*Neuro-news: innovazioni diagnostiche e terapeutiche in neurologia*

# *TUMORI CEREBRALI*

Roberta Rudà
U. O. di Neuro-Oncologia, Dipartimento di Neuroscienze
Città della Salute e della Scienza e Università di Torino

***SIN Triregionale, Ivrea 6 Dicembre 2019***

# *DISCLOSURES*

I received consultancy and advisory board fees from :

UCB Pharma

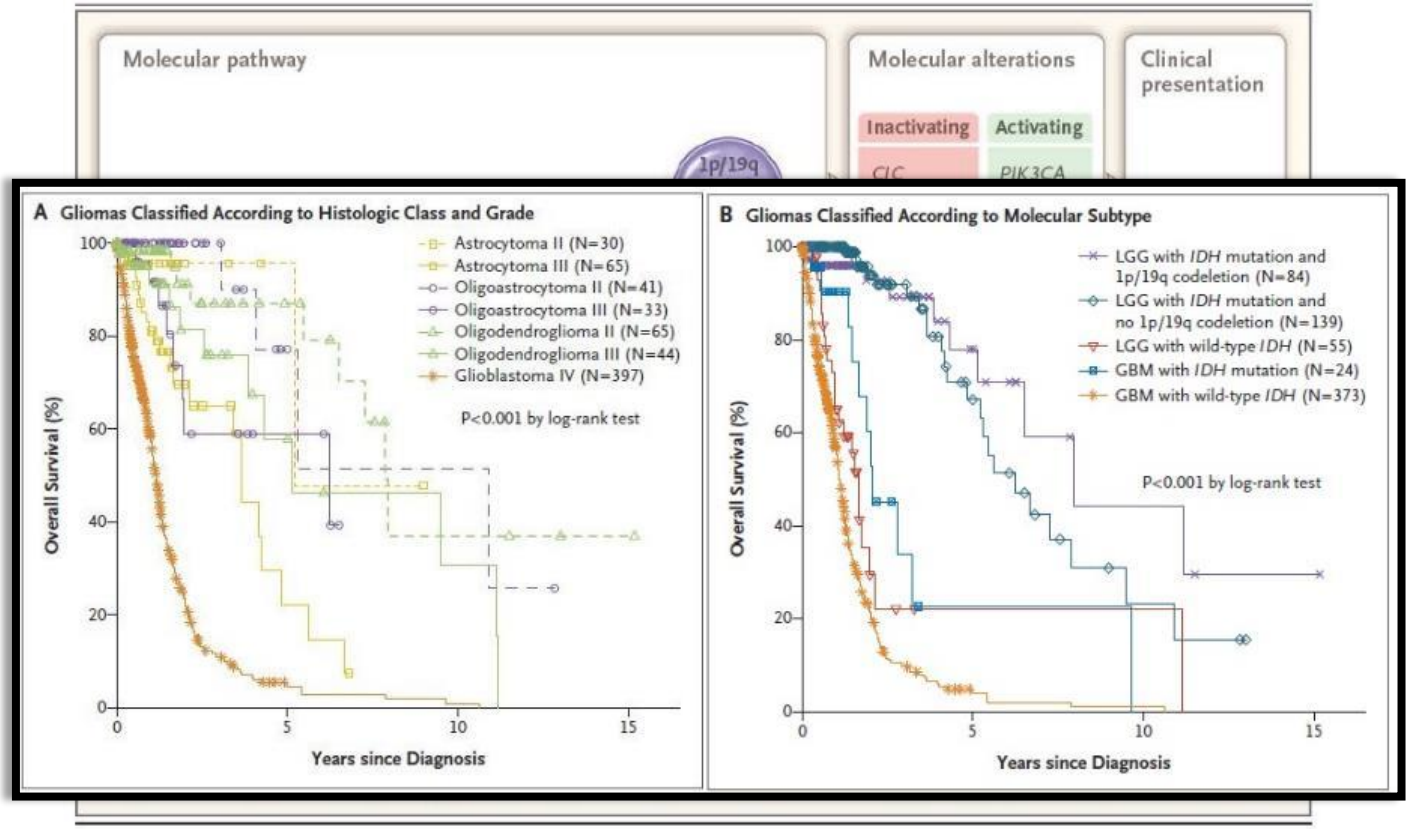
EISAI

Mundipharma

Novocure

# OUTLINE

- Innovazioni diagnostiche: gli avanzamenti in biologia molecolare
- Innovazioni terapeutiche: i risultati dei trials clinici di fase III nei gliomi di alto grado e le terapie target
- Liquid biopsy nei tumori cerebrali: nuovo strumento per il clinico?




Comprehensive, Integrative Genomic Analysis of Diffuse LGG
The Cancer Genome Atlas Research Network; NEJM, June 2015

Today we know that **different molecular arrangements can have stronger prognostic and predictive value** than the histotype itself.

## WHO 4 Ed. 2007

Diffuse astrocytoma, (II)
- Fibrillary astrocytoma
- Gemistocytic astrocytoma
- Protoplasmatic astrocytoma

Anaplastic astrocytoma, (III)

Glioblastoma, (IV)
Giant cell glioblastoma
Gliosarcoma
Gliomatosis cerebri

Oligodendroglioma, (II)
Anaplastic oligodendroglioma, (III)

Oligoastrocytoma, (II)
Anaplastic oligoastrocytoma, (III)

## WHO 4 Ed.+ 2016

Diffuse astrocytoma, IDH-1 mutant (II)
Gemistocytic astrocytoma, IDH-mutant (II)
*Diffuse astrocytoma, IDH-wildtype (II)*
Diffuse astrocytoma,NOS (II)

Anaplastic astrocytoma, IDH-mutant (III)
*Anaplastic astrocytoma, IDH-wildtype (III)*
Anaplastic astrocytoma, NOS (III)

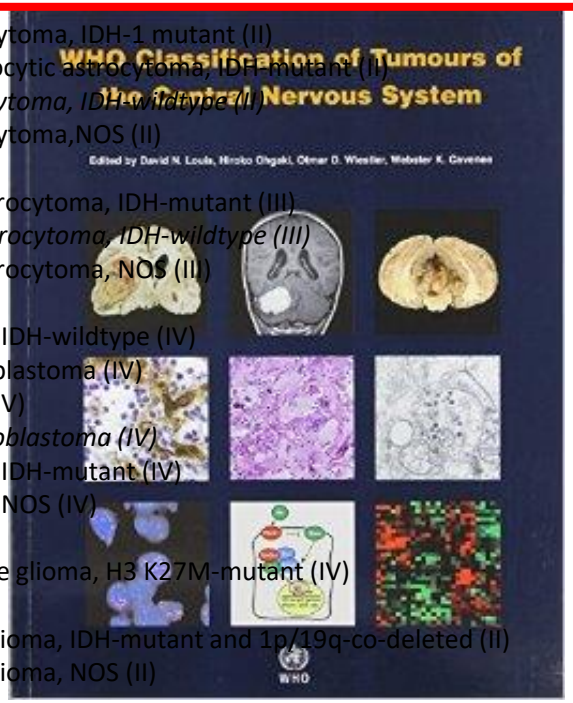
Glioblastoma, IDH-wildtype (IV)
Giant cell glioblastoma (IV)
Gliosarcoma (IV)
*Epithelioid glioblastoma (IV)*
Glioblastoma, IDH-mutant (IV)
Glioblastoma, NOS (IV)

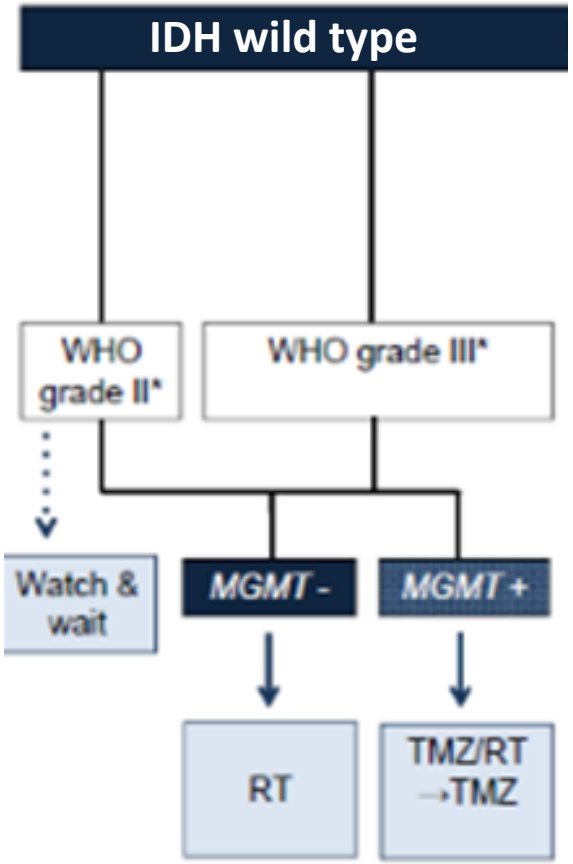
Diffuse midline glioma, H3 K27M-mutant (IV)

