Du profil moléculaire à la thérapeutique: l'exemple des gliomes

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Equipe Neuro-oncologie et Neuro-inflammation
Inserm U1028 – CNRS UMR5292

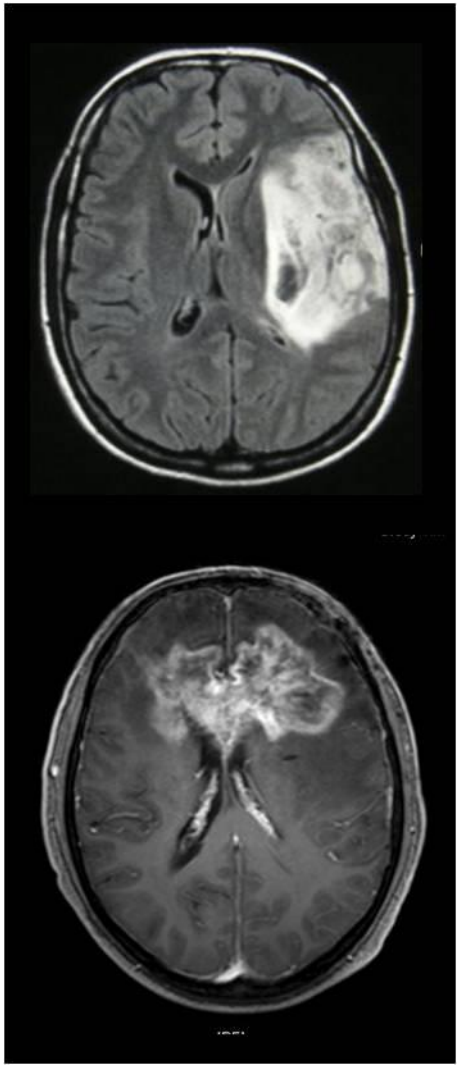
Les gliomes

Tumeurs cérébrales primitives les plus fréquentes de l'adulte

Environ 4000 cas / an

Tumeurs incurables:

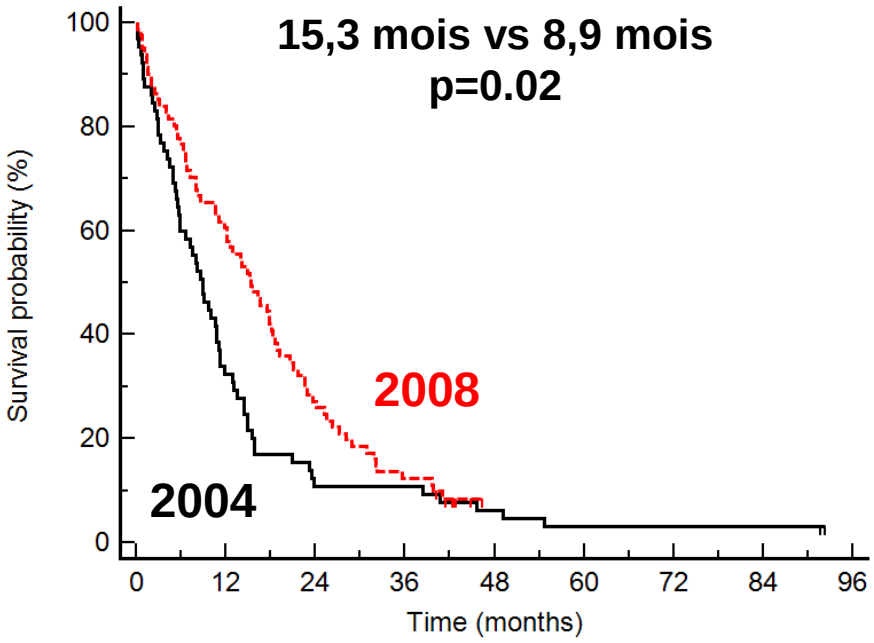
- **manque de traitements efficaces**
- **hétérogénéité**



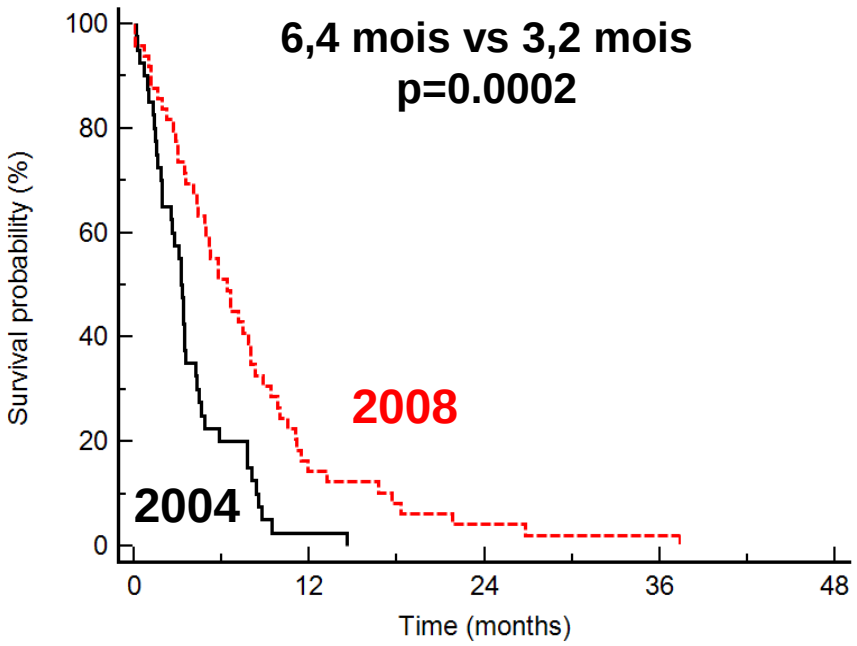
Ricard et al. Lancet 2012

Survie des glioblastomes à Lyon

< 70 ans

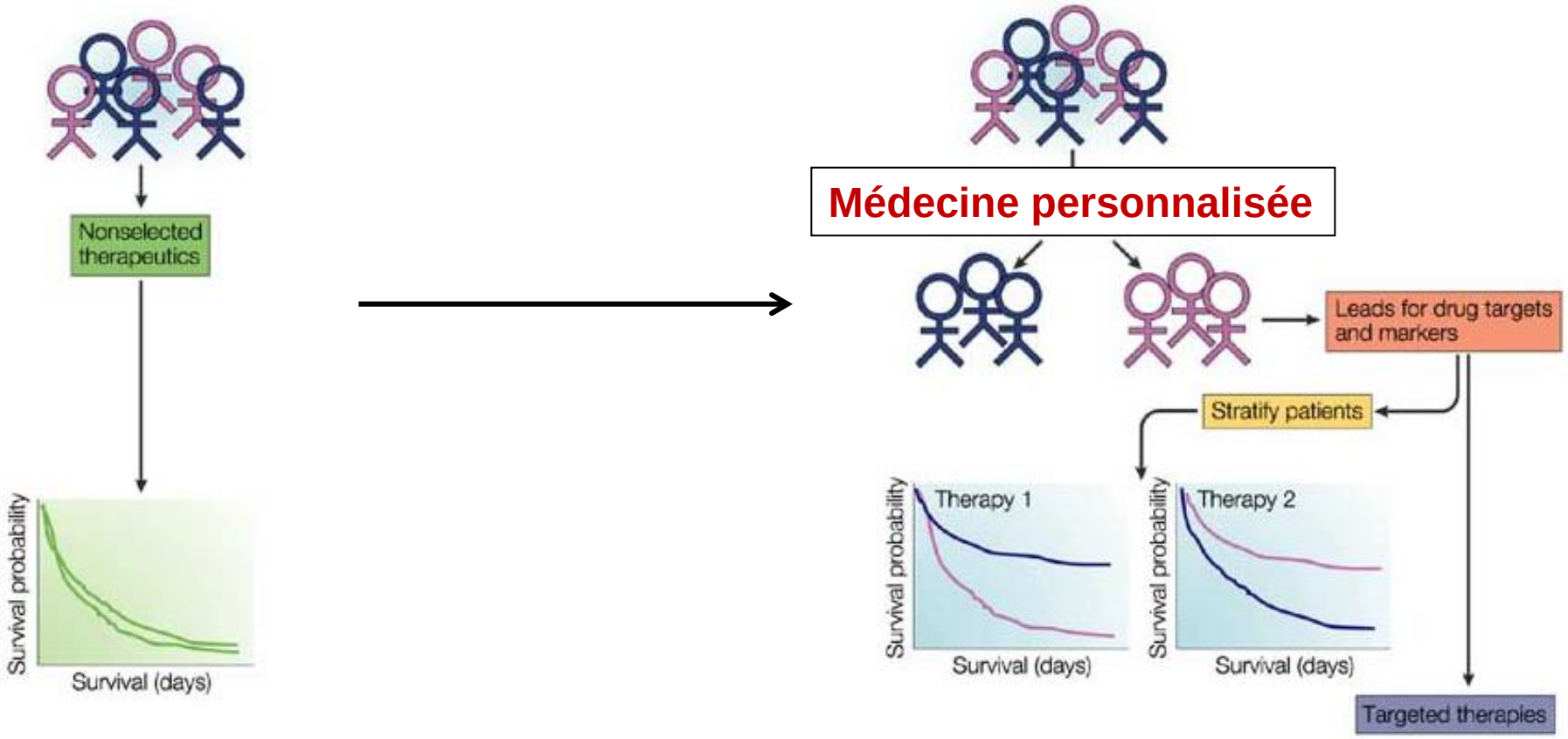


> 70 ans



- Badaoui et al. Revue Neurol 2014

Comment progresser ?

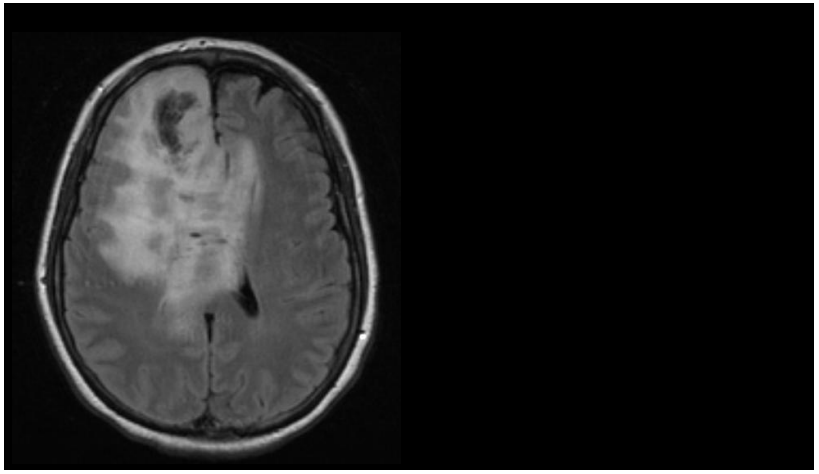


- Mischel et al. Nature Reviews Neuroscience 2004

Patiente de 59 ans
Crises, **oligodendrogliome**

Chimiothérapie (TMZ)

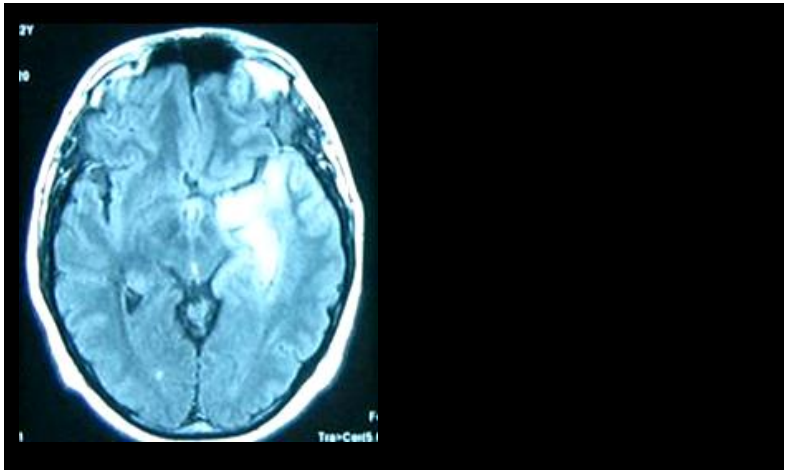
Avant Après



Patient de 43 ans
Crises, **oligodendrogliome**

Chimiothérapie (TMZ)

Avant Après



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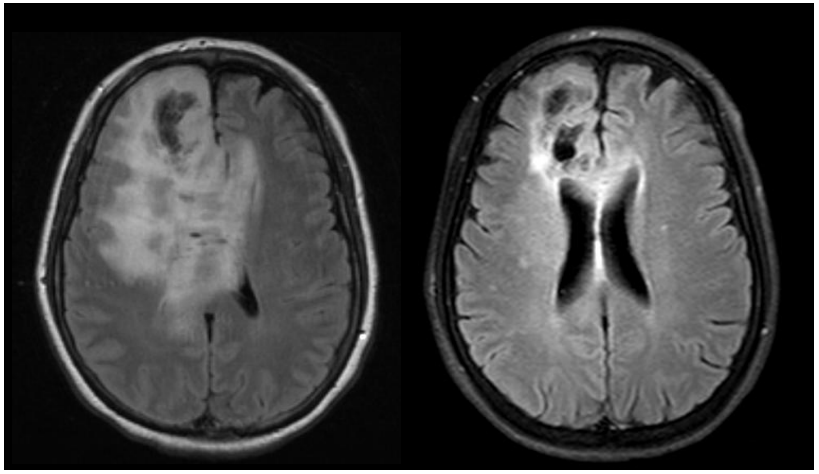
Avant Après

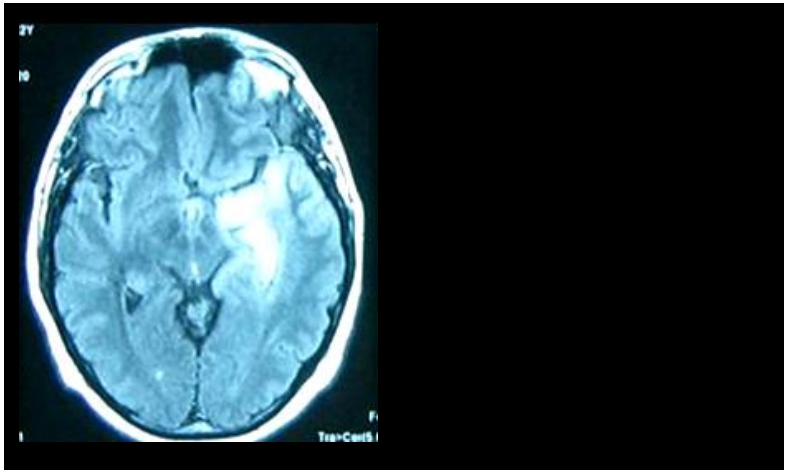


En vie à 5 ans, va bien

Patient de 43 ans
Crises, **oligodendrogliome**

Chimiothérapie (TMZ)

Avant Après



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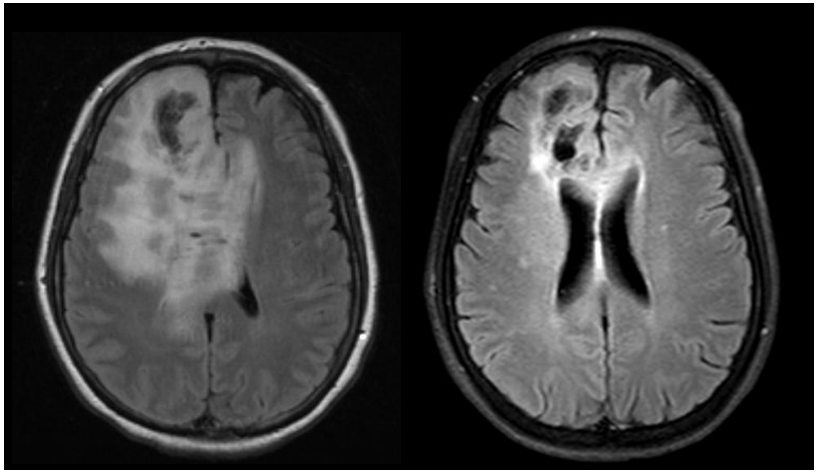

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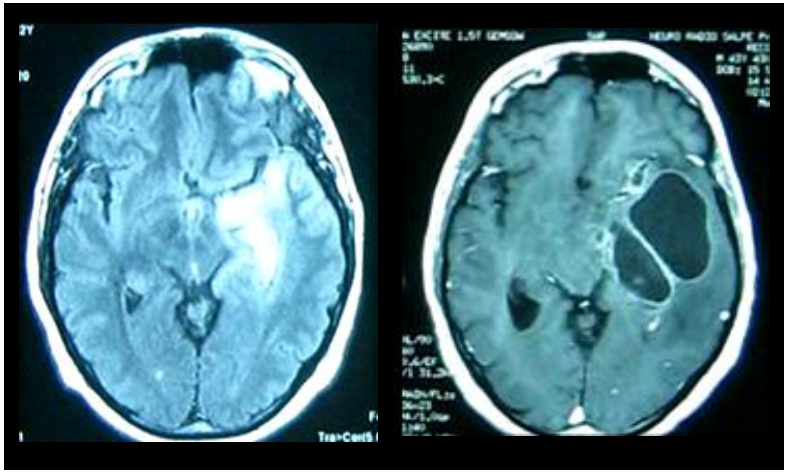
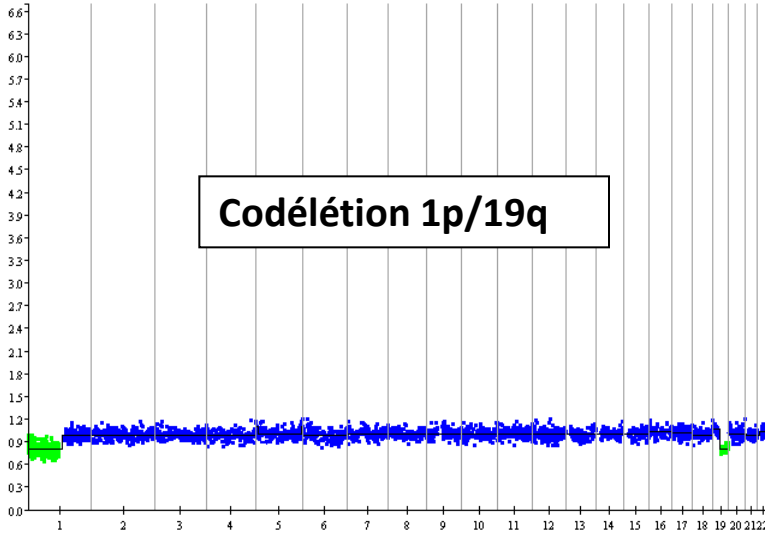


