How to improve the outcome of glioblastoma patients

Professor Bart Neyns MD PhD

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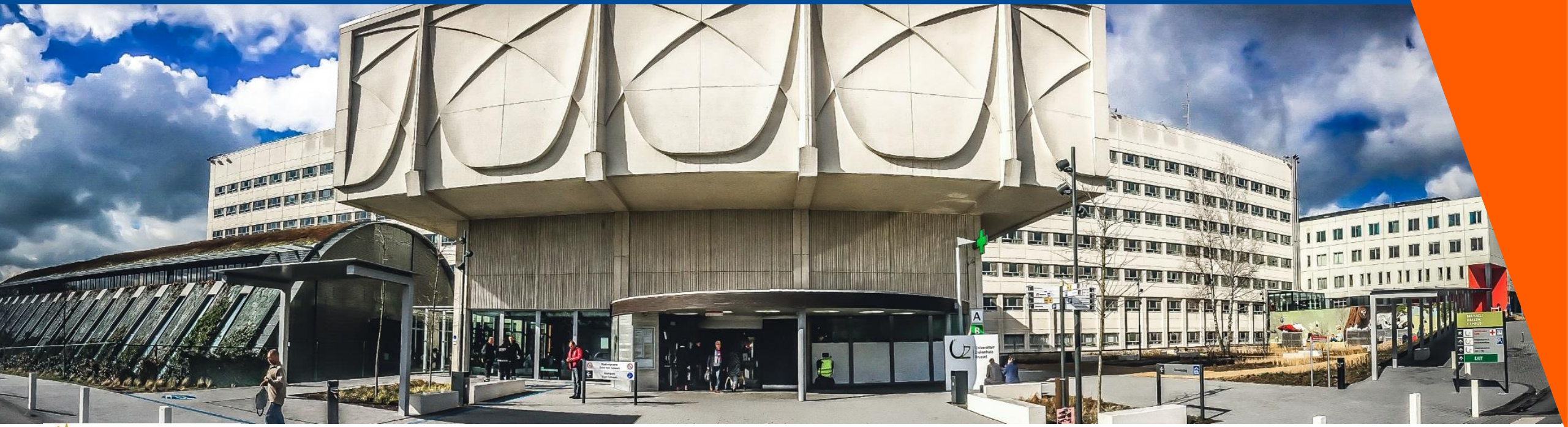

