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Centre Eugène Marquis RENNES

Nouveautés en neuro-oncologie congrès ASCO, ESMO, SNO 2015

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UNICANCER
Groupe des Centres de Lutte Contre le Cancer

Plan

- Classification anatomo-pathologique OMS 2016
- Glioblastome
  - TTF
  - Bevacizumab-LOMUSTINE
  - Molécules ayant effet antitumoral?
  - Nouvelles molécules
- Métastatases cérébrales

Plan

- **Classification anatomo-pathologique OMS 2016**

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  - Nouvelles molécules

- Métastatases cérébrales

Intégration des altérations génétiques dans prise en charge

- **Gliome anaplasique :**
  - 2012: Mise à jour phase III : RTOG 9402 et EORTC 26951
    Codélétion 1p 19 q : RT + PCV > RT
  - 2014: Mutation IDH: RT + PCV > RT

Van den Bent, J Clin Oncol 2012; Caincross, J Clin Oncol 2012 et 2014

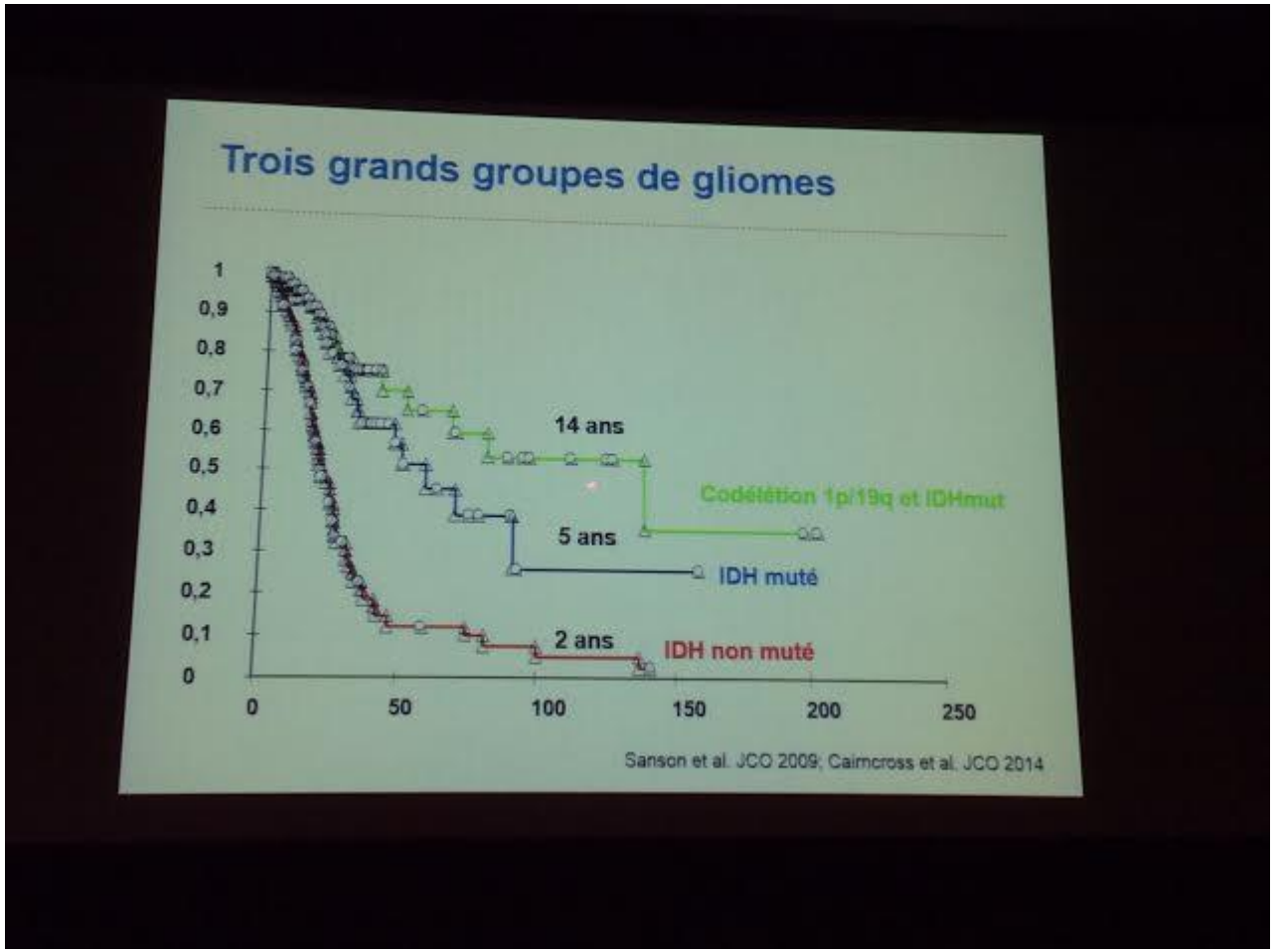
- **Gliome de bas grade :**
  - 2015: Sous-groupes pronostiques: IDH, codélétion, promoteur TERT…

Eckel-Passow NEJM 2015

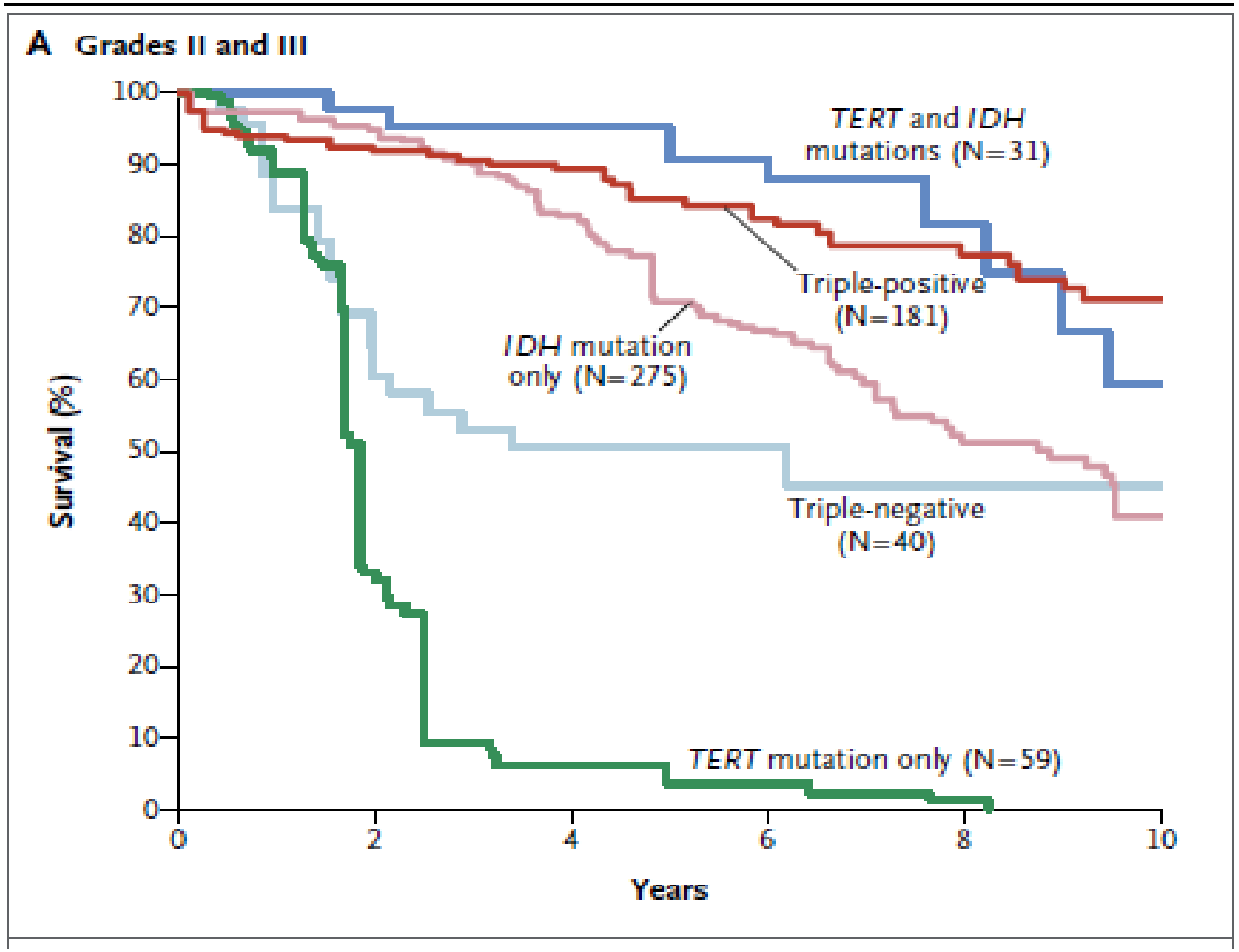
- **Glioblastome :**
  - 2016: Changement de classification diagnostique OMS

