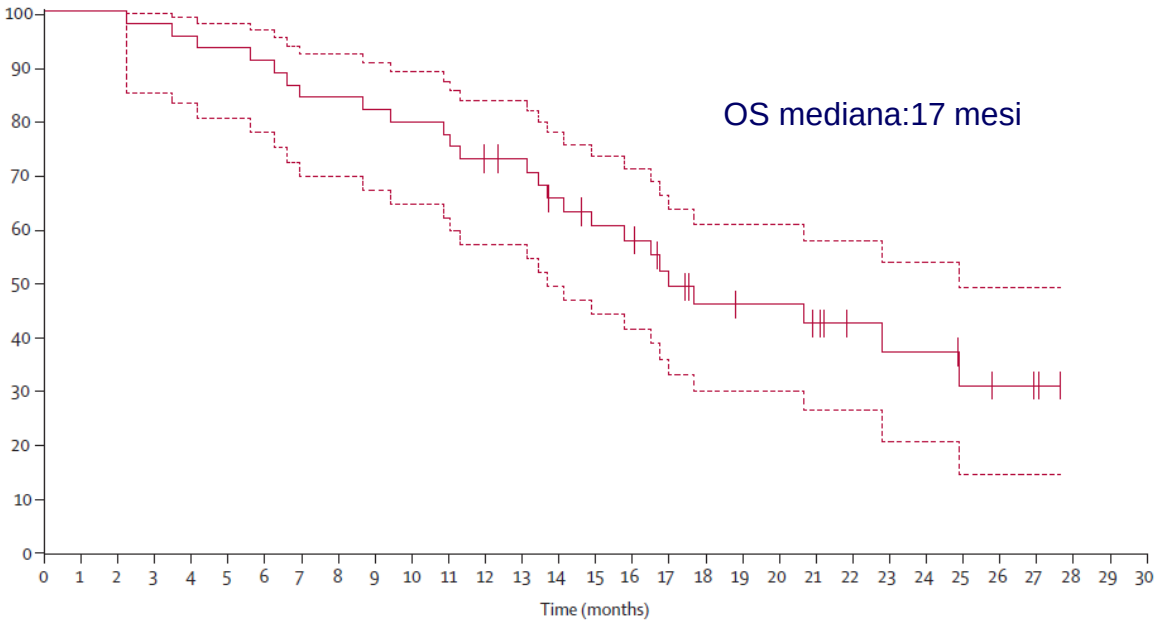
Risposte obiettive SNC

	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

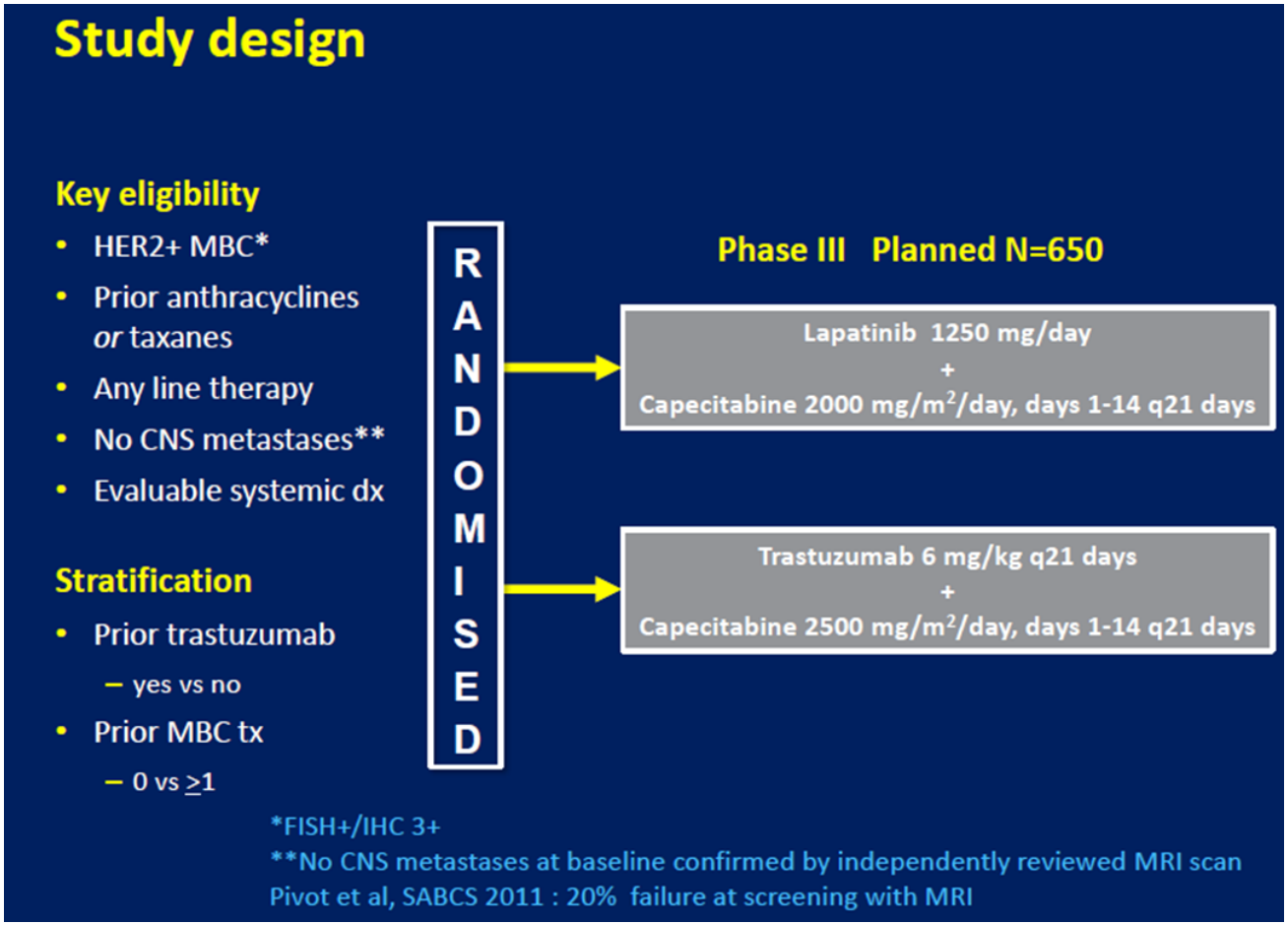
Sopravvivenza globale



OS mediana:17 mesi

Bachelot T et al, Lancet Oncol 2013;14:1-8

Lapatinib e prevenzione delle metastasi cerebrali: **studio CEREBEL**



End-point principale: incidenza delle metastasi cerebrali come primo sito di recidiva; secondari: PFS, OS, ORR, CBR, tempo alla prima progressione cerebrale, incidenza delle progressioni cerebrali, sicurezza

Pivot X, et al. Ann Oncol 2012;23(S9): abstract LBA11

Studio **CEREBEL**: risultati

Primary endpoint: CNS endpoints (modified ITT)

	Lapatinib + capecitabine (N=251)	Trastuzumab + capecitabine (N=250)	OR (95% CI)	p-value
CNS as first site of relapse, n (%)	8 (3)	12 (5)	0.65 (0.26, 1.63)	0.360
Incidence of CNS progression at any time, n (%)	17 (7)	15 (6)	1.14 (0.52, 2.51)	0.8646
Time to first CNS progression, median (range)	5.7 (2–17)	4.4 (2–27)	-	-

Pivot X, et al. Ann Oncol 2012;23(S9): abstract LBA11

Studio **CEREBEL**: conclusioni

Conclusions (1)

- Inconclusive for primary endpoint (CNS as first site of relapse)
  - There was a low incidence of brain metastases as the first site of progression in both arms
  - These are the first prospective data in subjects with HER2-positive MBC showing an approximate 20% incidence of asymptomatic brain metastases

(Pivot et al 2011)

- In the ITT population, PFS was longer for those who received trastuzumab plus capecitabine
- In the trastuzumab naïve group, trastuzumab plus capecitabine had superior efficacy
- In the group previously treated by trastuzumab no superiority was observed

Pivot X, et al. Ann Oncol 2012;23(S9): abstract LBA11

Nuovi farmaci

Trial	Planned accrual	Population	Treatment	Primary endpoint(s)	Status
Trastuzumab					