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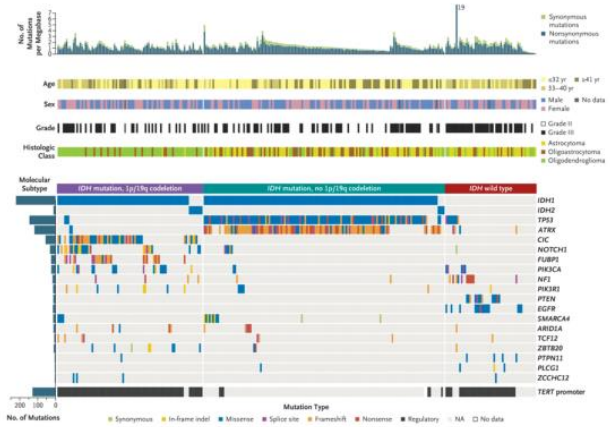
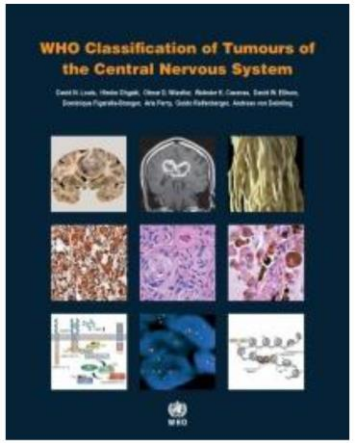
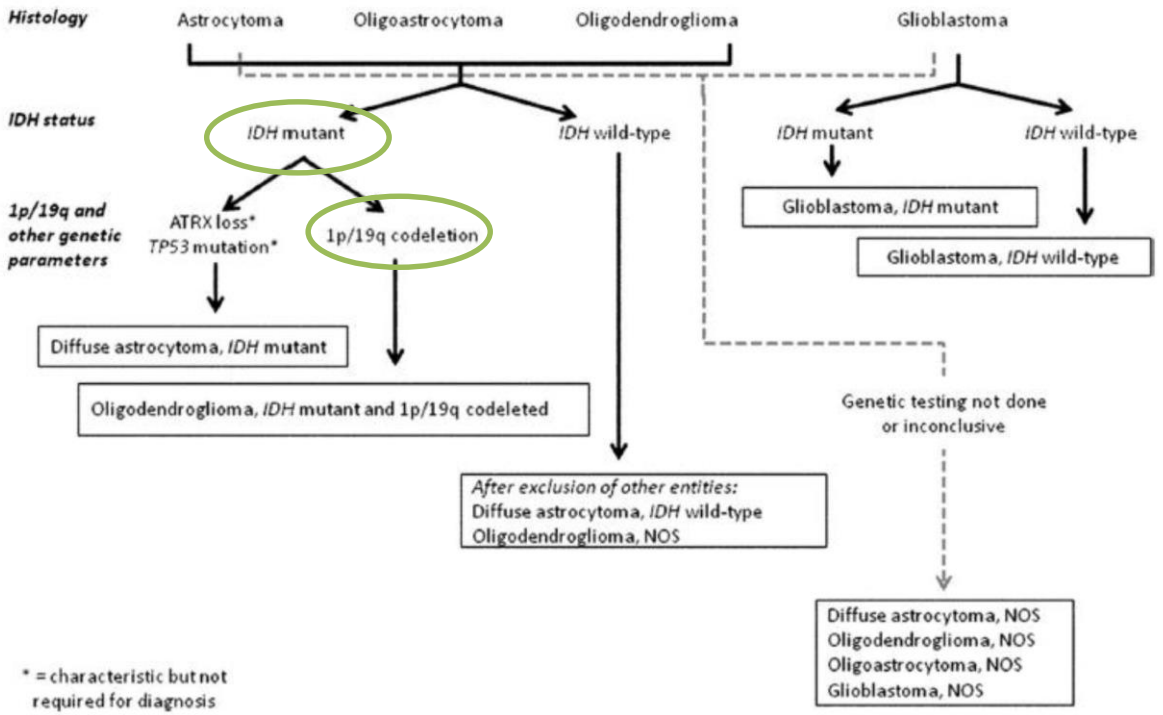
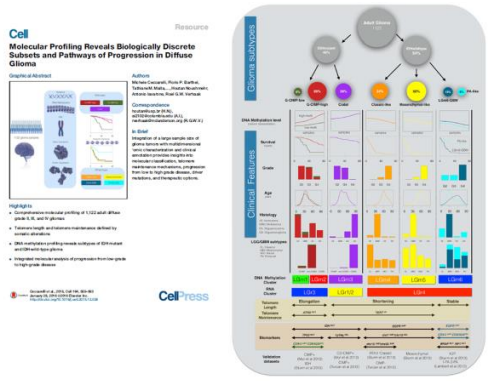
Classification of Diffuse Glioma



N Engl J Med 2015; 372:2481-2498
DOI: 10.1056/NEJMoa1402121







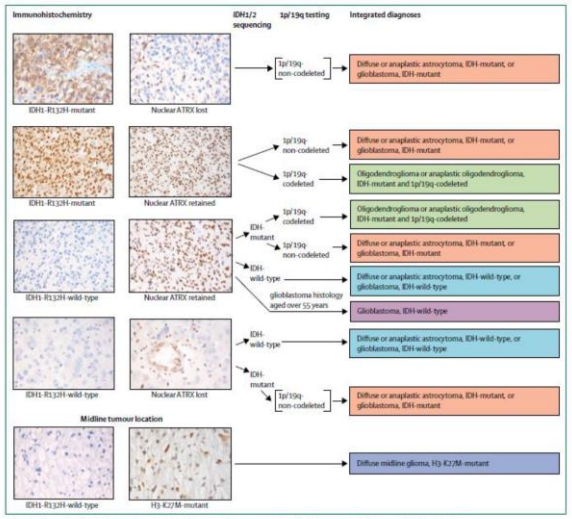
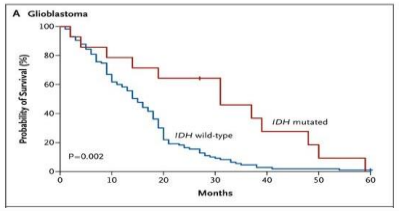
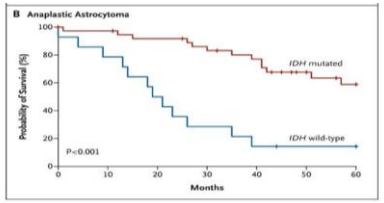


