Lessons from translational research in EORTC glioma trials

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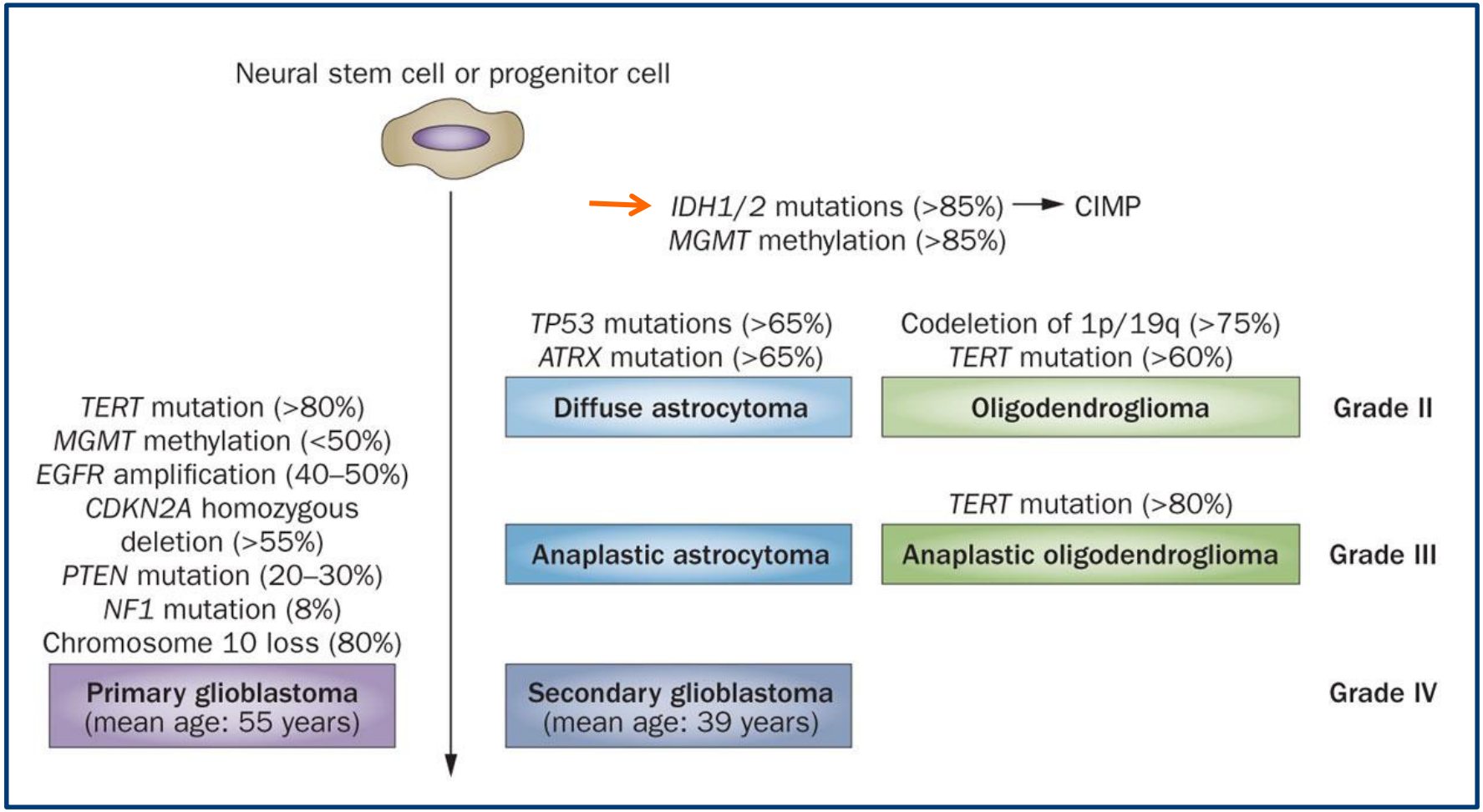
ICTR-PHE , CICG Geneva, February, 2016

Pathogenetic and Epigenetic Evolution of Glioma in Adults

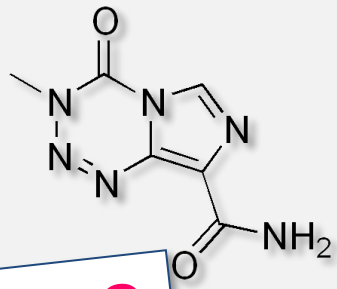


Hegi, M. E. & Stupp, R. (2013) *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2013.127; PMID 23817351

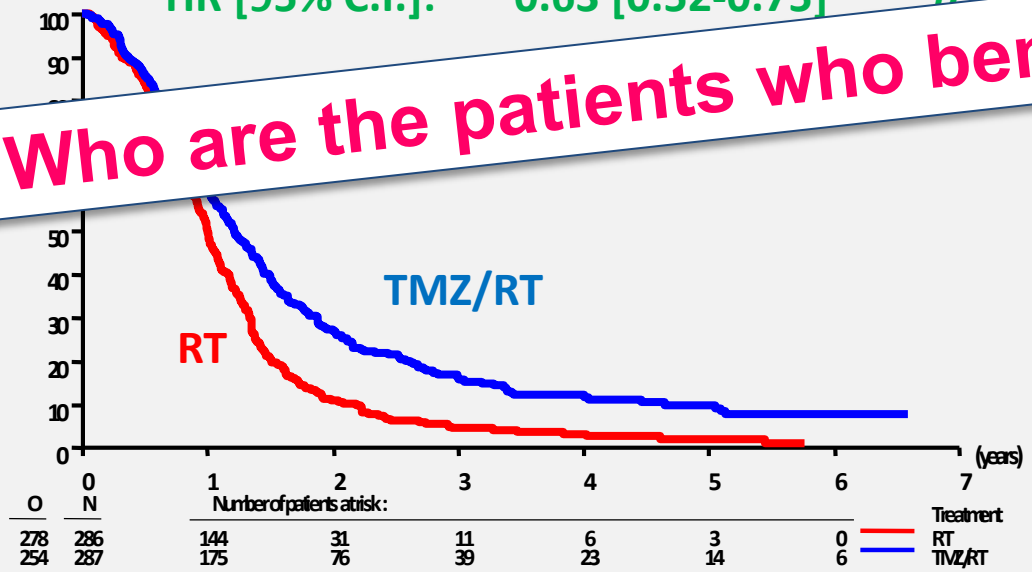
Predictive Factors for Benefit from the Addition of Temozolomide to RT EORTC-NCIC Trial

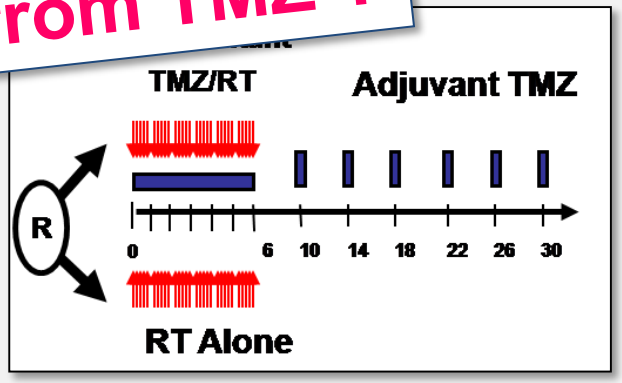
EORTC26981/22981 NCIC CE.3

	RT (95% ci)	TMZ/RT (95% ci)
Median OS, mo:	12.1 (11.2, 13.0)	14.6 (13.2, 16.8)
2-yr survival:	10.9% (7.6-14.8)	27.2% (22.2-32.5)
5-yr survival:	1.9% (0.6-4.4)	9.8% (6.4-14.0)
HR [95% C.I.]:	0.63 [0.52-0.75]	$p<0.0001$



Who are the patients who benefit from TMZ ?



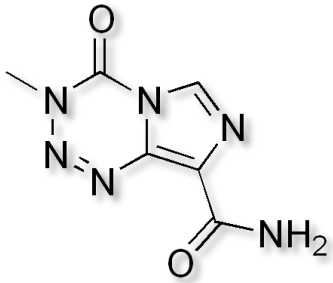


Stupp *et al*. N Engl J Med, 352:987-996, 2005
Stupp *et al*. Lancet Oncol, 10:559-66, 2009

Silencing of *MGMT* by promoter methylation renders tumor cells sensitive to alkylating agents