ESMO 2015

Gliomes anaplasiques

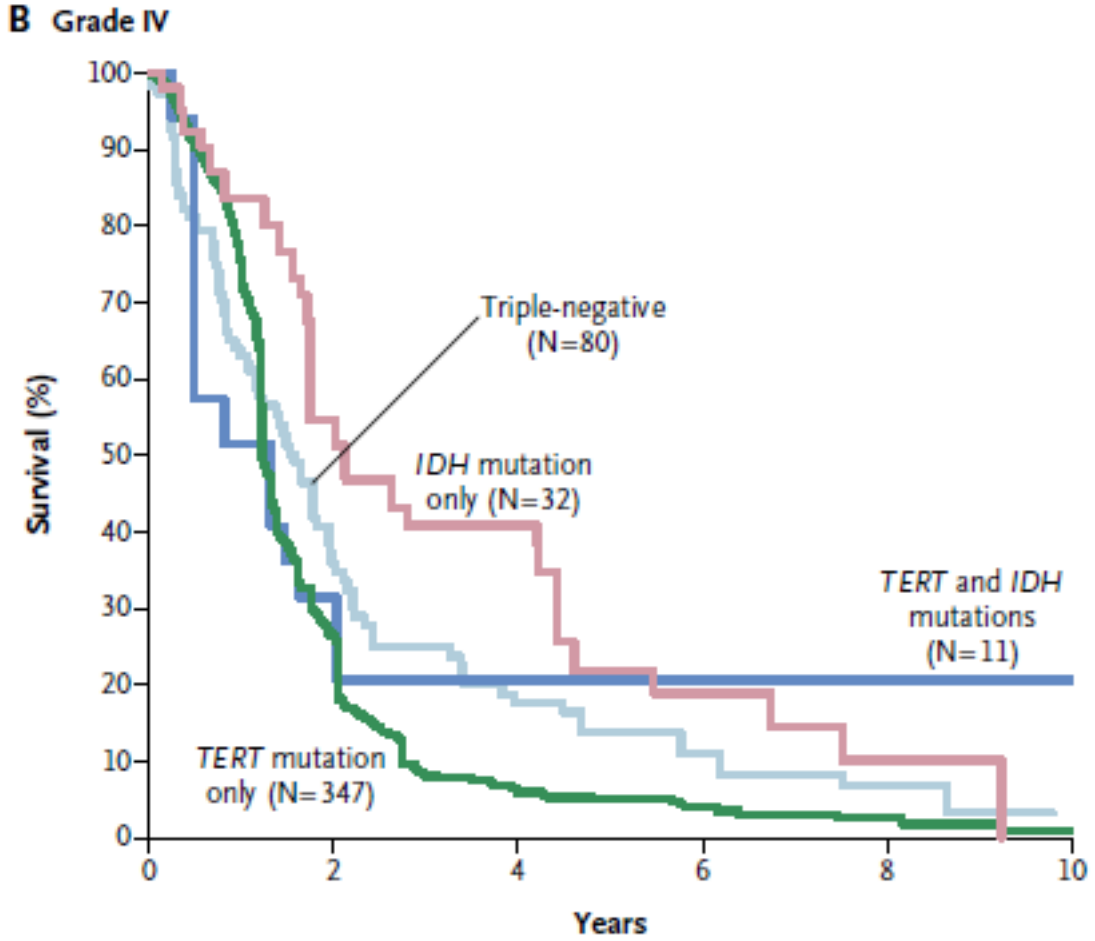


Gliomes de grade II et III



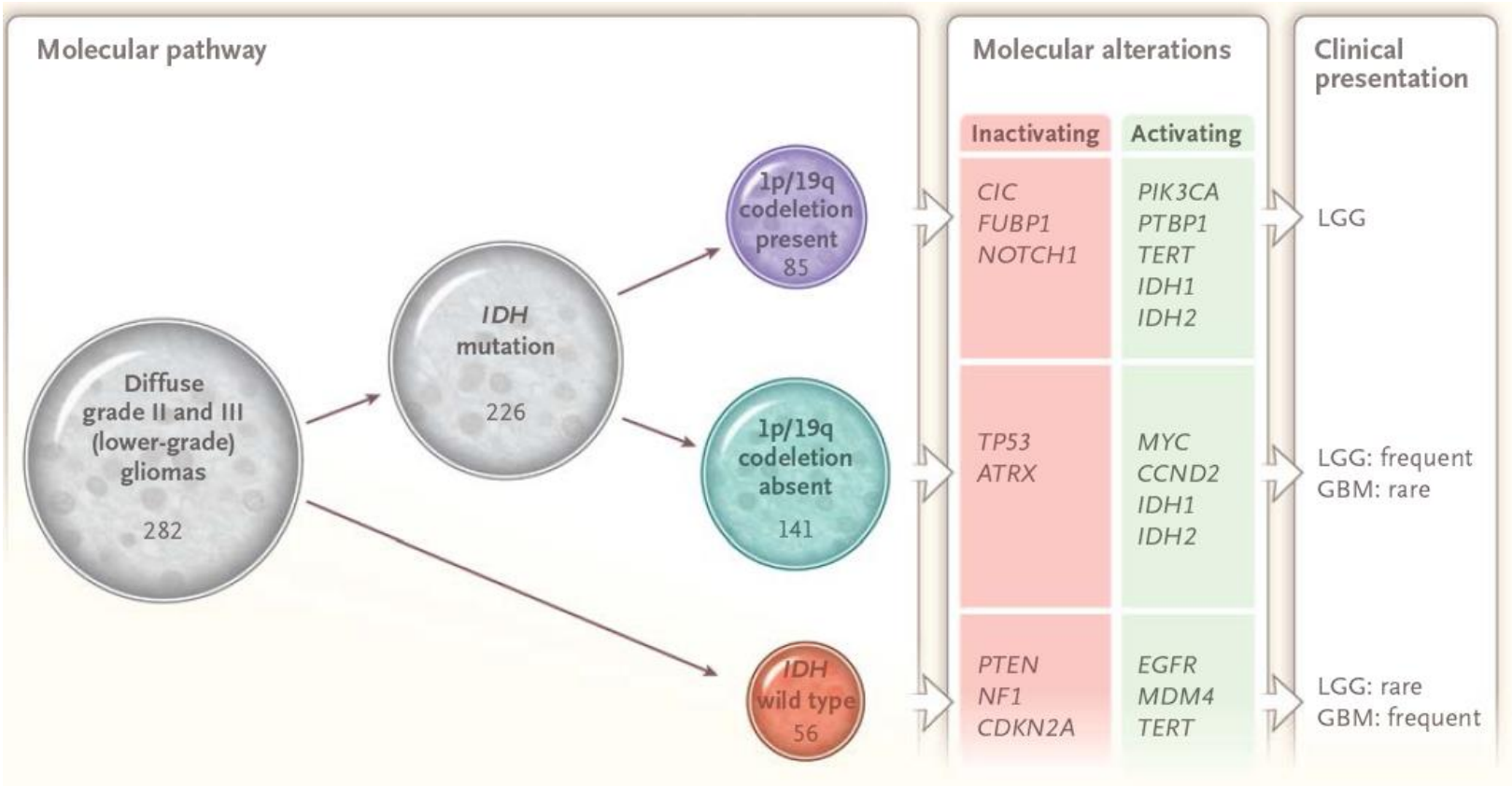
Eckel-Passow NEJM 2015

Glioblastomes



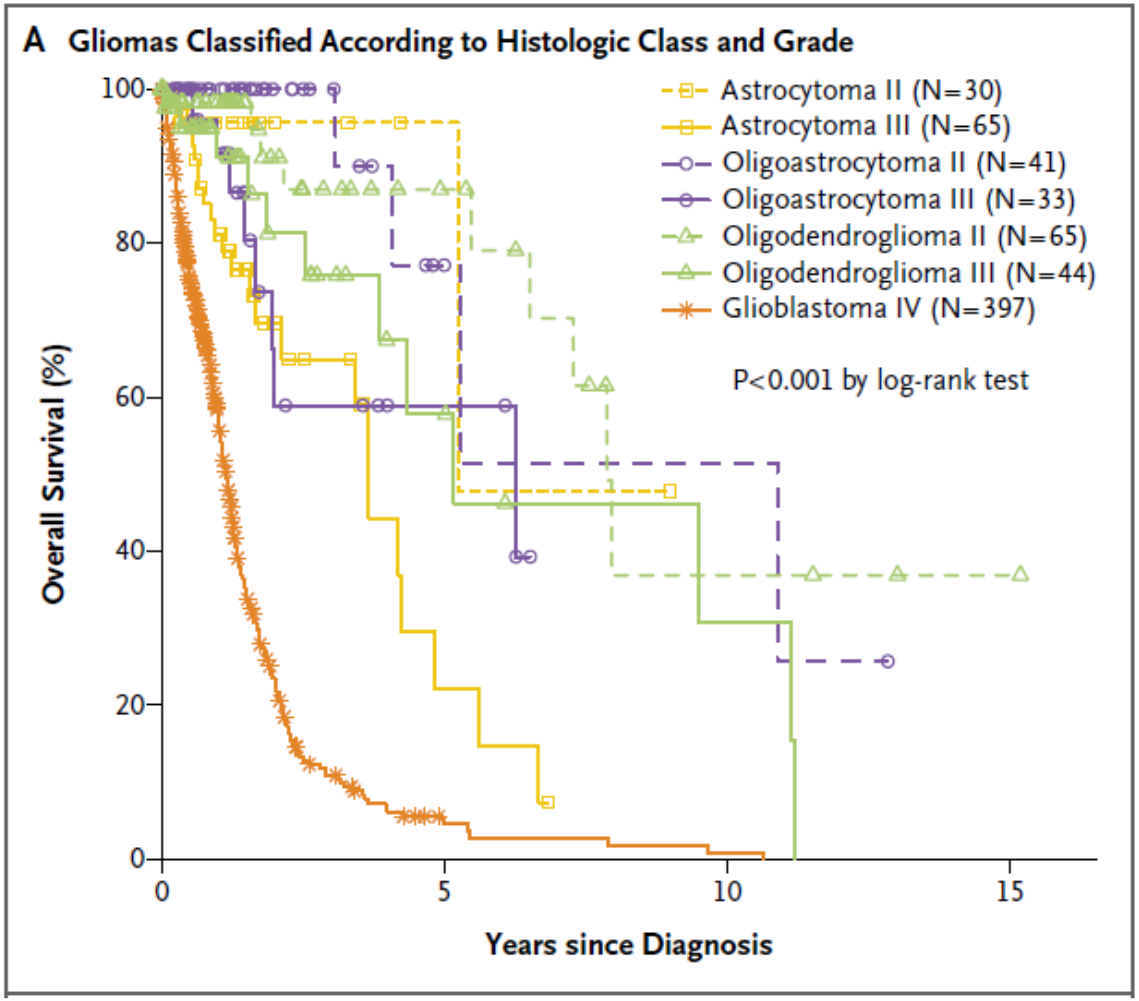
Eckel-Passow NEJM 2015

Gliomes: altérations moléculaires présentations cliniques



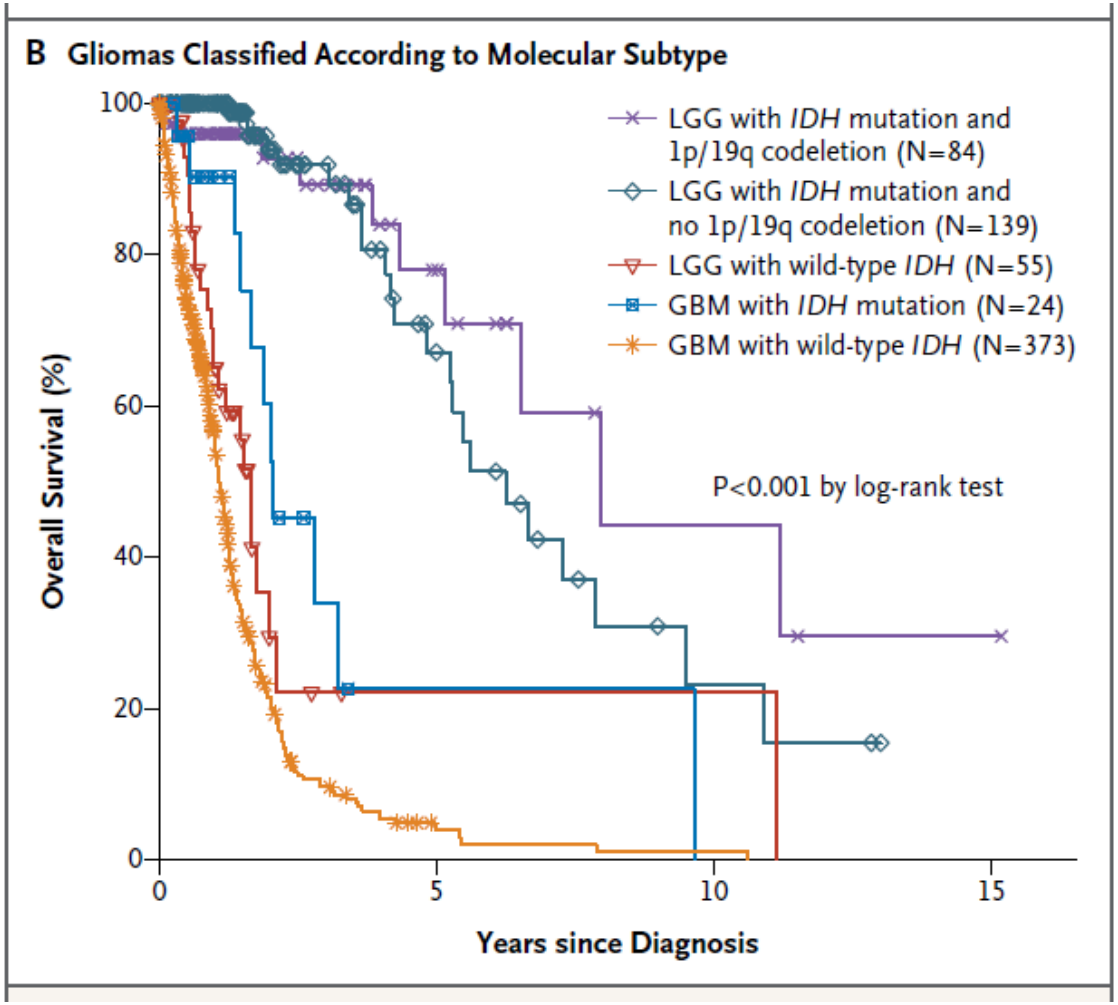
TCGA, NEJM 2015.

Survie globale des Gliomes histologie et grade



TCGA, NEJM 2015.

Survie globale des Gliomes sous-types moléculaires



TCGA, NEJM 2015.