Figure 1: Diagnostic algorithm for integrated classification of diffuse astrocytic and oligodendroglial gliomas, including glioblastoma

THE 2017 EANO GUIDELINELANCET ONCOLOGY 2017;18:E315-E329





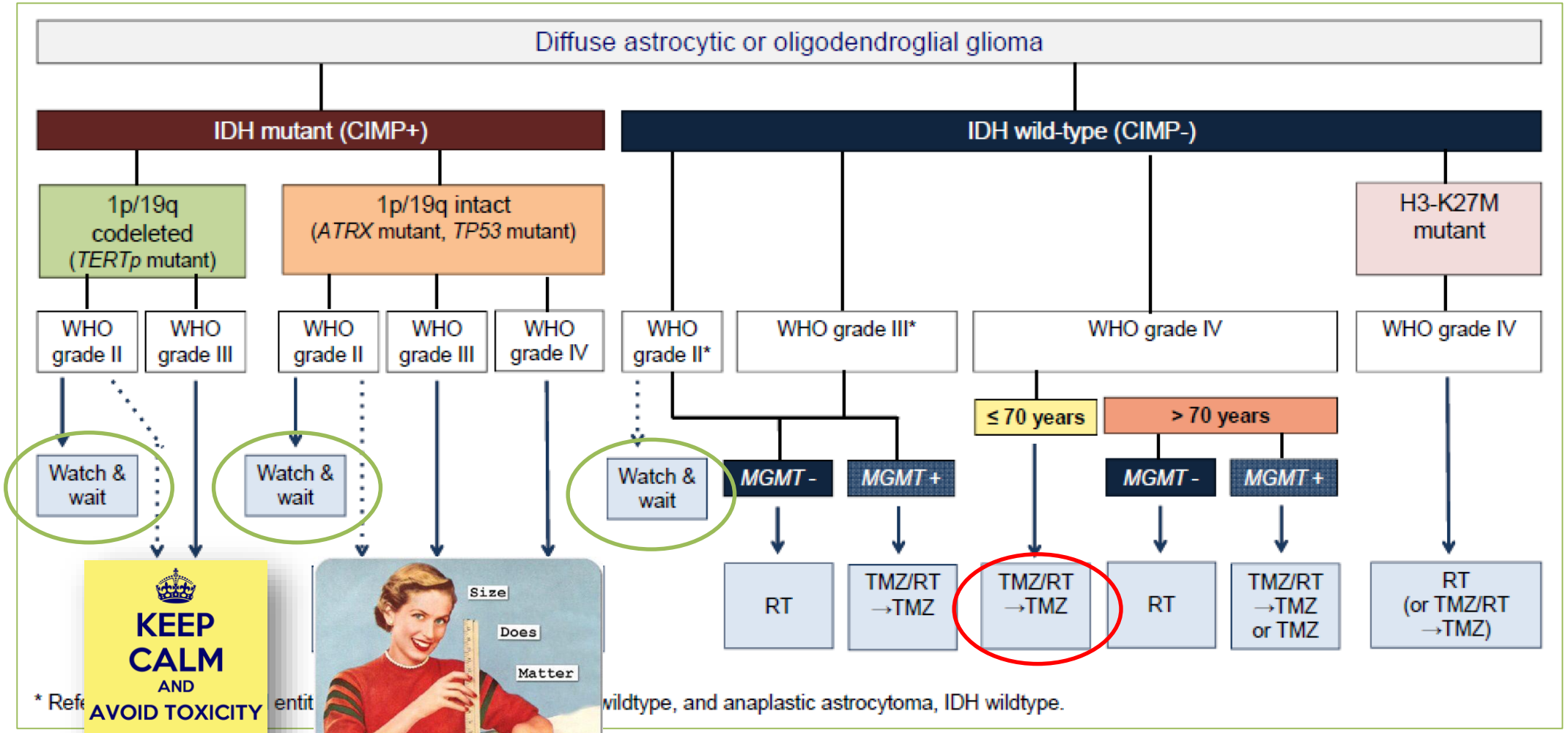
ORIGINAL ARTICLE

IDH1 and IDH2 Mutations in Gliomas

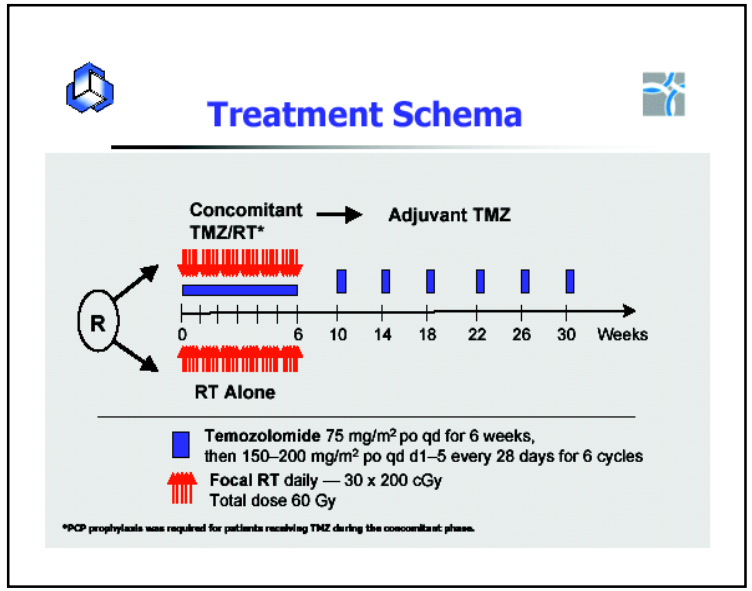
Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., et al.

Standard Treatment for Diffuse Glioma

THE 2017 EANO GUIDELINELANCET ONCOLOGY 2017;18:E315-E329



EORTC 26981/22981-NCIC CE3
Phase III Randomized Trial on RT vs. RT/TMZ + TMZ for GBM



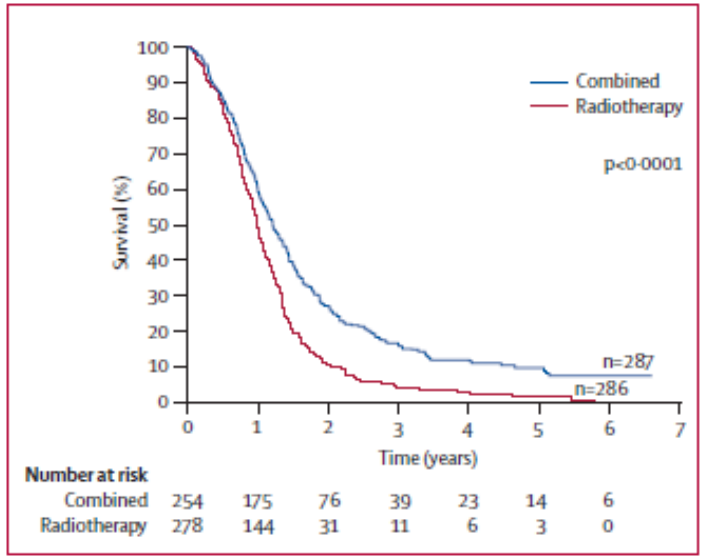
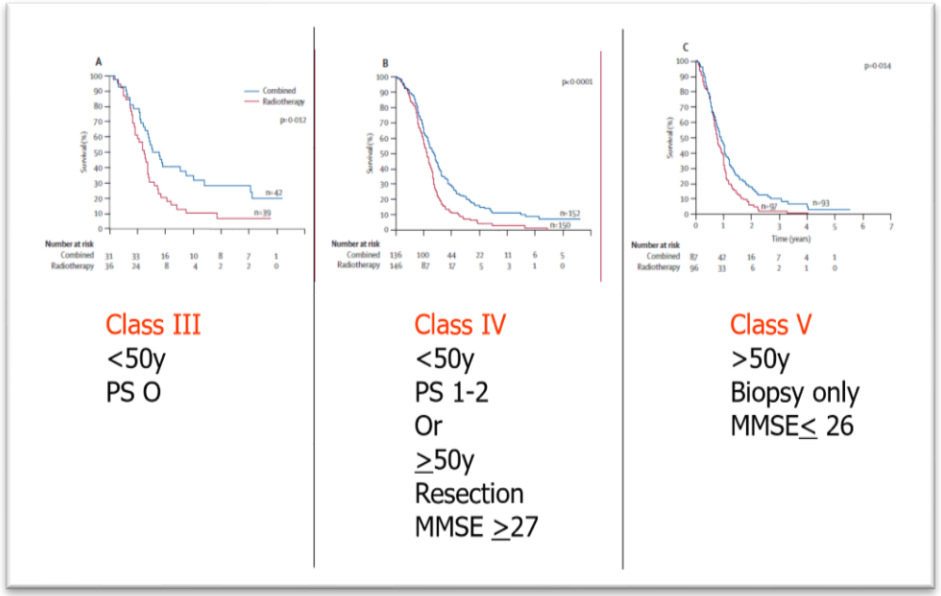