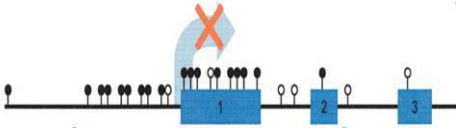
TREATMENT

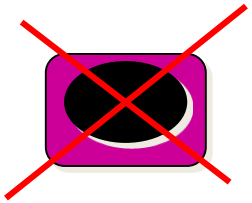
•Alkylating Agent
Temozolomide



TUMOR TISSUE

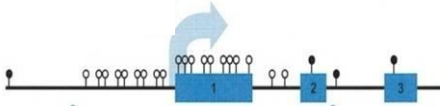
Methylated MGMT

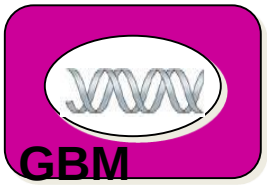




DNA damage
cell death via MMR

Unmethylated MGMT

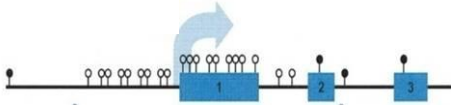


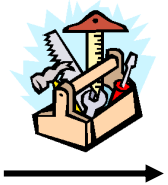


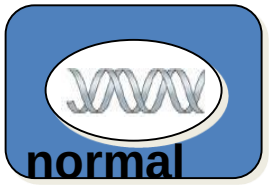
resistance

NORMAL TISSUE

Unmethylated



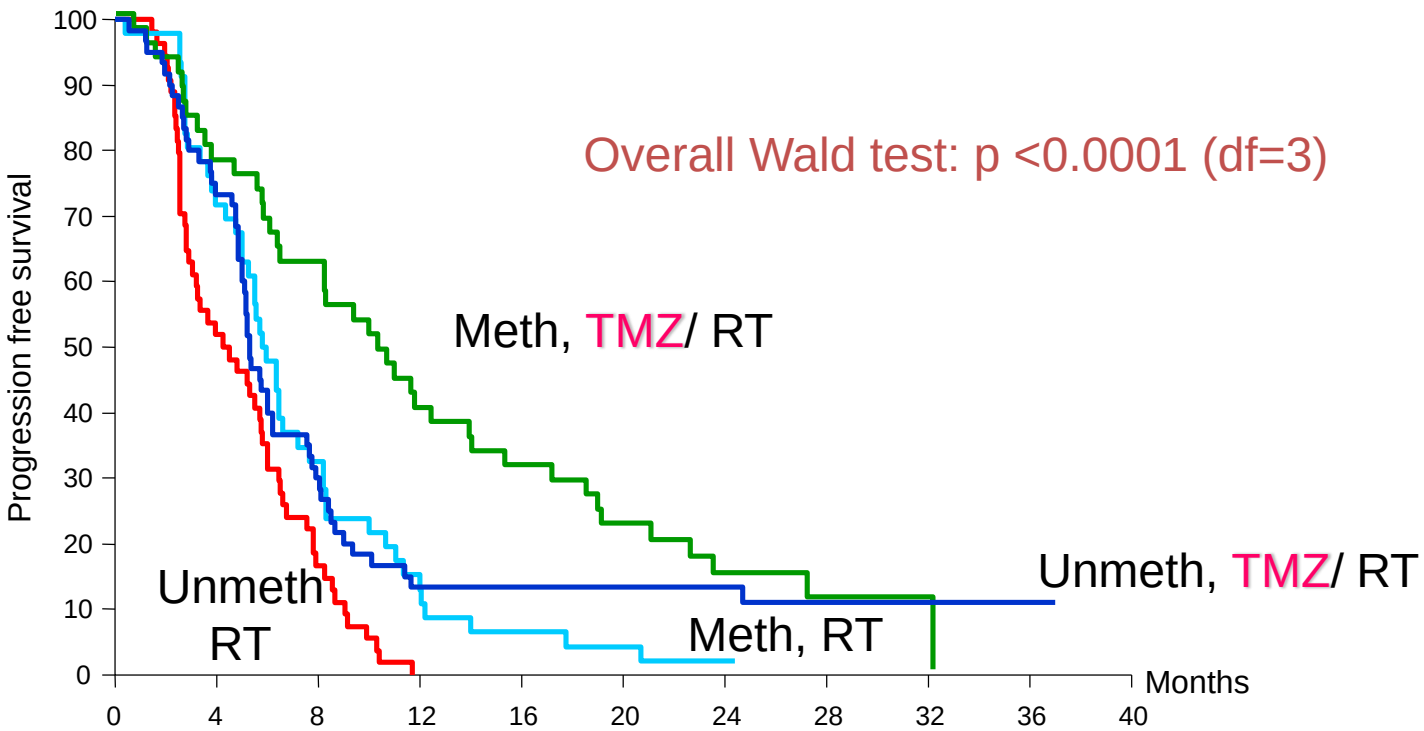




protected

Hegi ME, et al. Clin Cancer Res 2009;15:5026–5031

Progression-free survival supports MGMT methylation status as predictive factor for benefit from TMZ



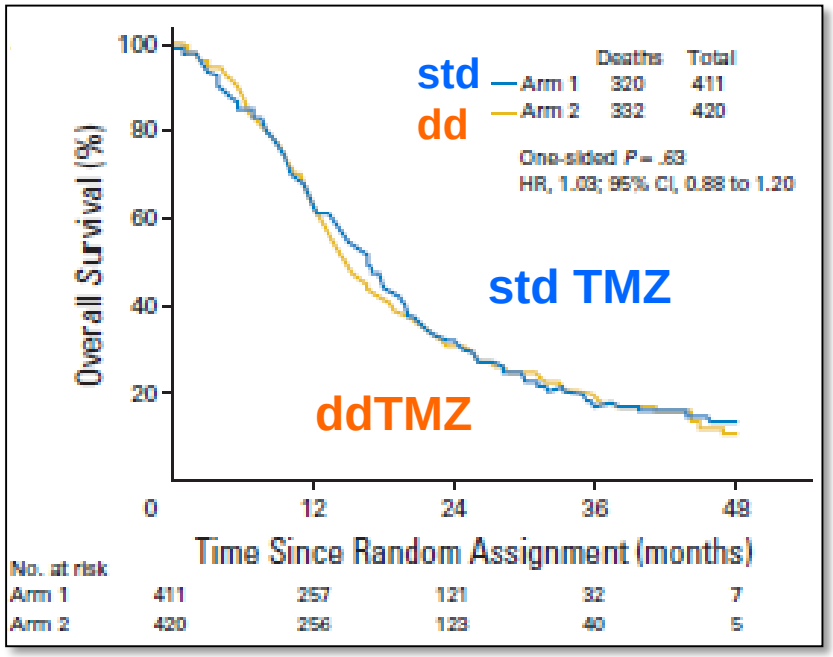
O	N	Number of patients at risk :								
54	54	28	9	0	0	0	0	0	0	0
53	60	44	18	8	8	8	7	5	3	1
45	46	33	15	7	3	2	1	0	0	0
40	46	35	28	18	14	10	6	3	1	0

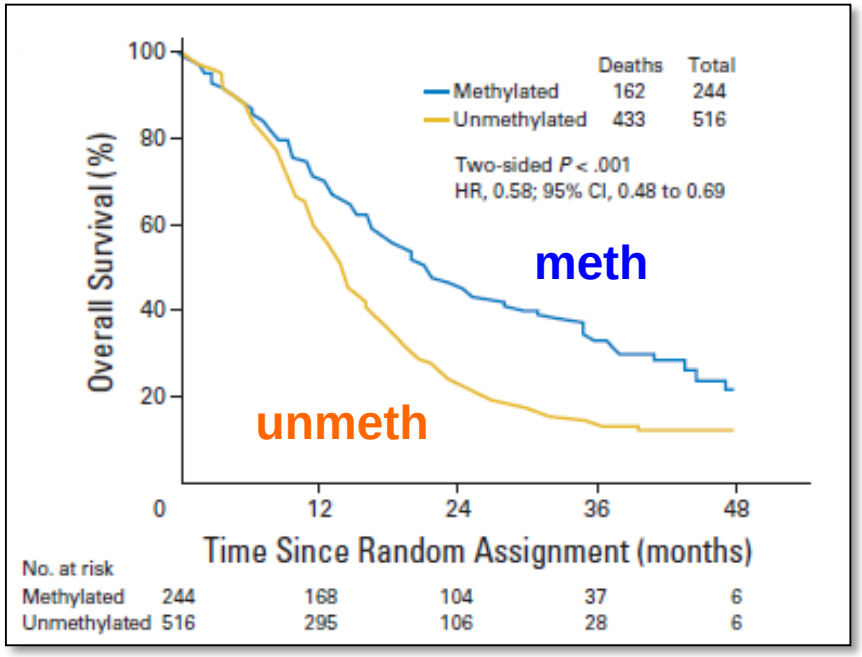
Unmeth, RT alone
Unmeth, TMZ/ RT
Meth, RT alone
Meth, TMZ/ RT

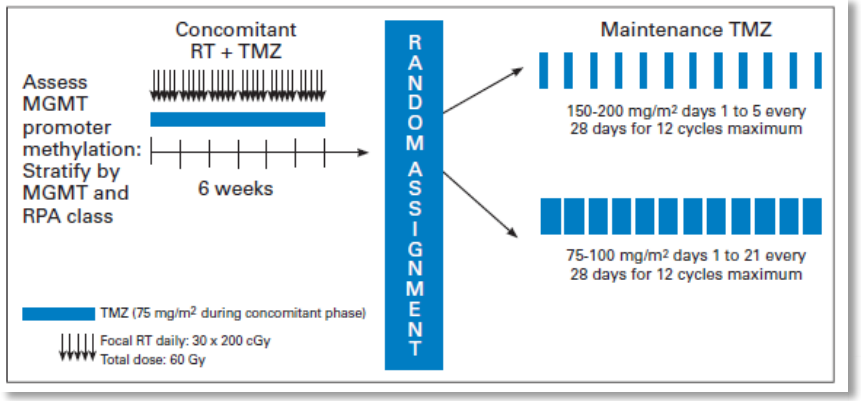
Hegi ME, et al. N Engl J Med 2005;352:997–1003

Testing dose dense TMZ in GBM

Prospective Validation of *MGMT* Methylation Status as Biomarker







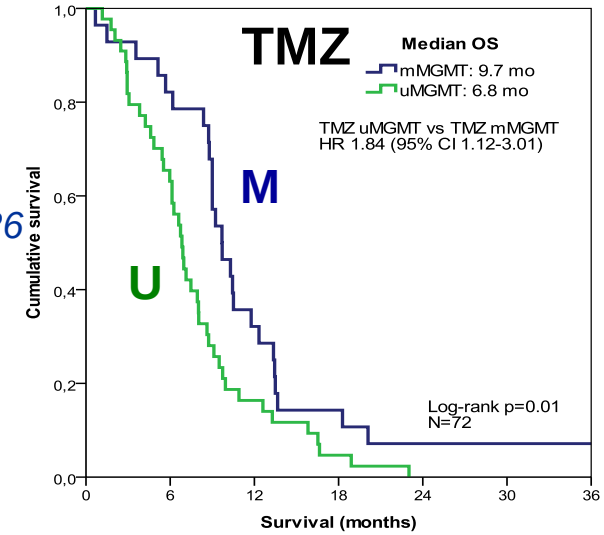
EORTC

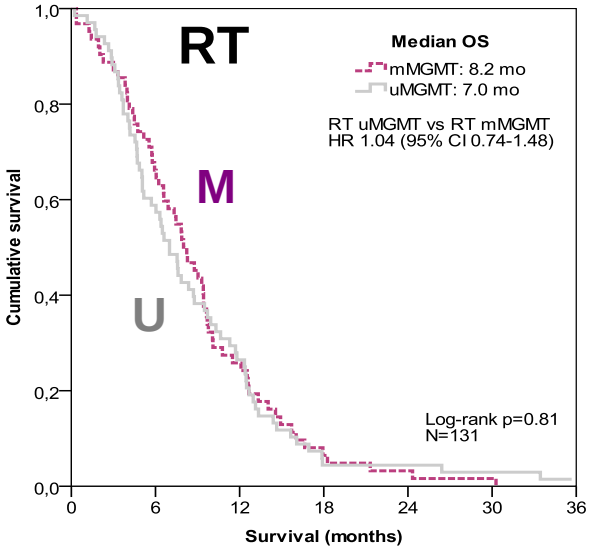
Gilbert *et al.* JCO 2013

Predictive Effect of *MGMT* in Elderly GBM Patients

Nordic Trial
RT vs TMZ

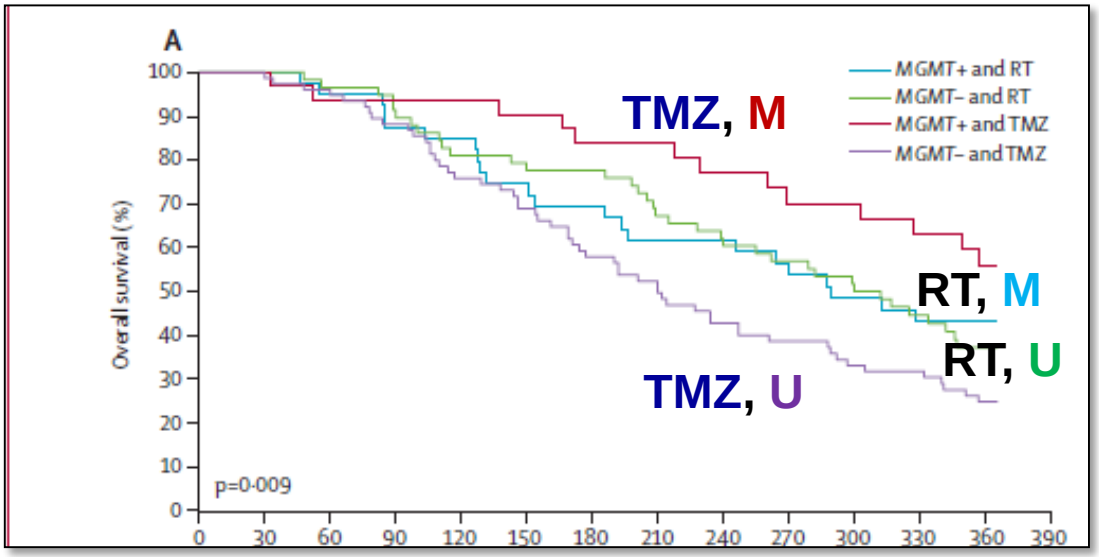
Malmström et al.
*Lancet Oncol **2012**; 13: 916-926*





NOA-08
RT vs TMZ

Wick et al.
*Lancet Oncol **2012**; 13(7):707-15*



MGMT methylation is a predicitve factor in GBM

- The presence of a methylated *MGMT* promoter is associated with benefit from alkylating agent therapy
- Patients with an unmethylated *MGMT* promoter profit very little from TMZ, if at all.
- Elderly patients should be treated according to their *MGMT* status
- Patients with unmethylated *MGMT* should be recruted into trials with new promising drugs

- **Terms**: predicitive versus prognostic
  - **predictive**, treatment dependent ; impact on choice of therapy
  - **prognostic**, independent of treatment; no direct impact on treatment

Patient Selection by *MGMT* Status randomized Phase I/II and III Trials for GBM

NO TMZ
- GLARIUS Irinotecan & Bev NCT00967330, rand. Phase II
- TORISEL Temsirolimus NCT01019434, rand. Phase I/II
- PPX and Concurrent Radiation NCT01402063, rand. phase II

With TMZ
- CENTRIC Cilengitide Phase III EORTC26071-22072 EMD 121974-011

Diagnosis

Step 1: central *MGMT* methylation status assay

Registration

***MGMT* unmethyl.**

Step 2: Randomization

R

versus RT/TMZ-TMZ

+ New Agent

Radiotherapy

Concomitant Phase Adjuvant (maintenance) Phase

***MGMT* methyl.**

Randomiz.