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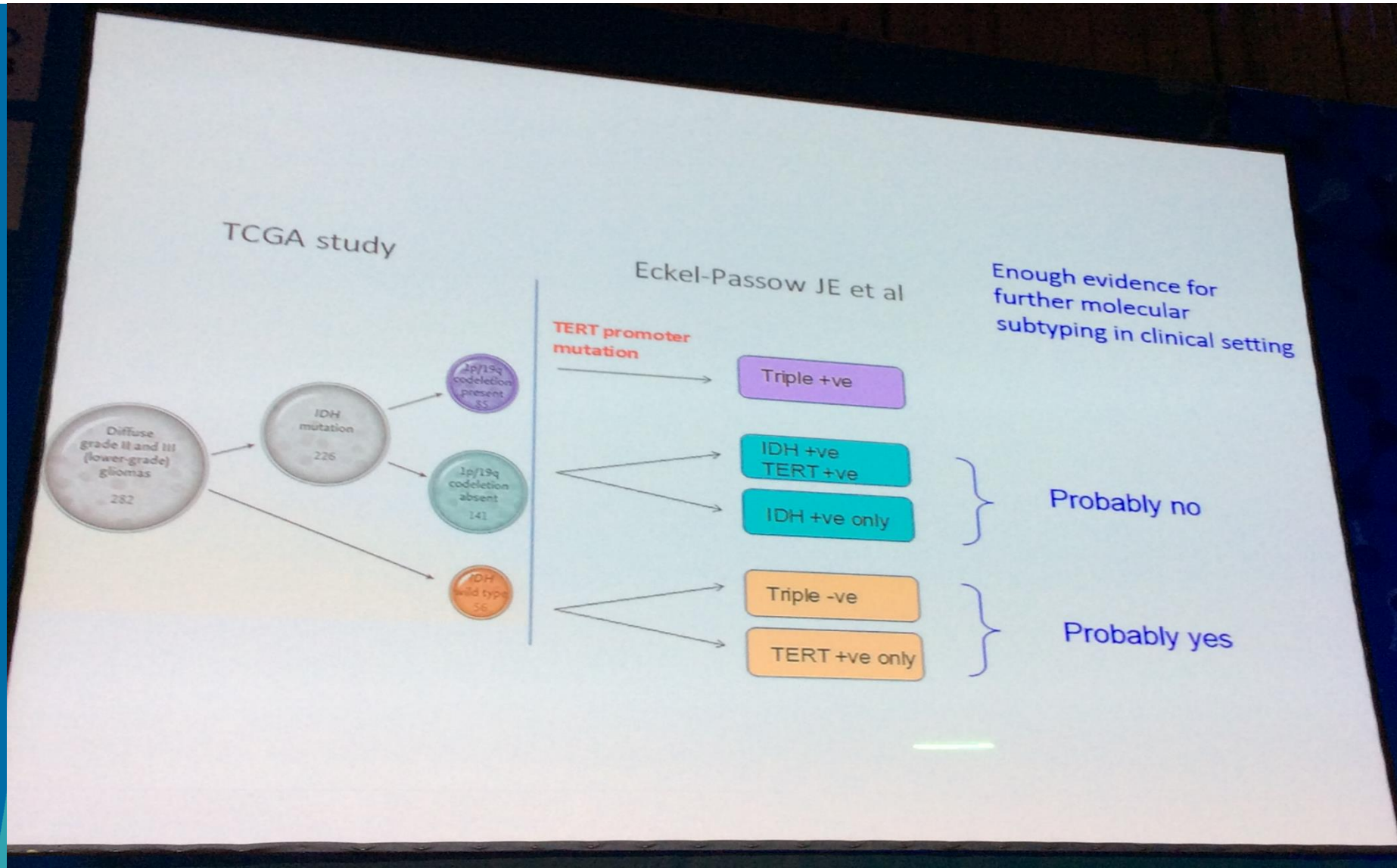
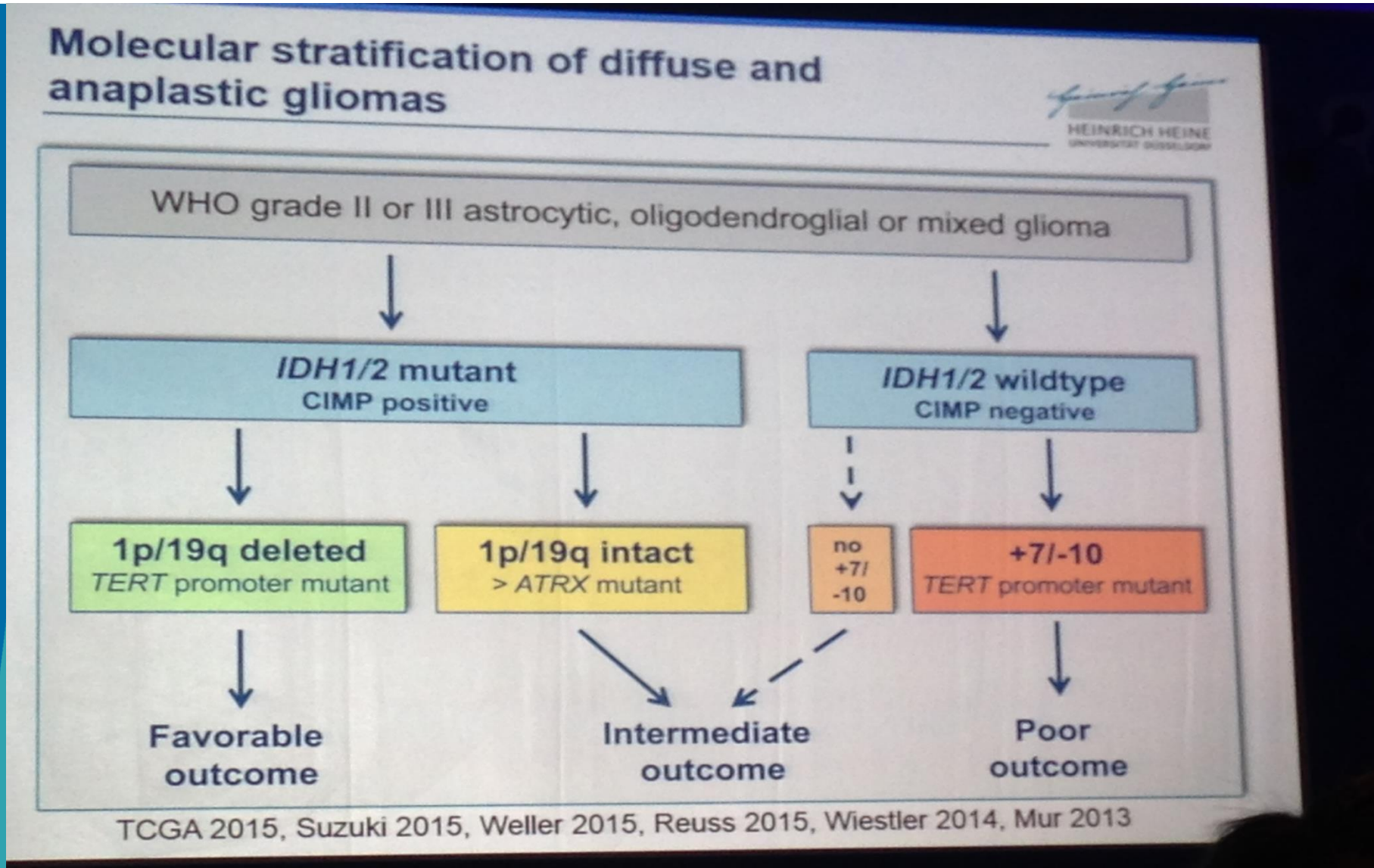
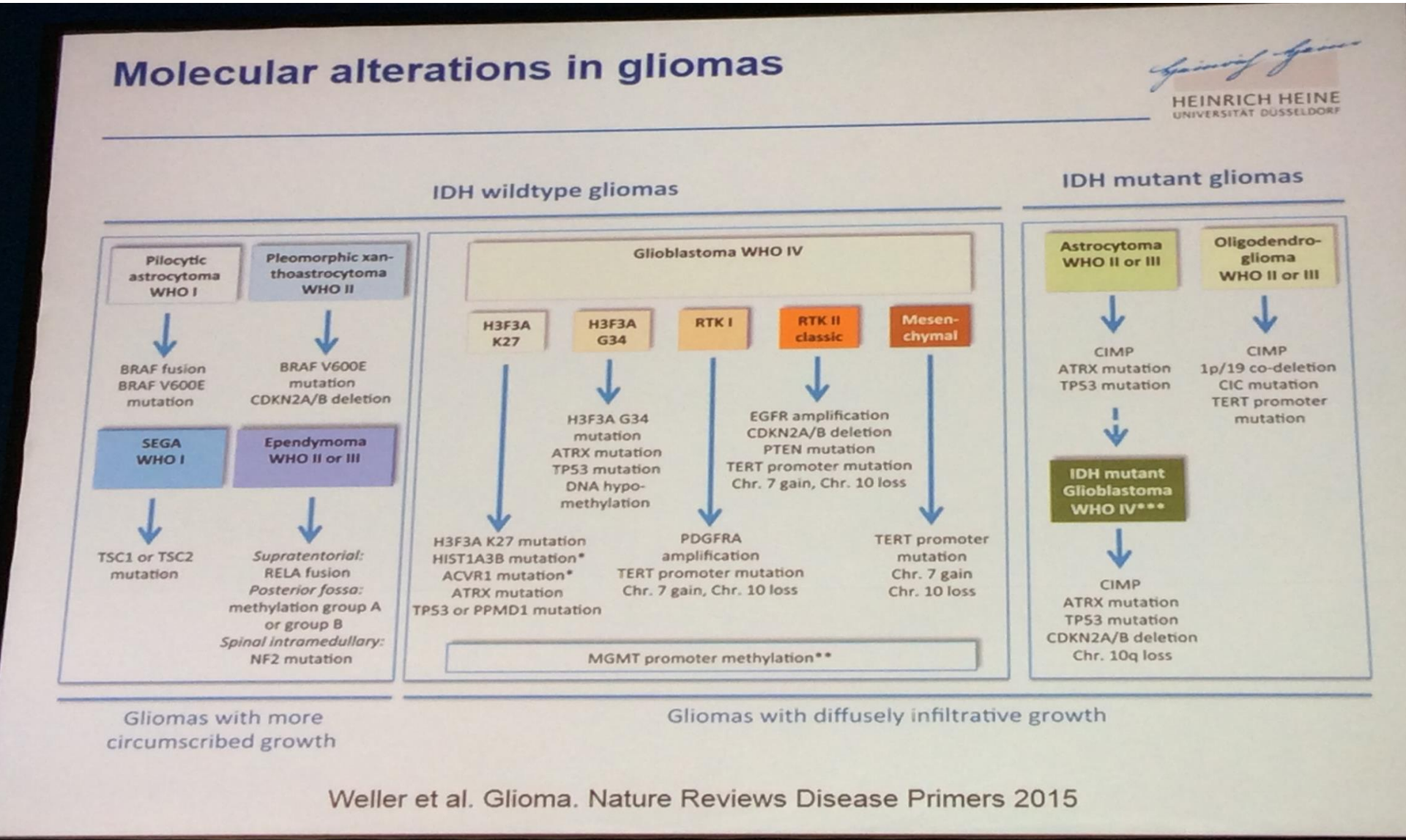
Changement de la classification diagnostique OMS



Gliomes grade II et III

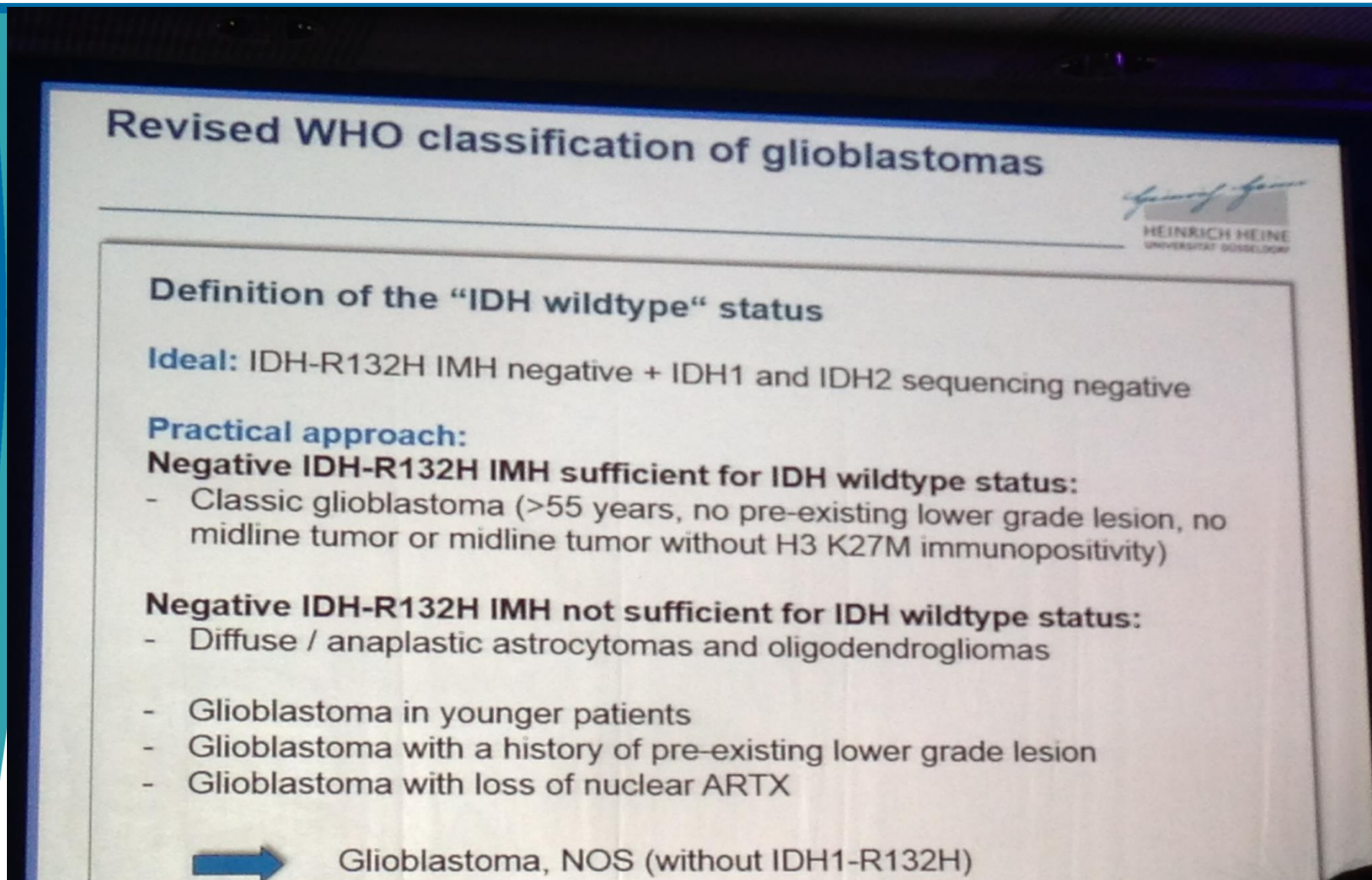


Nouvelles classifications moléculaires



Weller et al. Glioma. Nature Reviews Disease Primers 2015

Changement diagnostique

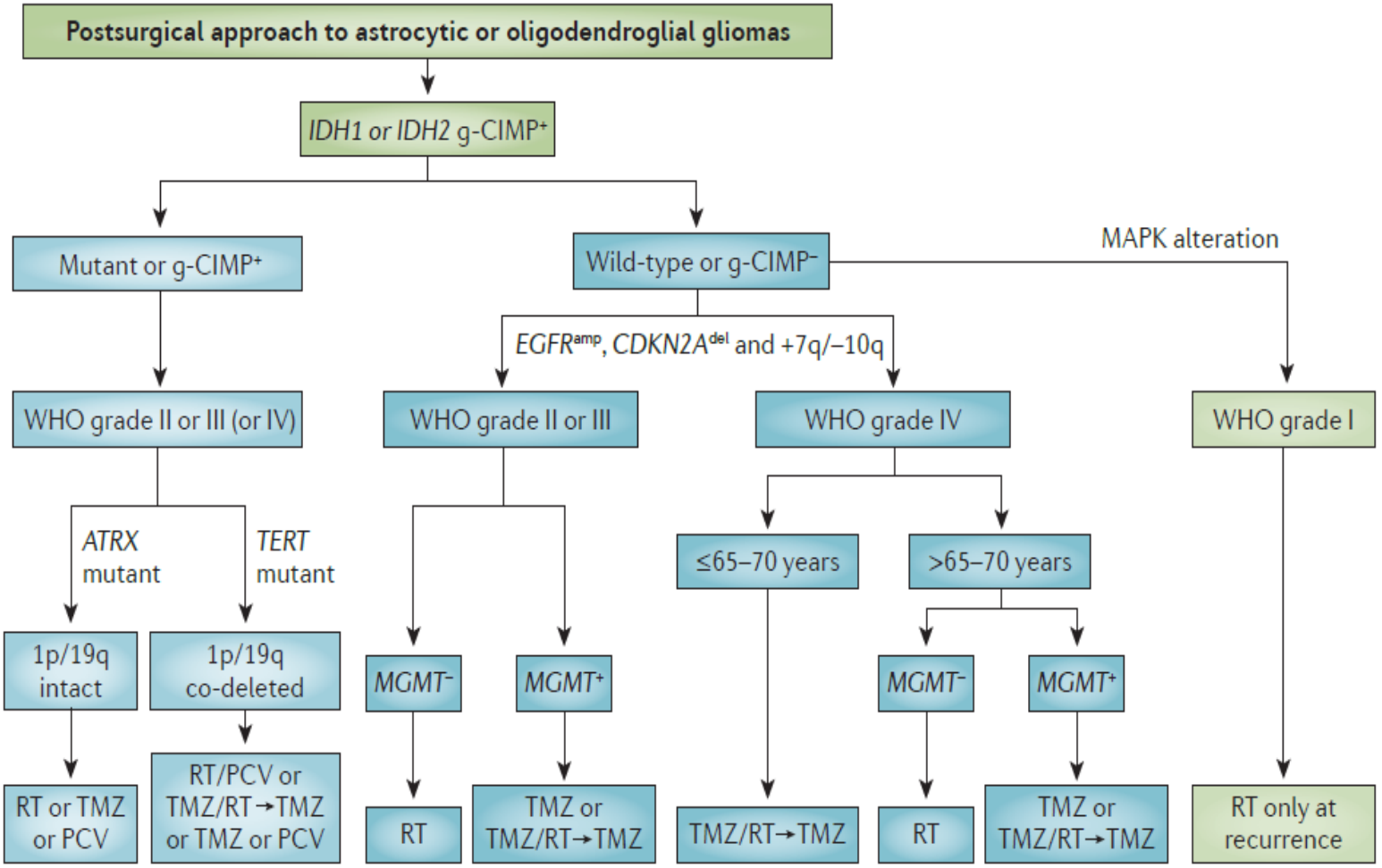


Changement diagnostique

- GBM: IDH wt ou muté /ATRX +/- MGMT
  - Nécrose
  - Prolifération endothélio-capillaire
  - CGH: gain du 7, perte du 10, nécessaire pour diagnostic si doute!
- Astrocytome diffus IDH muté, non codélété:
  - Mitose < 2 mitoses pour 10 champs à fort grossissement: II
  - Mitose > 2 mitoses: III anaplasique
- Oligodendrogliome avec codélétion 1p 19q
  - Nécrose ou prolifération ou mitose > 6 mitoses: III anaplasique
- Oligodendrogliome non codélété disparaît

>>> Publication attendue pour 1er mars 2016!