Décès en 1 an

Patiente de 59 ans
Crises, **oligodendrogliome**

Patient de 43 ans
Crises, **oligodendrogliome**

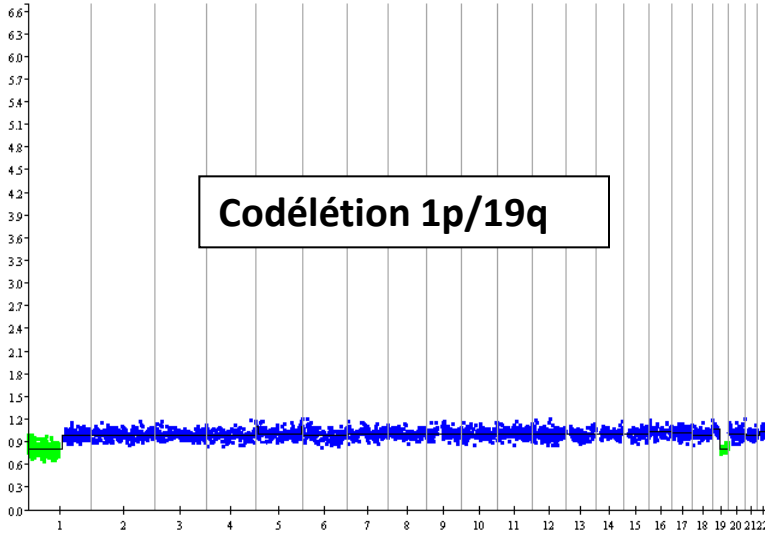
Profil génomique



Patiente de 59 ans
Crises, **oligodendrogliome**

Patient de 43 ans
Crises, **oligodendrogliome**

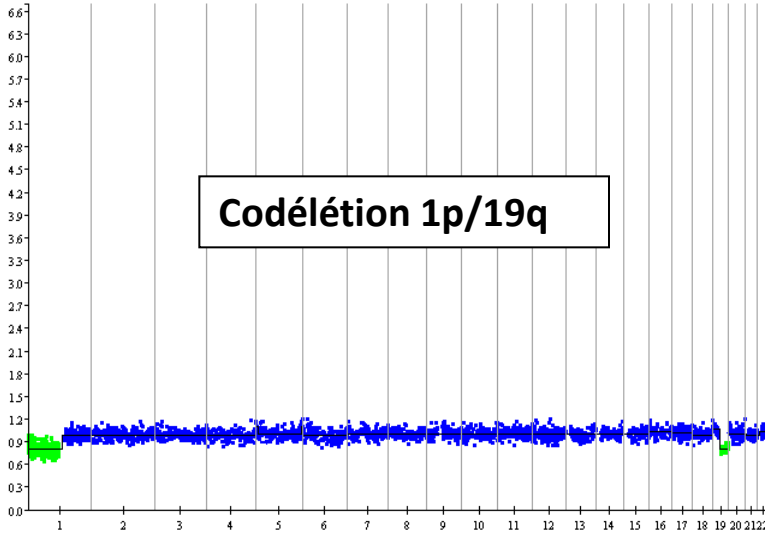
Profil génomique



profil typique d'oligodendrogliome, chimioS, survie: 15 ans

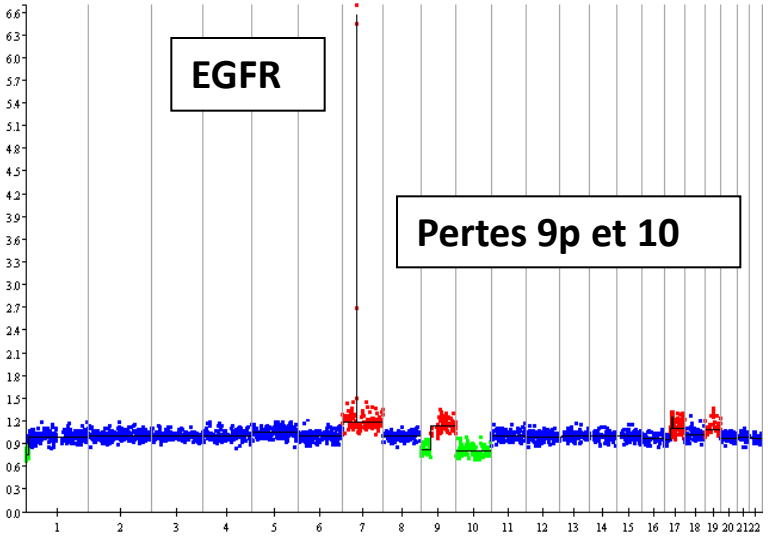
Patiente de 59 ans
Crises, **oligodendrogliome**

Profil génomique



Patient de 43 ans
Crises, **oligodendrogliome**

Profil génomique



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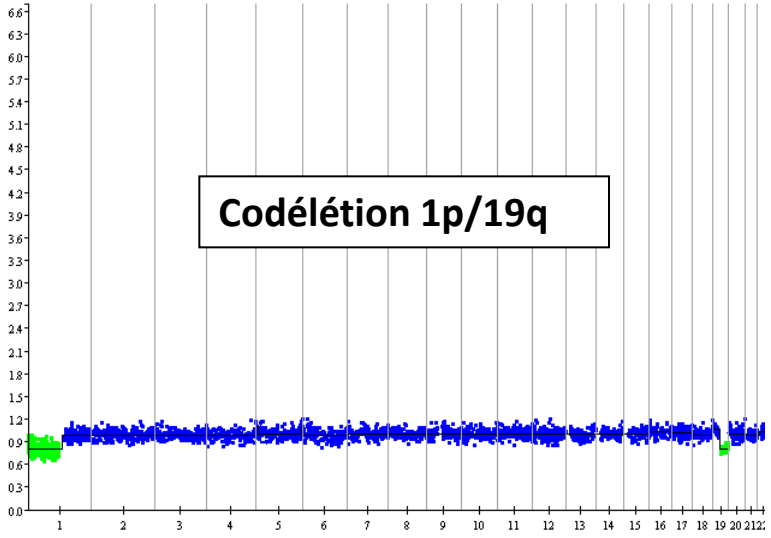

profil typique d'oligodendrogliome, chimioS, survie: 15 ans

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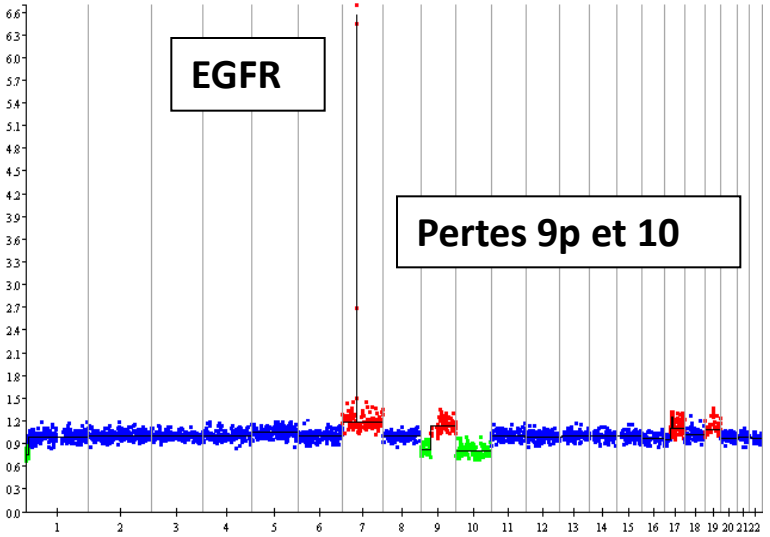
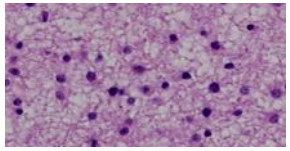
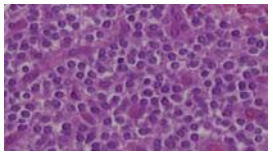


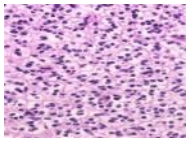
profil typique de glioblastome, chimioR, survie: 1 an

Classification OMS des gliomes

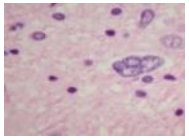




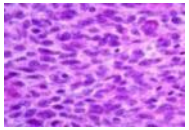
Densité



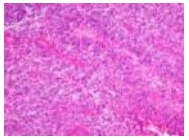
Atypies



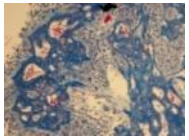
Mitoses



Prolif. endoth.



Nécrose

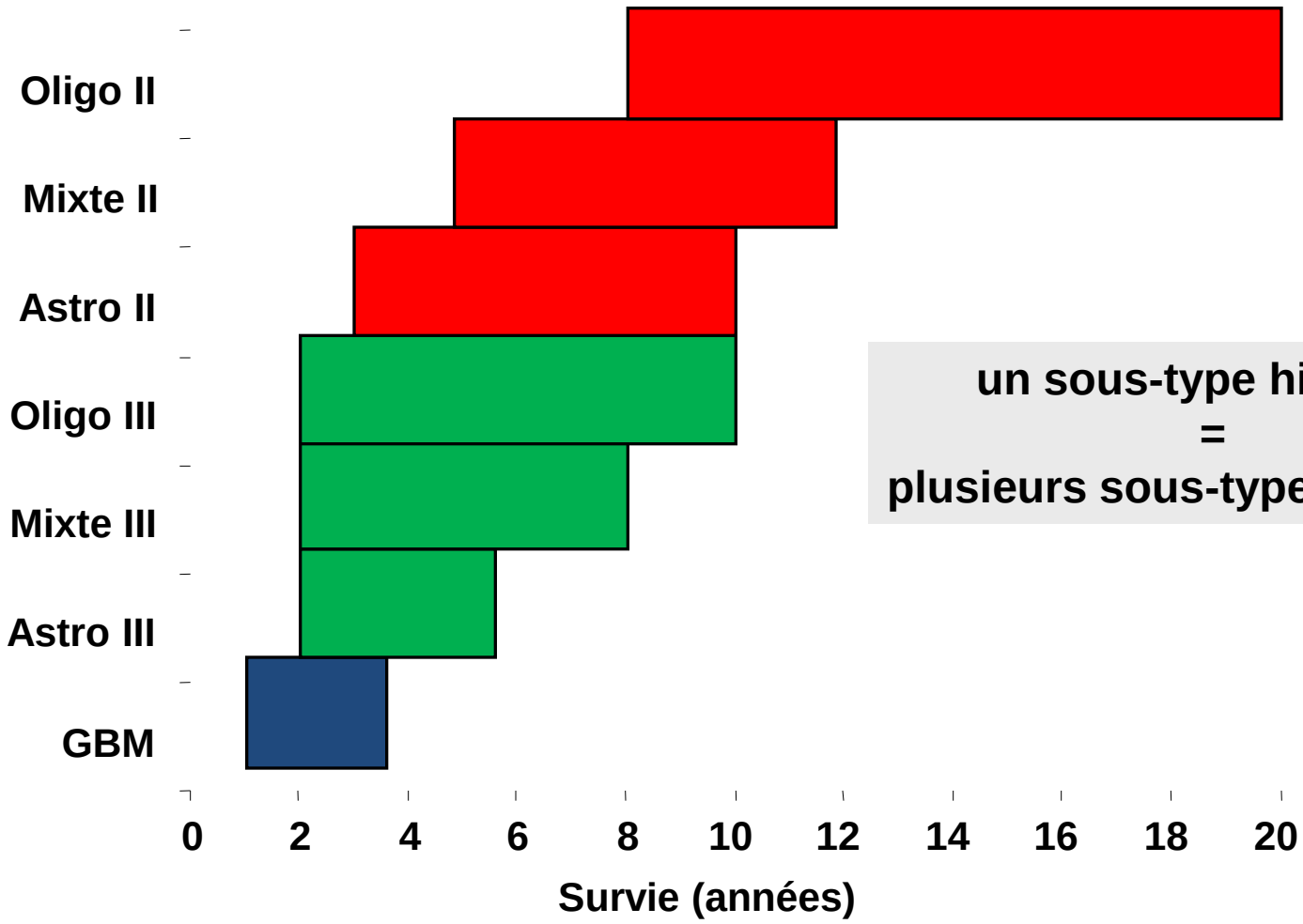


Grade	Astrocytome	Oligo-astrocytome	Oligodendrogliome	Survie médiane
I	A. pilocytique			>20
II	A. bas grade	OA bas grade	O bas grade	5-15
III	A. anaplasique	OA anaplasique	O anaplasique	3-15
IV	Glioblastome			1-1.5

Louis et al. Acta Neuropathol 2007

Limites de la classification OMS

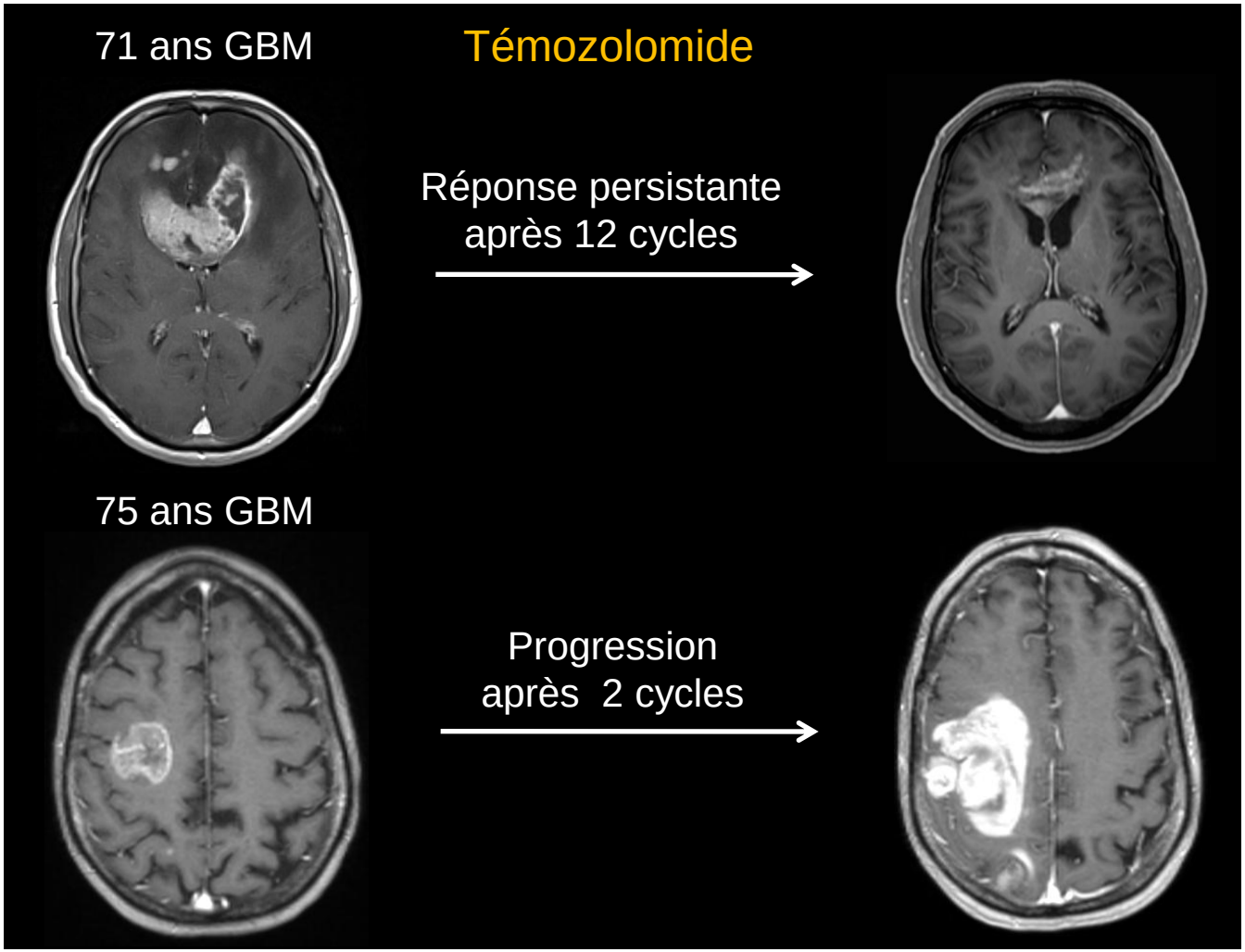
Manque de précision pronostique



un sous-type histologique
=
plusieurs sous-types moléculaires

Limites de la classification OMS

Manque de précision pour la prédiction de la réponse

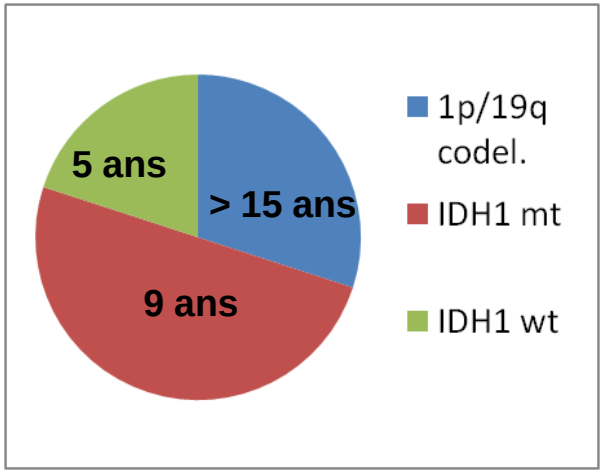


Classification histo-moléculaire

Pronostique et prédictive de l'efficacité des traitements

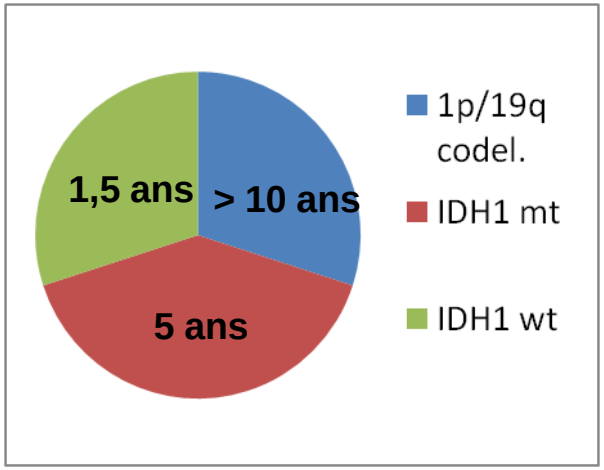
Grades II

(% des altérations et survie médiane)