Step 2: Randomization

R

versus RT/TMZ-TMZ

+ New Agent

TMZ

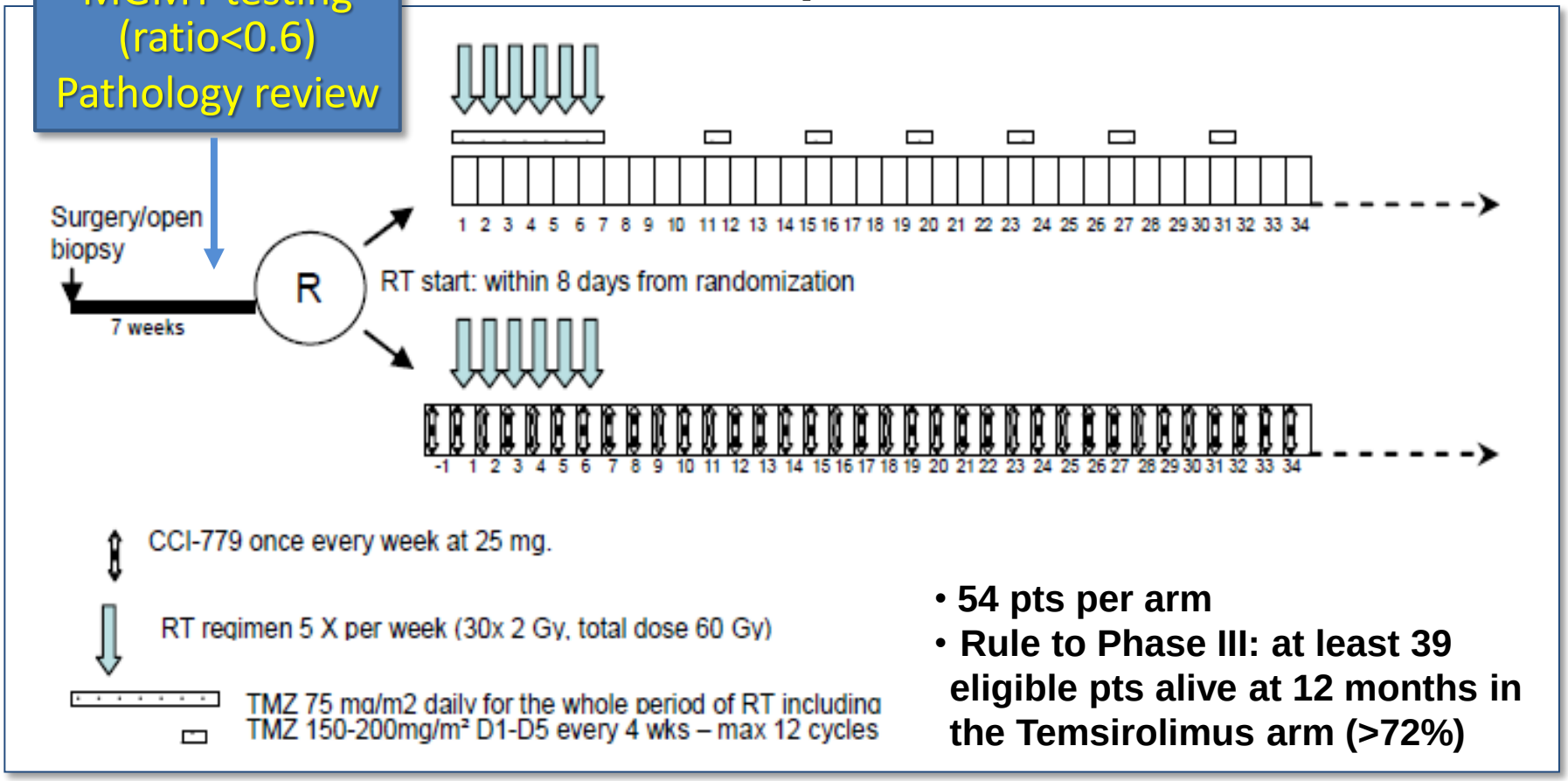
Radiotherapy

Concomitant Phase Adjuvant (maintenance) Phase

EORTC 26082/22081: Study Design

for newly diagnosed GBM with unmethylated *MGMT*

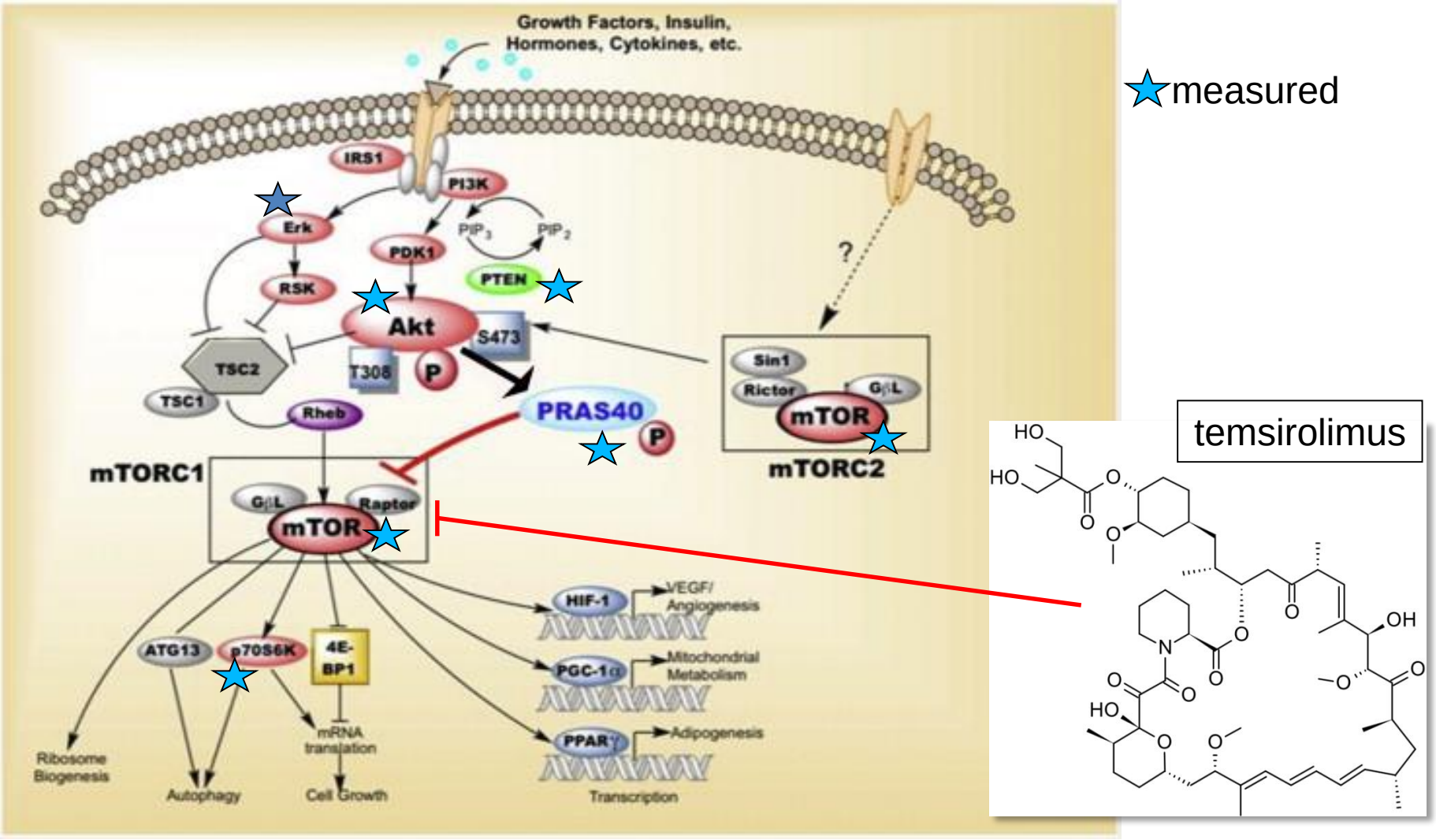
Randomized phase II – 2 arms



- **54 pts per arm**
- **Rule to Phase III: at least 39 eligible pts alive at 12 months in the Temsirolimus arm (>72%)**

EORTC *The future of cancer therapy*

mTOR pathway



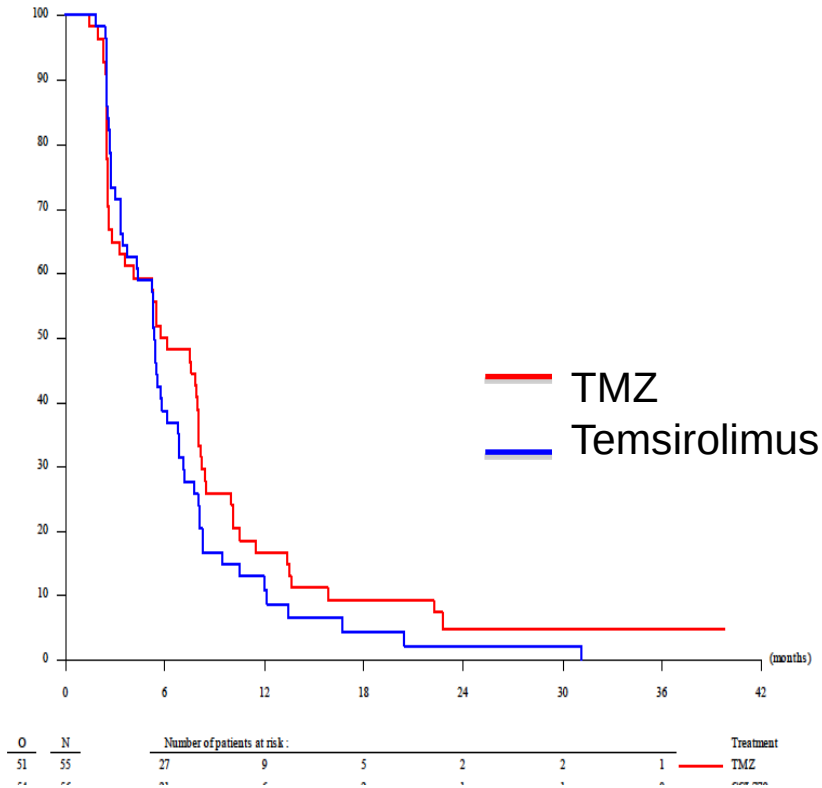
Taken from Malla *et al.* B B R C (463), 161-166, 2015