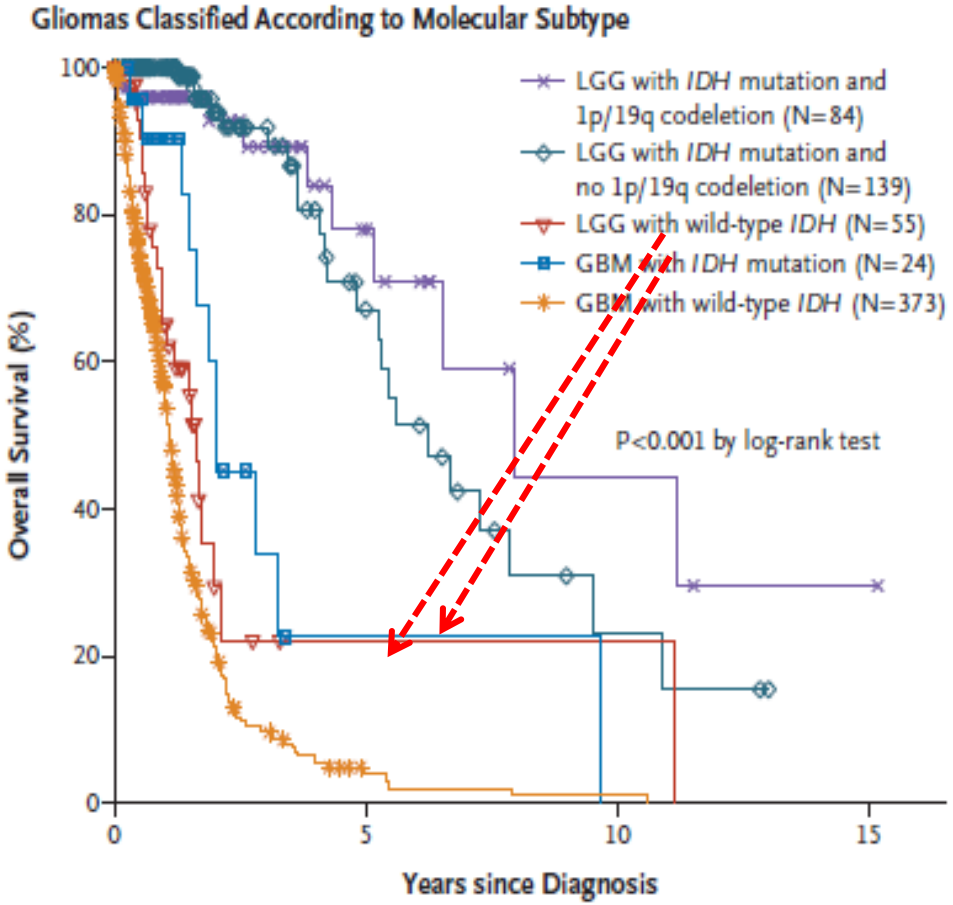
Oligodendroglioma, IDH-mutant and 1p/19q-co-deleted (II)
Oligodendroglioma, NOS (II)

Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted (III)
Anaplastic oligodendroglioma, NOS (III)

*Oligoastrocytoma (II)*
*Anaplastic oligoastrocytoma (III)*





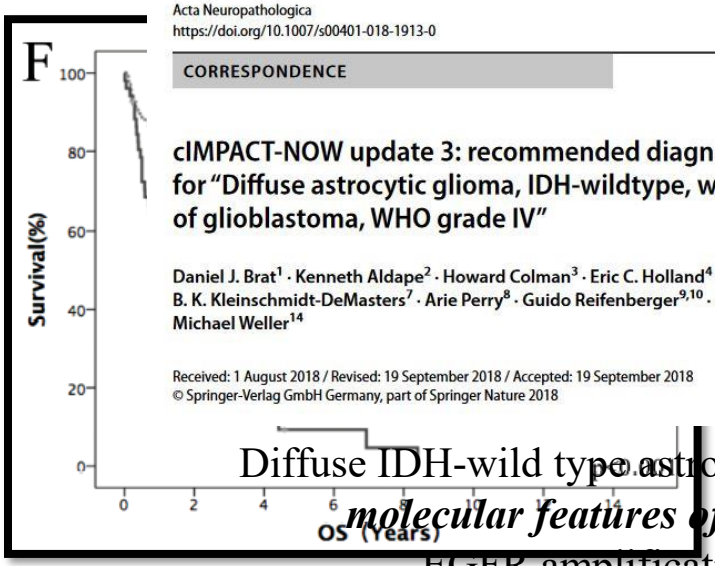




The Cancer Genome Atlas Research Network 2015; Weller 2017.

# Grade II IDH-wild type

With the current 2016 WHO Classification **all IDH-wild type tumours are classified as astrocytomas**, regardless of the tumour grade. Thus, cases originally diagnosed as either oligodendrogliomas or oligoastrocytomas according to WHO 2007 need to be reclassified as astrocytomas.

There is now increasing evidence of the **molecular heterogeneity** of the IDH-wild type grade II astrocytomas.




Aibadula et al, Neuro Oncol 2017;19(10):1327–1337

EGFR mutation
TERTp mutation
H3F3A K27 mutation
(BRAF-wild type)
(MYB amplification)

Diffuse IDH-wild type astrocytomas with
***molecular features of GBM***:
EGFR amplification
TERTp mutation
+7/-10 chromosomes alterations

Acta Neuropathologica (2018) 135:481–484
https://doi.org/10.1007/s00401-018-1808-0

CORRESPONDENCE

# cIMPACT-NOW update 1: Not Otherwise Specified (NOS) and Not Elsewhere Classified (NEC)

David N. Louis[1] · Pieter Wesseling[2,3,4] · Werner Paulus[5] · Caterina Giannini[6] · Tracy T. Batchelor[7] · J. Gregory Cairncross[8] · David Capper[9,10] · Dominique Figarella-Branger[11] · M. Beatriz Lopes[12] · Wolfgang Wick[13] · Martin van den Bent[14]

Acta Neuropathologica (2018) 135:639–642
https://doi.org/10.1007/s00401-018-1826-y

CORRESPONDENCE

# cIMPACT-NOW update 2: diagnostic clarifications for *diffuse midline glioma, H3 K27M-mutant* and *diffuse astrocytoma/anaplastic astrocytoma, IDH-mutant*

David N. Louis[1] · Caterina Giannini[2] · David Capper[3] · Werner Paulus[4] · Dominique Figarella-Branger[5] · M. Beatriz Lopes[6] · Tracy T. Batchelor[7] · J. Gregory Cairncross[8] · Martin van den Bent[9] · Wolfgang Wick[10,11,12] · Pieter Wesseling[13,14]

Acta Neuropathologica (2018) 136:805–810
https://doi.org/10.1007/s00401-018-1913-0

CORRESPONDENCE

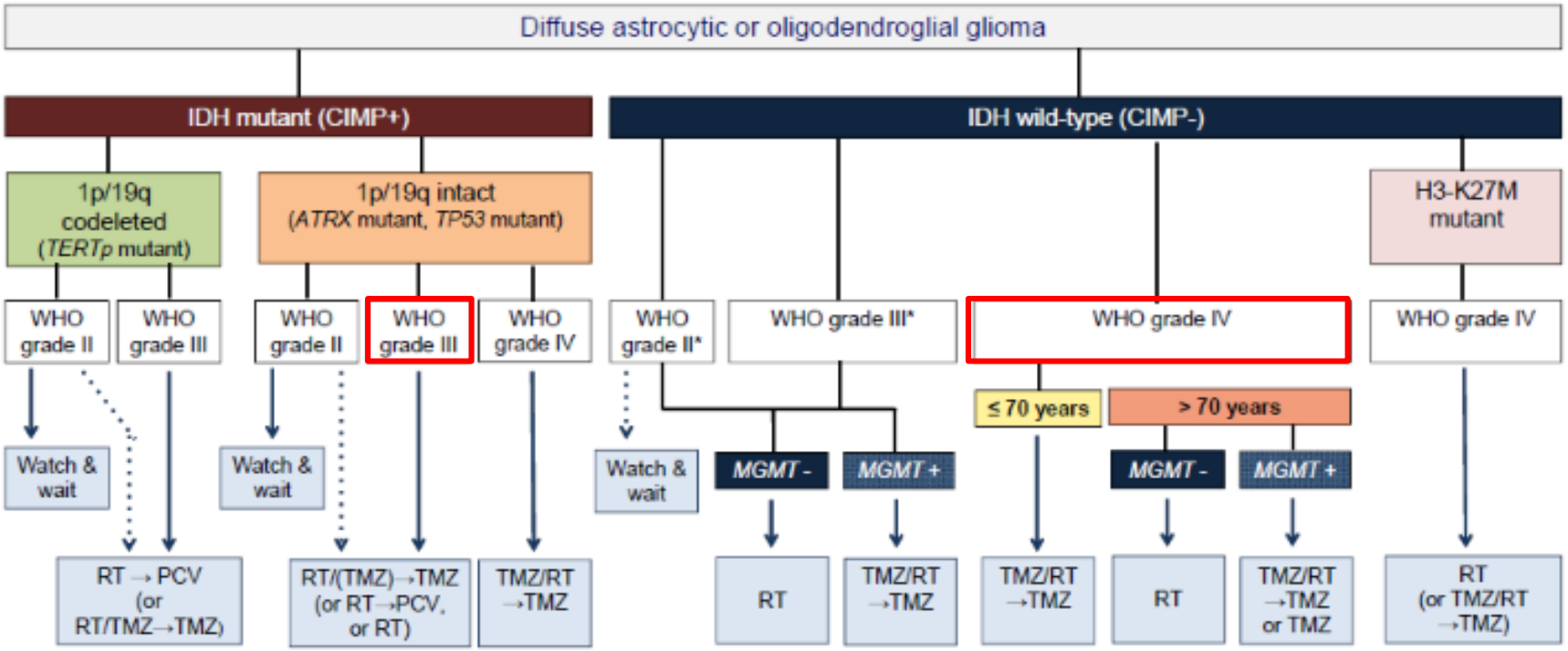
# cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV"

Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Eric C. Holland[4] · David N. Louis[5] · Robert B. Jenkins[6] · B. K. Kleinschmidt-DeMasters[7] · Arie Perry[8] · Guido Reifenberger[9,10] · Roger Stupp[11] · Andreas von Deimling[12,13] · Michael Weller[14]

UniversitätsSpital Zürich

# The 2017 EANO guideline

## Lancet Oncology 2017;18:e315-e329




* Refers to the provisional entities of diffuse astrocytoma, IDH wildtype, and anaplastic astrocytoma, IDH wildtype.