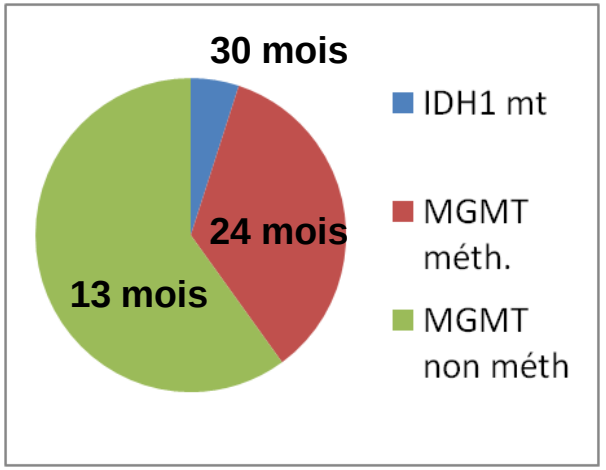
Grades III

(% des altérations et survie médiane)



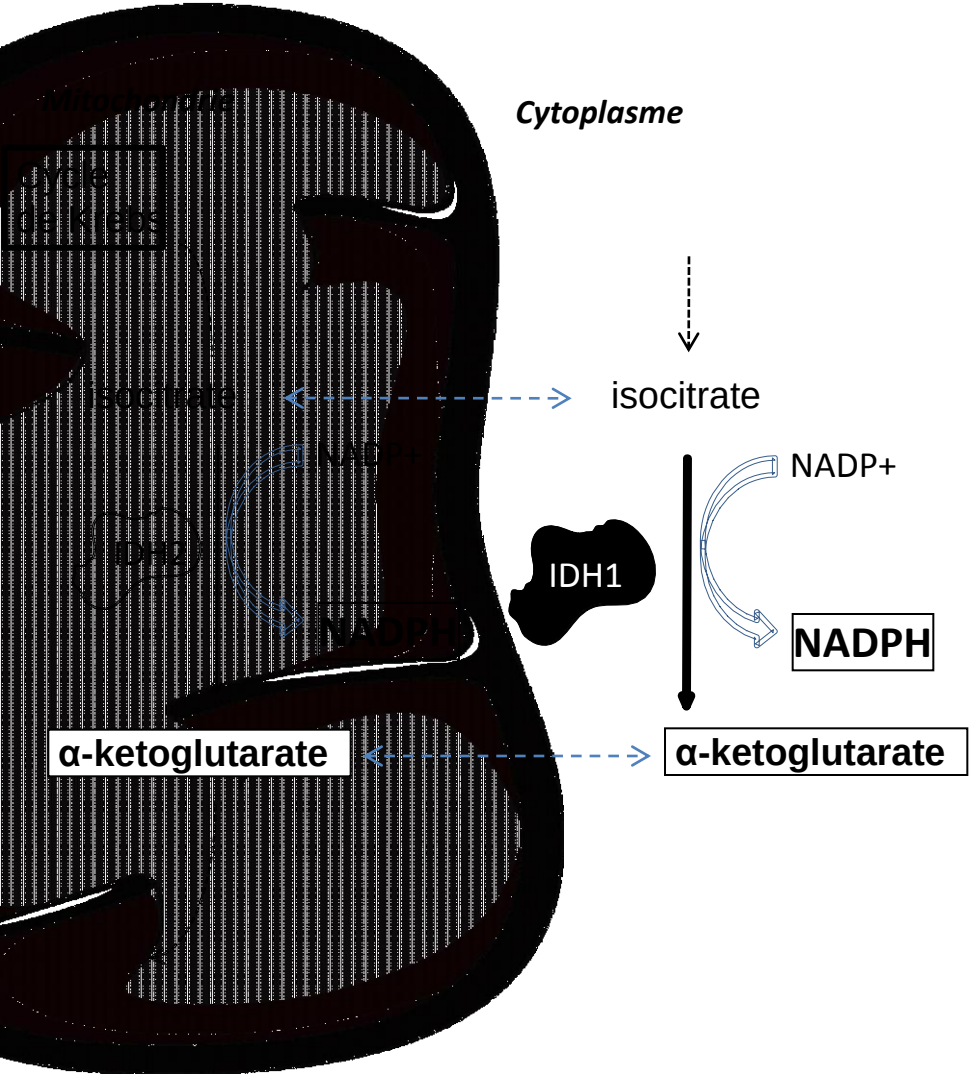
GBM

(% des altérations et survie médiane)



Mutation d'IDH

Isocitrate déshydrogénase



Spécifique des gliomes diffus

70-80% des grades II

50-60% des grades III

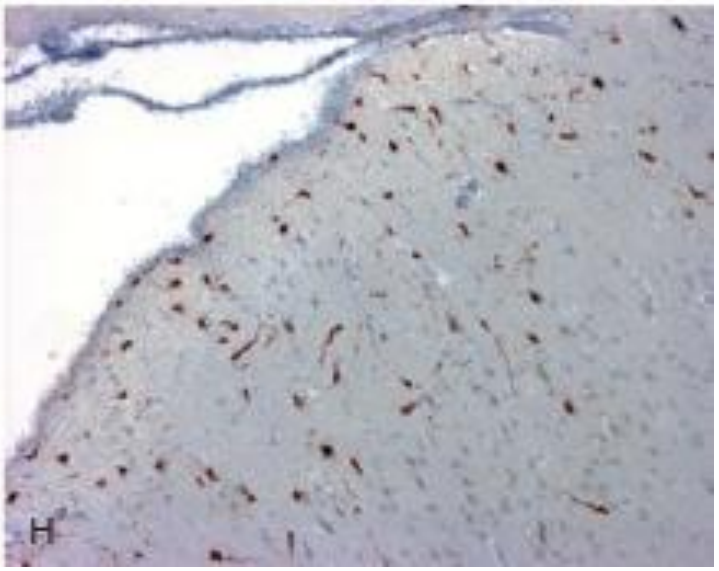
5-10% des GBM

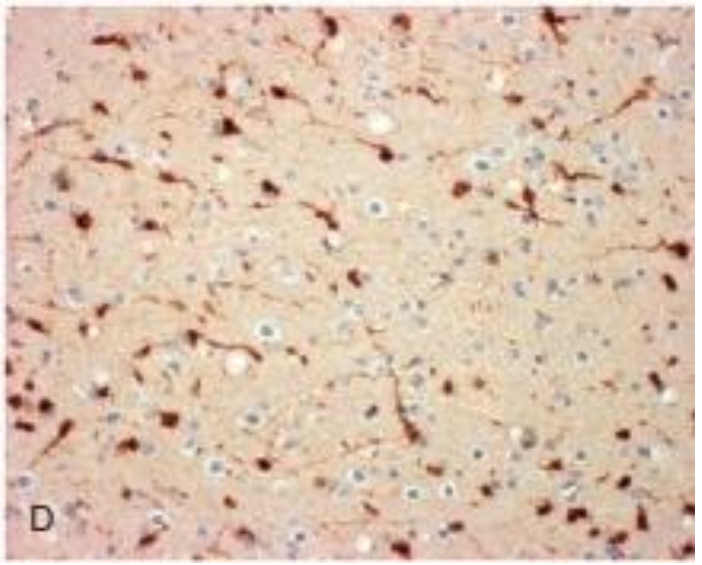
Parson s et al. Science 2008

Mutation d'IDH

Intérêts de l'immuno-histochimie anti-IDH1 R132H (>90% des mutations)

Marqueur diagnostique (mutation d'IDH1= gliome diffus)

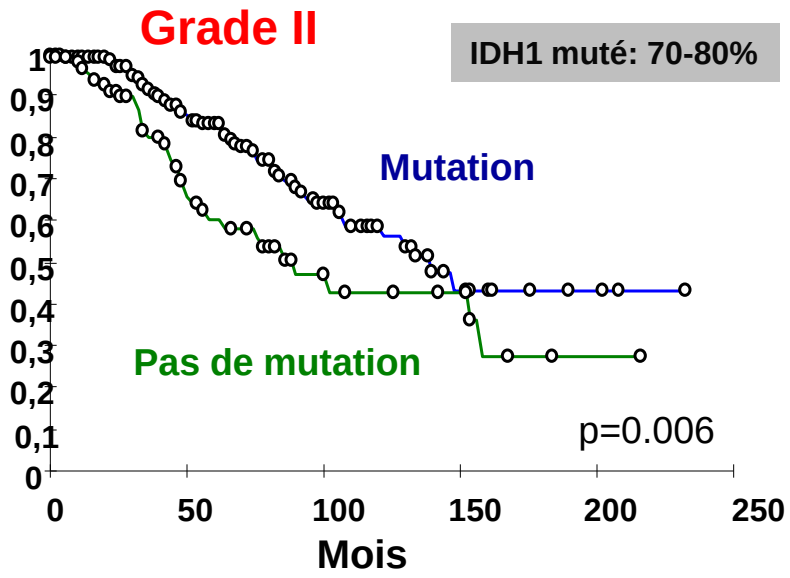


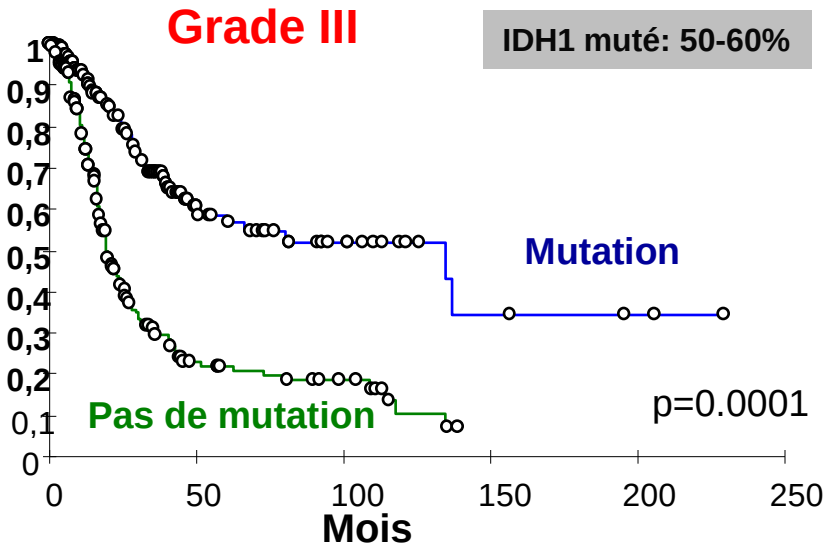


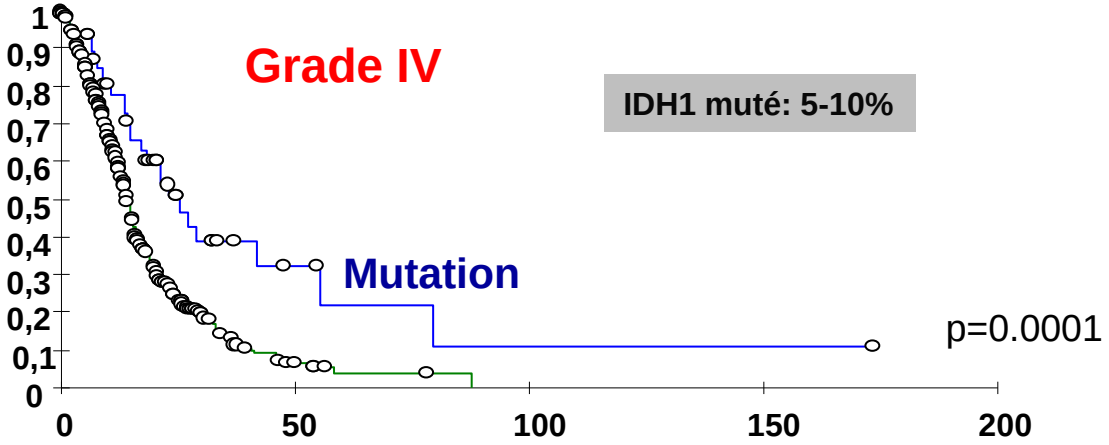
Capper et al. Brain Pathol 2009; Capper et al. Acta Neuropathol 2010