http://dx.doi.org/10.1016/j.bbrc.2015.05.041

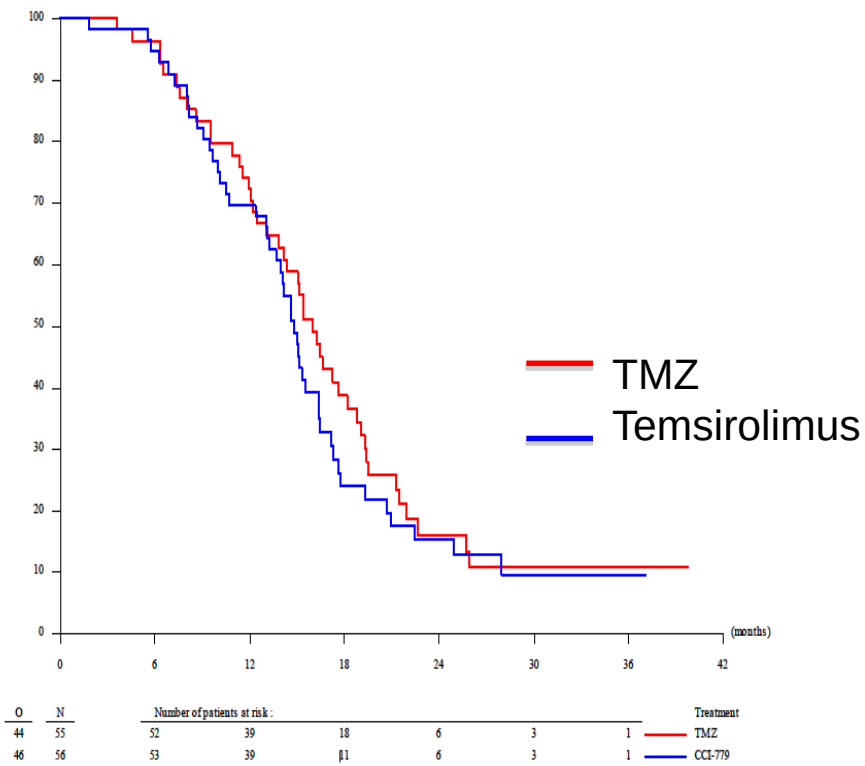
Temsirolimus/RT → Temsirolimus vs TMZ/RT→TMZ (EORTC26082)

Non-comparative

Progression-free survival



Survival

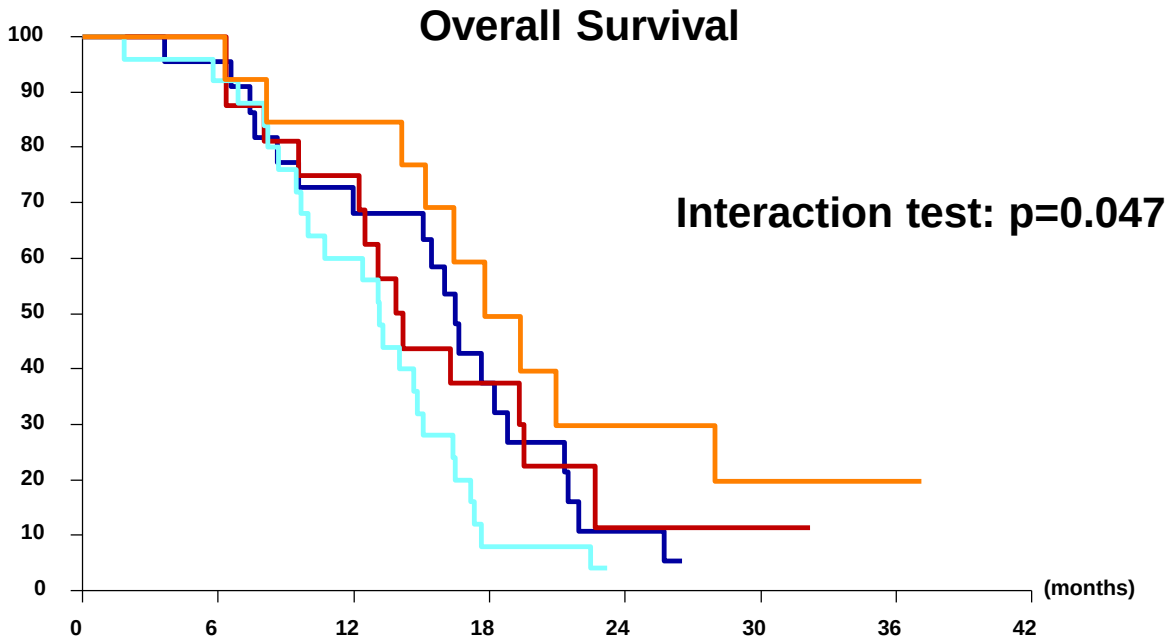


EORTC *The future of cancer therapy*

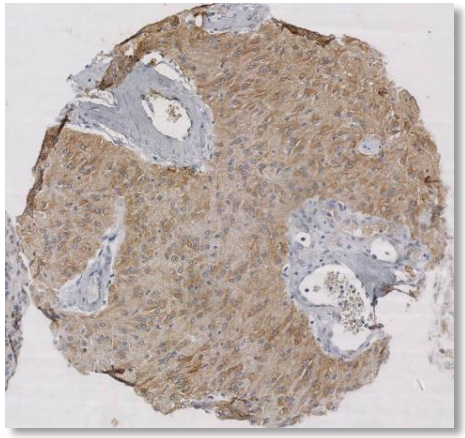
Wick et al. Proc ASCO 2014 {abstr 2003}
Hegi et al. Mol Markers 2015

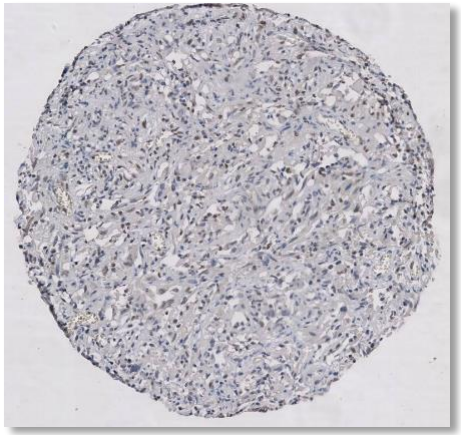
OS by p-mTOR expression and treatment

p-mTOR is predicitve for benfit from temsirolimus



O	N	Number of patients at risk :						Trt/p-mTOR
19	23	21	15	7	2	0	0	TMZ/Neg
13	16	16	12	5	1	1	0	TMZ/Pos
24	25	23	15	2	0	0	0	CCI-779/Neg
9	13	13	11	5	3	2	1	CCI-779/Pos