Figure 2: Kaplan-Meier estimates of overall survival by treatment group



	Deaths/ patients	Hazard ratio (95% CI)	Median (months; 95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
Overall							
Radiotherapy	278/286	1·0	12·1 (11·2–13·0)	10·9 (7·6–14·8)	4·4 (2·4–7·2)	3·0 (1·4–5·7)	1·9 (0·6–4·4)
Combined	254/287	0·6 (0·5–0·7)	14·6 (13·2–16·8)	27·2 (22·2–32·5)	16·0 (12·0–20·6)	12·1 (8·5–16·4)	9·8 (6·4–14·0)

Without a negative effect on HRQOL

Stupp R et al. N Engl J Med 2005; Taphoorn et al. Lancet Oncology 2005; Stupp R et al Lancet Oncology 2009; Mirimanoff RO et al., JCO 2006

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

James R. Perry, M.D., Normand Laperriere, M.D., Christopher J. O'Callaghan, D.V.M., Alba A. Brandes, M.D., Johan Menten, M.D., Claire Phillips, M.B., B.S., Michael Fay, M.B., Ch.B., Ryo Nishikawa, M.D., J. Gregory Cairncross, M.D., Wilson Roa, M.D., David Osoba, M.D., John P. Rossiter, M.B., B.Ch., Arjun Sahgal, M.D., Hal Hirte, M.D., Florence Laigle-Donadey, M.D., Enrico Franceschi, M.D., Olivier Chinot, M.D., Vassilis Golfinopoulos, M.D., Laura Fariselli, M.D., Antje Wick, M.D., Loic Feuvret, M.D., Michael Back, M.B., B.S., Michael Tills, M.B., B.S., Chad Winch, M.Sc., Brigitta G. Baumert, M.D., Wolfgang Wick, M.D., Keyue Ding, Ph.D., and Warren P. Mason, M.D., for the Trial Investigators*

METHODS

We conducted a trial involving patients 65 years of age or older with newly diagnosed glioblastoma. Patients were randomly assigned to receive either radiotherapy alone (40 Gy in 15 fractions) or radiotherapy with concomitant and adjuvant temozolomide.