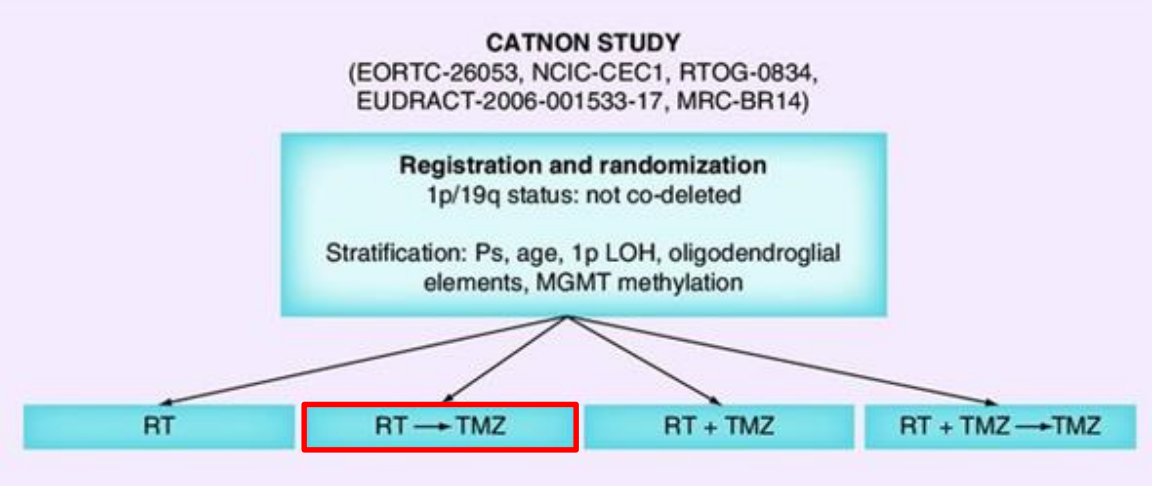
Lancet 2017; 390: 1645–53

CATI
con
delet

# Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study

with
-co-
label

Martin J van den Bent, Brigitta Baumert, Sara C Erridge, Michael A Vogelbaum, Anna K Nowak, Marc Sanson, Alba Ariela Brandes, Paul M Clement, Jean Francais Baurain, Warren P Mason, Helen Wheeler, Olivier L Chinot, Sanjeev Gill, Matthew Griffin, David G Brachman, Walter Taal, Roberta Rudà, Michael Weller, Catherine McBain, Jaap Reijneveld, Roelien H Enting, Damien C Weber, Thierry Lesimple, Susan Clenton, Anja Gijtenbeek, Sarah Pascoe, Ulrich Herrlinger, Peter Hau, Frederic Dhermain, Irene van Heuvel, Roger Stupp, Ken Aldape, Robert B Jenkins, Hendrikus Jan Dubbink, Winand N M Dinjens, Pieter Wesseling, Sarah Nuyens, Vassilis Golfinopoulos, Thierry Gorlia, Wolfgang Wick, Johan M Kros



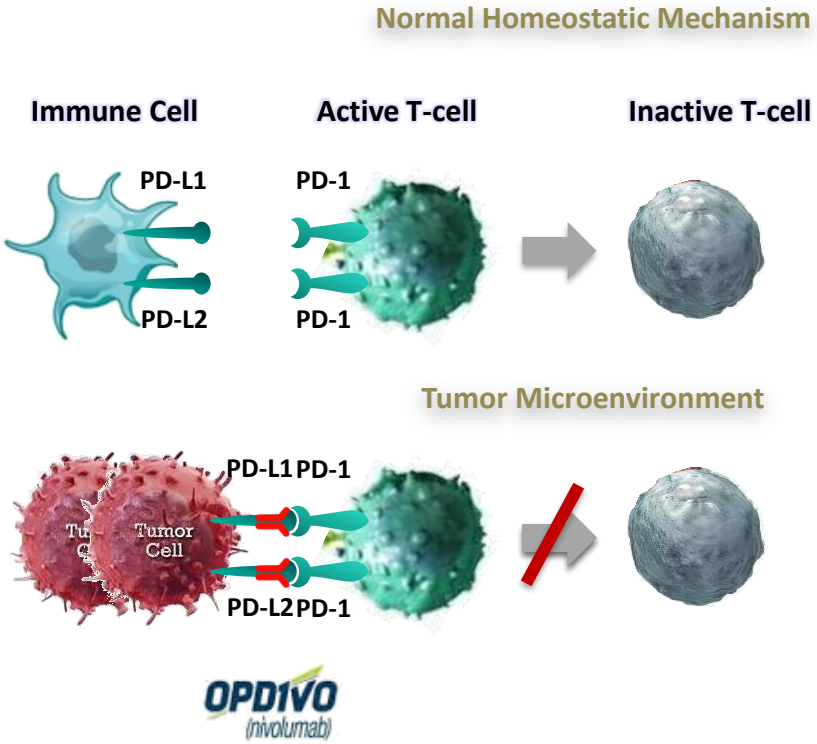

- **OS** HR 0.645 (95% CI 0.450, 0.926; p= 0.0014) adj TMZ
- **PFS** HR 0.586 (95% CI 0.472, 0.727; p < 0.0001) adj TMZ
- Benefit from adjuvant (adj) temozolomide (TMZ) on overall survival (OS) but remained inconclusive about concurrent (conc) TMZ.

Van den Bent, ASCO, SNO 2019

| Notable phase III novel agents targeting glioblastoma multiforme | | | | |
|---|---|---|---|---|
| **Project** | **Mechanism** | **Company** | **Trial ID** | **Notes** |
| Opdivo | Anti-PD-1 MAb | Bristol-Myers Squibb | NCT02617589<br>NCT02667587 | Checkmate-498, vs Temodar: failed May 2019.<br>Checkmate-548, on top of Temodar: data due this year. |
| Depatuxizumab mafodotin | Anti-EGFR ADC | Abbvie | NCT02573324 | Intellance-1 study, on top of Temodar in patients with EGFR amplification: failed May 2019. |
| Toca 511 & Toca FC | Gene therapy & pyrimidine analogue | Tocagen | NCT02414165 | Toca 5 study, on top of Temodar or Avastin. In May 2019 cleared to continue to final readout, due by end 2019. |
| DCVax-L | Cancer vaccine | Northwest Biotherapeutics | NCT00045968 | On top of Temodar. Recruitment halted 2015; still no final readout. |
| Trans sodium crocetinate | Vitamin A analogue | Diffusion Pharmaceuticals | NCT03393000 | Intact study, on top of Temodar, biopsy-only patients: primary completion 2021. |
| Marizomib | Proteasome inhibitor | Celgene | NCT03345095 | EORTC-1709-BTG study, on top of Temodar: primary completion 2022. |

*Source: EvaluatePharma and Clinicaltrials.gov.*

# Programmed Death Pathway and Nivolumab




- Normal function of PD-1 pathway is to attenuate immune response to avoid immune system attack of "self"
- A "brake" to prevent overreaction & overproliferation

- Tumor cells "co-opt" the PD-1 pathway to evade T-cell immune responses

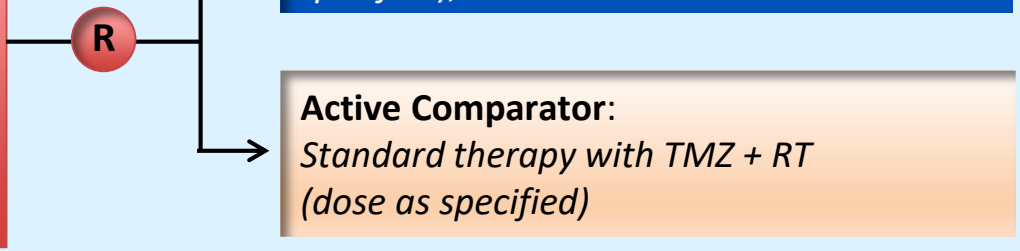
- Nivolumab occupies the PD-1 receptor of T-cells → prevents inhibitory ligand binding & T-cell inactivation

# CheckMate 498
# CA209-498 (NCT02617589): Phase 3 Randomized, Open-Label Study of RT in Combination With Nivolumab or TMZ in Newly Diagnosed *MGMT*-Unmethylated GBM[1]

Estimated enrollment N = 550

**Key inclusion criteria**

- Newly diagnosed brain cancer or tumor called GBM or GBM
- Males and females ≥ 18 years old
- Tumor test result shows MGMT unmethylated type
- KPS ≥ 70%




Start Date: February 2016
Estimated Study Completion Date: October 2019
Estimated Primary Completion Date: March 2019
Status: currently recruiting participants
Study Sponsor: Bristol-Myers Squibb
Collaborator: Ono Pharmaceutical Co. Ltd

- Primary Outcome Measure: 3-year OS
- Secondary Outcome Measure: PFS; 2-year OS

1. Clinicaltrials.gov. NCT02617589. Accessed April 17, 2018.

# CheckMate 498

## CA209-498 (NCT02617589): Phase 3 Randomized, Open-Label Study of RT in Combination With Nivolumab or TMZ in Newly Diagnosed *MGMT*-Unmethylated GBM[1]

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- Tumor test result sho… MGMT unmeth…
- KPS…