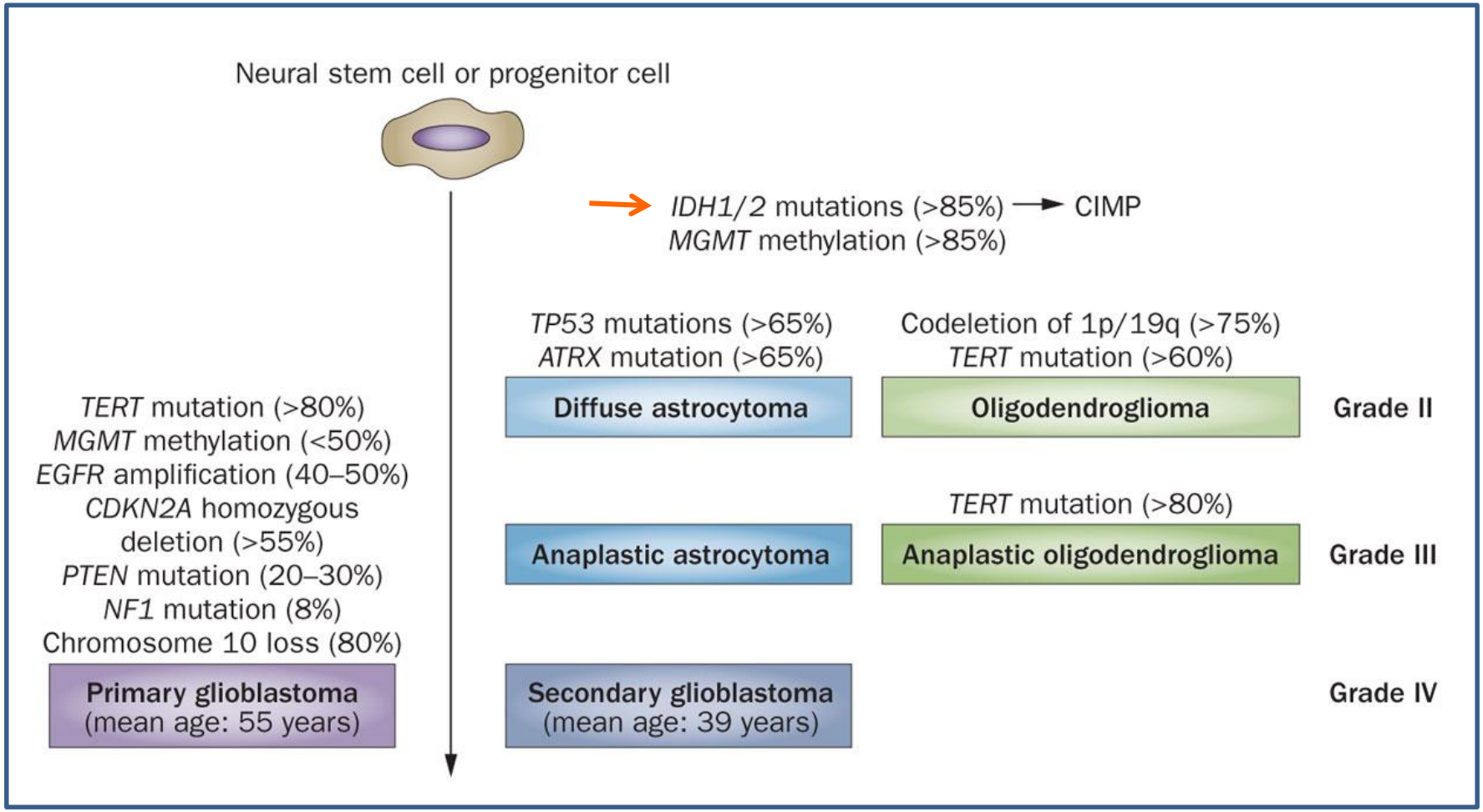




EORTC *The future of cancer therapy*

Wick et al. Clin Cancer Res, in revision

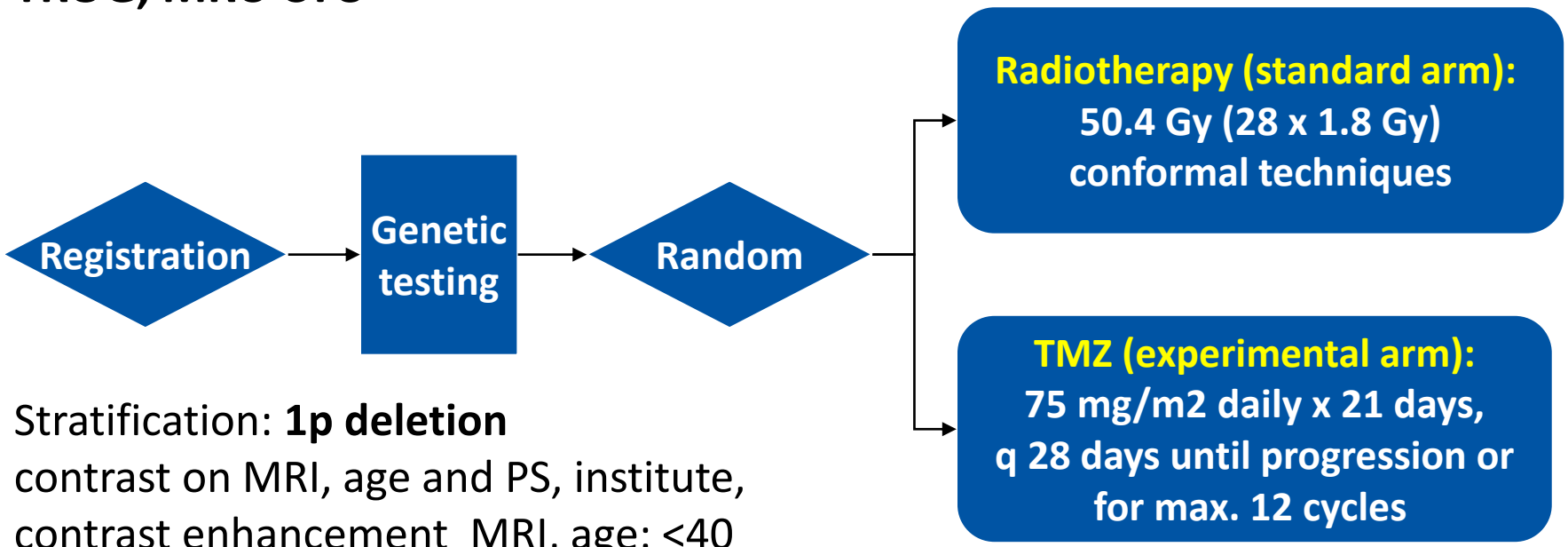
Pathogenetic and Epigenetic Evolution of Glioma in Adults



Hegi, M. E. & Stupp, R. (2013) *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2013.127; PMID 23817351

EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033) in patients with a high risk low-grade glioma

Participating groups: EORTC ROG and BTG, NCI-CTG, TROG, MRC-CTU



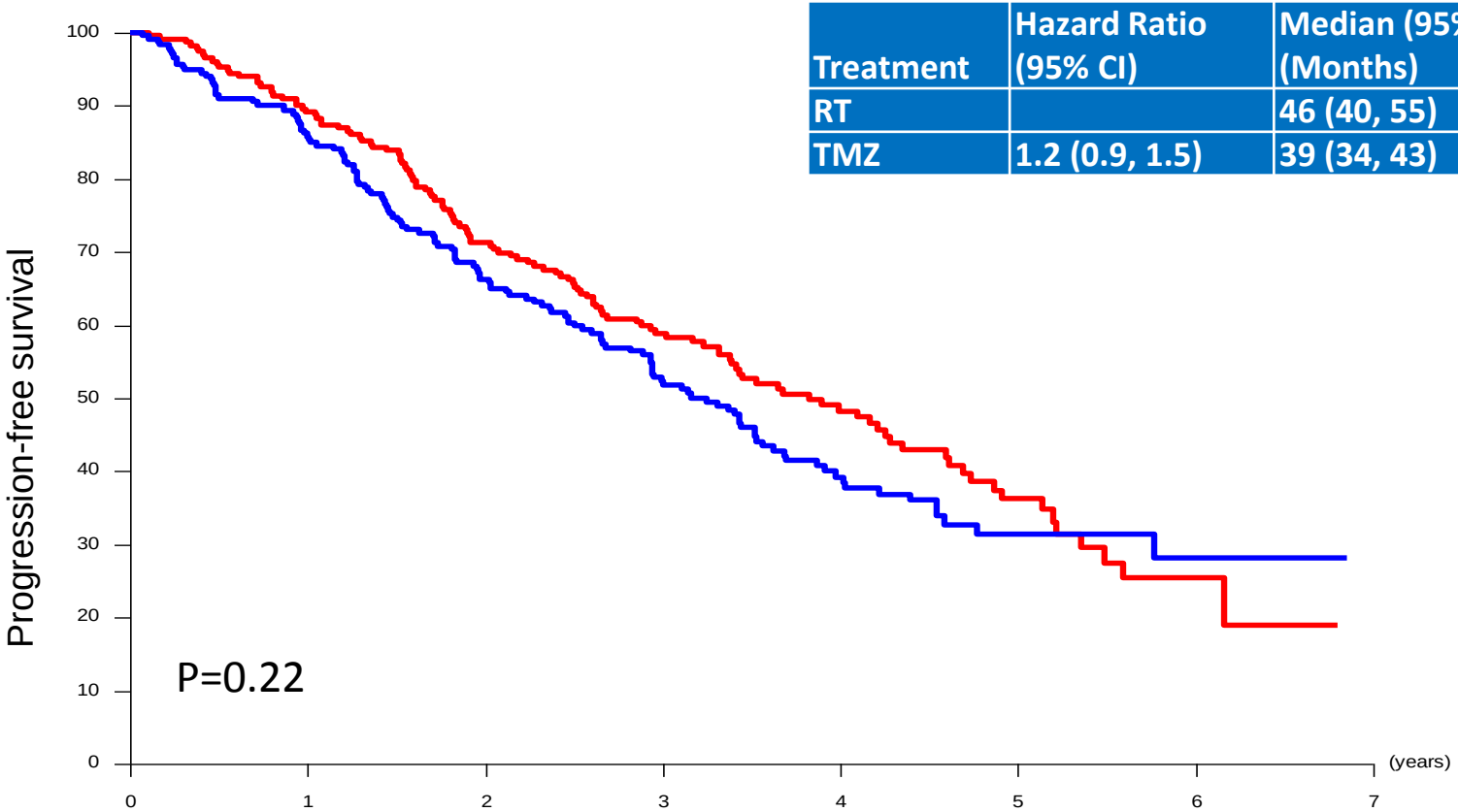
Stratification: **1p deletion**
contrast on MRI, age and PS, institute, contrast enhancement MRI, age: <40 vs ≥ 40 yrs, WHO PS 0 /1 versus 2

Accrual: **2005 – 2012**
707 patients registered
477 randomized

Baumert, Hegi,…Stupp. Submitted

Progression-Free Survival

Treatment	Hazard Ratio (95% CI)	Median (95% CI) (Months)
RT		46 (40, 55)
TMZ	1.2 (0.9, 1.5)	39 (34, 43)

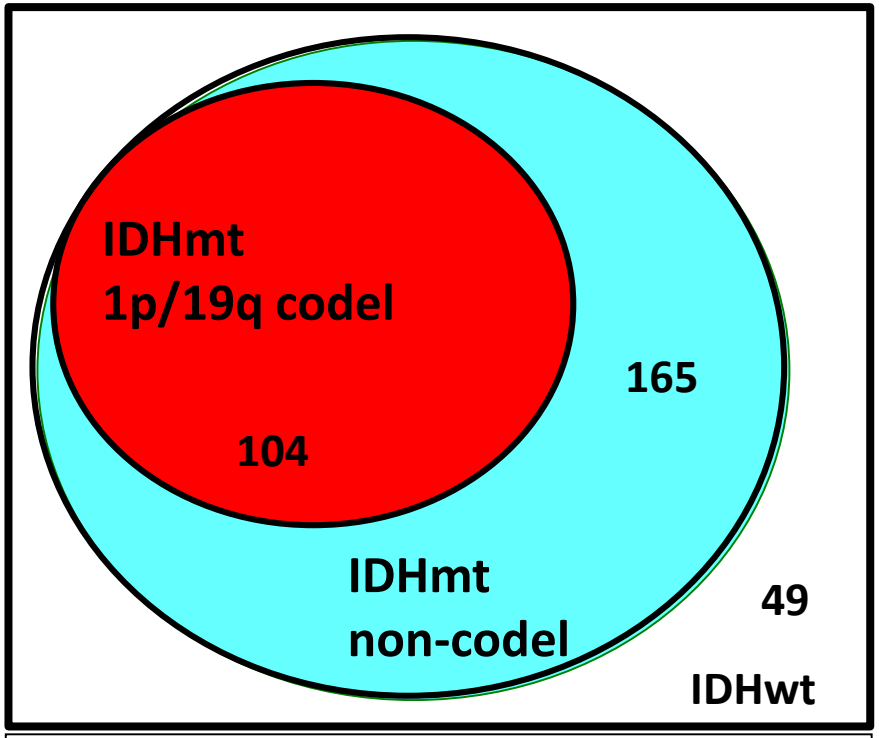


O	N	Number of patients at risk :						Treatment
126	240	203	156	110	60	25	5	RT
136	237	197	148	100	51	19	8	TMZ

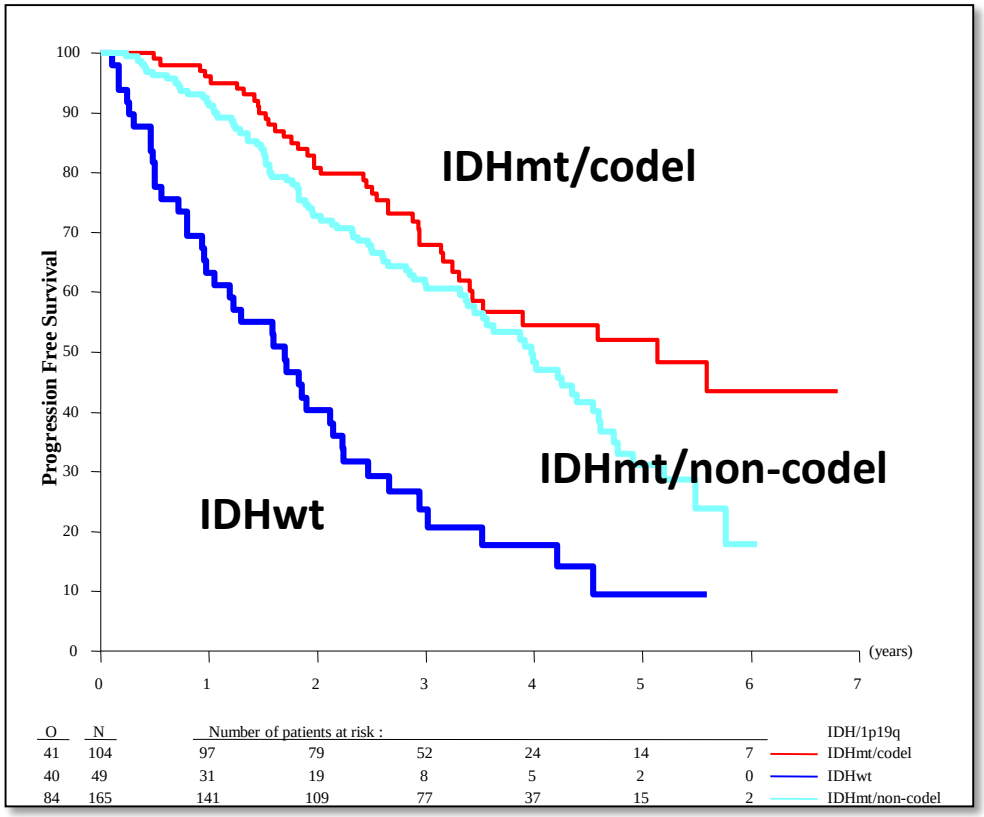
Baumert et al., Proc ASCO 2013 (abstr #2007)