Prise en charge des gliomes



Weller, Nat Rev Dis Prim, 2015

Plan

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Essai Adjuvant avec NovoTTF 100A

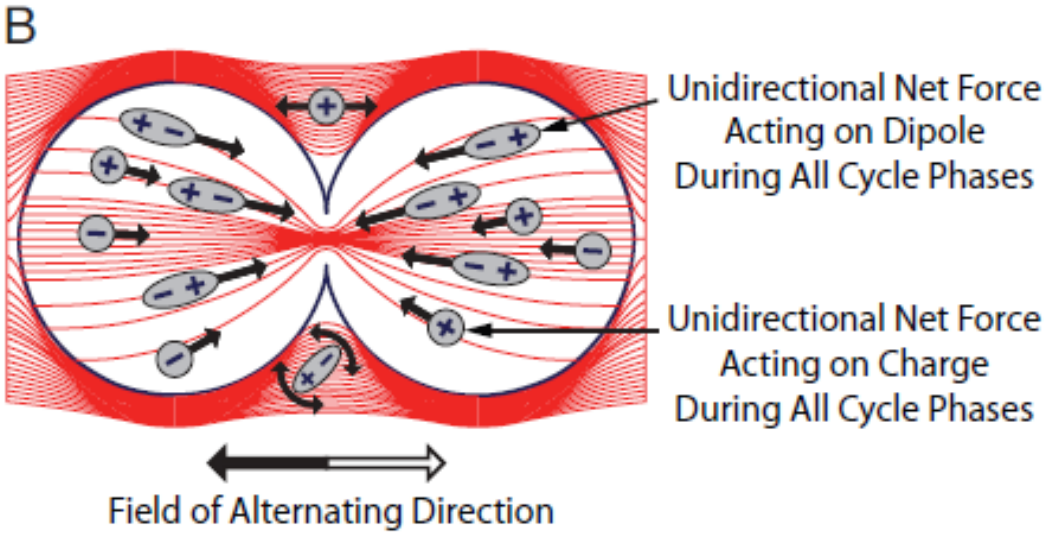
- Champs électriques alternatifs de faible amplitude

- Crâne rasé,
- Port au moins 18H /24
- Sac 3 kg pour batterie autonome 4h

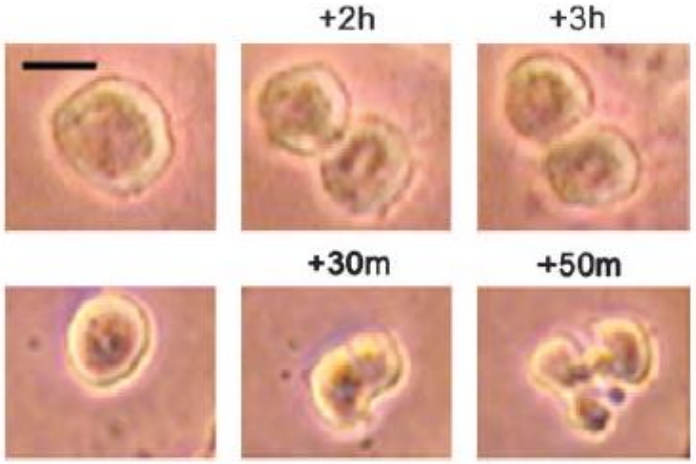
Abstract 2000, Stupp R, JAMA 2015

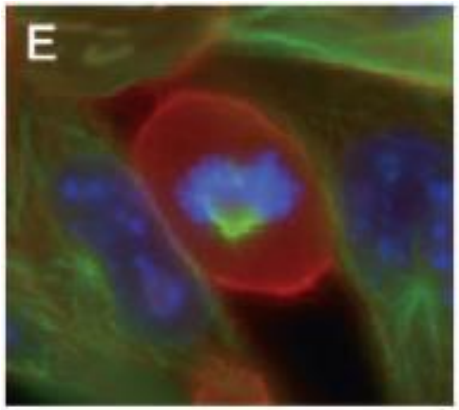
Rationnel biologique TTF 100A

- Activité anti-mitotique



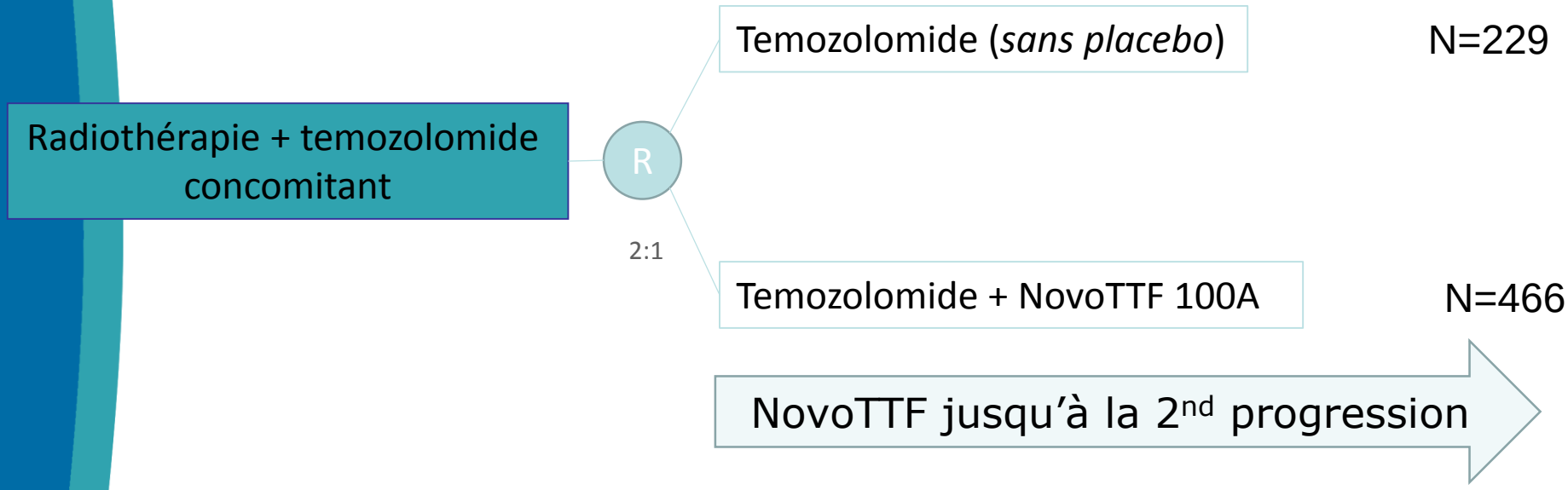
- Perturbation alignement des faisceaux mitotiques





Essai EF-14

- Phase III: Glioblastome au diagnostic



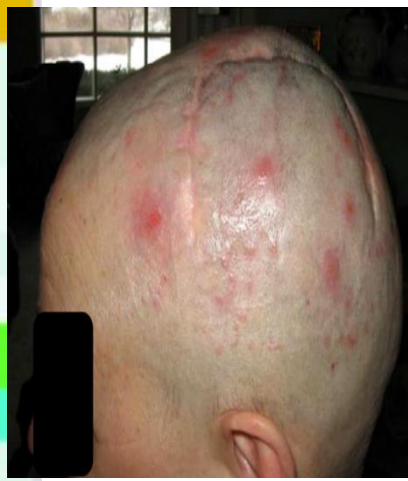
- **Critère principal de jugement** : survie sans progression PFS (*ITT*)
- **Objectifs secondaires** : survie globale = OS (*Per Protocol*), qualité de vie

#2000, Stupp R.

Résultats : tolérance

- Alopécie !

	Grade 1 – 2: mild – moderate		Grade 3 – 4: severe	
System Organ Class Number patients with ≥1 TEAE	TTFields/TMZ N=437 %	TMZ alone N=207 %	TTFields/TMZ N=437 %	TMZ alone N=207 %
Neutropenia/Thrombocytopenia	5 / 13	3 / 18	3 / 7	1 / 5
Gastrointestinal Disorders	46	37	4	2
Cardiac (arrhythmia, etc)	3	3	1	3
Medical device site reaction (skin)	44	1	1	0
Nervous system disorders	43	36	19	20
headache	21	14	2	3
convulsion	13	14	6	6
Psychiatric Disorders	25	18	4	3
depression	10	9	<1	<1
insomnia	9	0	5	<1
anxiety	7	3	<1	0
Vascular Disorders	11	9	4	5
Fatal Events			3%	3%

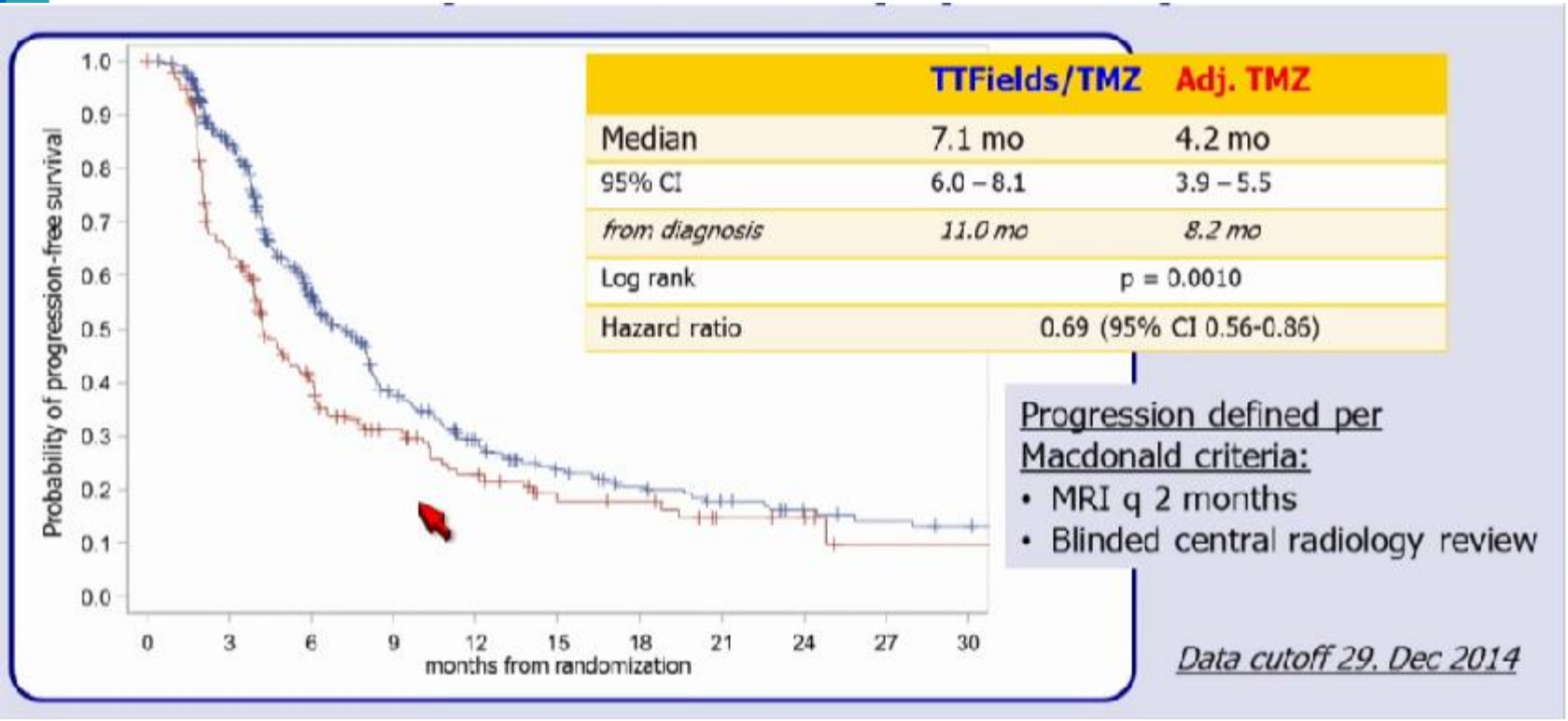


- > Prix : 21 000/mois

#2000, Stupp R.