Mutation d'IDH

Marqueur pronostique







Yan et al. NEJM 2009; Sanson et al. JCO 2009

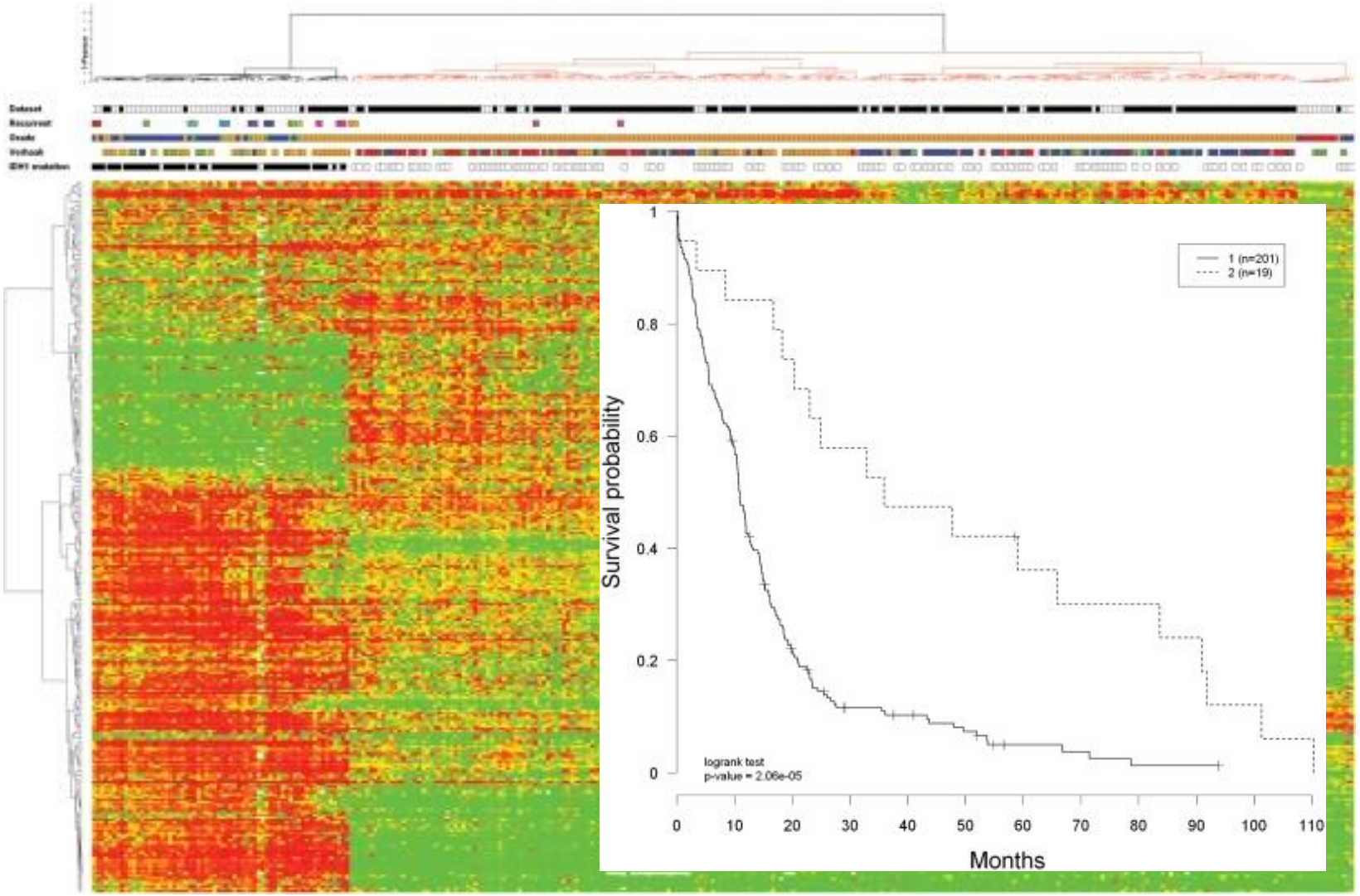
Mutation d'IDH

Associée à un phénotype hyperméthylé

- Laffaire et al. Neuro-oncol 2011

Mutation d'IDH

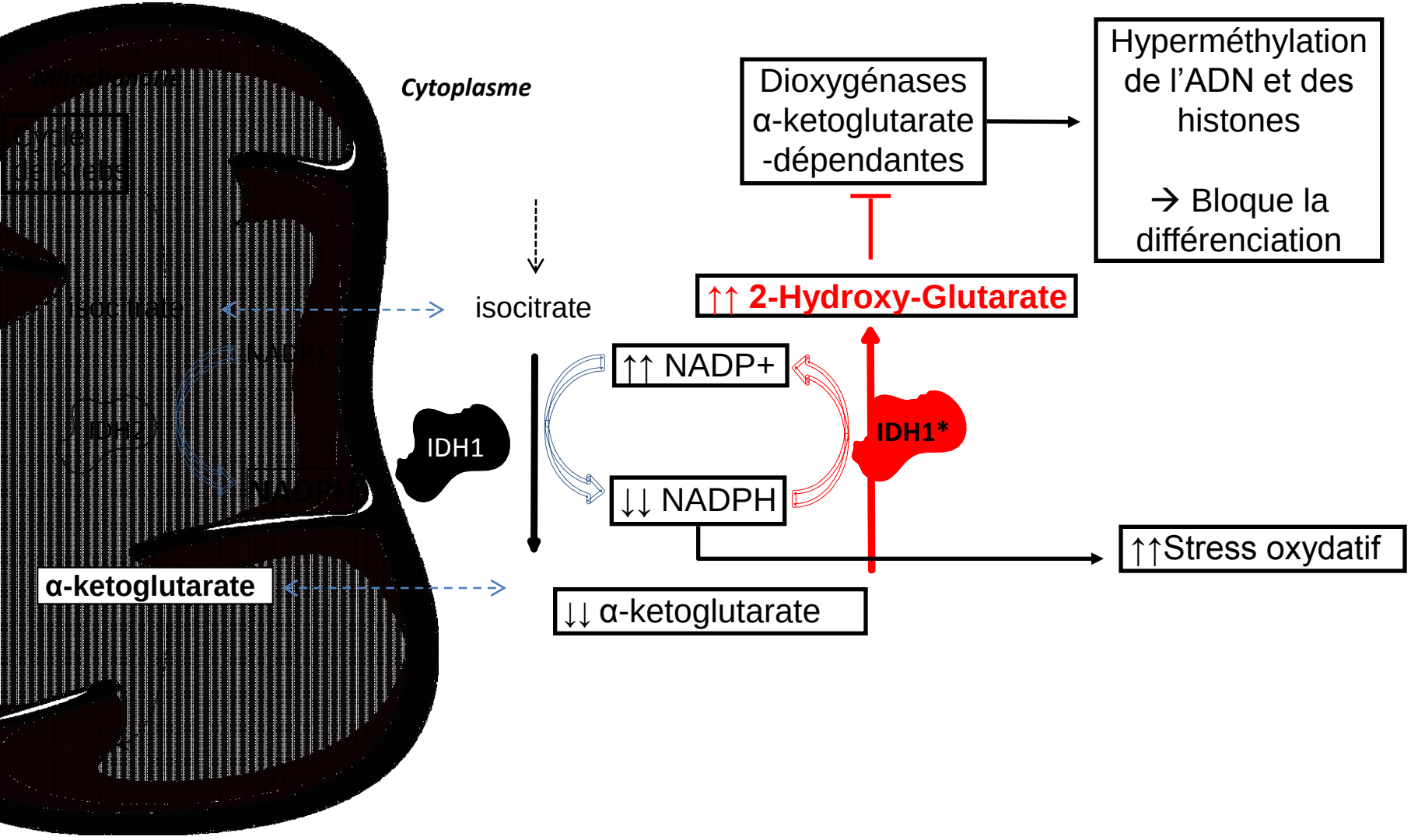
Associée à un phénotype hyperméthylé



- Laffaire et al. Neuro-oncol 2011

Mutation d'IDH

Physiopathologie

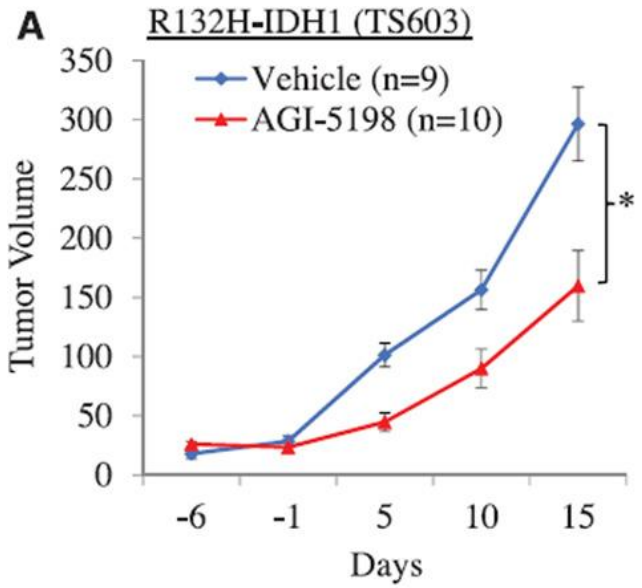


Dang et al. Nature 2010; Turcan et al. Nature 2012; Lu et al. Nature 2012; Koivunen et al. Nature 2012; Rohle Science 2013

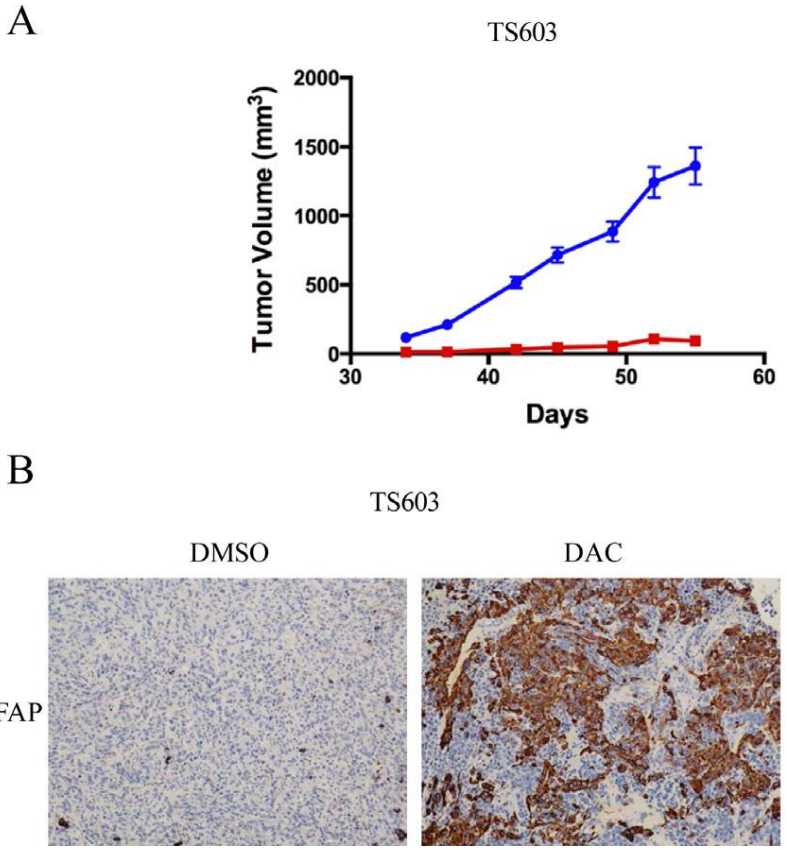
Mutation d'IDH

Une cible thérapeutique prometteuse

Inhibiteur spécifique



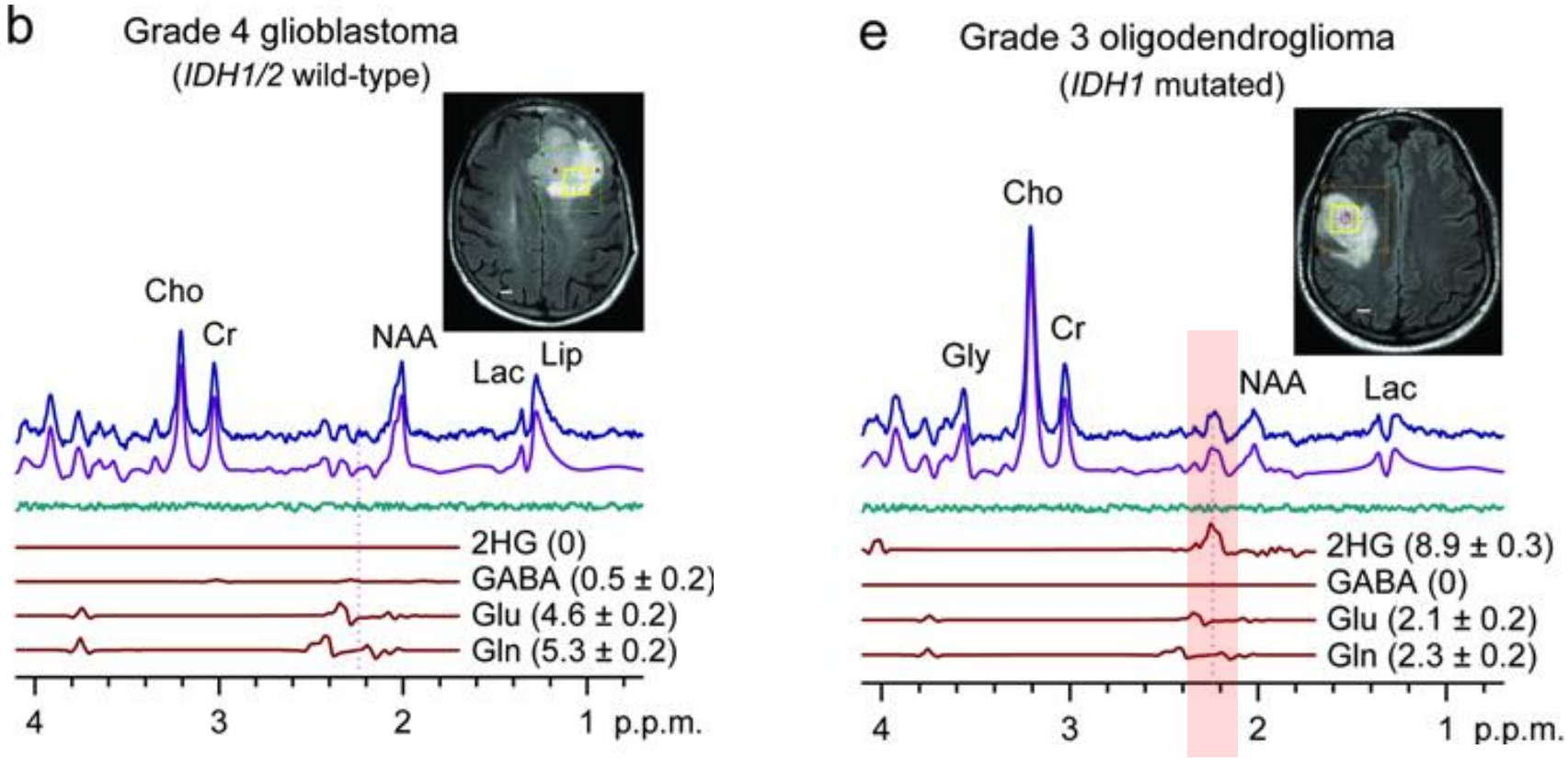
Agents déméthylants
5-(deoxy)azacytidine



Rohle et al. Science 2013; Turcan et al. Oncotarget 2013; Borodovsky et al. Oncotarget 2013