PFS by Molecular Marker Subgroups: Prognostic value

EORTC 22033



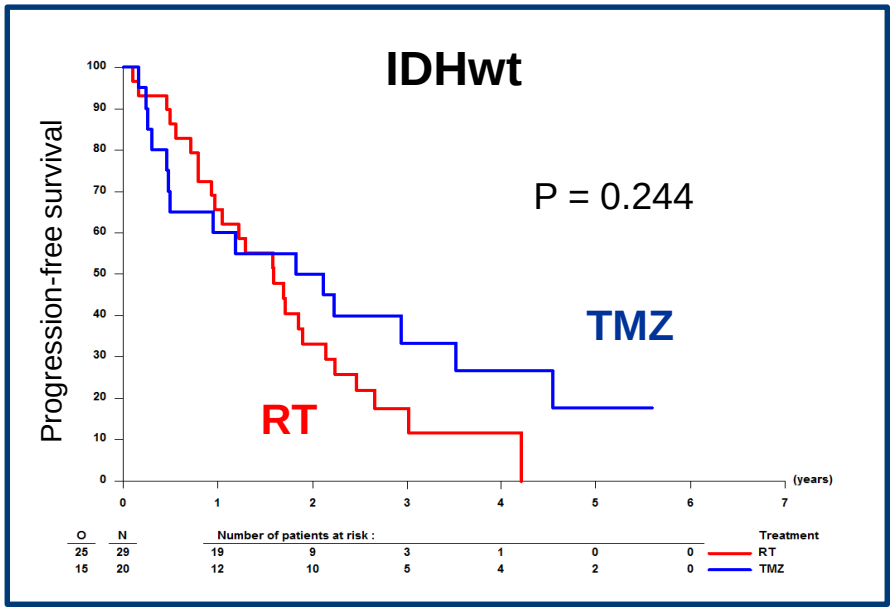
N=318

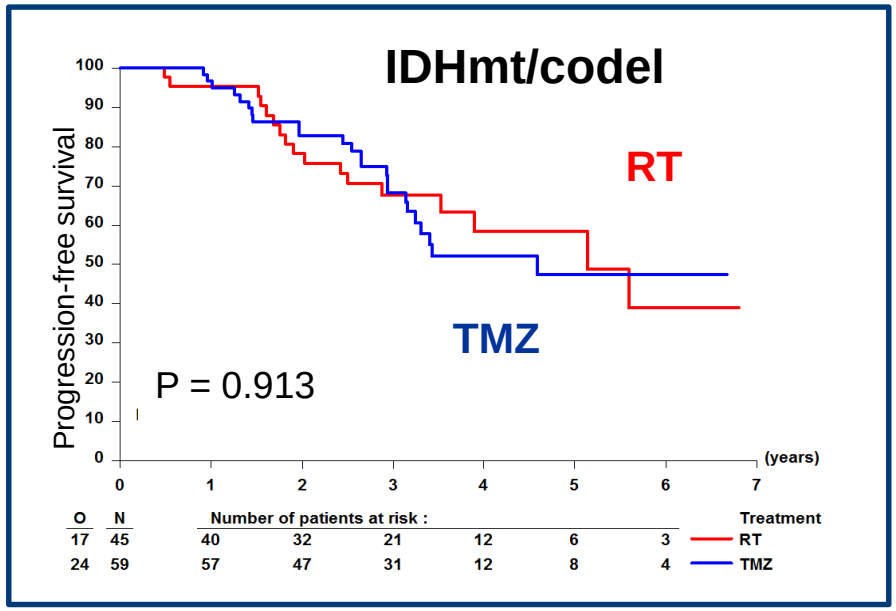


EORTC

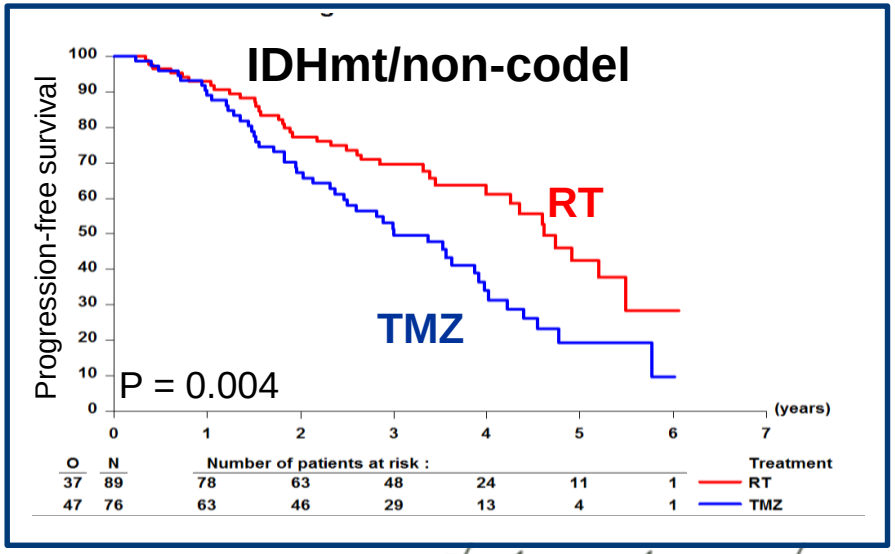
Baumert et al. ASCO 2015

Molecular subgroups and treatment





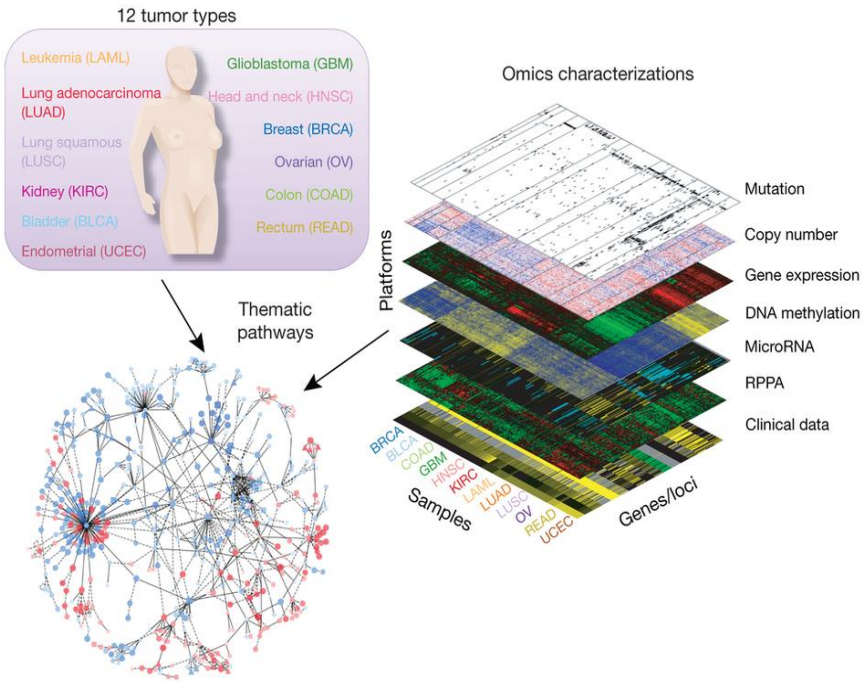
Subgroup	Patients (N)	Events (O)	Median (95% CI) (Months)
RT-IDHmt/codel	45	17	61.63 (42.32, N)
RT-IDHwt	29	25	19.09 (11.27, 25.69)
RT- IDHmt/non-codel	89	37	55.36 (47.87, 65.87)
TMZ-IDHmt/codel	59	24	55.03 (37.95, N)
TMZ-IDHwt	20	15	23.69 (5.55, 42.25)
TMZ-IDHmt/non-codel	76	47	36.01 (28.42, 46.95)



EORTC

The future of cancer therapy

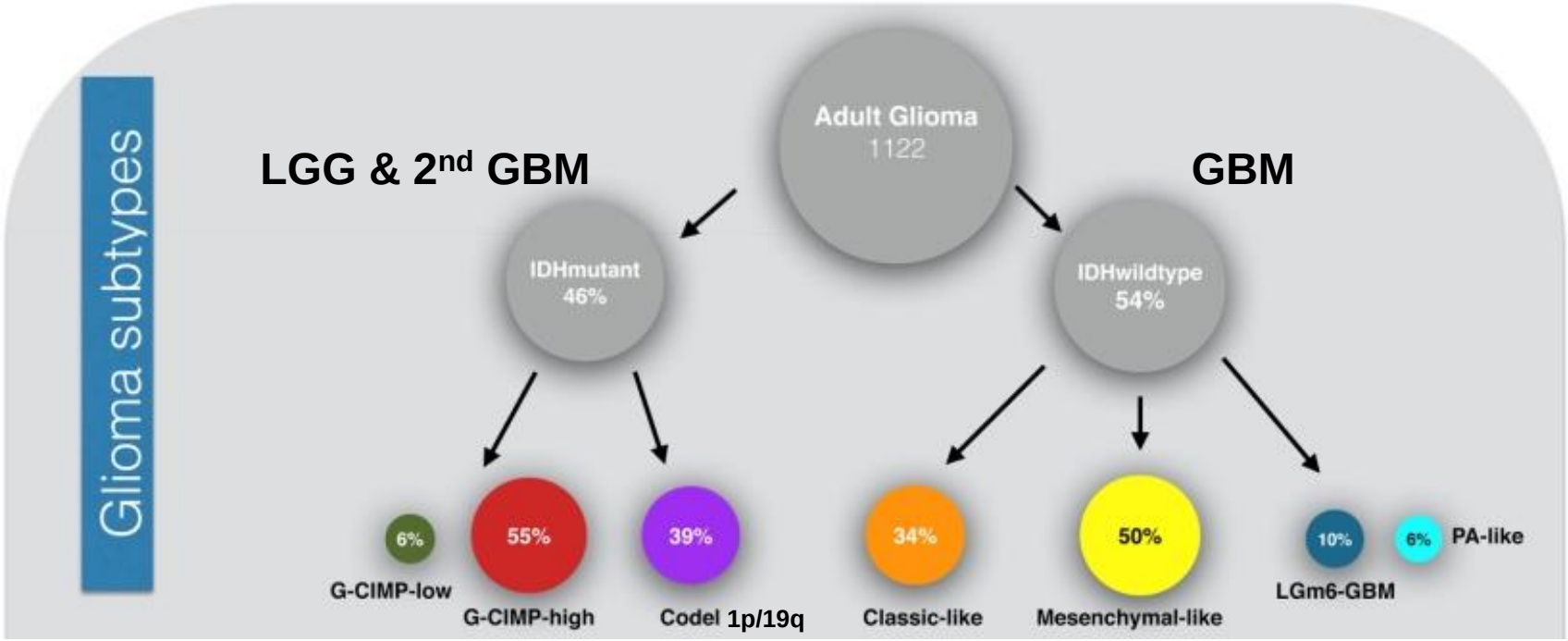
Translation of molecular knowledge into patient care



- Classification
- Outcome prediction
- Targets /treatment options
- Biomarkers for treatment choices
- Tumor heterogeneity

Adapted from : TCGA network, Nature Genetics, 1113–1120 (2013)

Molecular Glioma Subtypes



Astros
2nd GBM

Oligos

GBM

Adapted from Ceccarelli et al.,*Cell* 2016 164, 550-563DOI: (10.1016/j.cell.2015.12.028)