Résultats : survie

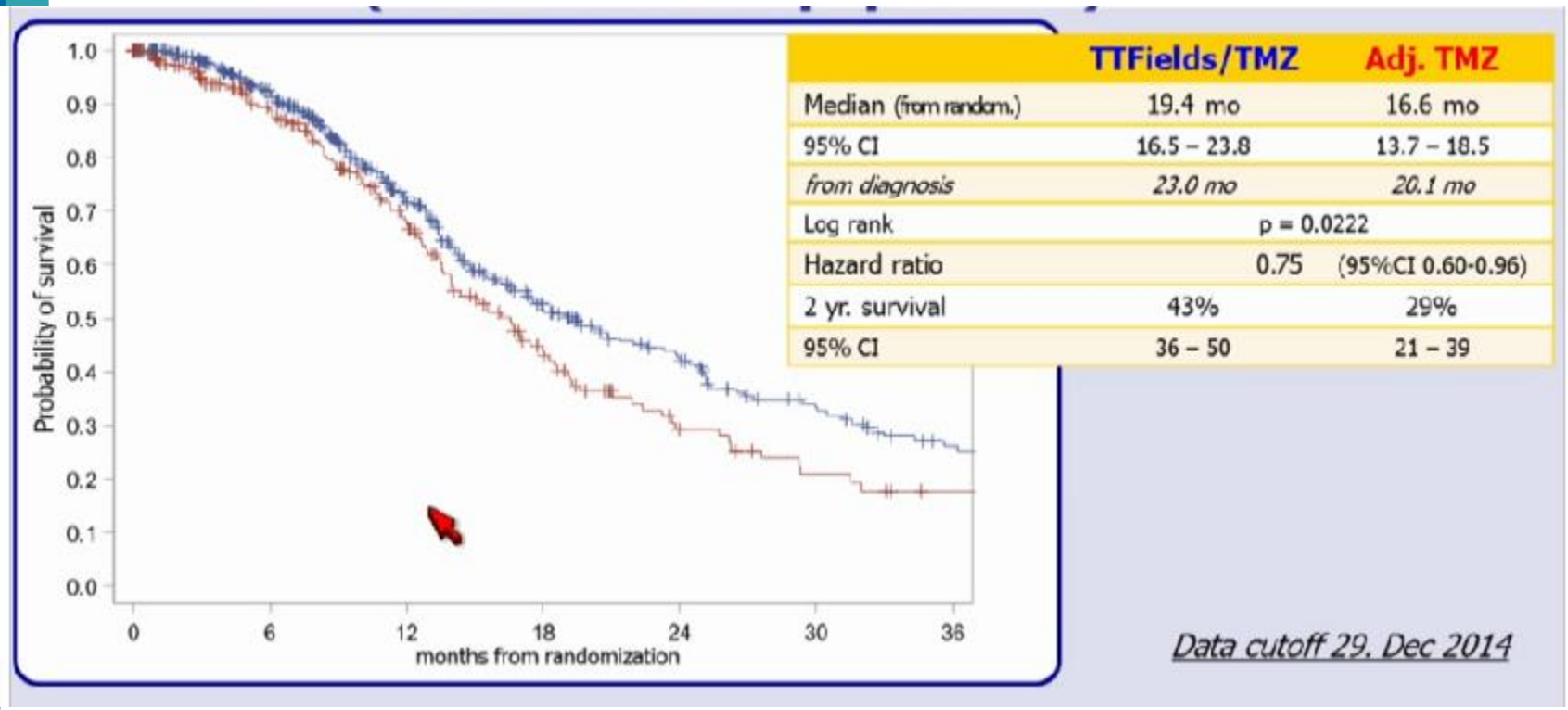
- Survie sans progression = PFS (ITT)
  - 7.1 *versus* 4.2 mois



#2000, Stupp R.

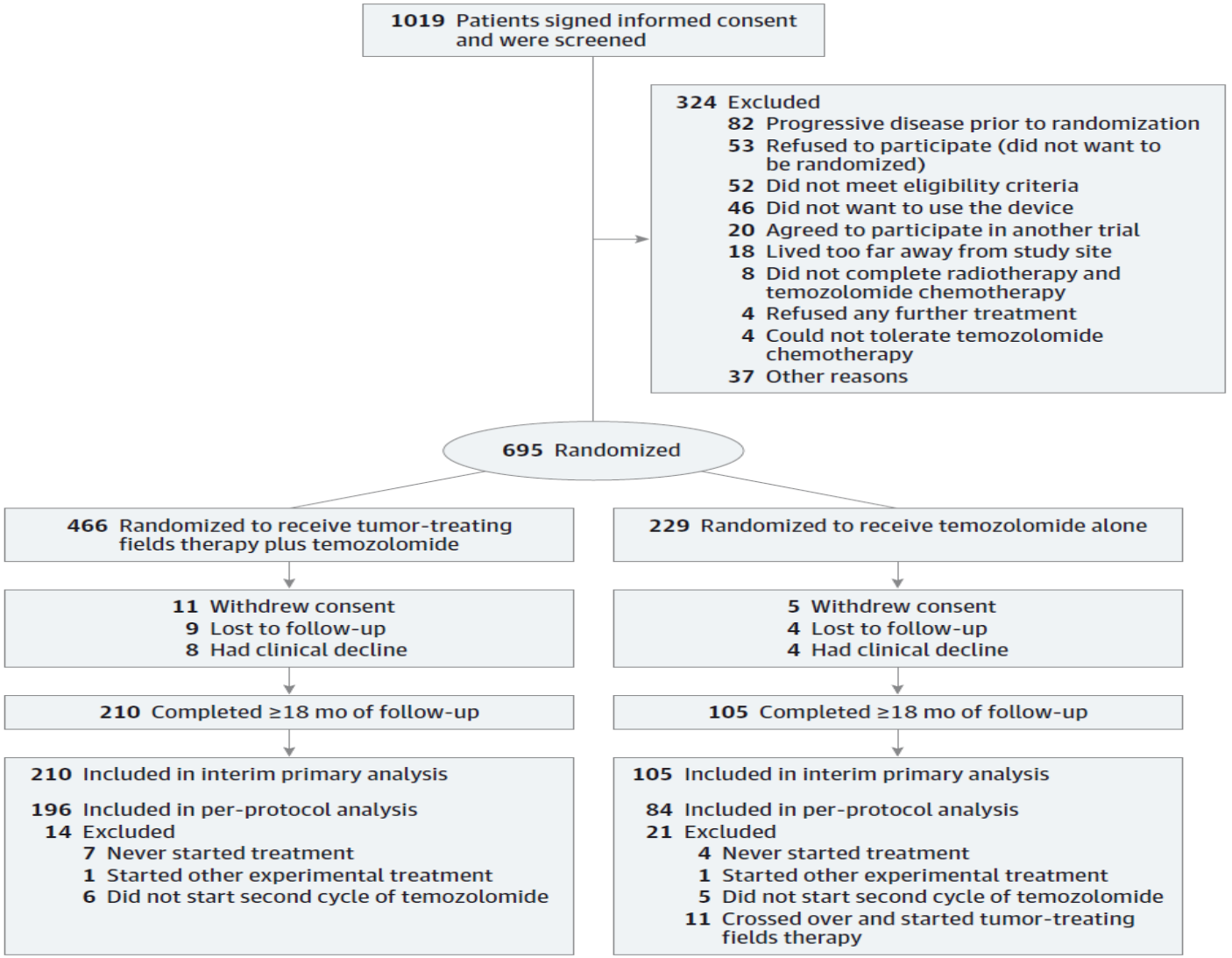
Résultats : survie

- Survie globale = OS (PP)
  - 19.4 *versus* 16.6 months

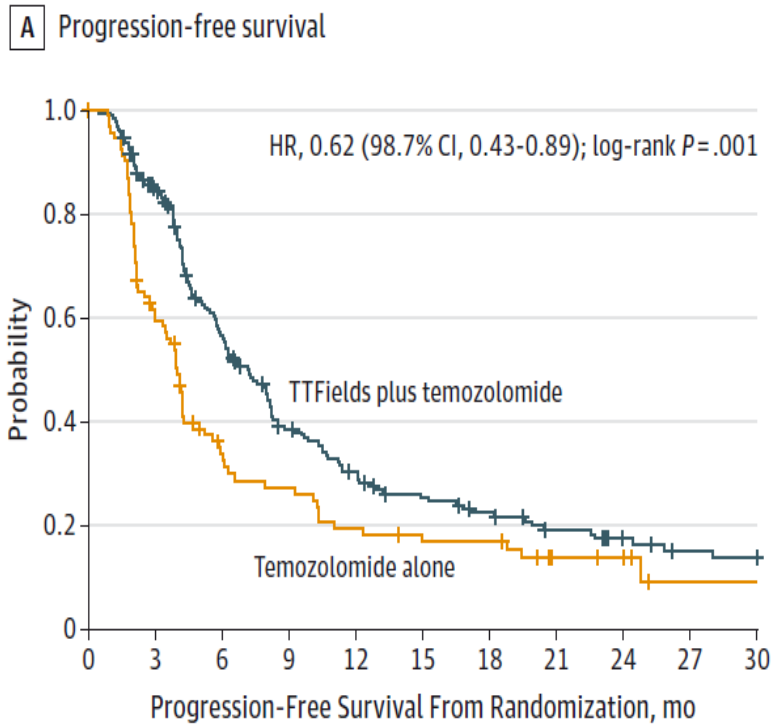


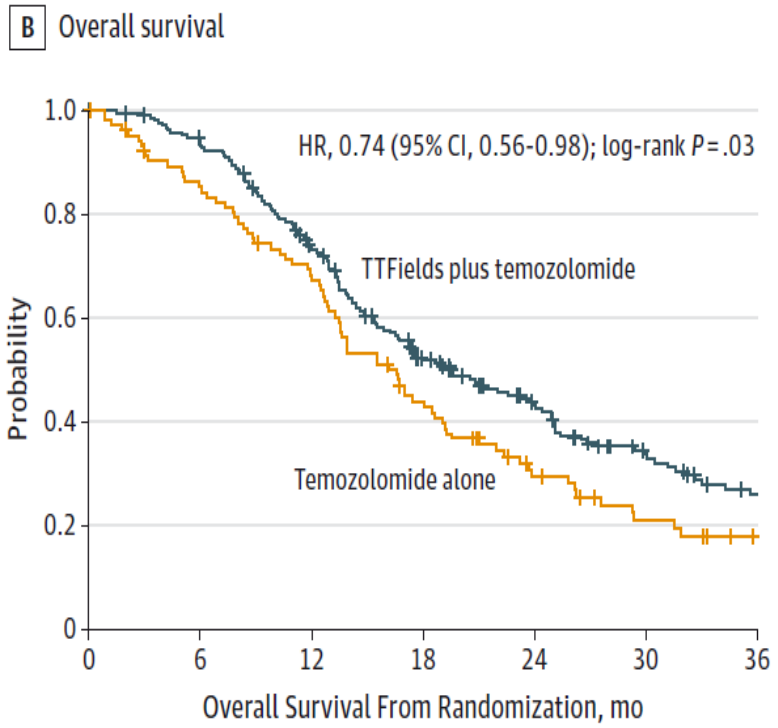
#2000, Stupp R.

ITT /PP


1019 Patients signed informed consent and were screened
324 Excluded
82 Progressive disease prior to randomization
53 Refused to participate (did not want to be randomized)
52 Did not meet eligibility criteria
46 Did not want to use the device
20 Agreed to participate in another trial
18 Lived too far away from study site
8 Did not complete radiotherapy and temozolomide chemotherapy
4 Refused any further treatment
4 Could not tolerate temozolomide chemotherapy
37 Other reasons
695 Randomized
466 Randomized to receive tumor-treating fields therapy plus temozolomide
229 Randomized to receive temozolomide alone
11 Withdrew consent
9 Lost to follow-up
8 Had clinical decline
5 Withdrew consent
4 Lost to follow-up
4 Had clinical decline
210 Completed ≥18 mo of follow-up
105 Completed ≥18 mo of follow-up
210 Included in interim primary analysis
196 Included in per-protocol analysis
14 Excluded
7 Never started treatment
1 Started other experimental treatment
6 Did not start second cycle of temozolomide
105 Included in interim primary analysis
84 Included in per-protocol analysis
21 Excluded
4 Never started treatment
1 Started other experimental treatment
5 Did not start second cycle of temozolomide
11 Crossed over and started tumor-treating fields therapy

Résultats : survie ITT





No. at risk

TTFields plus temozolomide	210	149	94	60	45	35	29	22	16	12	11
Temozolomide alone	105	55	26	21	15	12	12	6	5	1	1

210	195	147	94	65	43	28
105	86	68	42	23	14	8

- essai en récidive avec TTF 100A : négatif.

>>> prochain standard ?