R

**Experimental:**

*Nivolumab IV…*

*spe…*

…Measure: 3-year OS

…ry Outcome Measure: PFS; 2-year OS

**Bristol-Myers Squibb Announces Phase 3 CheckMate -498 Study Did Not Meet Primary Endpoint of Overall Survival with Opdivo (nivolumab) Plus Radiation in Patients with Newly Diagnosed MGMT-Unmethylated Glioblastoma Multiforme**

**Category:**

Corporate/Financial News

Thursday, May 9, 2019 6:59 am EDT

1. Clinicaltrials.gov. NCT02617589. Accessed April 17, 2018.

# CheckMate 548
# CA209-548 (NCT02667587): Phase 3, Randomized, Single-Blind Study of TMZ + RT With Nivolumab in Newly Diagnosed *MGMT*-Methylated GBM[1]

Estimated enrollment N = 693

## Key inclusion criteria

- Males and females ≥ 18 years old
- Newly diagnosed brain cancer or tumor called GBM or GBM
- Tumor test result shows MGMT methylated / indeterminate tumor
- KPS ≥ 70%
- Substantial recovery from surgical resection

R

## Experimental:

- Nivolumab IV infusion specified dose on specified days
- RT: 2 gray units 5 times/week for 6 weeks
- TMZ 75 mg/m$^2$ daily during RT, followed by a 4-week treatment break; then TMZ 150 mg/m$^2$ days 1-5 of cycle 1 and increased to 200 mg/m$^2$ days 1-5 of cycles 2-6 as tolerated (additional cycles may be permitted with approval of sponsor)

## Placebo Comparator:

- Placebo IV infusion specified dose on specified days
- RT: 2 gray units 5 times/week for 6 weeks
- TMZ 75 mg/m$^2$ daily during RT, followed by a 4-week treatment break; then TMZ 150 mg/m$^2$ days 1-5 of cycle 1 and increased to 200 mg/m$^2$ days 1-5 of cycles 2-6 as tolerated (additional cycles may be permitted with approval of sponsor)

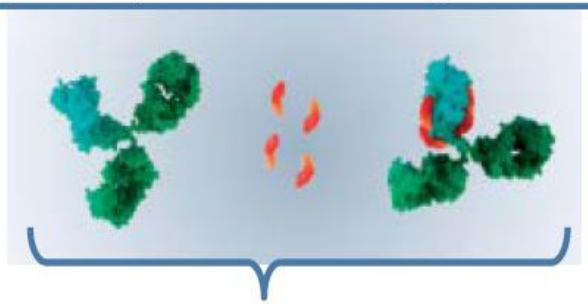
Start Date: May 2016
Estimated Study Completion Date: August 2023
Estimated Primary Completion Date: February 2021
Status: currently recruiting participants
Study Sponsor: Bristol-Myers Squibb
Collaborator: Ono Pharmaceutical Co. Ltd

- Primary Outcome Measures: OS, PFS[a]
- Secondary Outcome Measures: OS, PFS[b]

[a]Determined by BICR; [b]Determined by investigator.

1. Clinicaltrials.gov. NCT02667587. Accessed April 17, 2018.

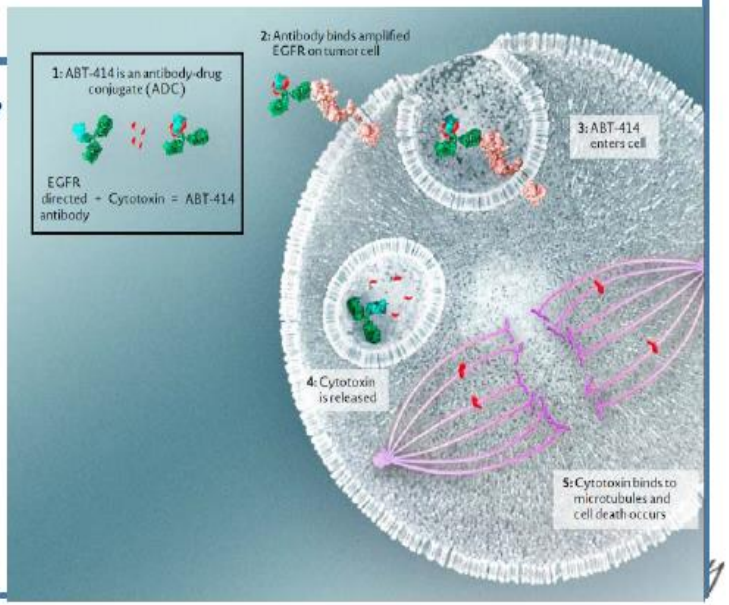
# Depatux-M (ABT-414) is a monoclonal Antibody Drug Conjugate (ADC) directed against EGFR



Antibody (ABT-806) + Toxin (MMAF) = Antibody Drug Conjugate (Depatux-M)

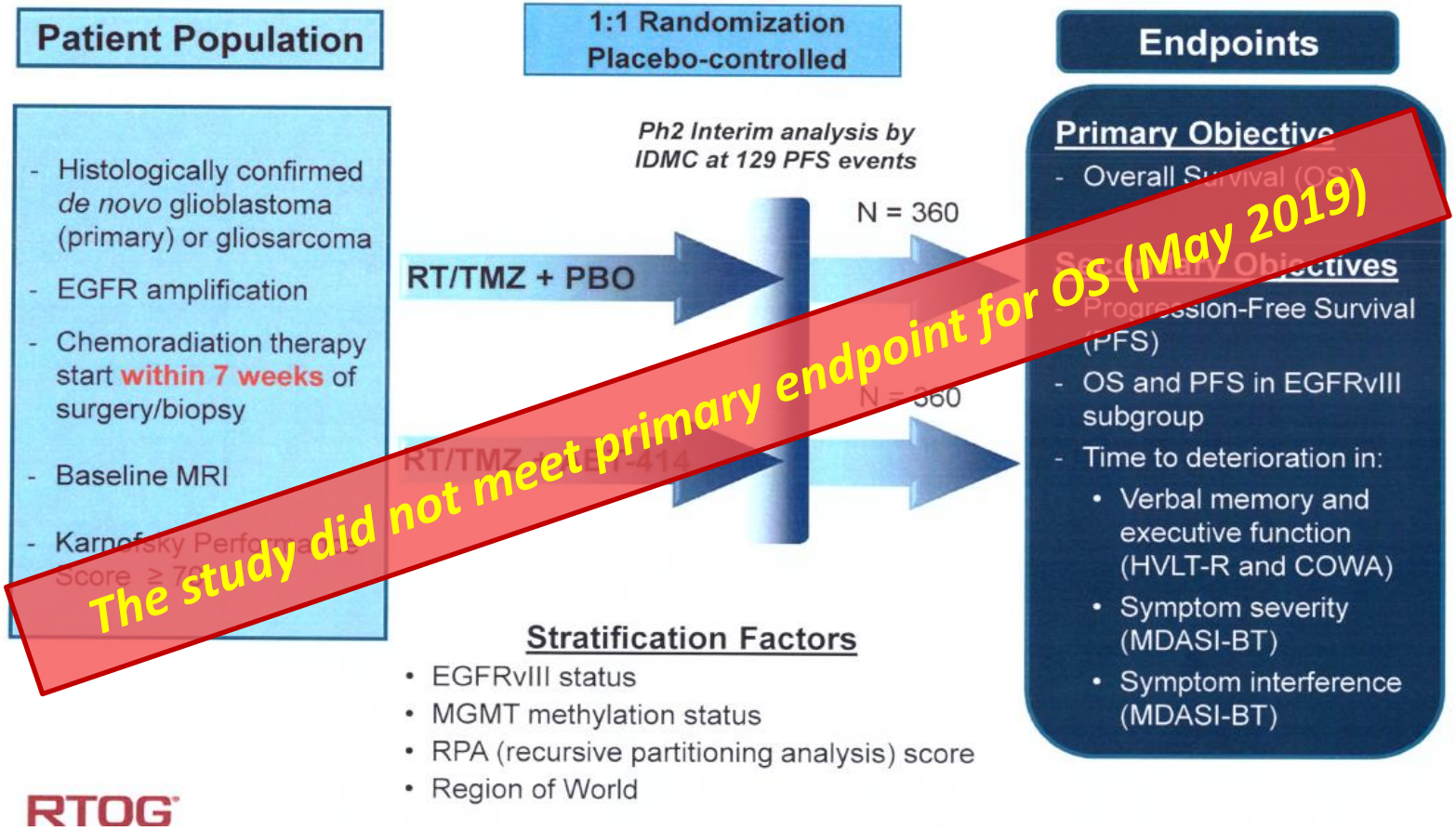
Depatux-M is an **antibody-drug conjugate (ADC),** comprised of an antibody that ***selectively targets activated EGFR*** and a cytotoxin that is **only released inside the *tumor* cell**

- EGFR amplification (~50% of GBM) leads to ***preferential exposure of a unique epitope*** of the EGFR protein that binds Depatux-M
- Unlike other EGFR directed therapies, there is **limited binding to EGFR in normal tissue** such as skin and other epithelial tissue.
- Depatux-M uses ***activated* EGFR** only as a target for **intracellular toxin delivery** and does not inhibit EGFR signaling; therefore, it can work in glioblastoma cells that are **resistant to classical EGFR inhibition**