Phase I/II (NCT00397501)	78	HER2-positive or HER2-negative MBC with CNS or brain metastases	Trastuzumab, methotrexate, and carboplatin with osmotic BBB disruption	OS	Not yet recruiting
Phase II (NCT01363986)	66	HER2-positive breast cancer and ≥1 measurable brain metastasis	Trastuzumab plus WBRT	Brain RR	Recruiting
Afatinib					
Phase II [100] (NCT01441596; LUX-breast 3)	120	HER2-positive MBC with CNS metastasis (≥1 measurable brain lesion)	Afatinib, afatinib/vinorelbine, or investigator's choice of therapy	Benefit at 12 weeks[a]	Recruiting
Lapatinib					
Phase I (NCT00614978; LAPTEM)	18	HER2-positive MBC with recurrent or progressive brain metastases after surgery, WBRT, or SRS (or unsuitable for these standard treatments)	Lapatinib plus temozolomide	MTD and DLT	Ongoing, not recruiting
Phase I (NCT00470847)	39	HER2-positive MBC, ≥1 parenchymal brain lesion, and CNS progression	Lapatinib plus WBRT	MTD and feasibility	Ongoing, not recruiting
Neratinib					
Phase II (NCT01494662)	45	HER2-positive MBC, ≥1 parenchymal brain lesion, and any number and type of prior therapy (other than neratinib) allowed	Neratinib (progressive brain metastases) or neratinib/ surgical resection (if eligible for craniotomy)		Recruiting
Everolimus					
Phase II (NCT01305941)	35	HER2-positive breast cancer with brain metastases (≥1 measurable brain lesion), and any number and type of prior therapy (other than mTOR inhibitors or Navelbine) allowed	Everolimus plus trastuzumab and vinorelbine	Intracranial RR[b]	Recruiting

Chien AJ et al.Breast Cancer Res Treat 2013;137:1-12

Conclusioni

- Mal. extracranica controllata
- Metastasi cerebrali ≤3
- PS buono

→ Chirurgia/radioterapia stereotassica +/- RT panencefalica → terapia sistemica*

- Mal. extracranica NON controllata
- Metastasi cerebrali >3
- PS scarso

→ RT panencefalica→ event. terapia sistemica*

* Nelle pz HER2+: chemioterapia + terapia anti-HER2