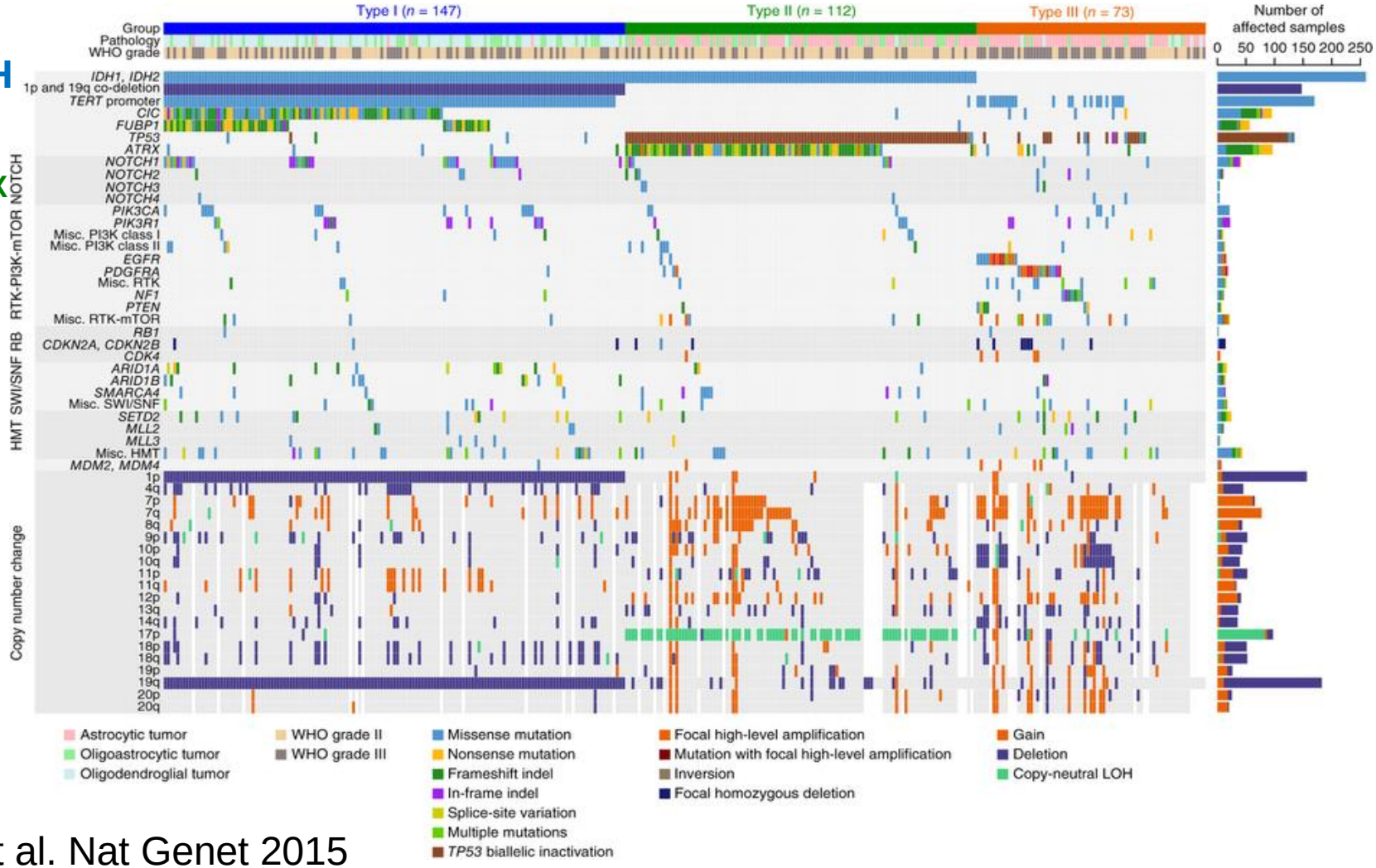
Landscape of genetic lesions in grade II and III gliomas

IDH mutant **IDH wild-type**

1p/19 codel **1p/19 non-codel**

IDH

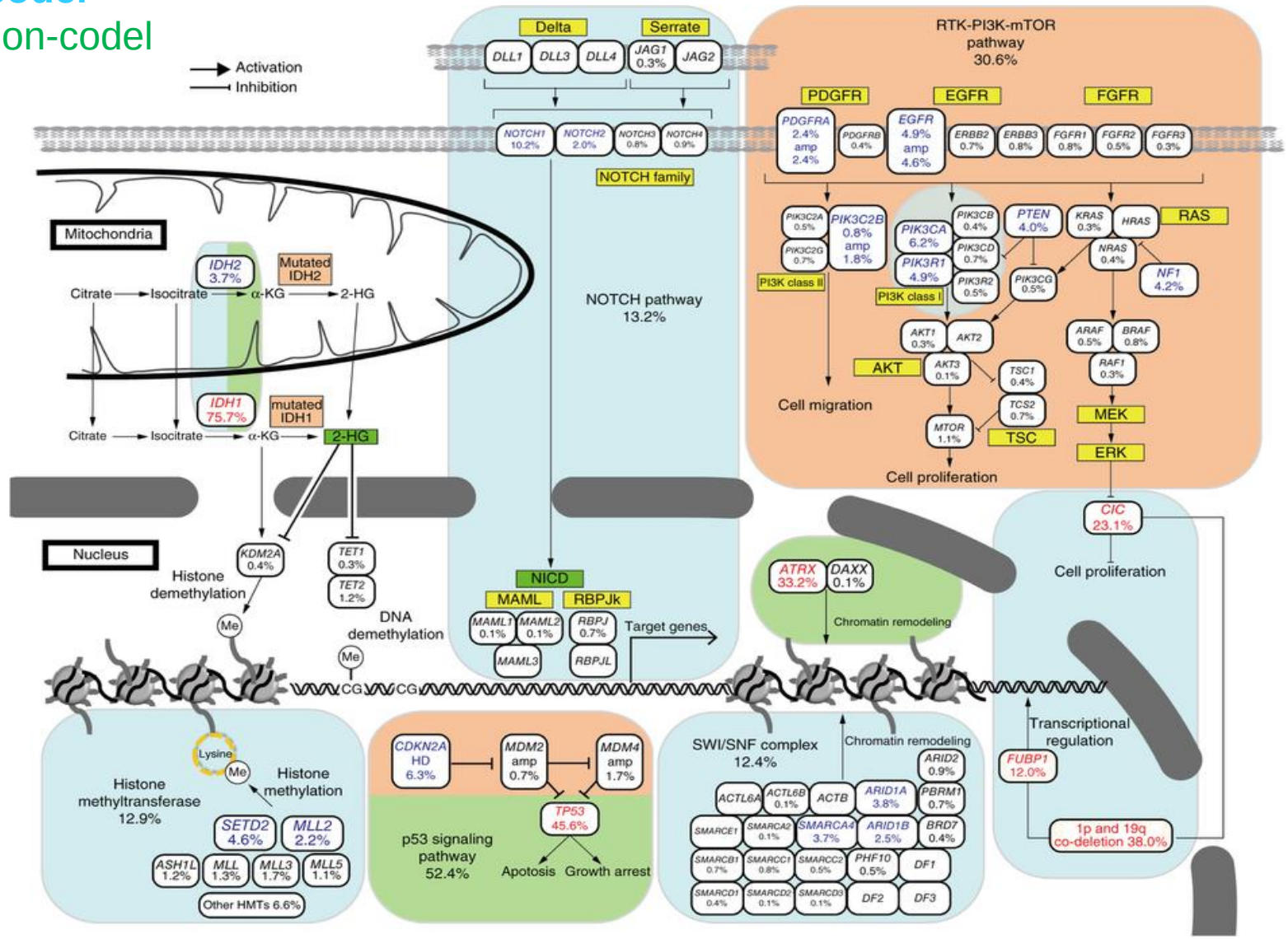
- **hTERT**
- **TP53**
- **ATRX**



Suzuki et al. Nat Genet 2015

Driver genes and functional pathways involved in grade II and III gliomas.

- **IDHmt/codel**
- IDHmt/non-codel
- **IDHwt**



Suzuki et al. Nat Genet 2015

Treatment Recommendations

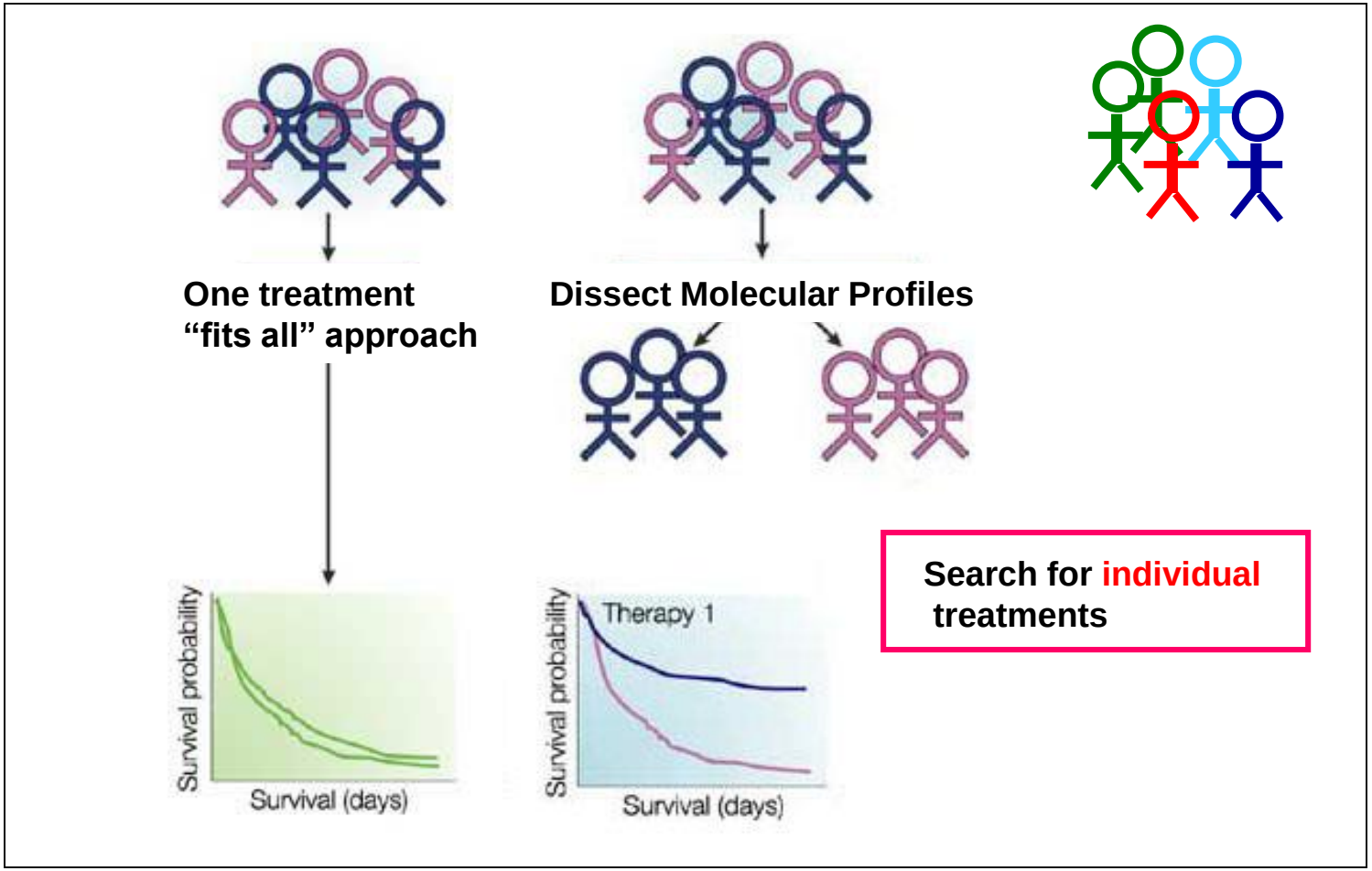
	Newly diagnosed	Progression
Anaplastic astrocytoma, WHO grade III	Resection or biopsy followed by radiotherapy or chemotherapy (or combined modality treatment)	Resection [illegible]
Anaplastic oligodendroglioma or oligoastrocytoma, WHO grade III, with 1p/19q co-deletion	Resection or biopsy [illegible] chemothe[illegible]	[illegible]ation and chemotherapy, radiotherapy, or bevacizumab
Anaplastic oligodendrogl[illegible] oligoastrocytom[illegible] with[illegible]	[illegible]biopsy, followed by [illegible]therapy or chemotherapy (or combined modality treatment)	Resection and chemotherapy, radiotherapy, or bevacizumab
[illegible] grade IV, [illegible] 70 years)	Resection or biopsy, followed by radiotherapy plus concurrent temozolomide, followed by adjuvant temozolomide	Re-resection, reirradiation, rechallenge chemotherapy, or bevacizumab
Glioblastoma, WHO grade IV (age >65–70 years)	Resection or biopsy, followed by radiotherapy, or temozolomide with or without radiotherapy based on MGMT and performance status	Resection and chemotherapy or radiotherapy

Table 1: Management options for newly diagnosed and progressive malignant gliomas

Variations of RT with TMZ or other chemotherapy!!!