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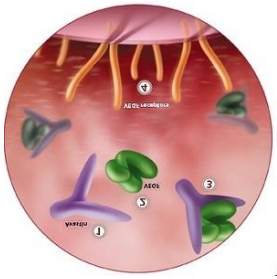
Essai de phase III GBM récidivant: Lomustine +/- Bevacizumab

Glioblastome à la récidive
Phase III

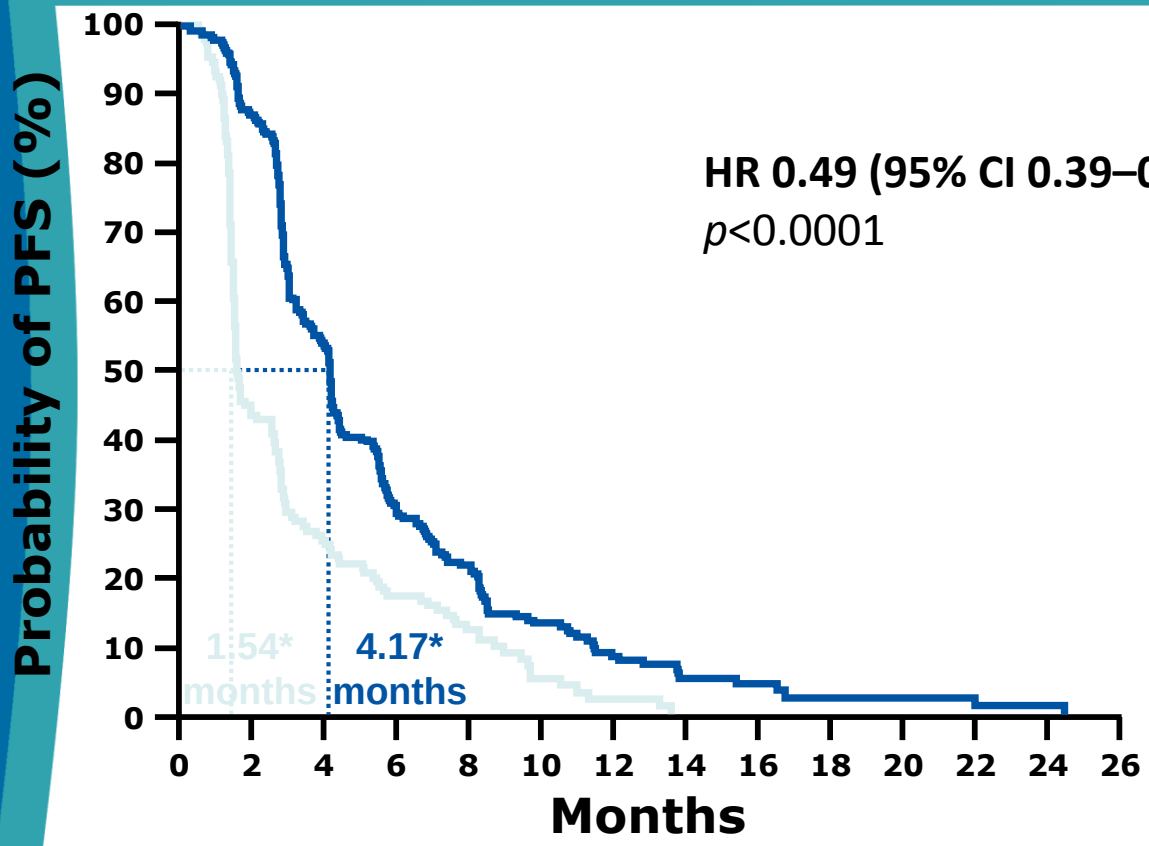


R

- Lomustine (LOM) + bevacizumab (bev) — N= 288
- Lomustine (LOM) — N= 149

Stratification
- Institution
- OMS: 0 vs >0
- Corticoides
- Diamètre tumoral ≤40mm *vs* >40mm

Survie sans progression



HR 0.49 (95% CI 0.39–0.61)

p<0.0001

	O	N	Patients at risk, N											
LOM	143	149	64	37	25	17	5	2	0	0	0	0	0	0
Bv+LOM	260	288	249	154	82	54	27	15	7	5	2	2	2	1

Wick, SNO 2015

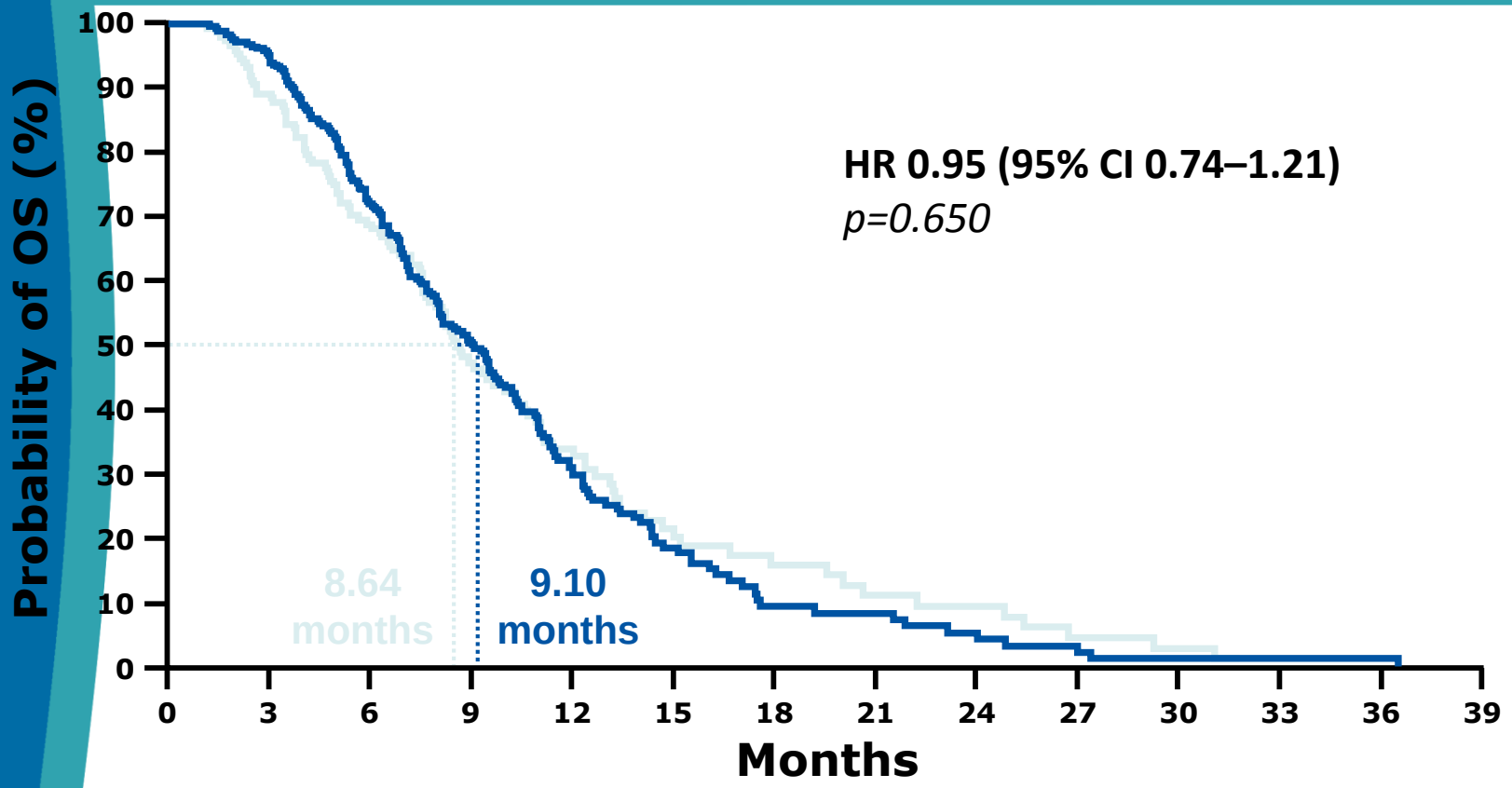
Réponses objectives

Traitement	Patients, N	PFS médiane (95% IC)	Patients non progressifs à un an	N cycles
LOM	149	1.54 months (1.48–2.53)	1.9% (0.4–6.0)	1 (1-8)
BEV+LOM	288	4.17 months (3.65–4.27)	8.8% (5.5–13.0)	3 (1-8) – 9 (1-48)

Response [%]	LOM	LOM+BEV
Réponse objective	**14 %**	**41.5 %**
p<0.0001		
Réponse complète	0.7 %	1.9 %

Wick, SNO 2015

Survie globale



HR 0.95 (95% CI 0.74–1.21)

p=0.650

	O	N	Patients at risk, N											
LOM	113	149	132	102	55	32	17	11	7	6	3	2	0	0
Bv+LOM	216	288	273	207	122	58	25	10	9	6	4	1	1	1

Bv, bevacizumab; CI, confidence interval;
HR, hazard ratio; LOM, lomustine; O, observed events

Wick, SNO 2015

Traitements à la récidive : cross over ?

	LOM	LOM + BEV
Ligne à la progression [%]	66	53
Chimiothérapie	33	38
Bevacizumab	36	19
Temodal ®	9	17
Thérapie ciblée	42	24
Radiothérapie	14	10
Chirurgie	9	7
Autre	5	5

Nouvelle étude qui montre gain en PFS et non en OS
Etude de Qualité de vie en attente.
>>> remboursement Bévacizumab?...

Wick, SNO 2015

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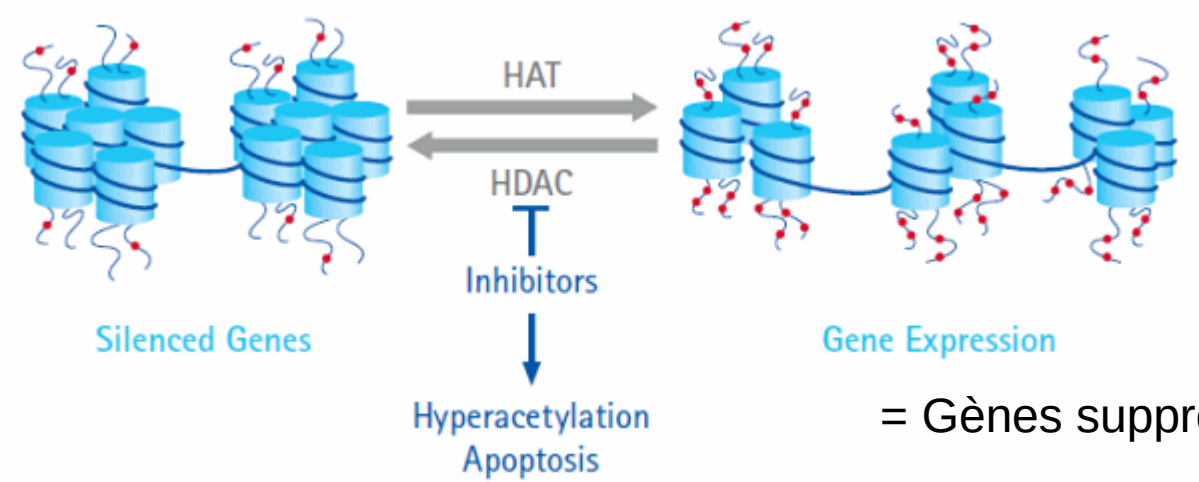
Impact de l'acide valproique ?

- Acide Valproique (Dépakine ®)
- Activité HDAC inhibiteur → activité anti-tumorale ?
  - Bénéfice de la dépakine *versus* autres anti-épileptiques ?



= Gènes suppresseur de tumeur

  - Effets secondaires : anti-épileptique inducteur enzymatique

- **Analyse du bénéfice potentiel de l'acide valproïque = VPA**
  - EORTC NCIC : protocole Stupp
  - Cohorte « contrôle »: CENTRIC, CORE, AVAglio, RTOG0825

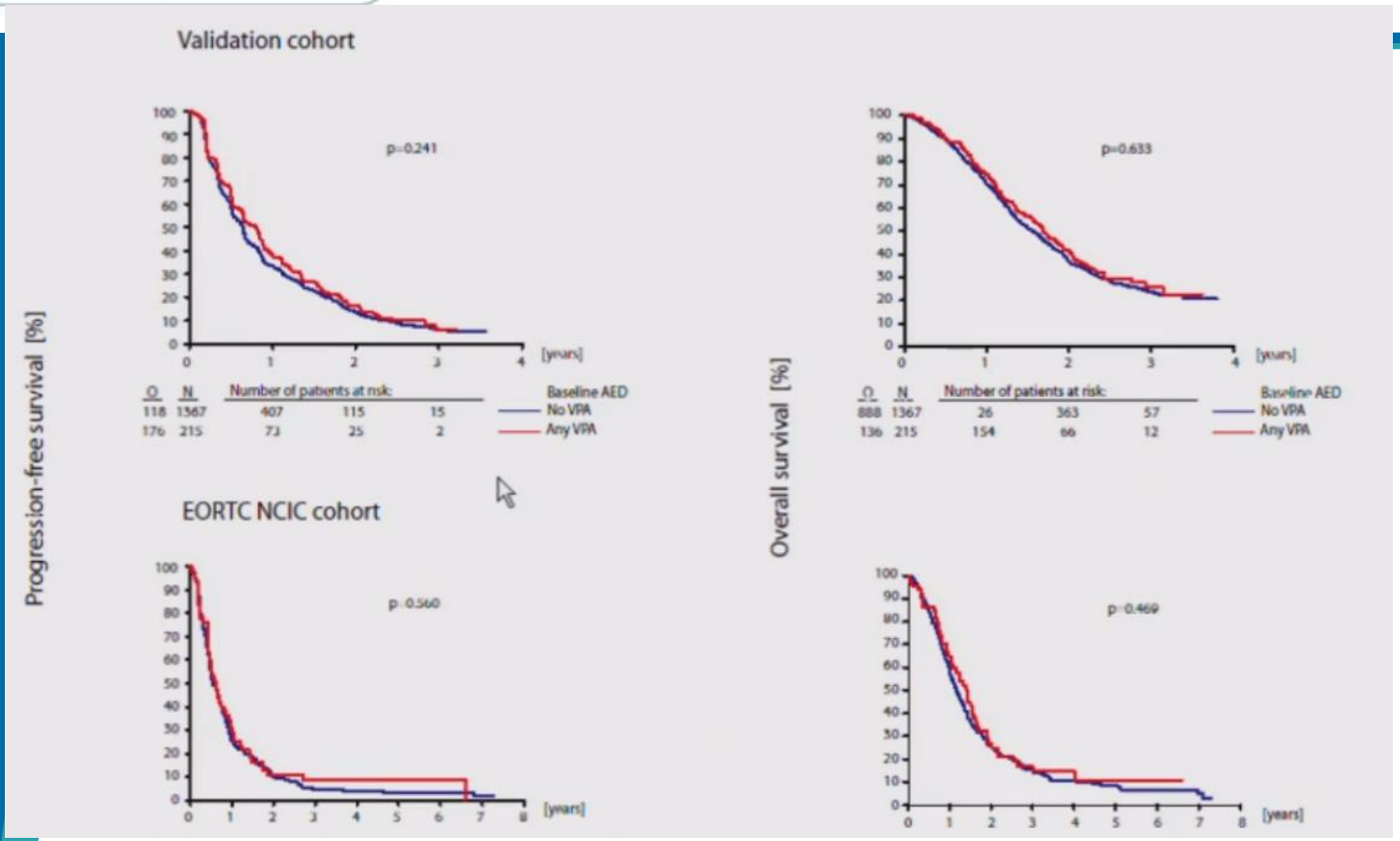
Traitements anti-épileptiques

- Patients sous anti-épileptiques = **57%**
- Patients sous acide valproïque (VPA) = **15%**