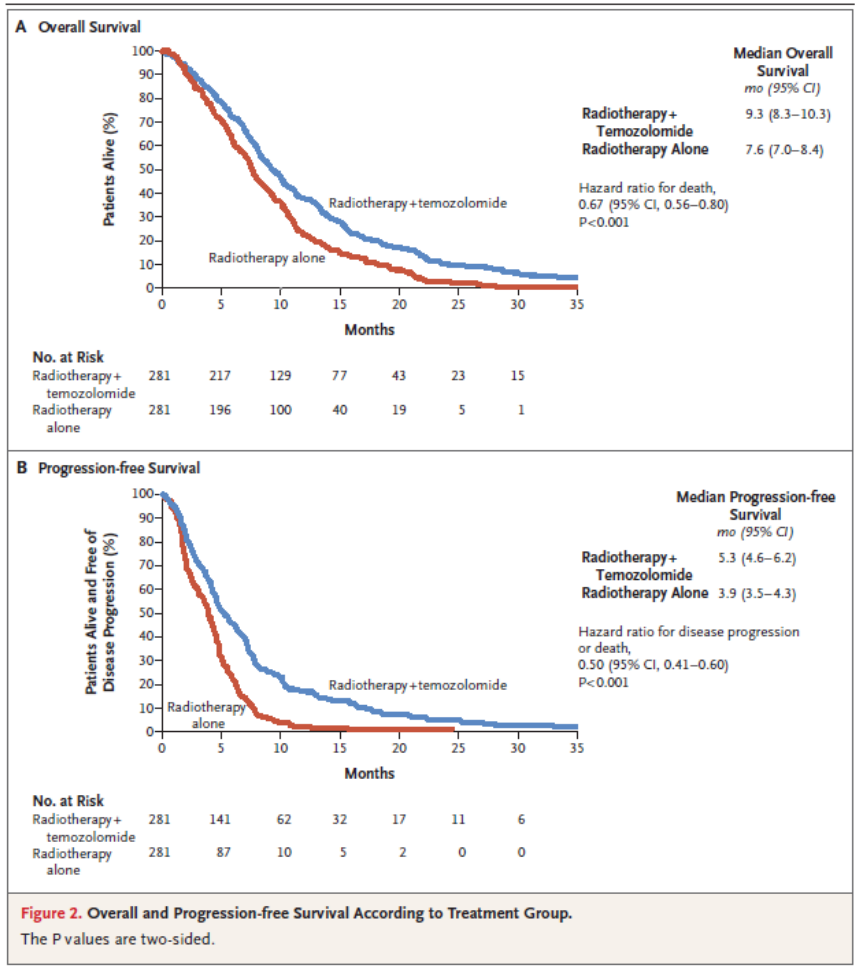
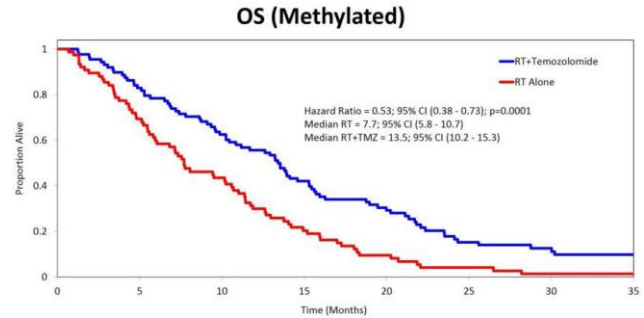
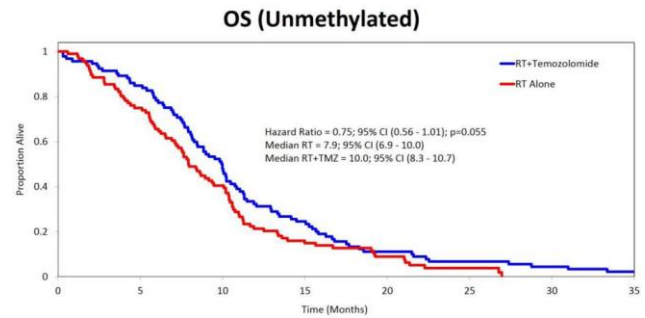


Figure 2. Overall and Progression-free Survival According to Treatment Group.
The P values are two-sided.





CONCLUSIONS

In elderly patients with glioblastoma, the addition of temozolomide to short-course radiotherapy resulted in longer survival than short-course radiotherapy alone. (Funded by the Canadian Cancer Society Research Institute and others; ClinicalTrials.gov number, NCT00482677.)