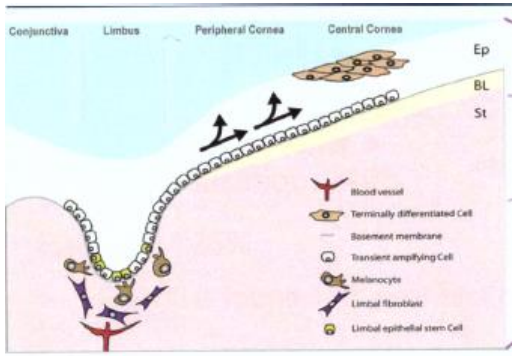

Gan et al, 2012; Trail et al, 2013

# Abbvie

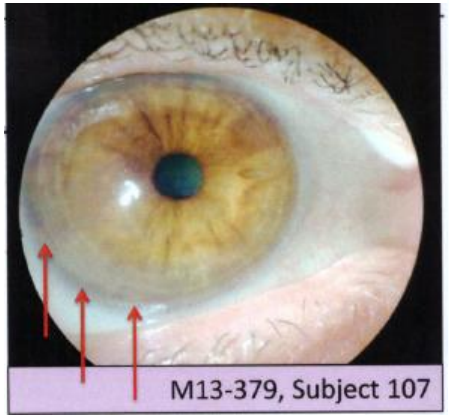



**The study did not meet primary endpoint for OS (May 2019)**

## Microcystic keratopathy and corneal epithelial microcysts



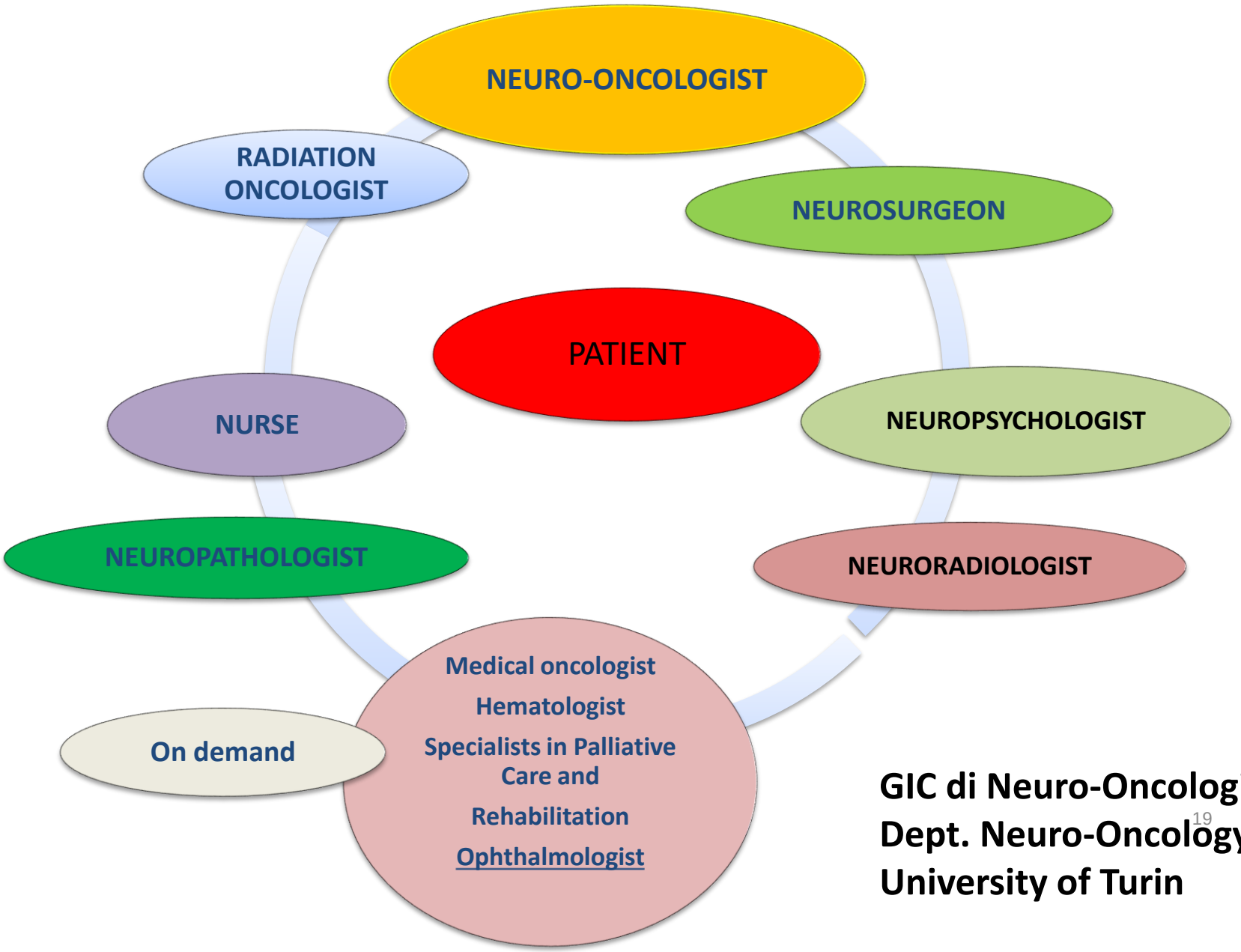

Secker *et al.*, 2010




## Microcystic Keratopathy – Clinical Presentation

- Both eyes typically affected
- Symptoms develop 7 – 28 days from 1st ABT-414 infusion
  - Blurred vision
  - Photophobia
  - Foreign body sensation
  - Dry Eye
  - Eye Pain
- Symptoms are reversible, resolving by 4 – 6 weeks
- Prophylactic steroid eye drops mitigate but do not prevent

**Only 3% discontinued ABT-414 due to eye toxicity**




**GIC di Neuro-Oncologia**
**Dept. Neuro-Oncology,**
**University of Turin**

# Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial

*Giuseppe Lombardi, Gian Luca De Salvo, Alba Ariela Brandes, Marica Eoli, Roberta Rudà, Marina Faedi, Ivan Lolli, Andrea Pace, Bruno Daniele, Francesco Pasqualetti, Simona Rizzato, Luisa Bellu, Ardi Pambuku, Miriam Farina, Giovanna Magni, Stefano Indraccolo, Marina Paola Gardiman, Riccardo Soffietti, Vittorina Zagonel*

*Lancet Oncol* 2019; 20: 110–119

Published Online
December 3, 2018
http://dx.doi.org/10.1016/
S1470-2045(18)30675-2

# REGOMA: study design

**A randomized, multicenter, controlled open-label phase II clinical trial**

**rGBM after RT/TMZ (Stupp protocol)**

- *PD by RANO criteria at least 12 weeks after completion of radiotherapy, unless the recurrence is outside the radiation field or has been histologically documented*
- *At least 1 bi-dimensionally measurable target lesion with 1 diameter of at least 10mm*
- *Histologically confirmed GBM*
- *ECOG PS 0-1 (KPS≥70)*

R

1:1

**Regorafenib**
**160mg/day (3 weeks on, 1 week off)**

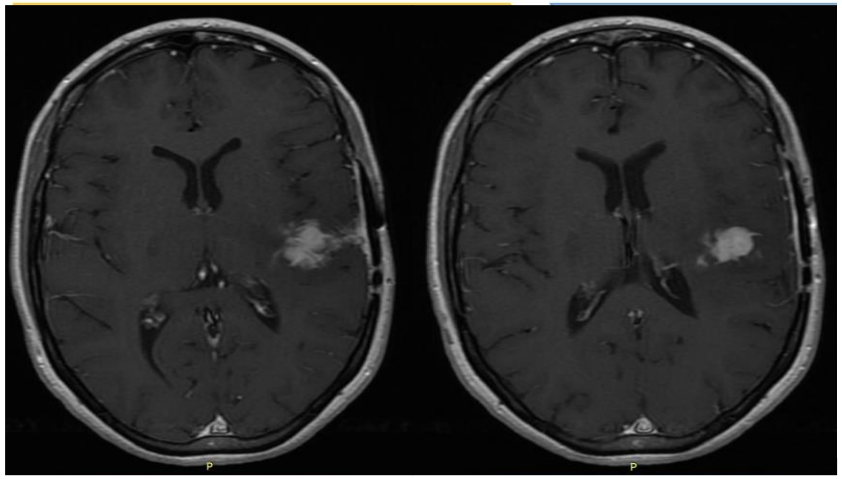
**Lomustine**
**110mg/m2 day1 (every 6 weeks)**

**Treat until PD** *(RANO criteria)*

- Stratification factors: center and surgery at recurrence
- Study location: 10 centers in Italy

Lancet Oncology, 2019

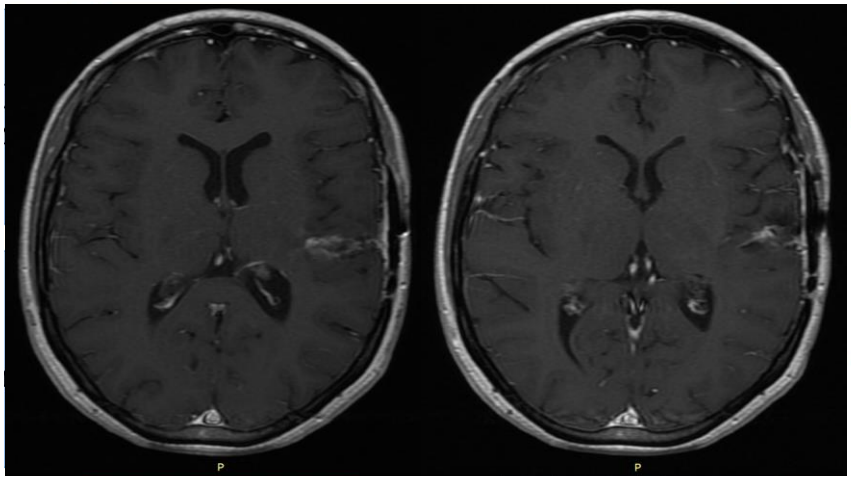
# From personalised to precision therapy



**Anaplastic ganglioglioma**

Relapse after chemoradiation before dabrafenib

Major partial response following 1 year of dabrafenib



*Pasqualetti F, …Rudà R et al, NeuroOncology, 2019*

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Central Nervous System Cancers