	Patient characteristics				
	EORTC 26981 (N=287) (2000-2002) N (%)	AVAGlio (N=463) (2009-2011) N (%)	RTOG 0825 (N=309) (2009-2011) N (%)	CORE/CENTRIC (N=810) (2008-2011) N (%)	Total (N=1869) N (%)
Baseline AED					
No AED	103 (35.9)	165 (35.6)	76 (24.6)	331 (40.9)	675 (36.1)
EI-AED only	113 (39.4)	104 (22.5)	47 (15.2)	101 (12.5)	365 (19.5)
EI-AED plus VPA	4 (1.4)	14 (3.0)	0 (0.0)	3 (0.4)	21 (1.1)
EI-AED plus non-EI-AED w/o VPA	5 (1.7)	20 (4.3)	11 (3.6)	12 (1.5)	48 (2.6)
VPA only	49 (17.1)	41 (8.9)	5 (1.6)	125 (15.4)	220 (11.8)
VPA plus another non-EI-AED	1 (0.3)	15 (3.2)	1 (0.3)	9 (1.1)	26 (1.4)
non-EI-AED (w/o VPA)	8 (2.8)	102 (22.0)	169 (54.7)	229 (28.3)	508 (27.2)
EI-AED plus VPA plus another non-EI-AED	1 (0.3)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.2)
Missing	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)

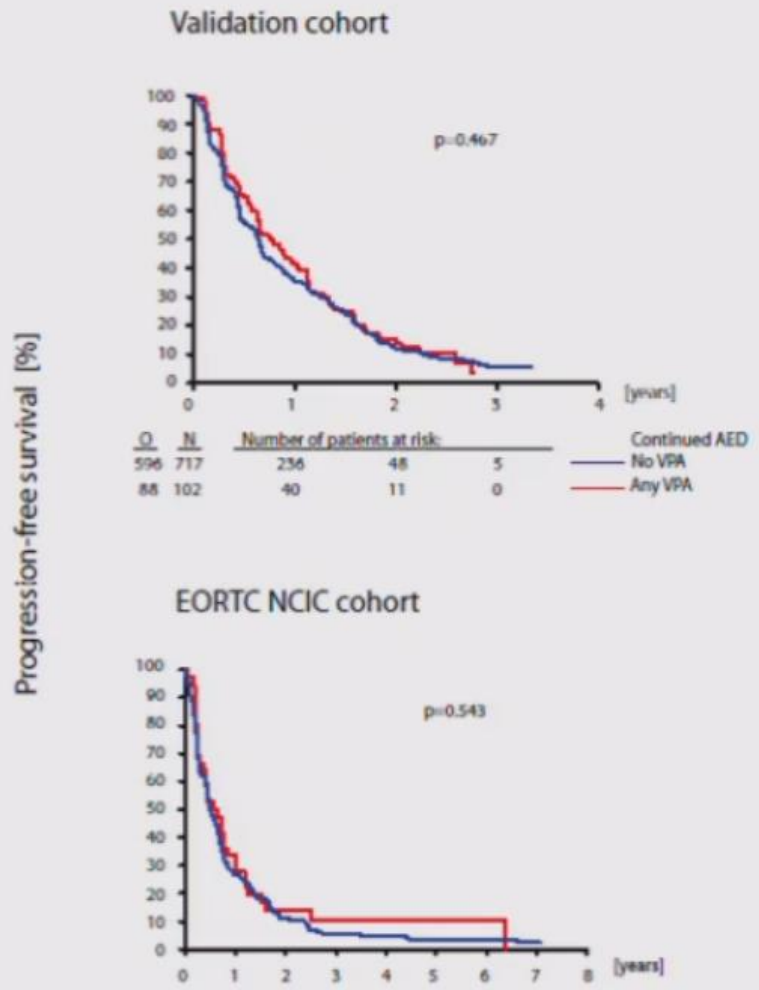
Weller, LBA26

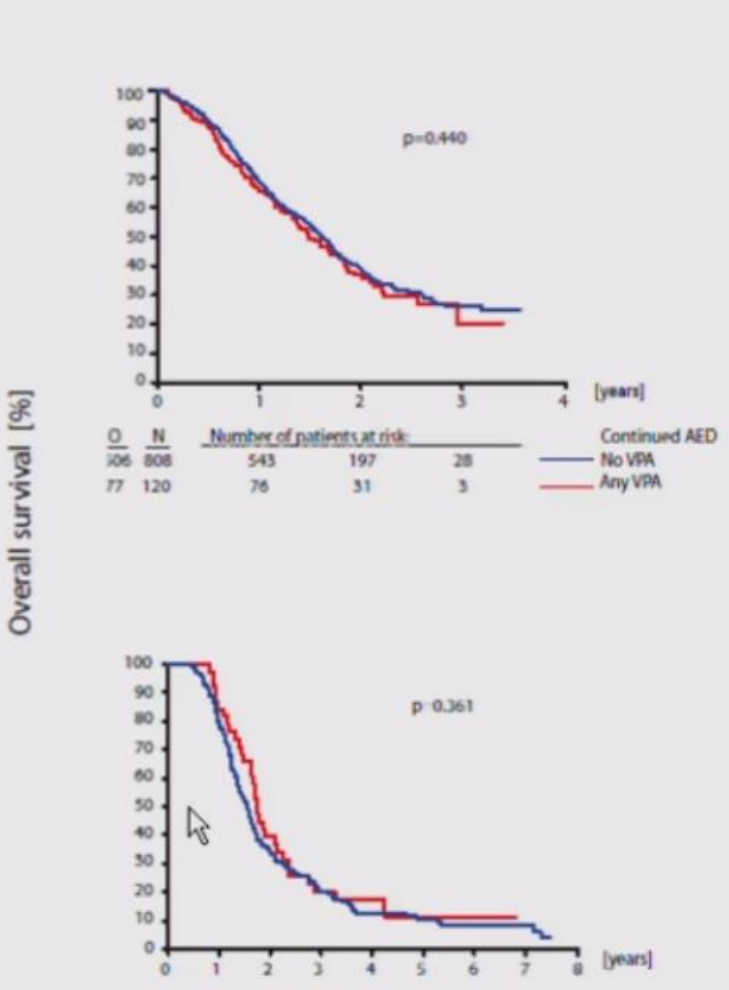
Patients sous VPA à l'inclusion



Weller, LBA26

VPA à l'inclusion et durant le TMZ

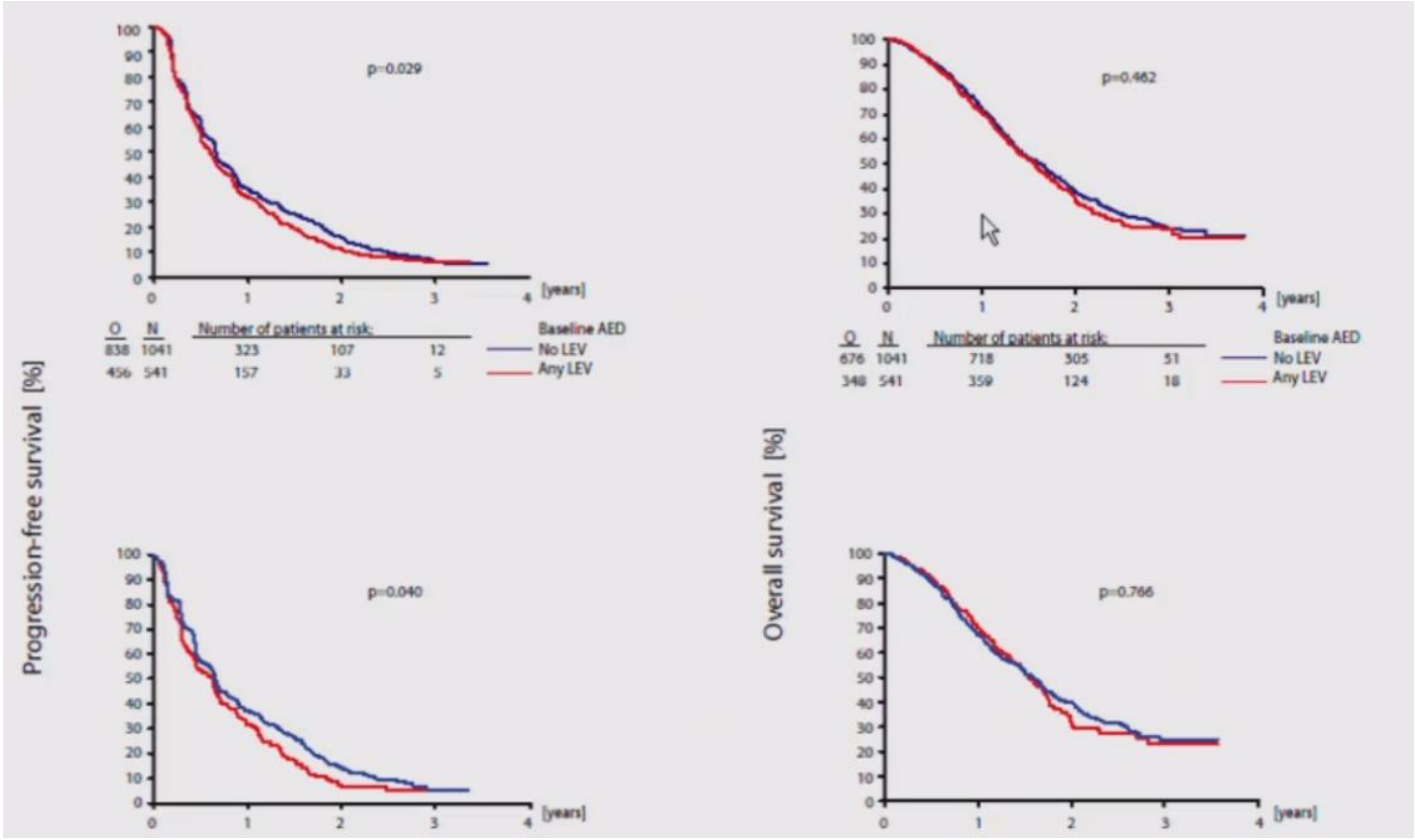




Weller, LBA26

Impact du lévétiracetam: keppra ®

- Effet MGMT-inhibiteur ?



Weller, LBA26

Effet anti-tumoral du CITALOPRAM?

- étude préliminaire
- Blocage canal K surexprimé dans GBM
- Effet cytotoxique sur lignée
- A évaluer chez homme

>>> anti-épileptique: moins toxique, plus efficace

>>> si besoin antidépresseur: proposer CITALOPRAM 20mg le soir…

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Nouvelles drogues ? Immunothérapie ?

- Axitinib: phase II positive, PFS 6 mo 27 vs 22%
  >>> phase II +/- associée à Lomustine

- Ipilimumab et nivolumab: peu toxicité nivolumab seul, survie 6 mois à 70%
  >>>phase II en cours

- Vaccination:

>>> ACT IV: cible EGFRvIII clos aux inclusions

>>> ABT-414: anticorps avec drogue conjugué anti-EGFR si amplification EGFR y compris EGFRvIII…

- Inhibiteur transcrit de fusion FGFR-TACC: rare 3%

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Essai de phase III : SRS +/- WBRT

Patients avec **1 à 3 métastases cérébrales**

R

- Radiochirurgie (SRS) *N*=111
- SRS + radiothérapie pan-cérébrale (WBRT) *N*=102

Stratification
- Age
- Maladie systémique
- Nombre de MC
- Institution

Objectif & critère principal

Dégradation cognitive à 3 mois

LBA4, Brown P.

Evaluations

- A 6 semaines, 3 mois, 6 mois, 9 mois et 12 mois
  - IRM
  - Qualité de vie
  - **Tests cognitifs**

Cognitive Domain	Test
Memory	HVLT (Hopkins Verbal Learning Test)
Processing Speed	TMT Part A (Trail Making Test)
Executive Function	TMT Part B
Verbal Fluency	COWA (Controlled Oral Word Association)
Motor Speed/Dexterity	GP-D (Grooved Pegboard Dominant)

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Résultats : dégradation cognitive

	SRS	SRS+WBRT	P-value
Cognitive Progression at 3 months (95% CI)	63.5% (50.5, 75.3)	91.7% (80.0, 97.7)	0.0007

- Déclin cognitifs à 3 mois :
  - SRS + WBRT > SRS seule

- Résultats persistants à 6 mois : **77.8**% *versus* **97.9**%
  - *p*=0.032

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Résultats : qualité de vie

- Consistant avec l'évaluation de la **qualité de vie**

QOL Test/Subtest	SRS	SRS+WBRT	P-value
Physical Well Being	-4	-18	0.053
Social/FamilyWB	1	-3	0.369
Emotional Well Being	13	5	0.129
Functional Well Being	3	-22	0.006
FACT General	0	-12	0.001
FACT Brain Specific	-1	-9	0.029
FACT-BR Total	-1	-11	0.002

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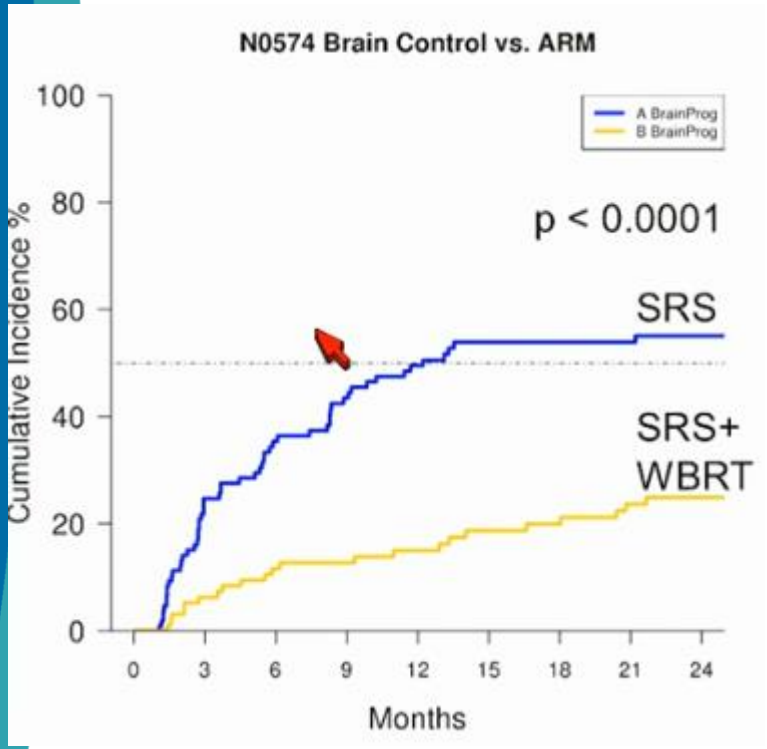
Résultats : survie