Mutation d'IDH

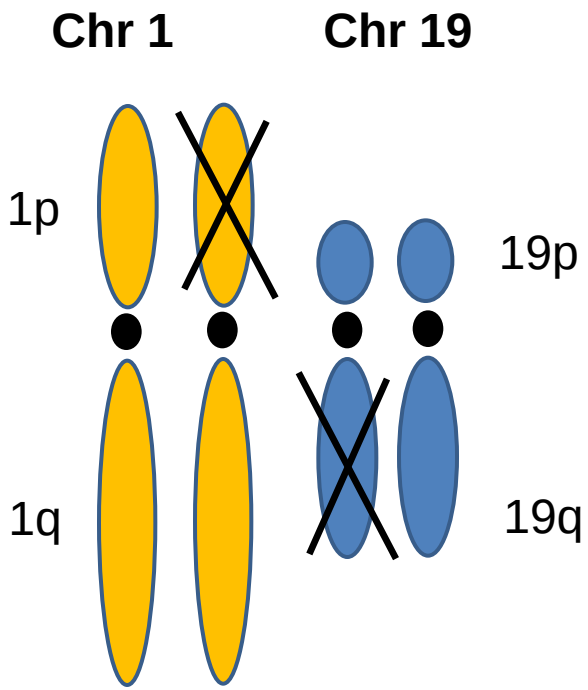
Détection du 2-HG en spectro-IRM



Choi et al. Nat Med 2012

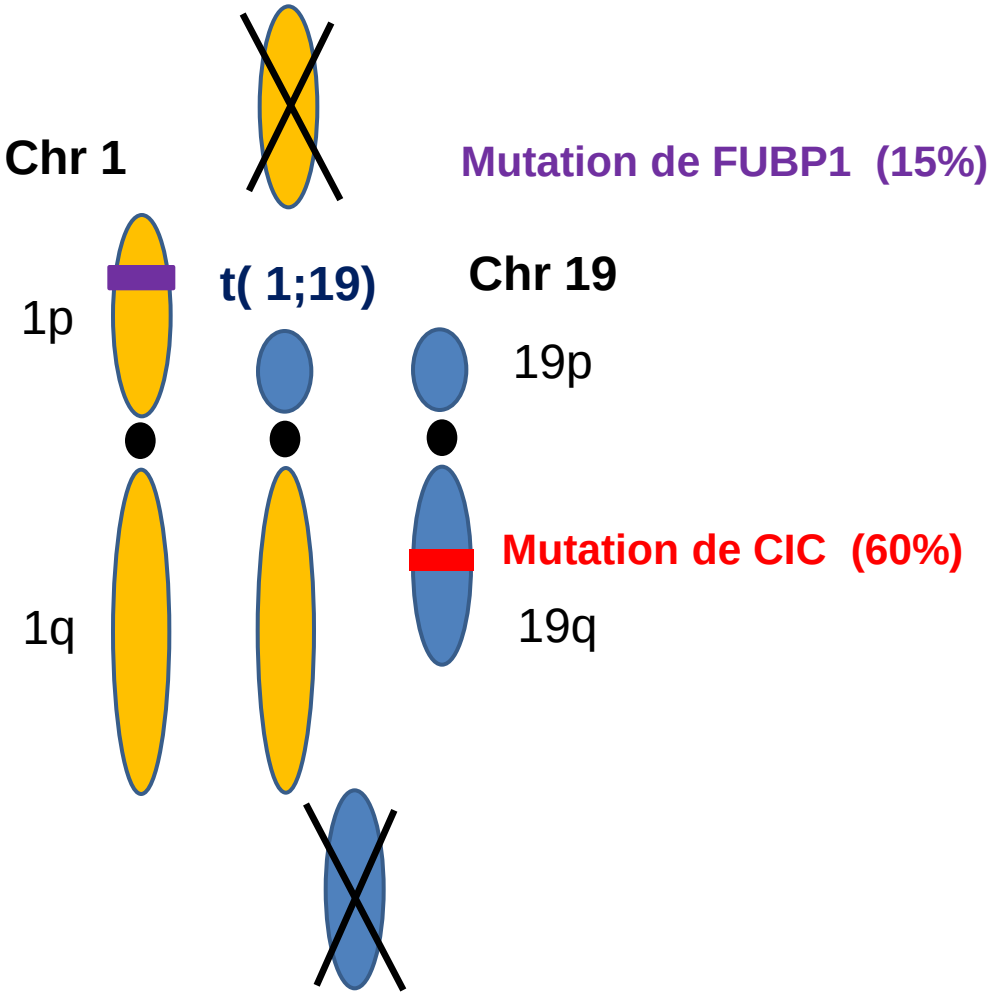
1p/19q codeletion

Definition

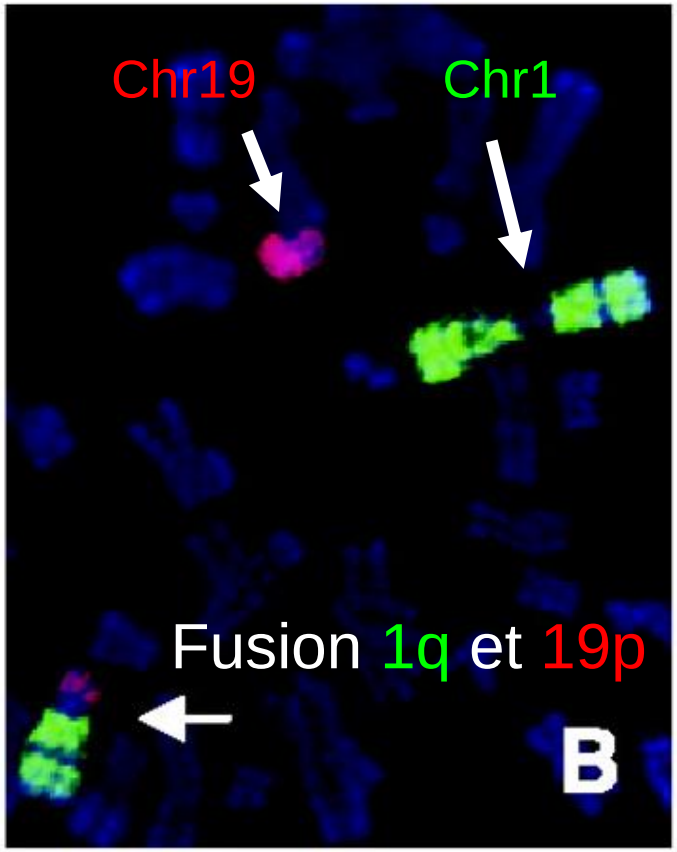


1p/19q codeletion

Definition



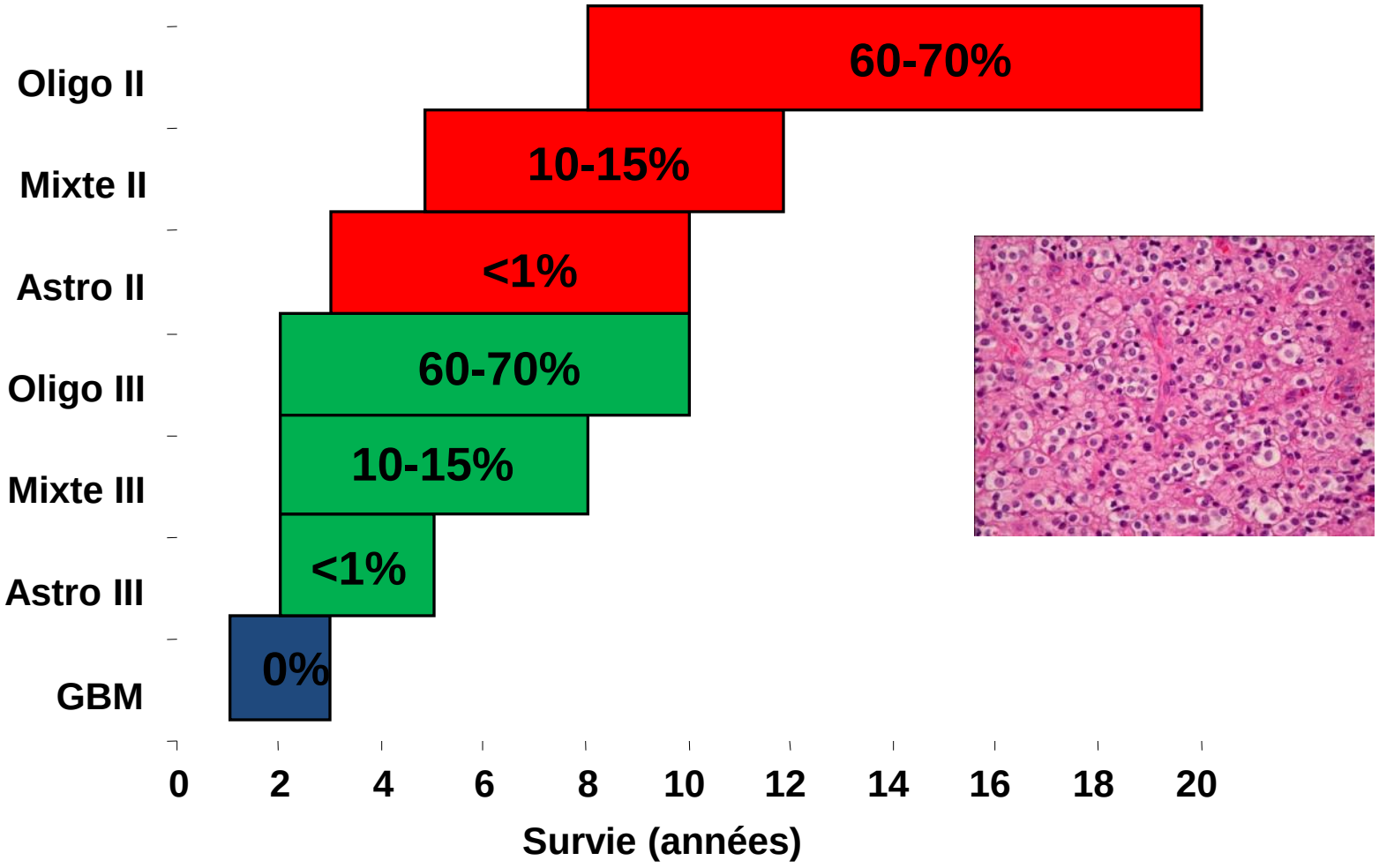
Translocation 1;19



Jenkins et al. Cancer Res. 2006, Bettegowda et al. Science 2011

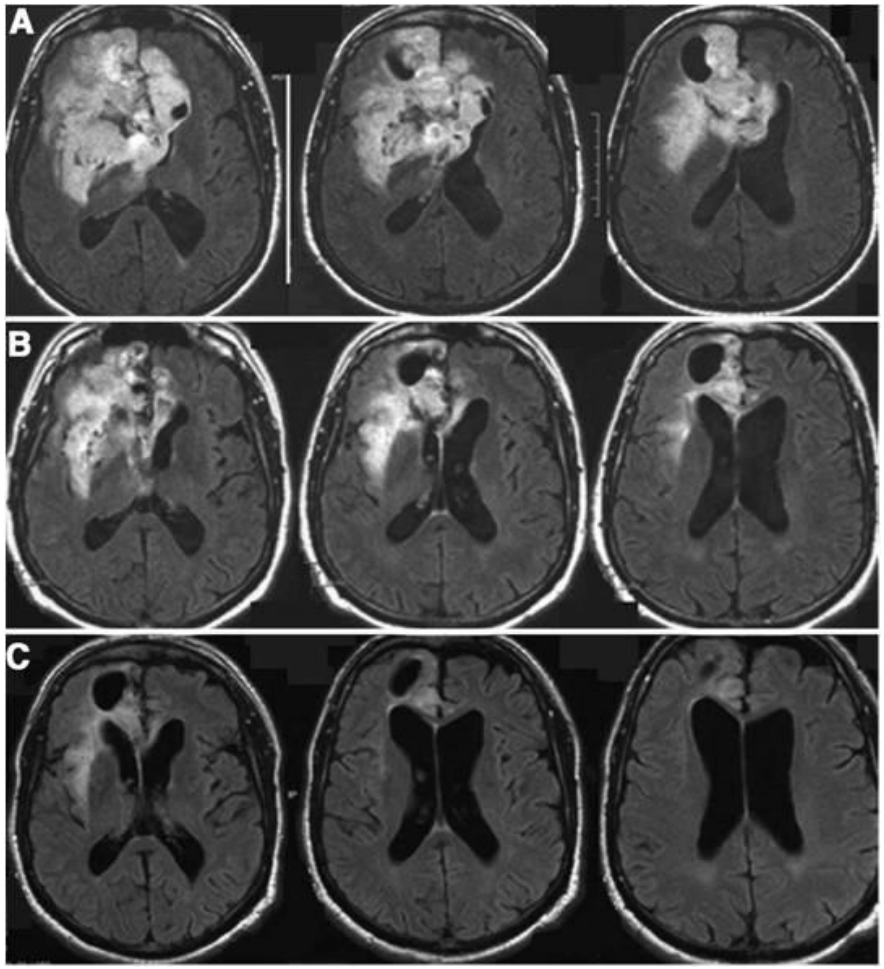
La codélétion 1p/19q

Associée au phénotype oligodendroglial pur



La codélétion 1p/19q

Marqueur de chimiosensibilité dans les gliomes de grade II



T0

+ 12 cycles de TMZ

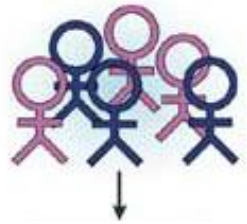
+ 24 cycles de TMZ

Cairncross et al. JNCI 1998; Hoang-Xuan et al. JCO 2004; Kaloshi et al. Neurology 2007

La codélétion 1p/19q

Marqueur de chimiosensibilité dans les gliomes de grade III

Grades III

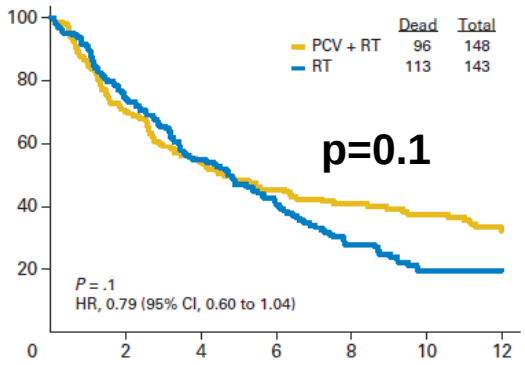


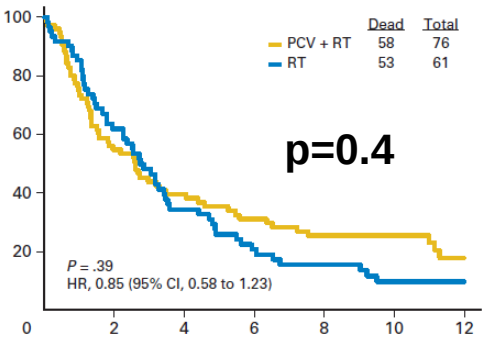
RT vs RT+PCV

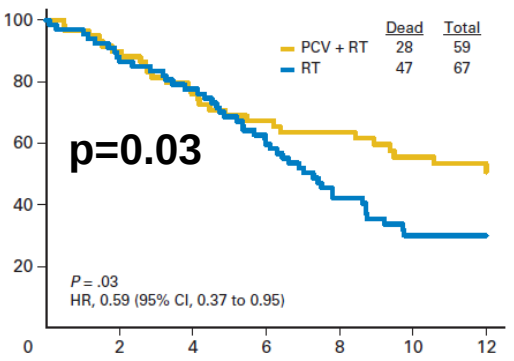
Codélétion 1p/19q

Non

Oui







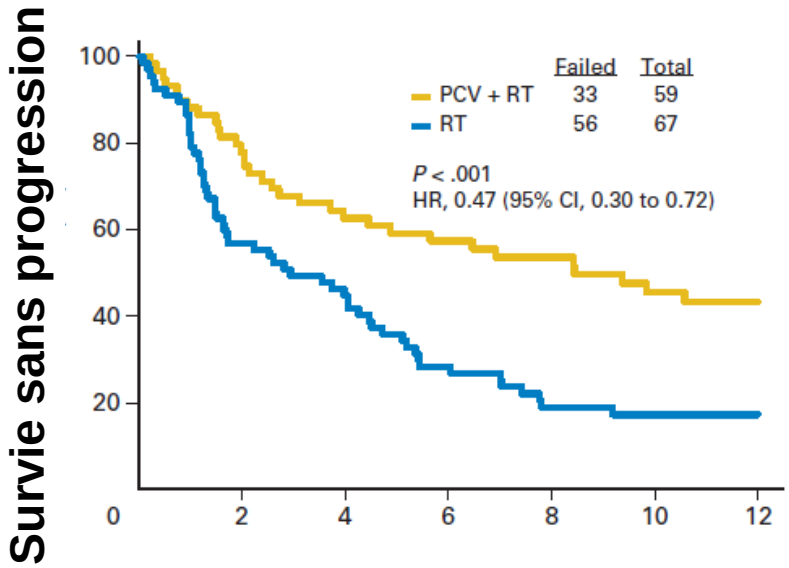
Cairncross et al. JCO 2012; van den Bent et al. JCO 2012

La codélétion 1p/19q

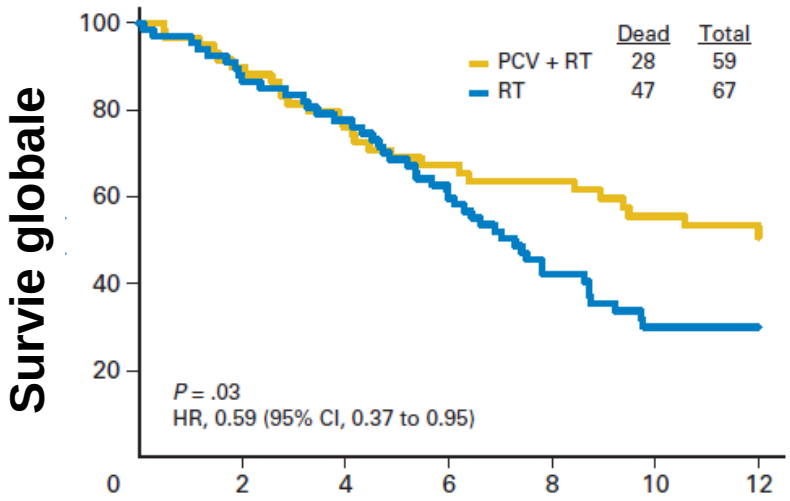
Marqueur de chimiosensibilité dans les gliomes de grade III

RT + PCV >> RT

8 ans vs 3 ans



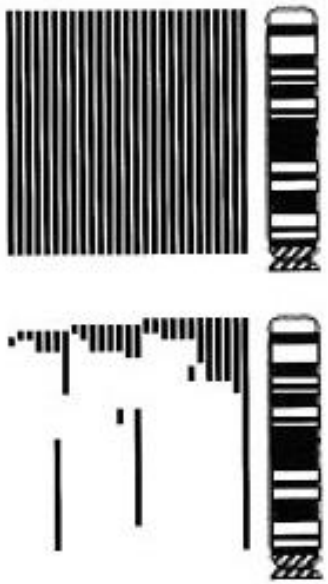
14 ans vs 7 ans



Cairncross et al. JCO 2012; van den Bent et al. JCO 2012

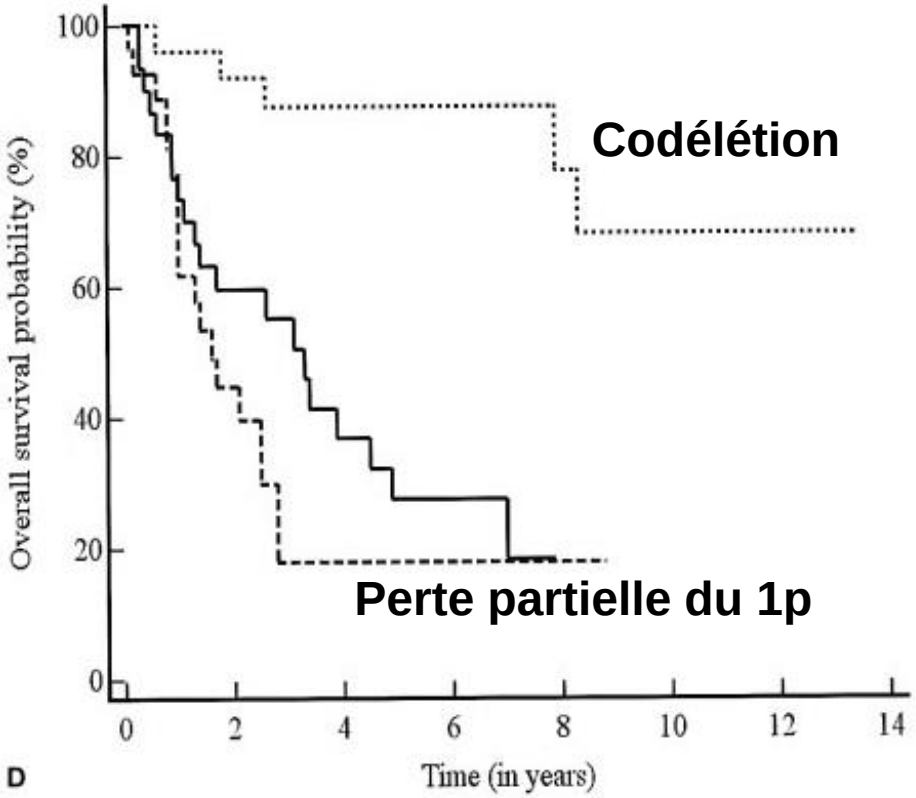
1p/19q codeletion

« Vraie » versus « fausse » codéletion



Perte complète

Perte partielle



Codélétion

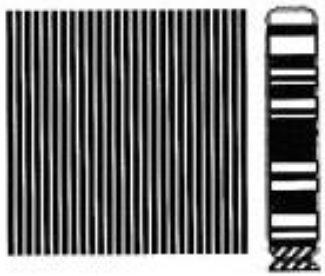
Perte partielle du 1p

Idbaih et al. Ann Neurol 2005; Idbaih et al. Int J Cancer 2008; Vogazianou et al. Neuro-Oncol 2010

1p/19q codeletion

« Vraie » versus « fausse » codélétion

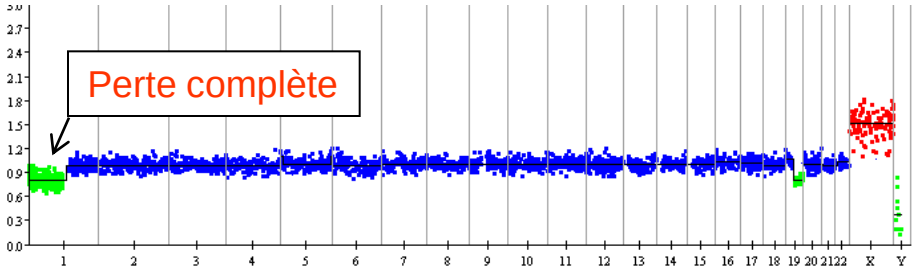
Chr 1p



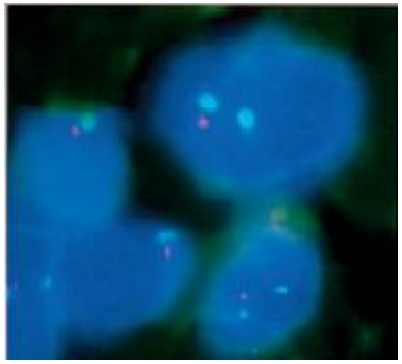
Perte complète

Perte partielle

Distinction « facile » en CGH array



Plus difficile en FISH



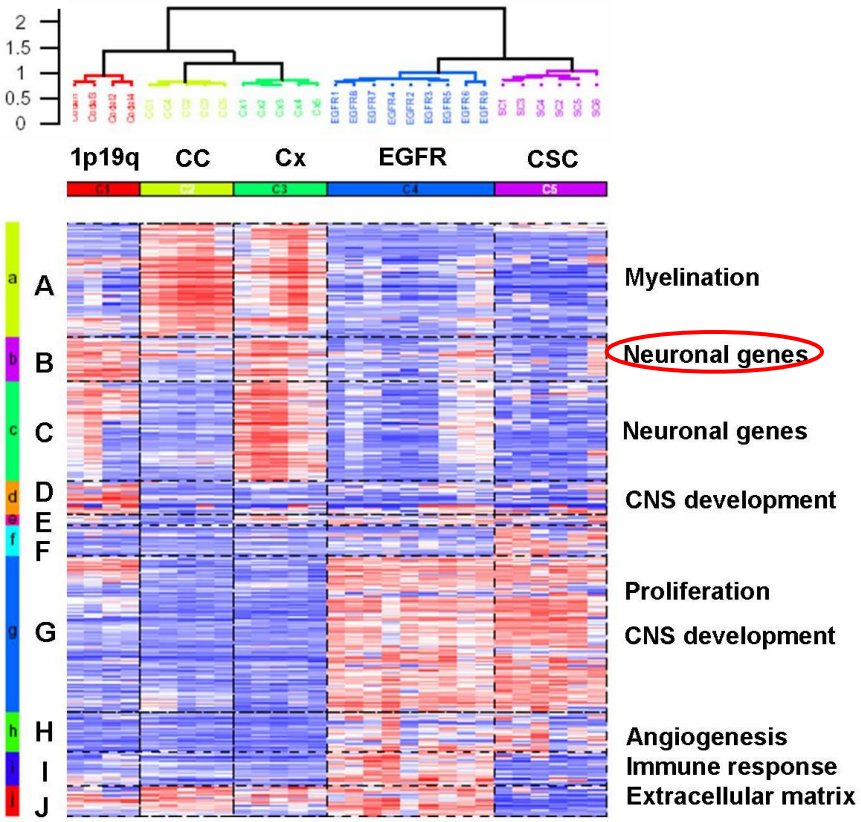
FISH
2 sonde
1p36
1q24

Perte complète ? Perte partielle ?