Weller et al, LancetOncol 2014; EANO Recommendations

Molecular Profiles to Stratify Treatments
Towards Personalized Therapy



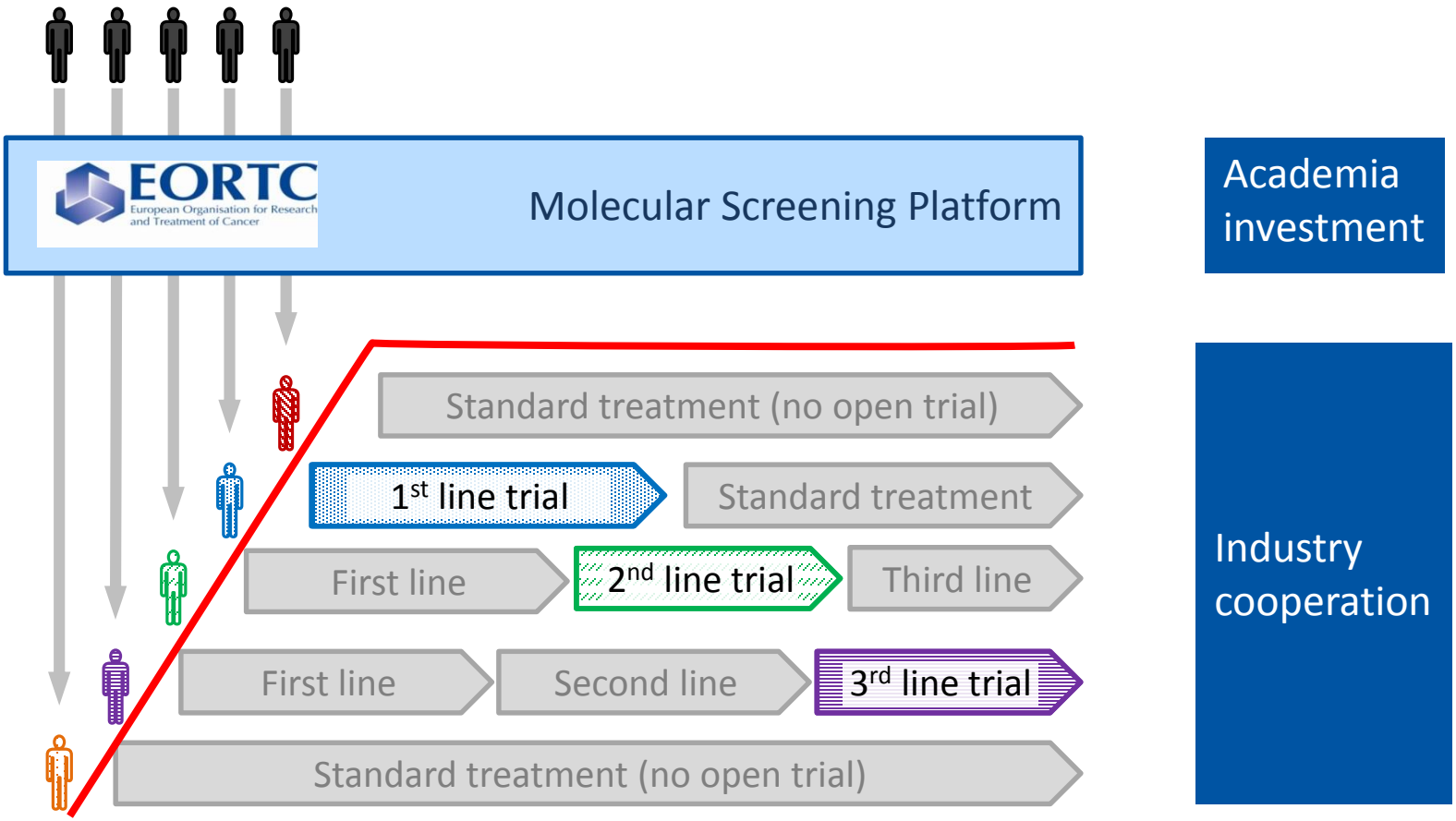
Adapted from Mischel, 2005

Nature Reviews | Neuroscience

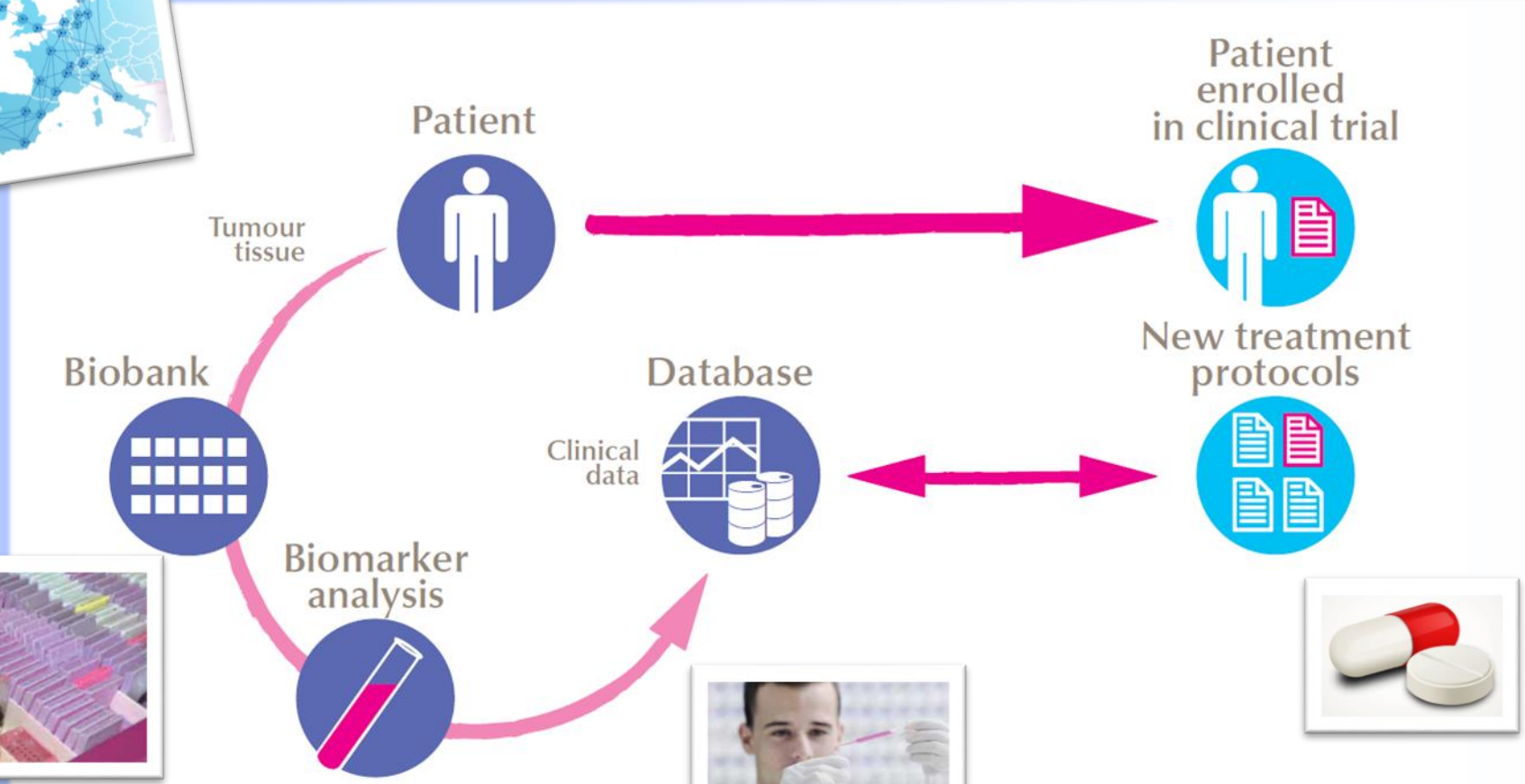
Identification of Patients for personalized therapy

- **Activating mutations in proto-oncogenes, infrequent**
- **Driver vs Passenger mutations, function not always known**
- **Are they actionable (can they be targeted for therapy)**
- **Are respective targeted drugs available**
- **Testing for presence of target(s)**
- **Take advantage of other mechanisms (pathway)**
- **Target altered pathways at multiple hubs - combination therapies**

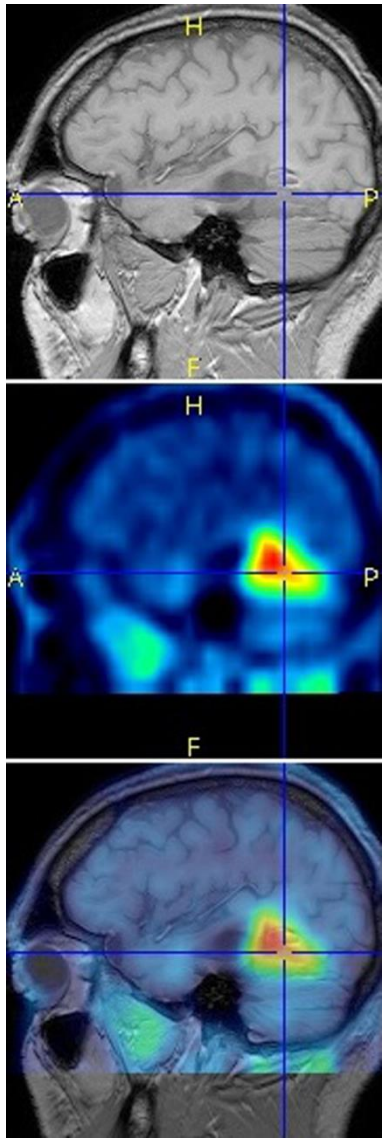
The SPECTA collaborative platform



SPECTA Platforms



- Targeted Exome Seq (>400 genes)
- **Gliomas, add** HM450K (DNA meth)



Conclusions

- Molecular targeting agents require presence of the target → enriched population (dx become rare)
- International collaboration needed
- Partnership academia-industry indispensable

Tissue is the Issue