Version 2.2019 — September 16, 2019

- **There are no identified targeted agents with demonstrated efficacy in glioblastoma. However, the panel encourages molecular testing of tumor because if a driver mutation is detected, it may be reasonable to treat with a targeted therapy on a compassionate use basis and/or the patient may have more treatment options in the context of a clinical trial. Molecular testing also has a valuable role in improving diagnostic accuracy and prognostic stratification that may inform treatment selection.**

Neuro-Oncology

XX(XX), 1–11, 2019 | doi:10.1093/neuonc/noz119 | Advance Access date 4 July 2019

## The medical necessity of advanced molecular testing in the diagnosis and treatment of brain tumor patients

Craig Horbinski, Keith L. Ligon, Priscilla Brastianos, Jason T. Huse, Monica Venere, Susan Chang, Jan Buckner, Timothy Cloughesy, Robert B. Jenkins, Caterina Giannini, L. Burt Nabors, Patrick Y. Wen, Kenneth J. Aldape, Rimas V. Lukas, Evanthia Galanis, Charles G. Eberhart, Daniel J. Brat, and Jann N. Sarkaria

# IDH mutations and brain tumour related epilepsy

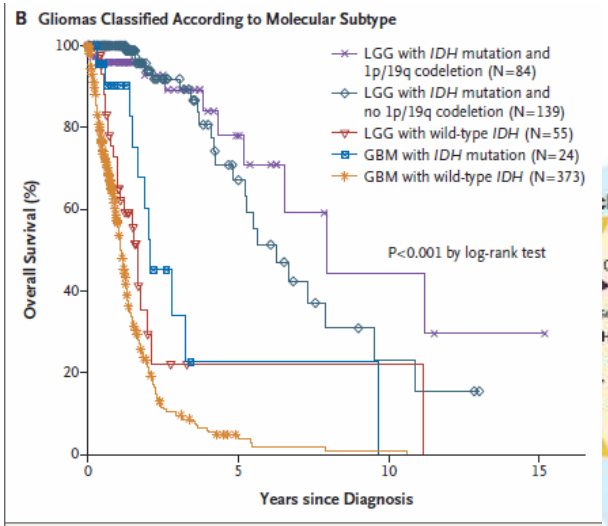
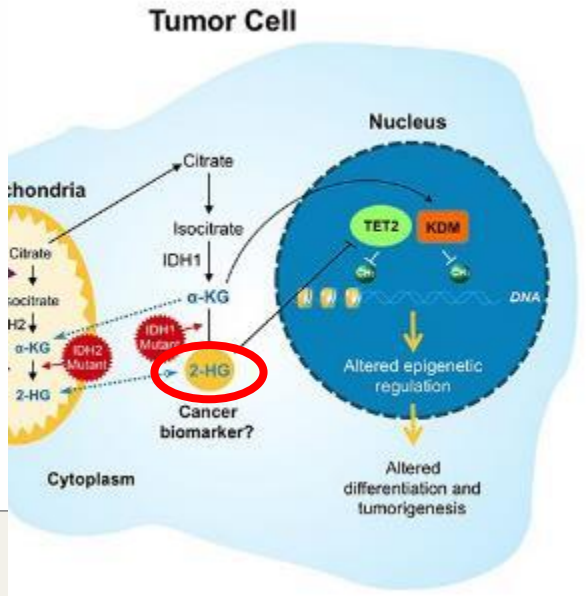



**Figure 6. Clinical Outcomes.**

Panel A shows Kaplan–Meier estimates of overall survival among patients with LGGs that are classified according to traditional histologic type and grade. GBM samples (from previously published Cancer Genome Atlas data[22]) are also included for comparison. Panel B shows overall survival among patients with LGGs that are classified according to *IDH* mutation and 1p/19q codeletion status. GBM samples classified according to *IDH* mutation status are also included. The results of an age-adjusted analysis are provided in Table S2 in Supplementary Appendix 1. [illegible] type, grade, and molecular subtype is shown in Fig. S22 in Supplementary Appendix 1.

*Brat et al N Engl J Med. 2015 ;372(26):2481-98.*




*Luibinas et al. Epilepsia 2014*

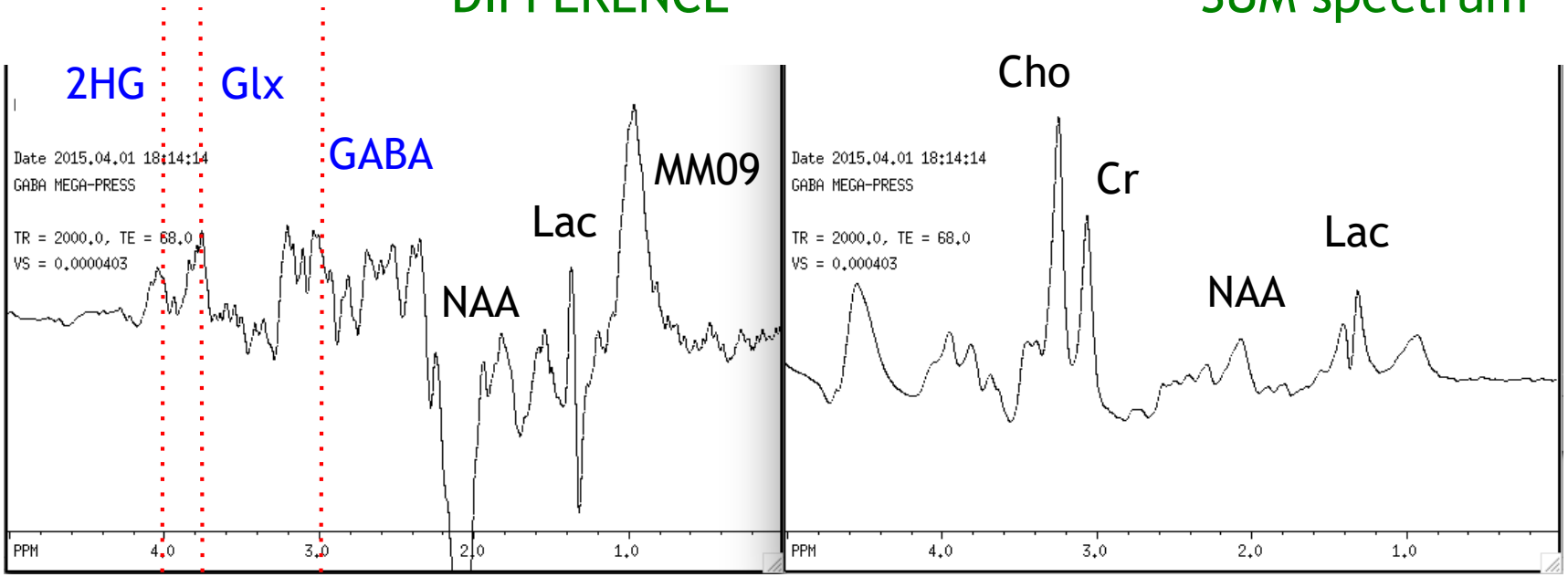
**2-HG may increase BTR epilepsy by mimicking glutamate on NMDA receptors**

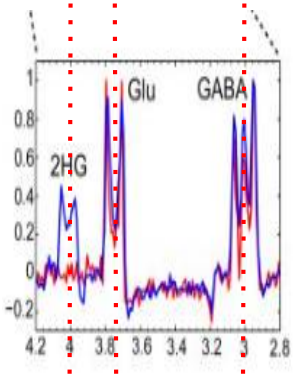
*H. Chen et al, Neurology 2017*

# 2HG and GABA in astrocytoma WHO-II (IDH mutant)

DIFFERENCE

SUM spectrum




MEGA-PRESS sequence

TR/TE= 2000/68 msec
VOI = 30 ml
NEX = 240
TA = 8 min

UNIVERSITÀ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

## Division of Neuro-Oncology
## Department of Neurosciences

**Roberta Rudà**

**Riccardo Soffietti**

Federica Franchino

Edoardo Pronello

Francesco Bruno

Francesca Mo

Alessia Pellerino

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## John Hopkins University

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M. G. Bruzzone

**Alberto Bizzi**

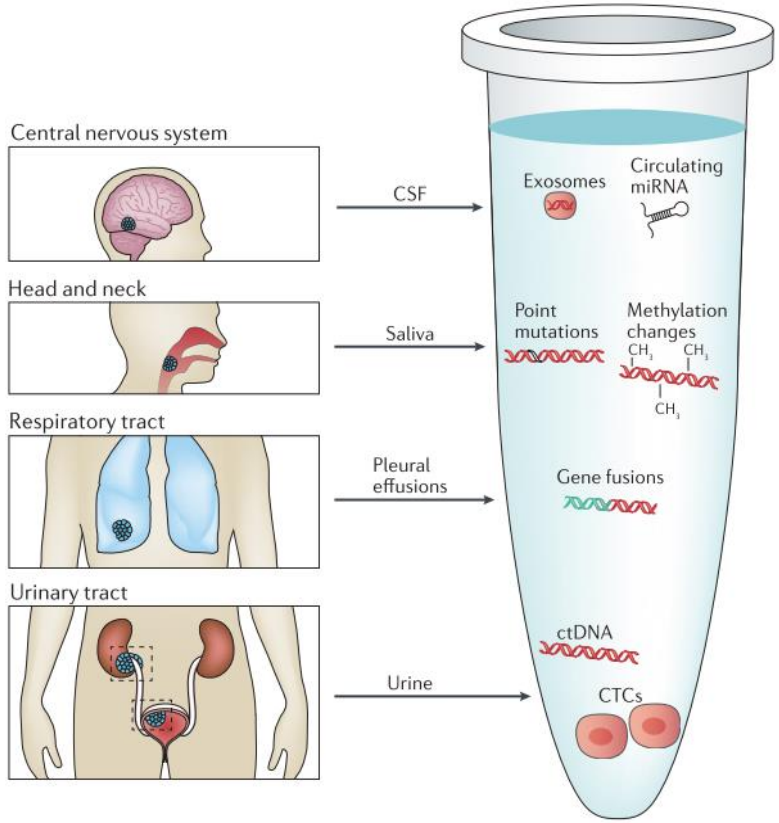
Riccardo Pascuzzo

# LIQUID BIOPSY
# IN PRIMARY BRAIN TUMOURS

# Which source for liquid biopsy?

- Blood
- CSF
- Other?