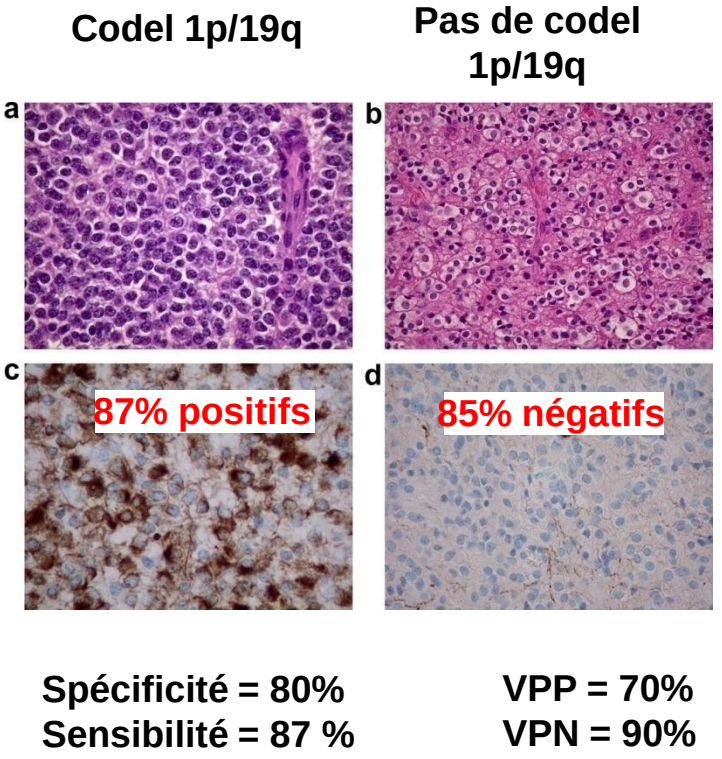
Idbaih et al. Ann Neurol 2005; Idbaih et al. Int J Cancer 2008; Vogazianou et al. Neuro-Oncol 2010

La codélétion 1p/19q

Associée à l'expression de gènes neuronaux



IHC anti-internexine alpha



Spécificité = 80%
Sensibilité = 87 %

VPP = 70%
VPN = 90%

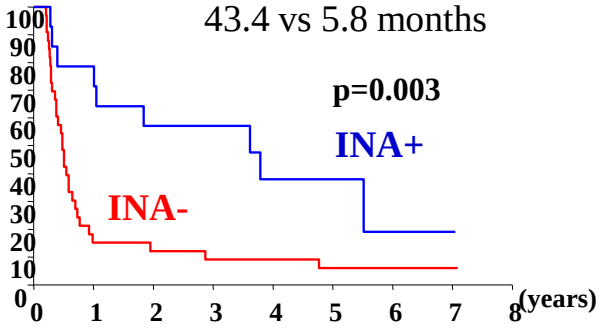
Ducray et al. Mol Cancer 2008; Ducray et al. Neurology 2009

La codélétion 1p/19q

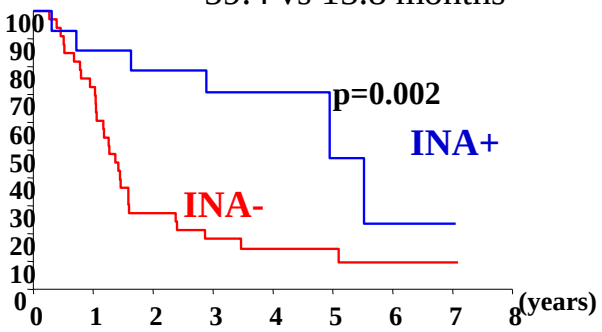
Intérêt de l'immunohistochimie anti-internexine alpha (INA)

RT

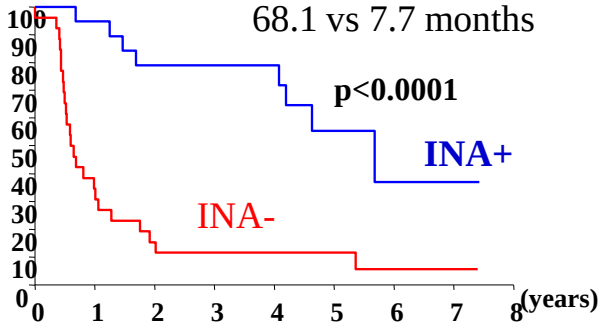
PFS

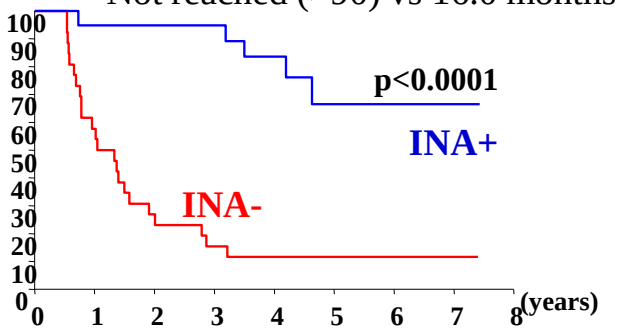


OS



RT-PCV



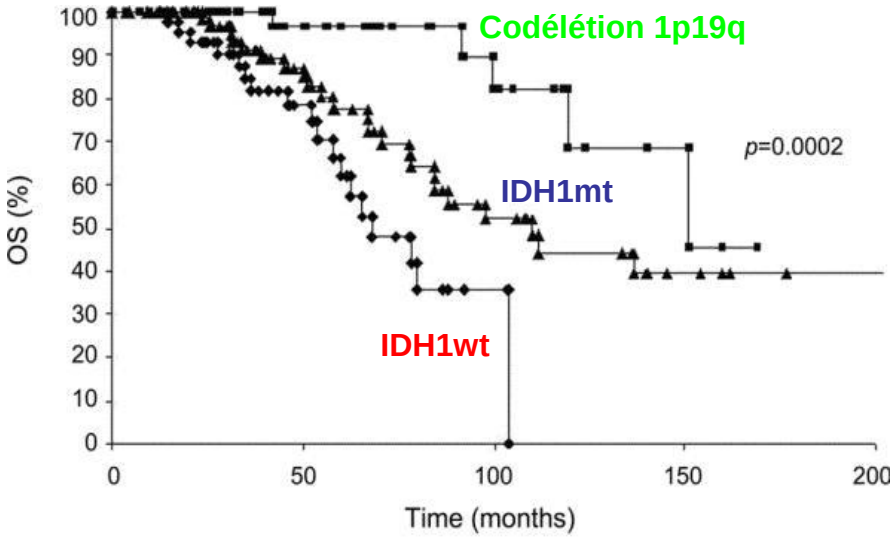


Ducray et al. Eur J Cancer 2011; Mokhtari et al. Cancer 2011

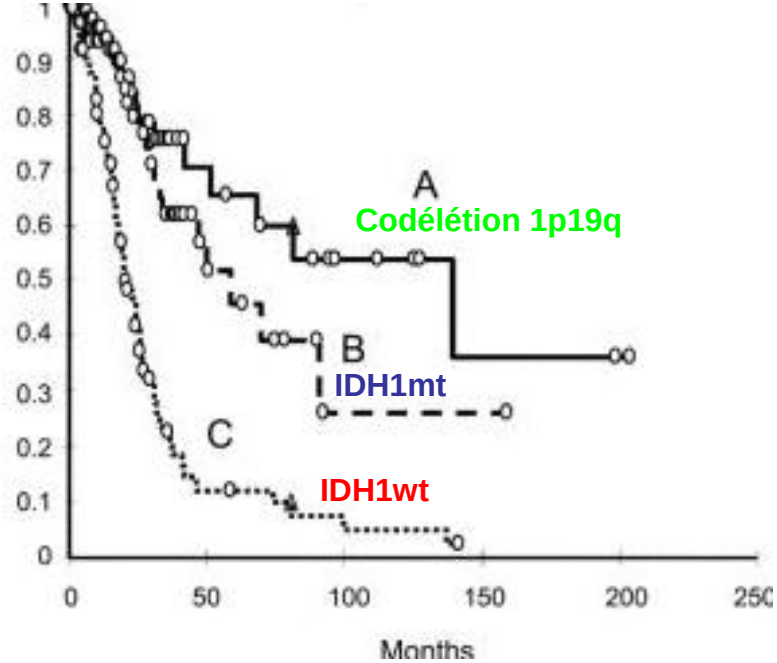
La codélétion 1p/19q

Marqueur pronostique indépendant des traitements dans les grades II et III

Grade II

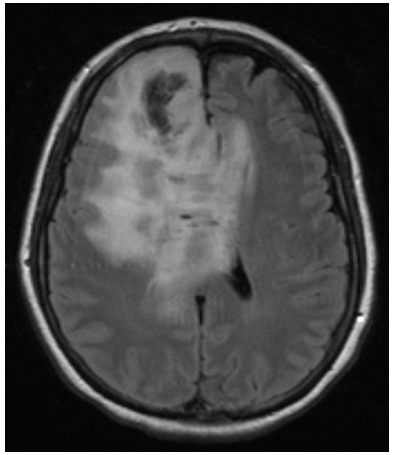


Grade III



Houillier et al. Neurology 2010, Labussiere et al. Neurology 2010

Essais cliniques selon le statut 1p/19q



65 ans

Oligo. grade III

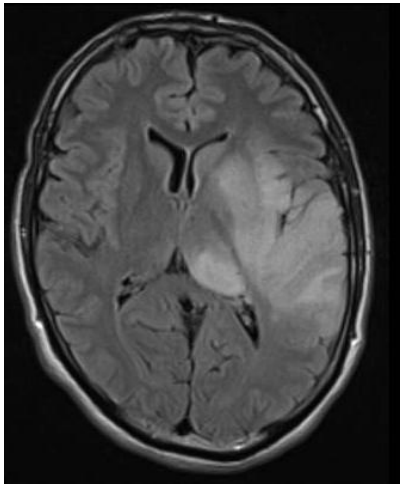
<u>Codélétion 1p/19q</u>

<u>Mutation IDH1</u>

Survie médiane > 10 ans

Problématique = neurotoxicité potentielle de la RT

→ Chimiothérapie première ?



50 ans

Oligo-astro grade III

<u>Pas de codélétion 1p/19q</u>

<u>Pas de mutation IDH1</u>

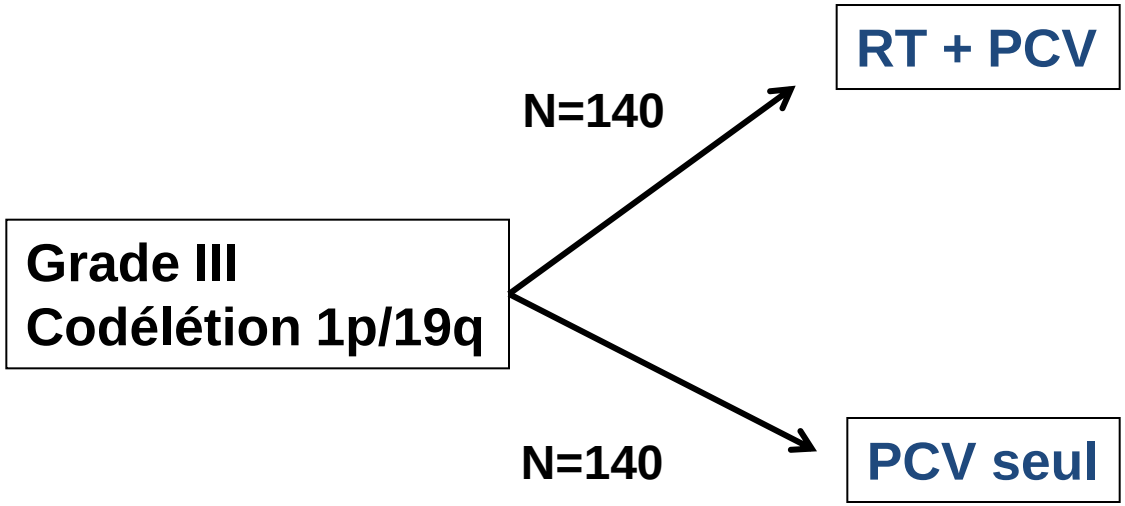
Survie médiane = 1,5 ans

Problématique = insuffisance du traitement classique des grades III (RT seule)

→ Essai RT + Témo. comme GBM

POLCA (**P**CV **O**n**L**y for **C**odeleted **A**naplastic gliomas)

Réseau POLA (Prise en charge des OLigo. Anaplasiques)

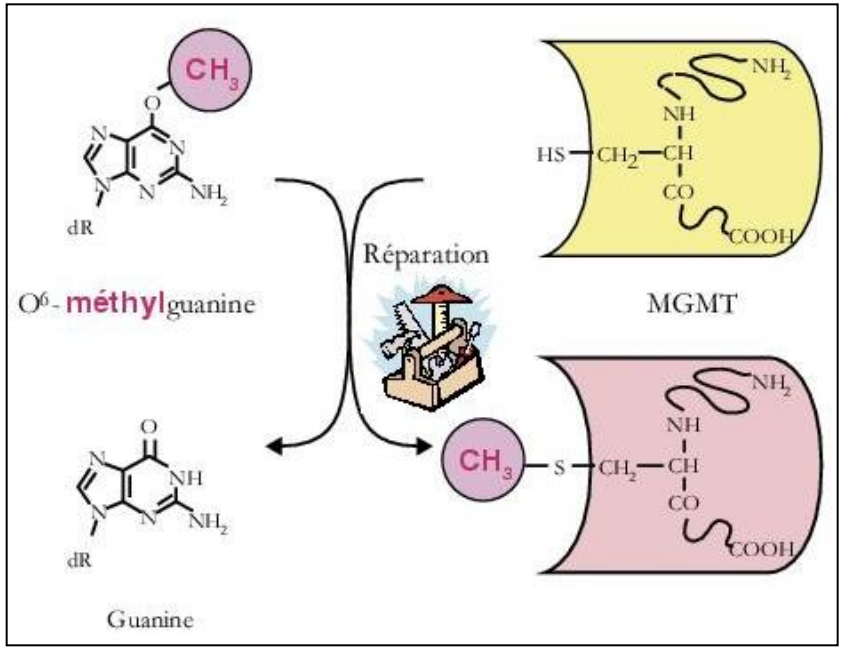


Objectif principal:

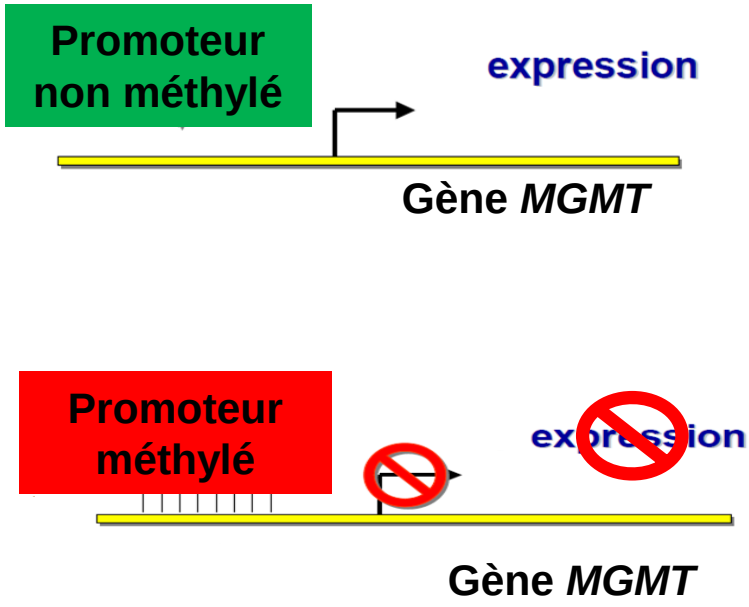
Montrer que commencer par la CT seule permet d'augmenter la survie sans détérioration cognitive