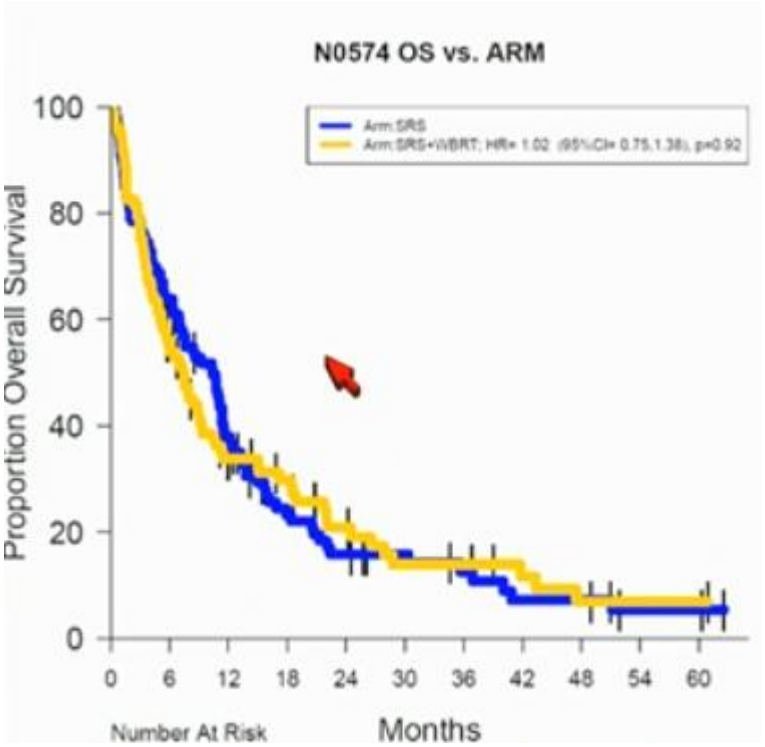
Progression cérébrale



Survie globale

Médiane SRS : 10.4 mois

Médiane SRS + WBRT : 7.4 mois



>>> radiochirurgie seule

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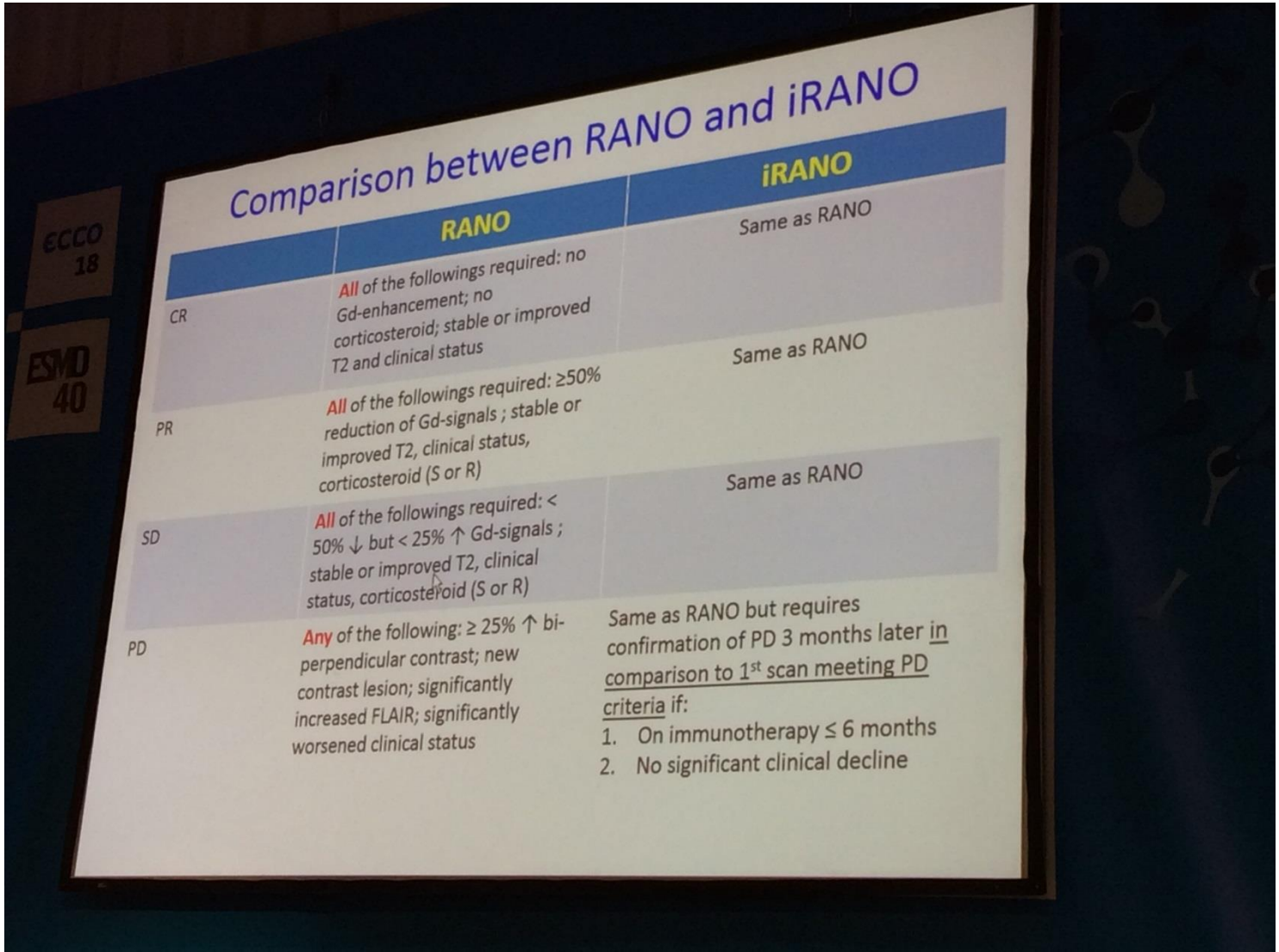
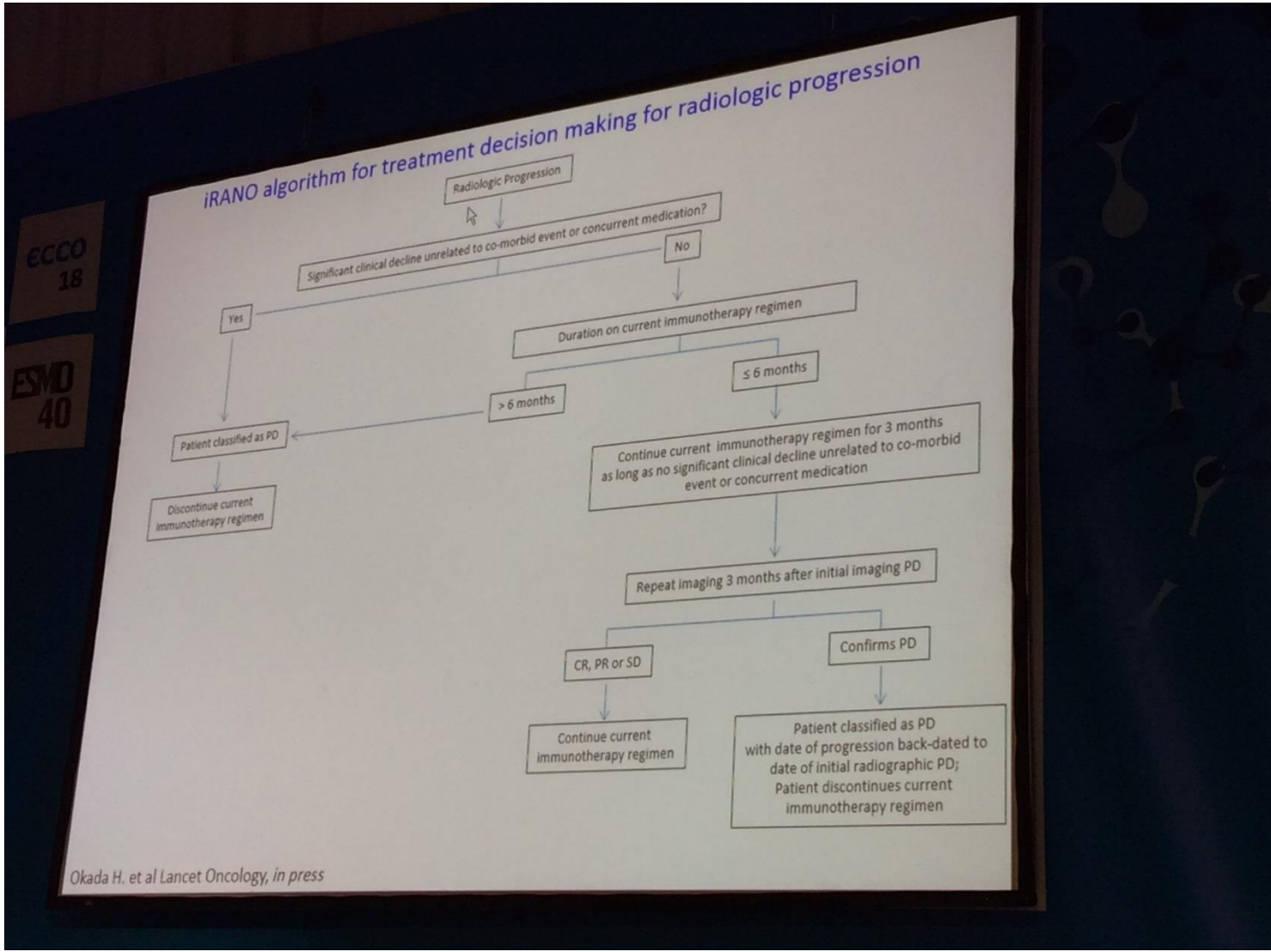
Evaluation de la réponse des métastases selon traitement



Évaluation immunothérapie



Critères iRANO

iRANO Criteria (Okada H et al. Lancet Oncology, *in press*)

	Malignant Glioma[16]	Low-Grade Glioma[17]	Brain Metastases[18]
Complete Response	-Disappearance of all enhancing disease for ≥ 4 weeks *AND* - No new lesions *AND* - Stable/improved T2/FLAIR *AND* - No more than physiologic steroids *AND* - Stable/improved clinically	-Disappearance of all enhancing and T2/FLAIR disease for ≥ 4 weeks *AND* - No new lesions *AND* - No more than physiologic steroids *AND* - Stable/improved clinically	-Disappearance of all enhancing target and non-target lesions for ≥ 4 weeks *AND* - No new lesions *AND* - No steroids *AND* - Stable/improved clinically
Partial Response	- ≥ 50% ↓ sum of biperpendicular diameters of enhancing disease for ≥ 4 weeks *AND* - No new lesions *AND* - Stable/improved T2/FLAIR *AND* - Stable/improved steroids *AND* - Stable/improved clinically	- ≥ 50% ↓ sum of biperpendicular diameters of T2/FLAIR disease for ≥ 4 weeks *AND* - No new lesions *AND* - Stable/improved steroids *AND* - Stable/improved clinically	- ≥ 30% ↓ sum of longest diameters of target lesions for ≥ 4 weeks *AND* - No new lesions *AND* - Stable/improved steroids *AND* - Stable/improved clinically
Minor Response	- Non-applicable	- 25-49% ↓ sum of biperpendicular diameters of T2/FLAIR disease for ≥ 4 weeks *AND* - No new lesions *AND* - Stable/improved clinically	Not applicable
Stable Disease	- Does not qualify for CR, PR, PD *AND* - No new lesions *AND* - Stable/improved T2/FLAIR *AND* - Stable/improved steroids *AND* - Stable/improved clinically	- Does not qualify for CR, PR, PD *AND* - No new lesions *AND* - Stable/improved T2/FLAIR *AND* - Stable/improved steroids *AND* - Stable/improved clinically	- Does not qualify for CR, PR, PD
Progressive Disease	- ≥ 25% ↑ sum of biperpendicular diameters of enhancing disease *OR* - New lesions *OR* - Significant worsened T2/FLAIR *OR* - Significant clinical decline	- ≥ 25% ↑ sum of biperpendicular diameters of T2/FLAIR disease *OR* - New lesions *OR* - Significant clinical decline	- ≥ 20% ↑ sum of longest diameters of target lesions *OR* -Unequivocal progression of enhancing non-target lesions *OR* - New lesions *OR* - Significant clinical decline
iRANO	Confirmation of progression on follow-up imaging 3 months after initial radiographic progression if: 1. No new or significantly worsened neurologic deficits not due to co-morbid event or concurrent medication *AND* 2. ≤ 6 months from initiation of immunotherapy If follow-up imaging confirms progression, the date of actual progression should be back-dated to the date of initial radiographic progression		

Conclusions

- Nouvelle classification OMS
- Nouveau traitement pour les glioblastomes au diagnostic: novo-TTF…
- Pas de bénéfice en survie globale pour le bevacizumab à la récidive
  - Attente de l'analyse de la qualité de vie
- Pas de bénéfice anti-tumoral de l'acide valproique, du levetiracétam, citalopram?
- Nouveau traitement standard pour les métastases cérébrales
  - Radiochirurgie seule
  - Critères RANO immunologique