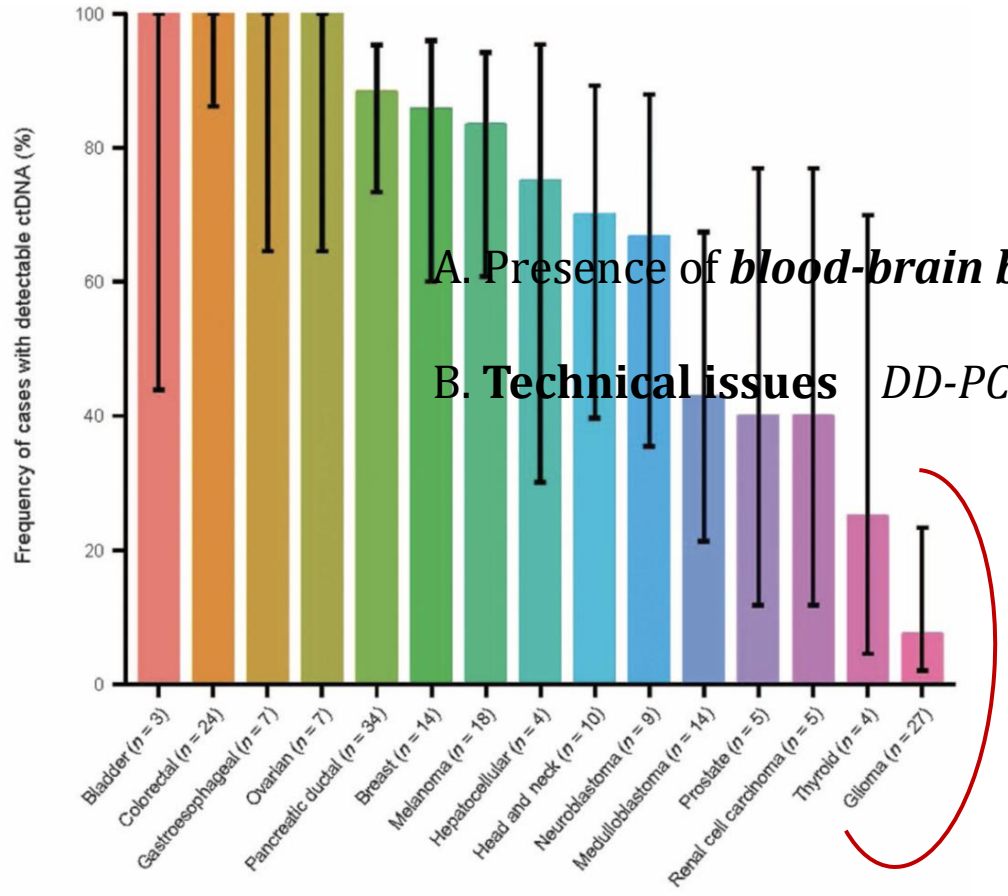
The source has to be *representative* of the specific disease of clinical interest




Siravegna G et al., *Nat Rev Clin Oncol* 2017

# Circulating Tumour DNA (ctDNA)

Blood ctDNA of primary brain tumour patients is **low compared to other tumours** that are able to transfer ctDNA fragments into blood




A. Presence of ***blood-brain barrier*** (BBB)

B. **Technical issues** *DD-PCR or NGS?*

Bettegowda et al, *Sci Tranl Med*, 2014

nature COMMUNICATIONS

ARTICLE

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DOI: 10.1038/ncomms9839 OPEN

# Cerebrospir fluid derived circulating tumour DNA better of brain tun erations

Leticia De Mattos-Arruda co Martínez-Ricarte[3,4], Davis Torrejon[1], Mafalda ena Guerini-Rocco[2], Elena Martínez-Sáez[4], Se oglio[2], Russel Towers[7], Ana Vivancos[1], Vicente P aría González-Cao[8], Josep Tabernero[1,3], Enriqu tes[1,3], Jorge S. Reis-Filho[2] & Joa

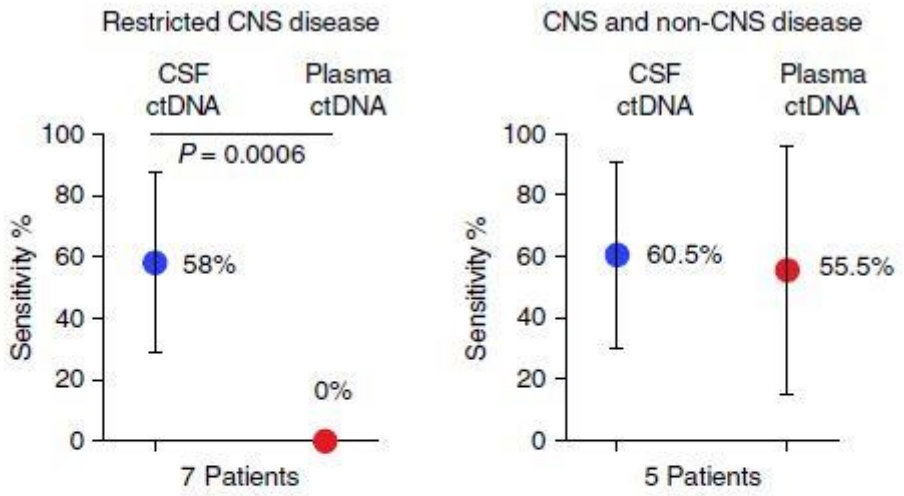


**Figure 2 | Sensitivity analysis of CSF ctDNA and plasma ctDNA.** Sensitivity was inferred based on gene mutations detected in central nervous system (CNS) tumours, which were either identified in CSF or plasma ctDNA (Supplementary Table 5). Data were pooled and the mean with standard deviation error bars is shown. A Mann–Whitney test was used for the analysis and *P* value is shown.

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DEGLI STUDI
DI TORINO

ISTITUTO DI CANDIOLO - IRCCS

## Division of Neuro-Oncology
## Department of Neurosciences

**Roberta Rudà**

**Riccardo Soffietti**

**Federica Franchino**

**Alessia Pellerino**

**Francesco Bruno**

## Division of Neurosurgery
## Department of Neurosciences

**Diego Garbossa**

Antonio Melcarne

R. Altieri

P. Zeppa

## Pathology Unit
## Department of Medical Science

Paola Cassoni

**Luca Bertero**

# Laboratory of Cancer Stem Cell Research

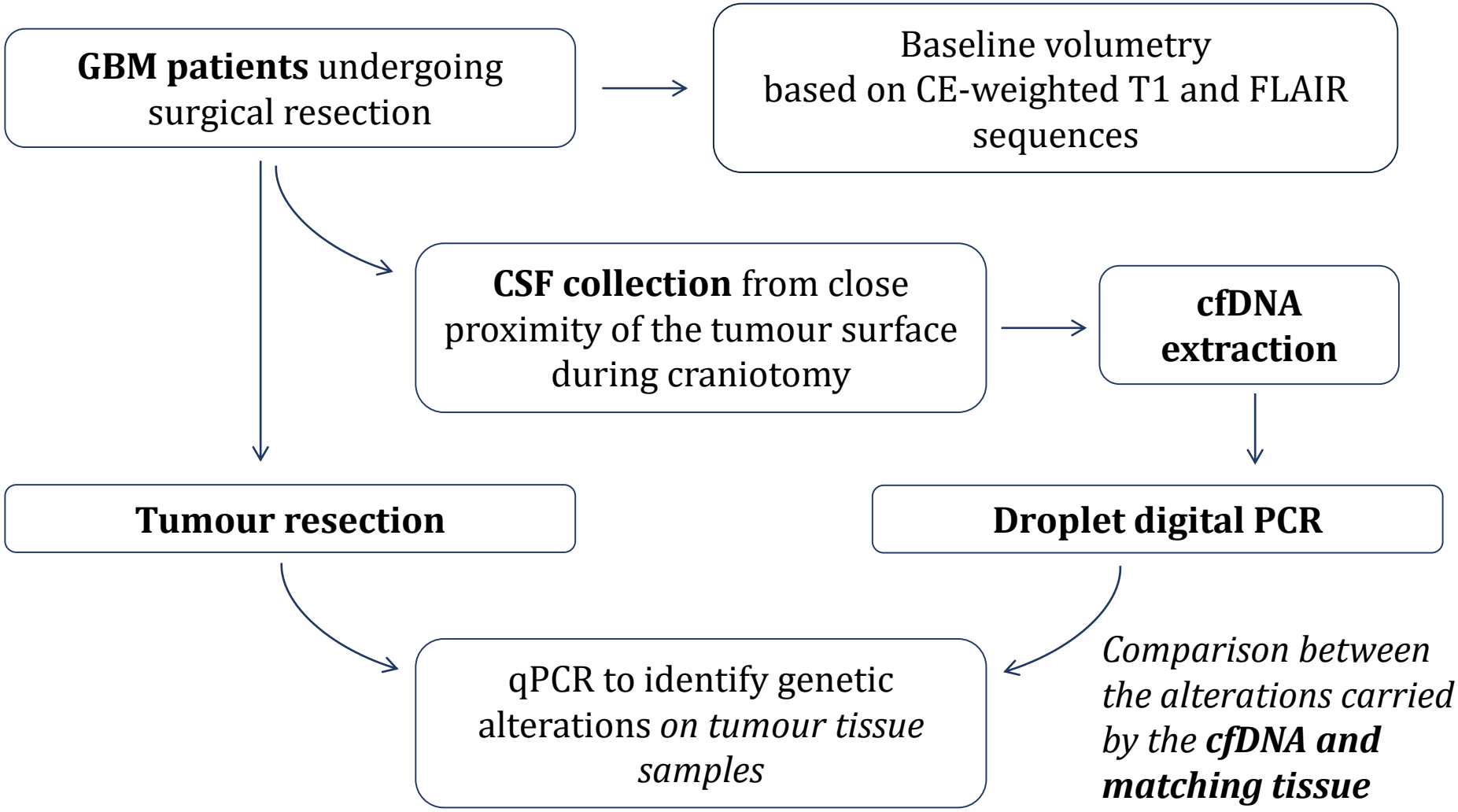
Candiolo Cancer Institute
University of Turin