Méthylation de MGMT

Méthylguanine Méthyltransférase



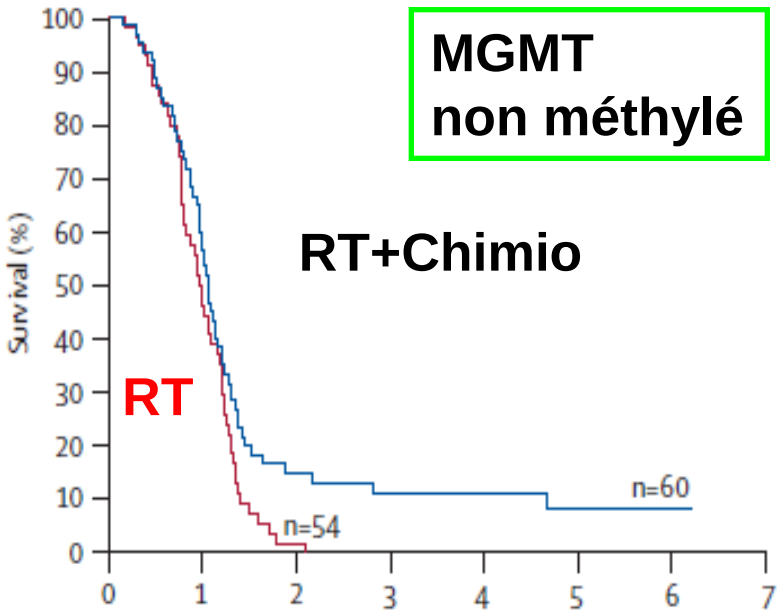
S'oppose à l'action des alkylants

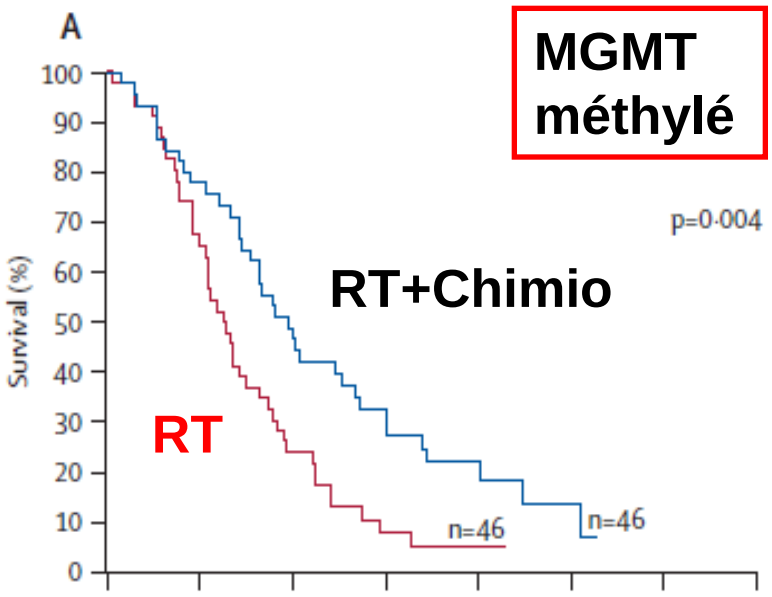


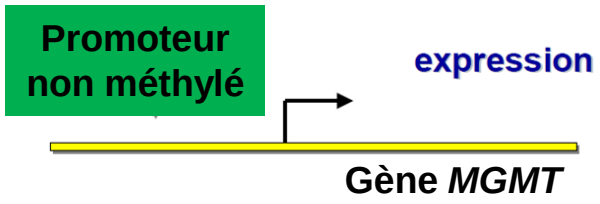
Hegi et al. Bull Cancer 2007

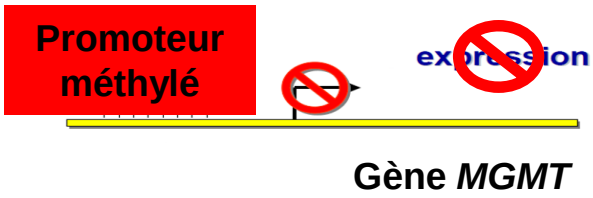
Méthylation de MGMT

Marqueur de chimiosensibilité dans les GBM





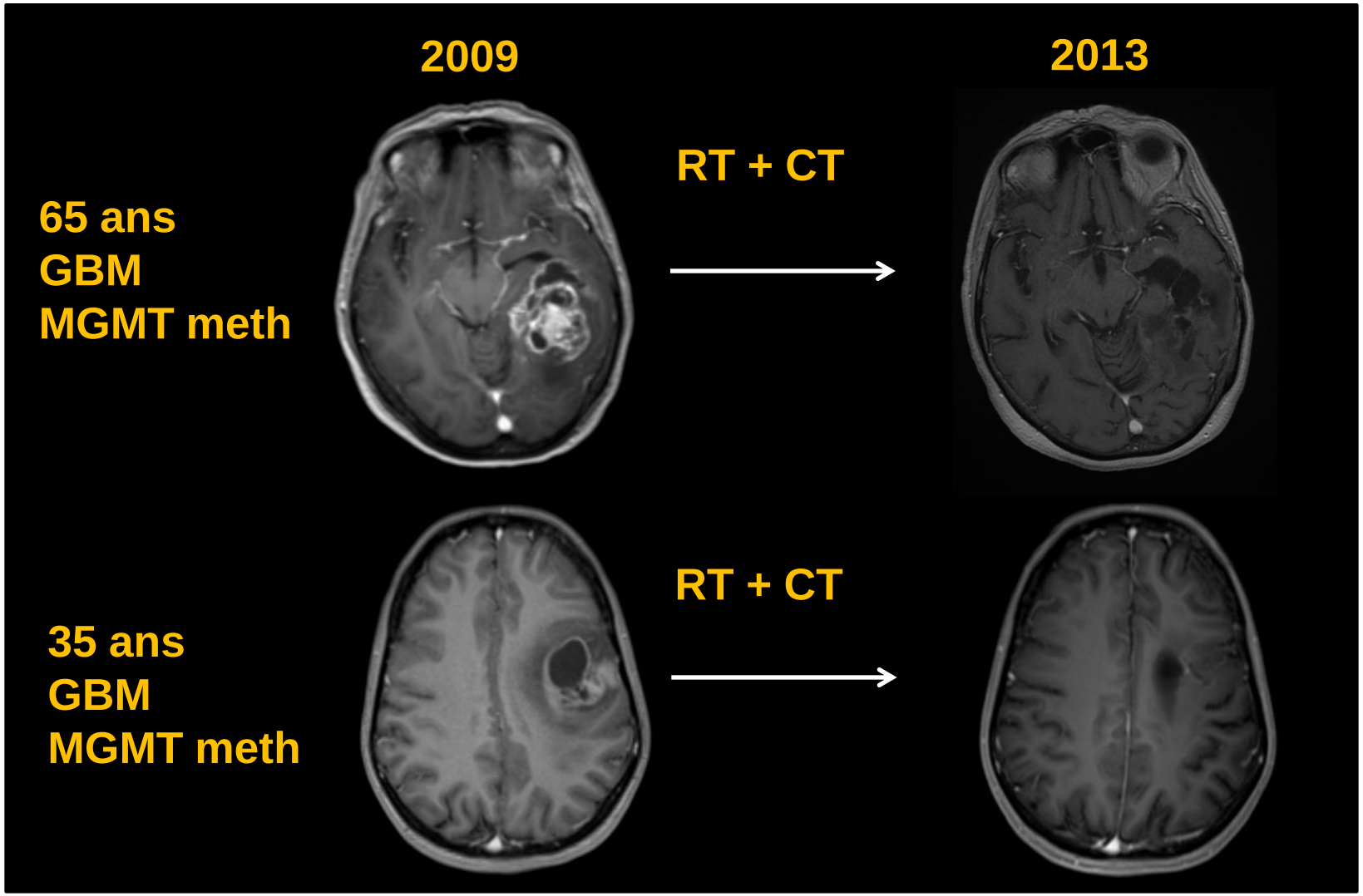




Hegi et al. NEJM 2005; Stupp et al. Lancet Oncol 2009

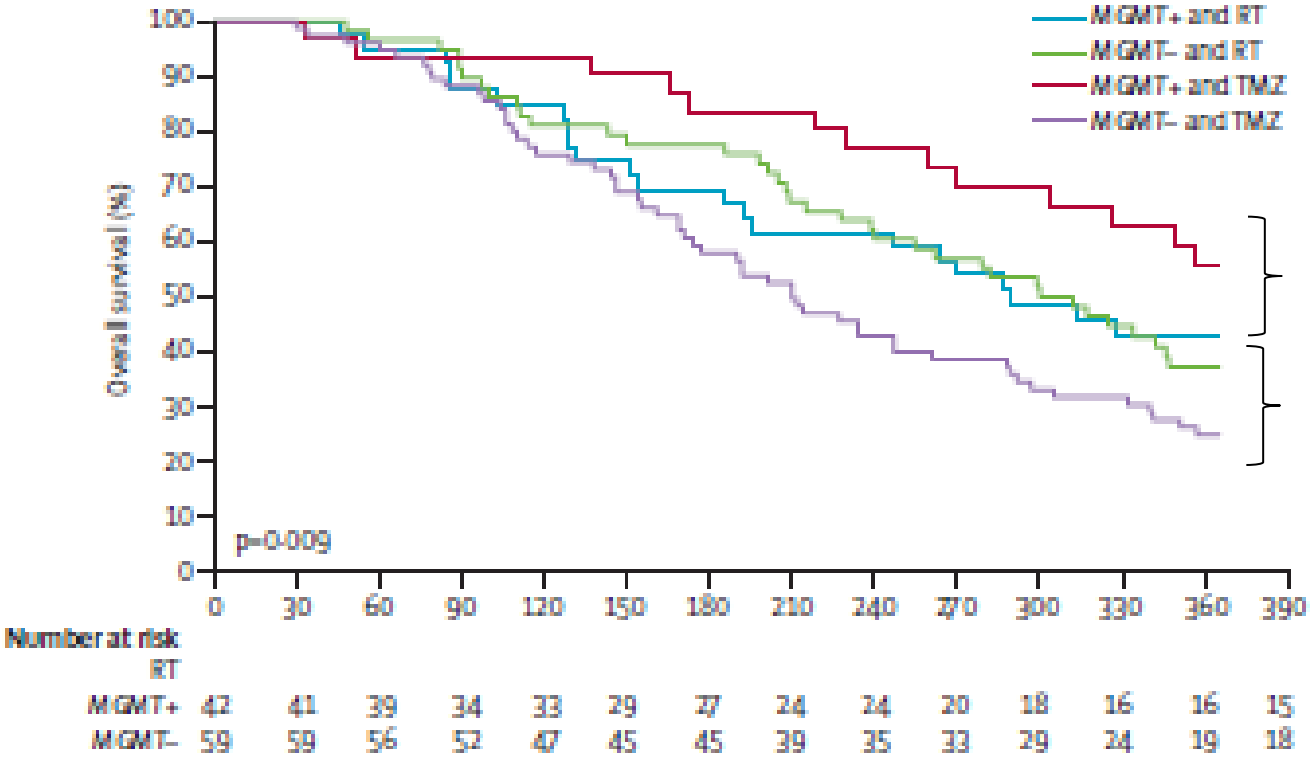
Méthylation de MGMT

Marqueur de chimiosensibilité dans les GBM



Méthylation de MGMT

Pourrait guider le traitement dans les GBM des sujets âgés



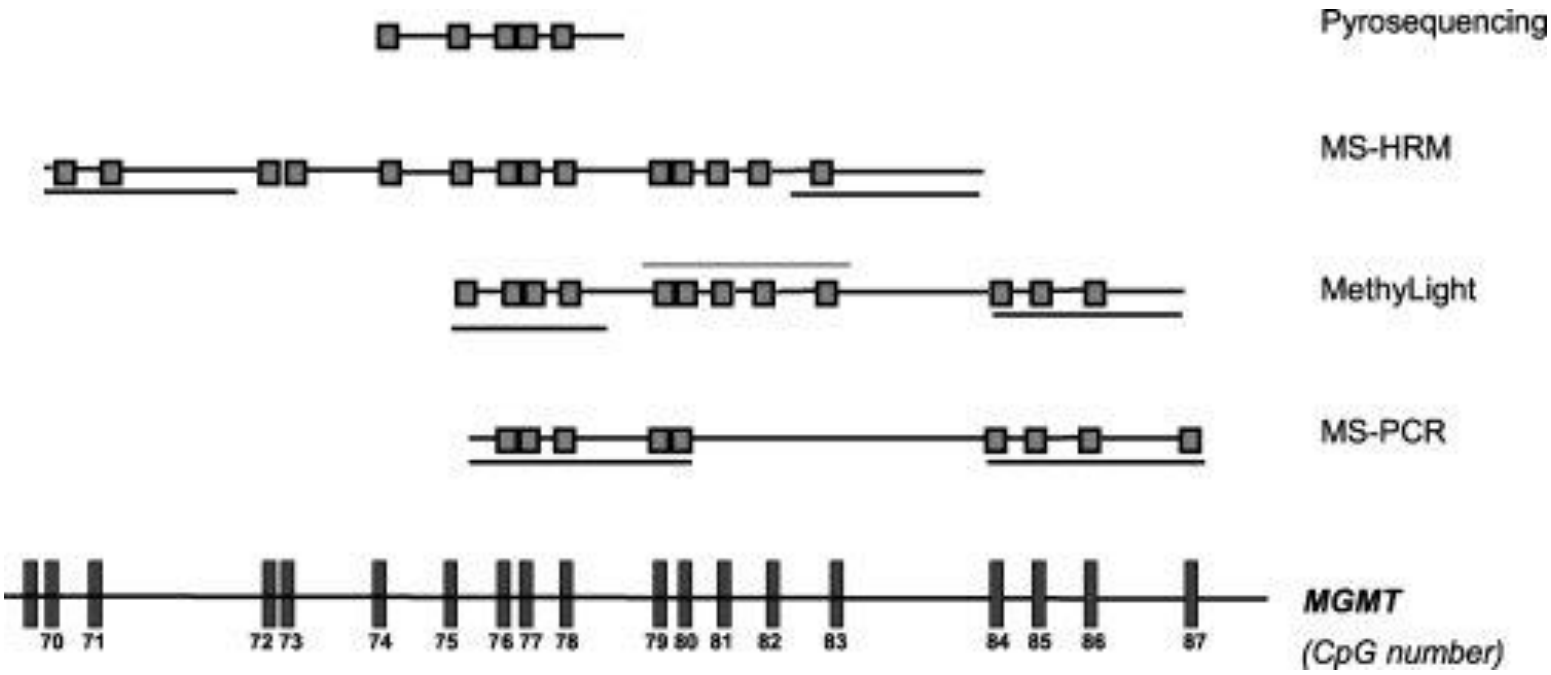
CT > RT si MGMT+

RT > CT si MGMT-

Wick et al. Lancet Oncol 2012

Méthylation de MGMT

Difficultés: 30 à 60% de patients méthylés selon la technique

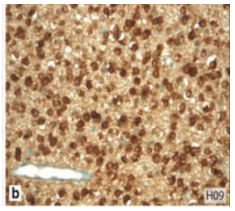


Quillien et al. Cancer 2012

Biomarqueurs des gliomes

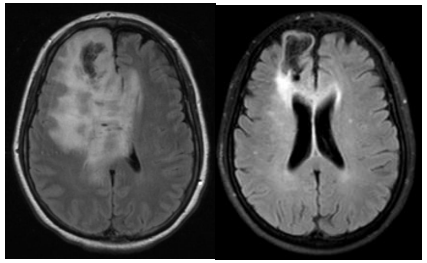
Synthèse en 2014

Un marqueur diagnostique:



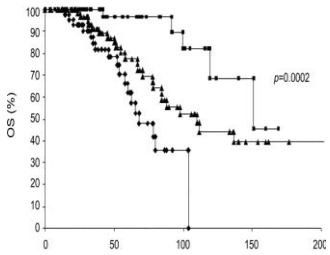
mutation d'IDH1 (présente = gliome)

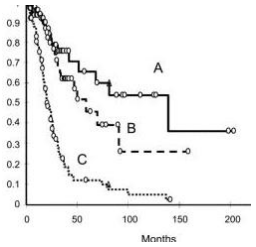
Deux marqueurs de chimio-sensibilité:

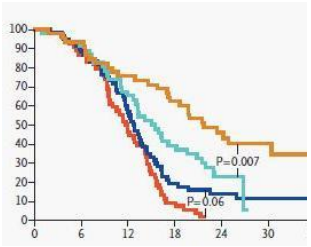


codélétion 1p/19q (grades 2 et 3)
méthylation MGMT (GBM)

Trois marqueurs pronostiques:



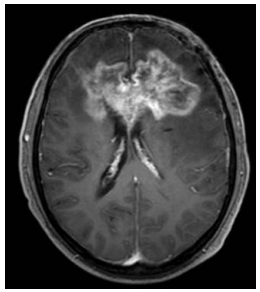




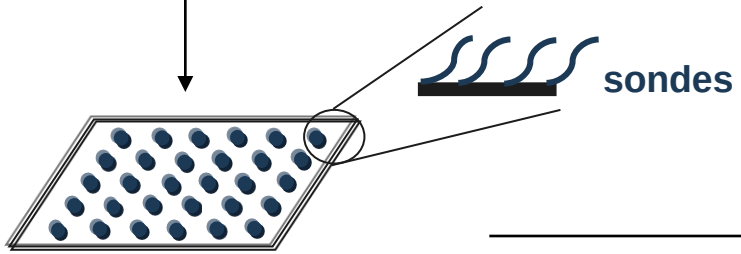
mutation d'IDH1 (grades 2, 3, 4)
codélétion 1p/19q (grades 2 et 3)
méthylation MGMT (GBM)