**Carla Boccaccio**

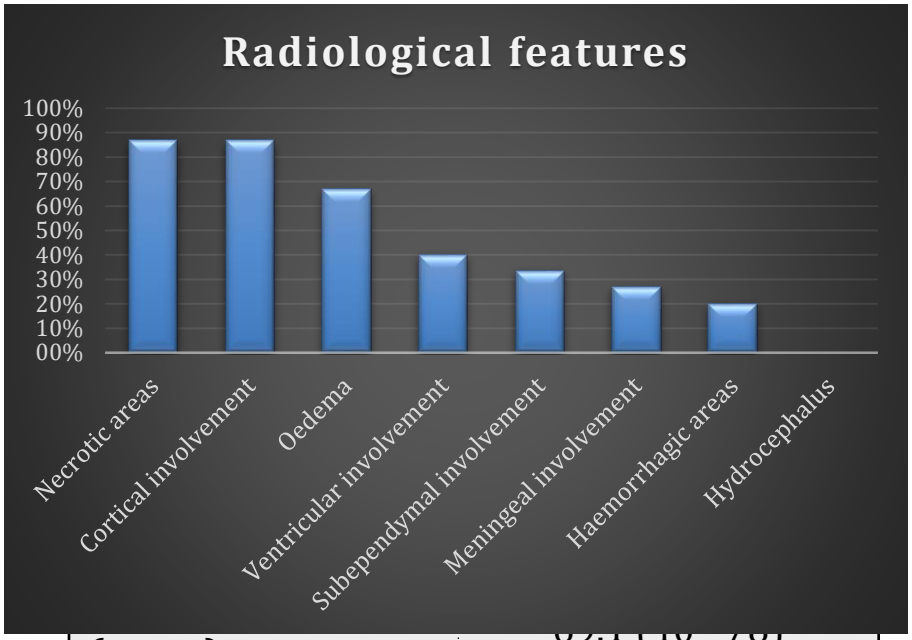
F. N. Orzan

F. De Bacco

# PATIENTS AND METHODS



# RESULTS

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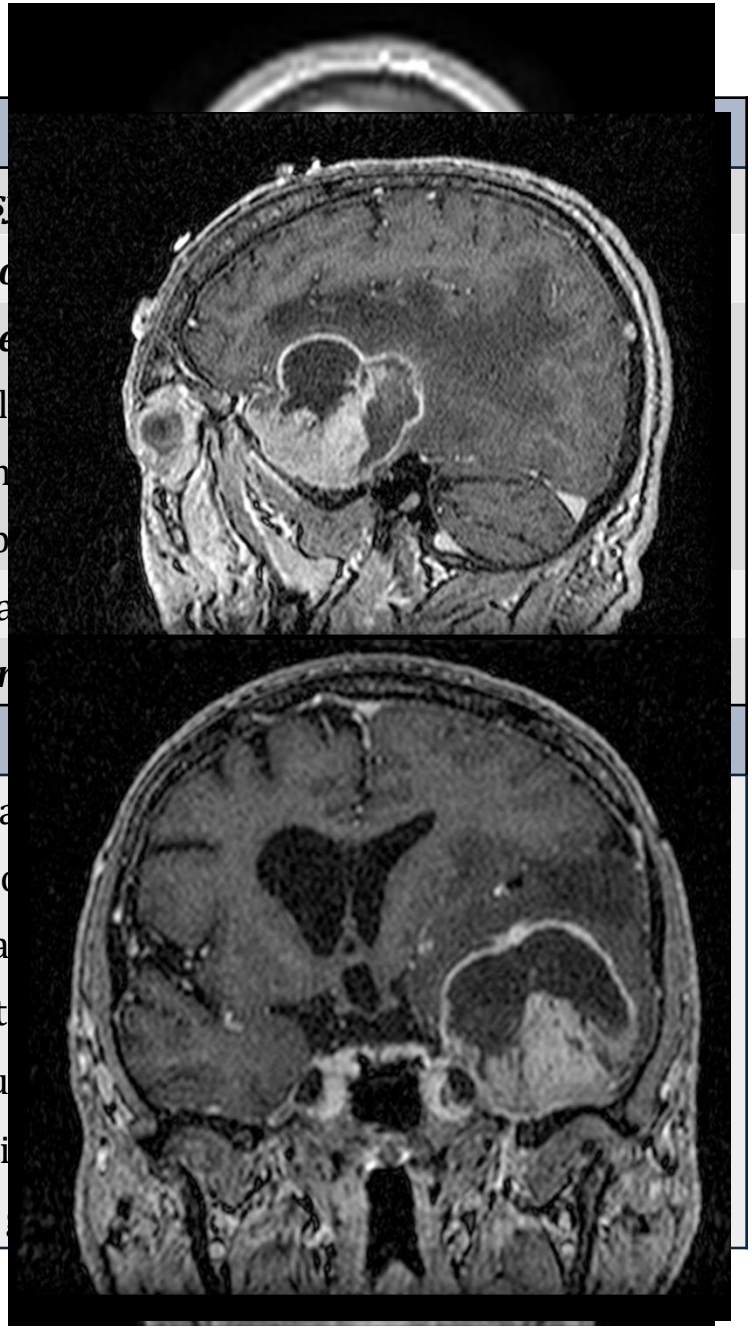
| Basal | |



# RESULTS

Tissue

CSF

| ID | Copy number variations | | | | | Point mutations | | | | | | Alterations tested on CSF | | Processable DNA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Profiling | EGFR | PDGFRA | CDK4 | MDM2 | CKDN2A | TP53 | PTEN | IDH1 | NRAS | PI3KR1 | pTERT | Copy number | Mutation | |
| 31002098 | amp | 0 | 0 | 0 | del | NA | NA | NA | NA | NA | NA | EGFR | | 1 |
| 31002100 | 0 | gain | 0 | 0 | del | 0 | 0 | 0 | 0 | 1 | NA | | PI3KR1 | 1 |
| 31002108 | 0 | 0 | amp | 0 | 0 | 1 | 0 | 0 | NA | NA | 1 | CDK4 | | 1 |
| 31002112 | amp | gain | amp | amp | del | 0 | 0 | 0 | NA | NA | 1 | EGFR / CDK4 / MDM2 | | 1 |
| 31002107 | 0 | amp | gain | 0 | del | 1 | 1 | 0 | NA | NA | NA | PDGFRA | | 1 |
| 31002093 | 0 | 0 | 0 | 0 | del | 0 | 0 | 0 | 0 | 0 | NA | CKDN2A | | 1 |
| 31002088 | gain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NA | EGFR | | 1 |
| 31002080 | amp | 0 | amp | amp | 0 | 0 | 1 | 0 | NA | NA | NA | EGFR / CDK4 / MDM2 | | 1 |
| 31002103 | 0 | gain | amp | 0 | 0 | 1 | 0 | 1 | 0 | NA | NA | PDGFRA / CDK4 | TP53 / IDH1 | 2 |
| 31002119 | amp | 0 | 0 | 0 | del | NA | NA | NA | NA | NA | 1 | EGFR / CKDN2 | pTERT | 2 |
| 31002095 | 0 | 0 | 0 | amp | del | 0 | 0 | 0 | 0 | 0 | 1 | MDM2 / CKDN2 | pTERT | 2 |
| 31002110 | amp | 0 | 0 | 0 | del | NA | NA | NA | NA | NA | 1 | EGFR / CKDN2 | pTERT | 0 |
| 31002091 | 0 | gain | 0 | 0 | del | 1 | 1 | 0 | NA | NA | NA | PDGFRA / CKDN2 | TP53 / PTEN | 0 |

# RESULTS

**CtDNA concentration in the CSF** seems significantly related to **baseline contrast-enhancement volume** and **FLAIR/contrast enhancement ratio** ($p$ = 0.018 and $p$ = 0.025 respectively).

| DNA concentration | | | | | |
|---|---|---|---|---|---|
| | Not standardised coefficients | | Standardised coefficients | | |
| ***Model*** | ***B*** | ***Standard deviation Error*** | ***Beta*** | ***t*** | ***Sig.*** |
| **Constant** | 0.388 | 0.54 | | 0.719 | 0.524 |
| **C.E. volume** | 0.029 | 0.006 | 0.98 | 4.766 | 0.018 |
| **FLAIR volume** | -0.007 | 0.004 | -0.292 | -1.883 | 0.156 |
| **FLAIR / C.E.** | 0.124 | 0.029 | 0.716 | 4.208 | 0.025 |
| **CSF volume** | -1.294 | 0.672 | -0.298 | -1.926 | 0.15 |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