Classification moléculaire globale

Basée sur les études génomiques à haut débit

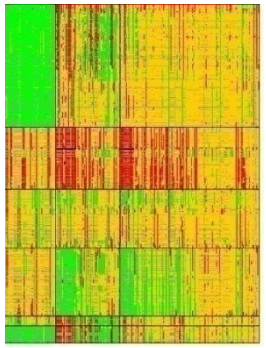


ADN ou **ARN**
marqués par un **fluorochrome**

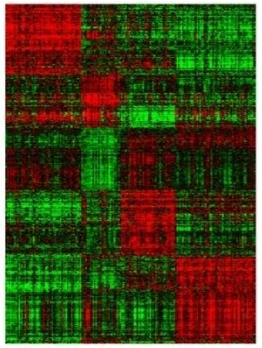


Classification moléculaire intégrée

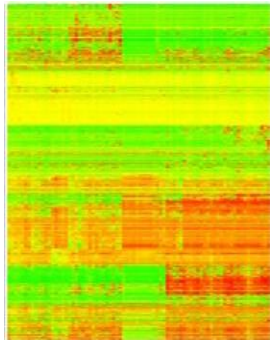
Classification génomique



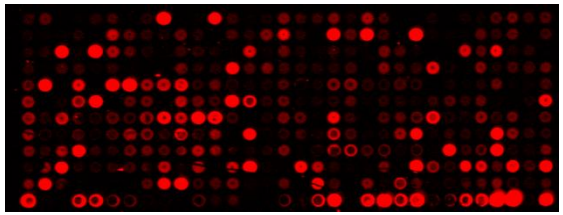
Classification transcriptomique



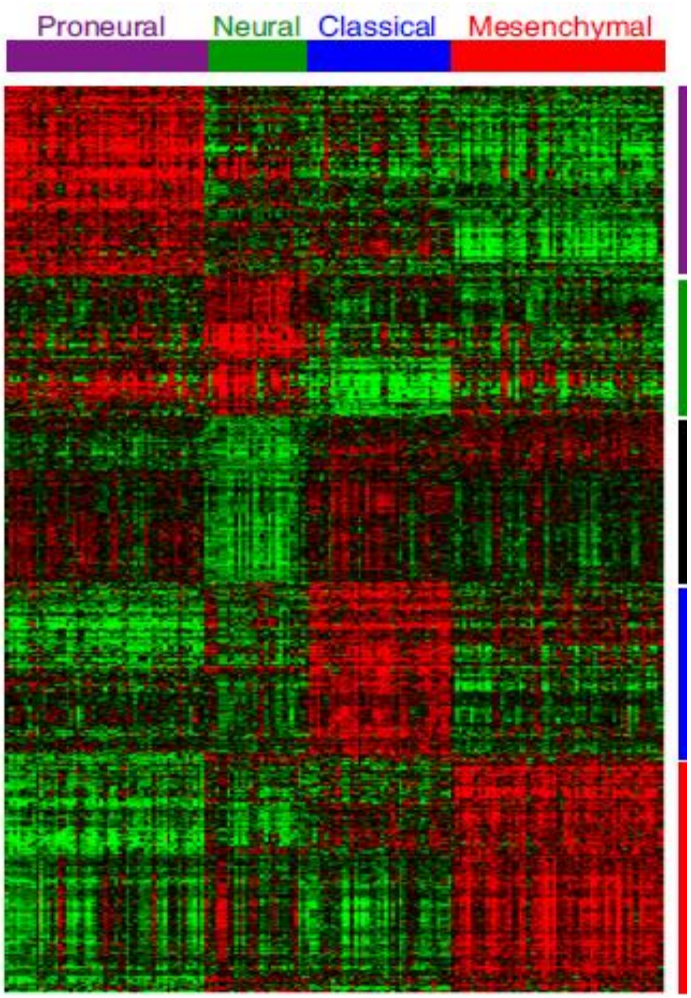
Classification épigénétique

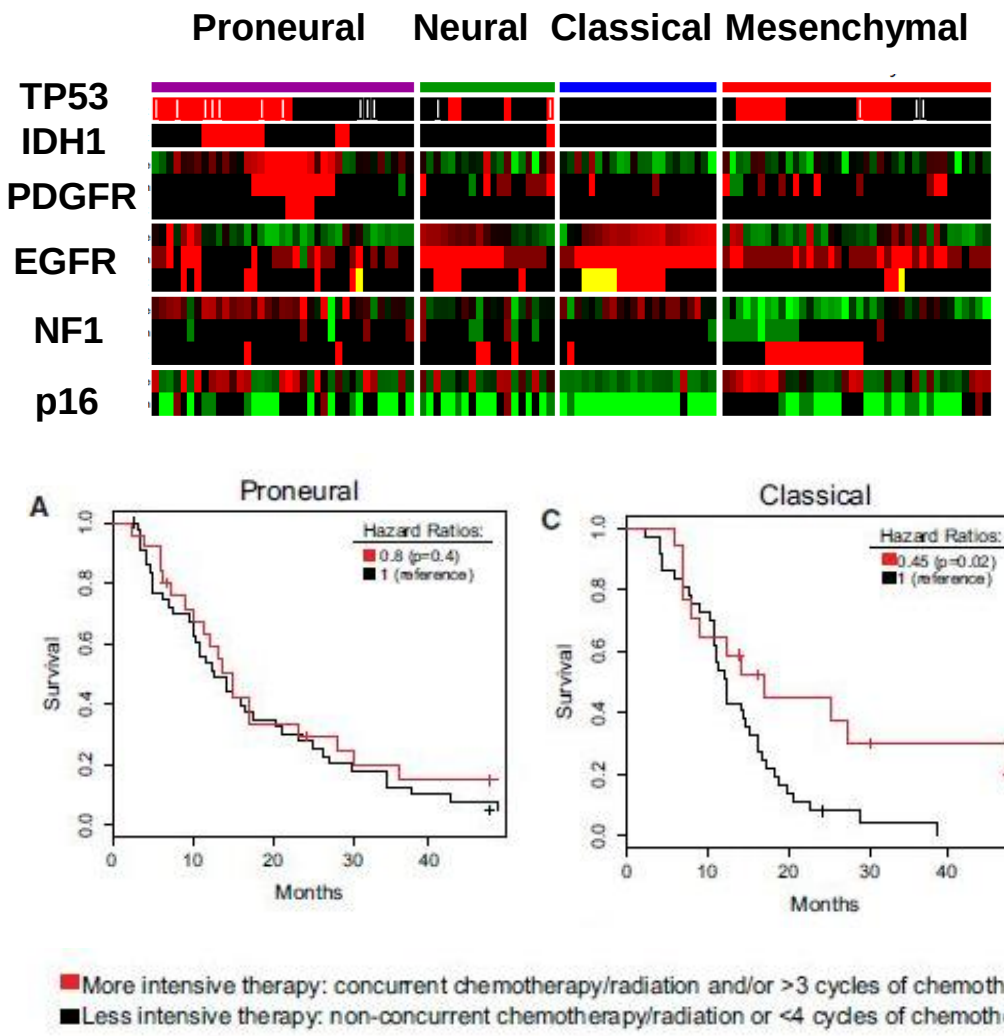


Vision globale génome / transcriptome / méthylome



Classification transcriptomique des GBM





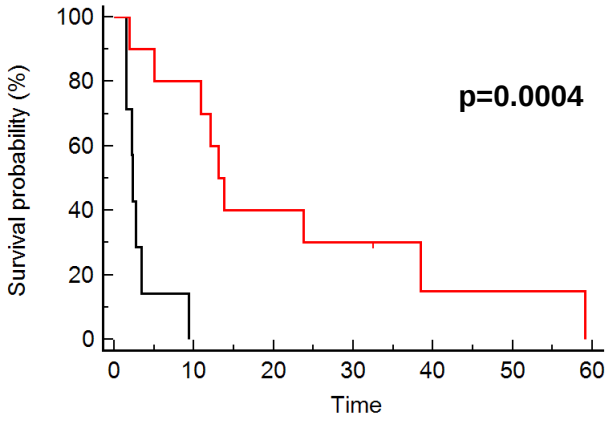
Verhaak et al. Cancer Cell 2010

Classification transcriptomique des GBM

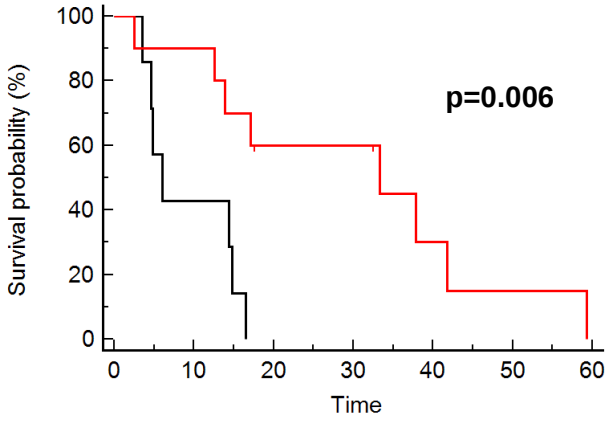
Valeur prédictive

GBM Mesenchym.

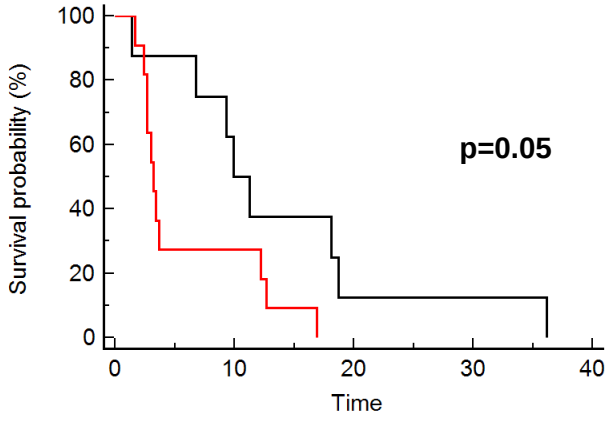
Survie sans progression

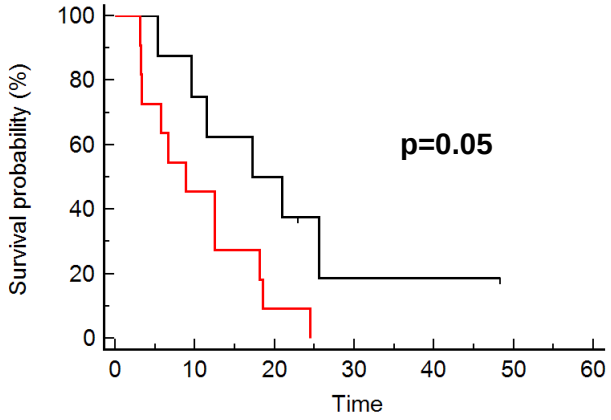


Survie globale



GBM Classiques





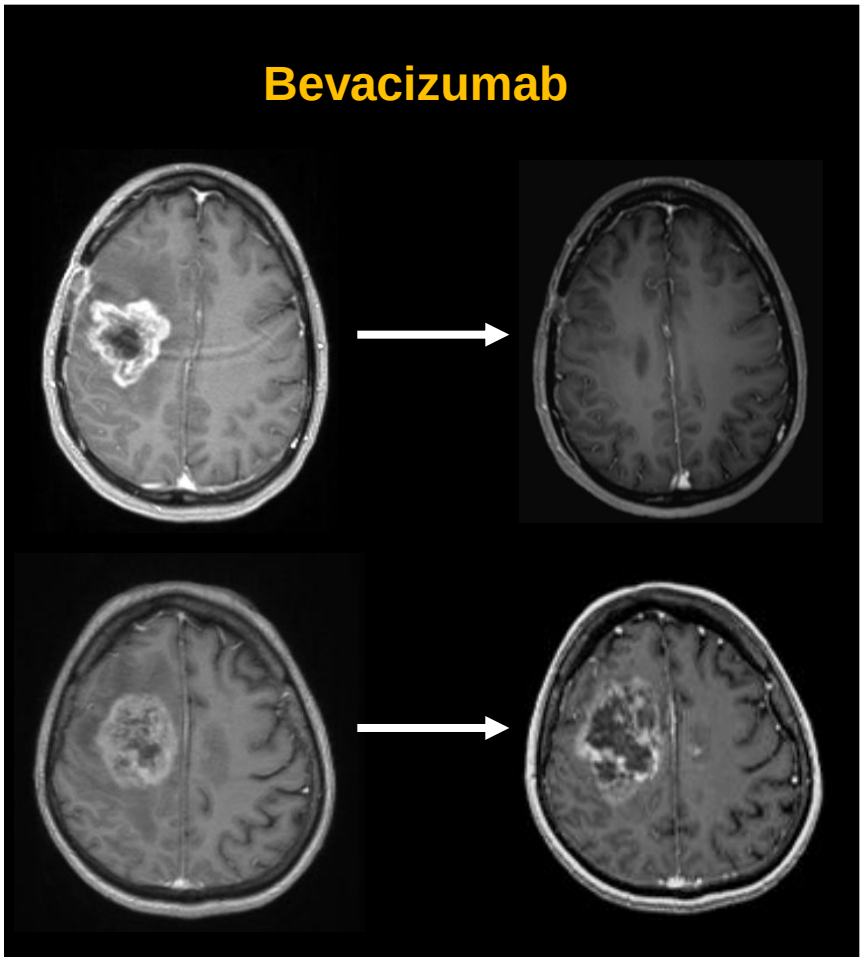
Radiotherapy ——

Chemotherapy ——

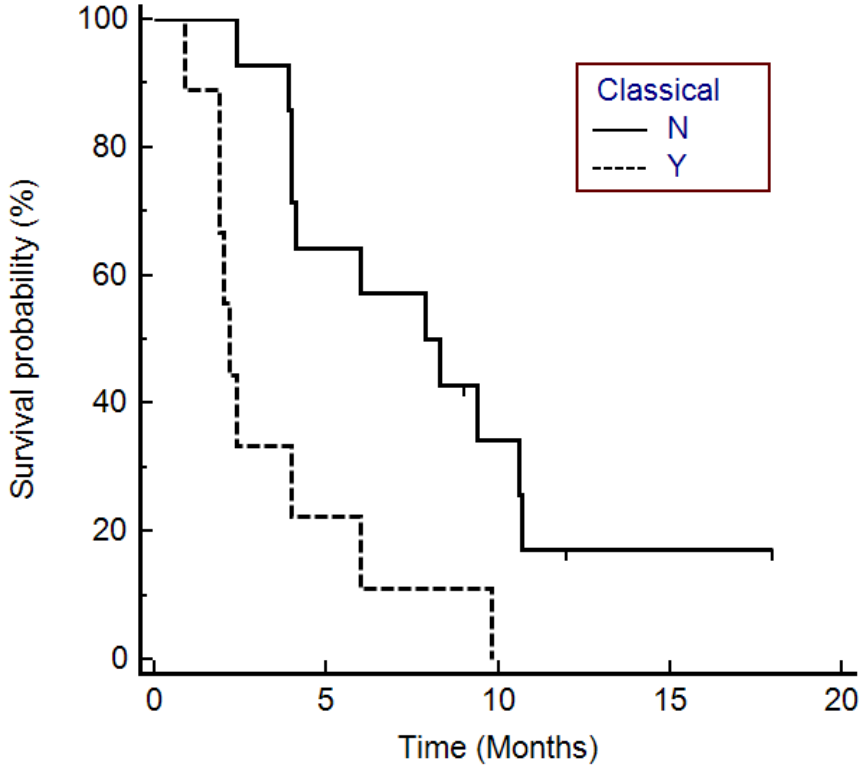
Ducray et al. Mol Cancer 2010

Classification transcriptomique des GBM

Valeur prédictive



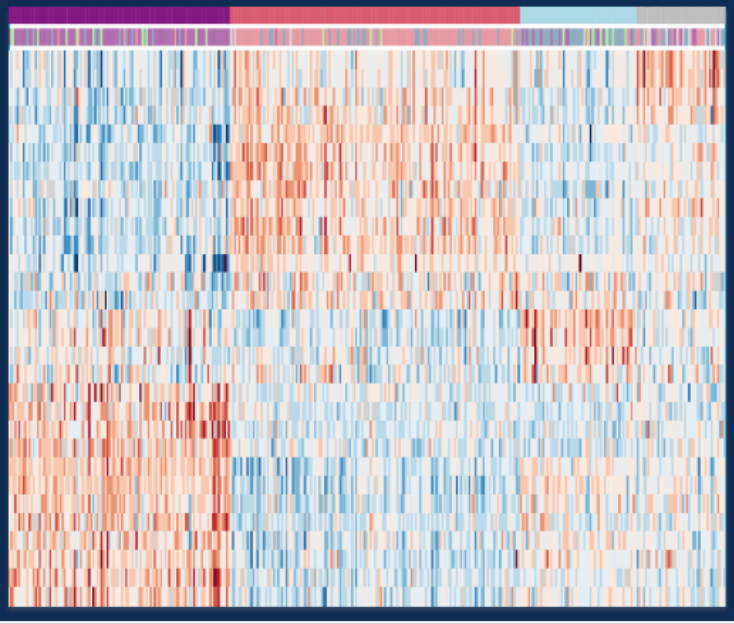
Durée de la réponse



Laffaire et al. BioMed Research International 2014

Classification transcriptomique des GBM

Laquelle chosir ?

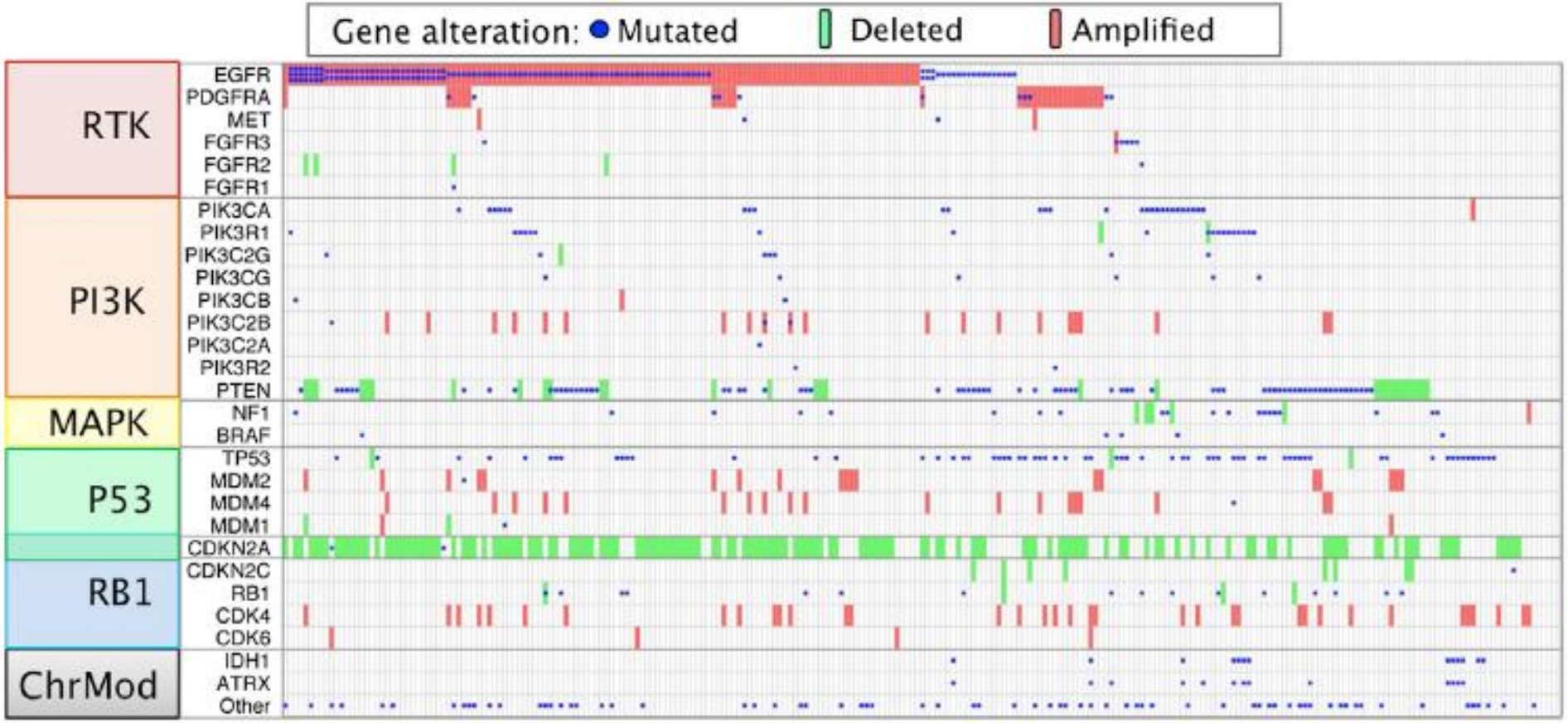


Subtype by Verhaak *et al*, 2010 (TCGA)[2]	Subtype by Phillips *et al*, 2006[1]			
	Proneural	Mesenchymal	Proliferative	Unclassified
Proneural	79	1	13	8
Mesenchymal	6	109	3	14
Classical	12	24	33	10
Unclassified	0	3	1	11
Neural	11	4	7	0

9

[1]Phillips *et al*, Cancer Cell 2006
[2]Verhaak *et al*, Cancer Cell 2010

« Paysage moléculaire » des GBM



Brennan et al. Cell 2013