N Engl J Med 2017;376:1027-37.
DOI: 10.1056/NEJMoa1611977

EORTC

The future of cancer therapy

Second interim and 1st molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion

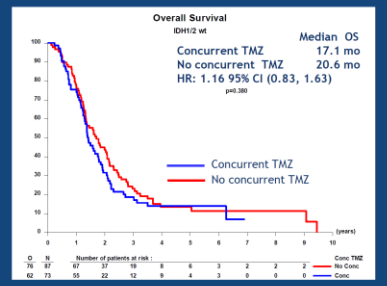
M J van den Bent, S Erridge, M A Vogelbaum, AK Nowak, M Sanson, A A Brandes, W Wick, P M Clement, J F Baurain, W Mason, H Wheeler, M Weller, K Aldape, P Wesseling, J M Kros, C M S Tesileanu, V Golfinopoulos, T Gorlia, B G Baumert, P French

on behalf of the EORTC Brain Tumor Group and partners

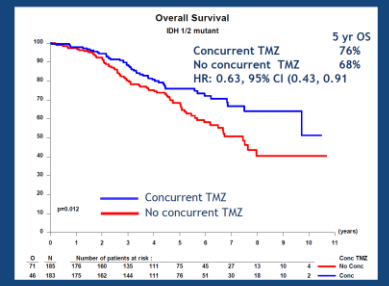
NOA Neuroonkologische Arbeitsgemeinschaft | NRG ONCOLOGY | MRC Medical Research Council | COGNO Cooperative Trials Group for Neuro-Oncology | Canadian Cancer Trials Group

Concurrent temozolomide in IDHwt and IDHmt anaplastic astrocytoma

IDH wild type



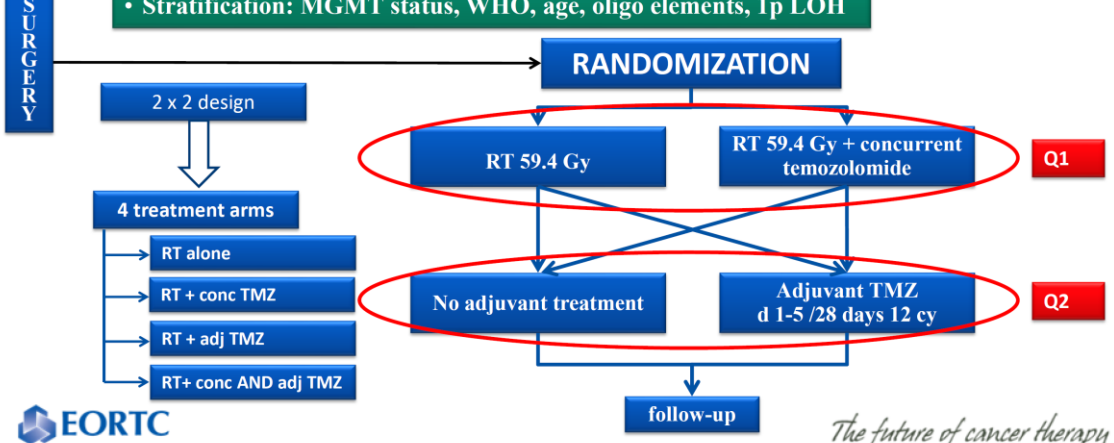
IDH mutant



➢ Concurrent temozolomide improves outcome in IDH mutant anaplastic astrocytoma

Intergroup phase III trial on concurrent and adjuvant temozolomide in non-1p/19q deleted anaplastic glioma

- Centrally confirmed grade III glioma
- No 1p/19q co-deletion
- Stratification: MGMT status, WHO, age, oligo elements, 1p LOH

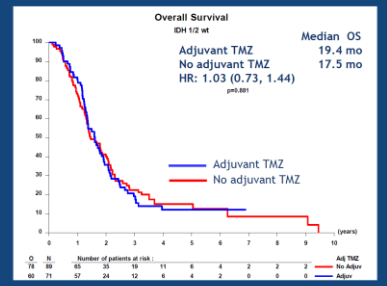


EORTC

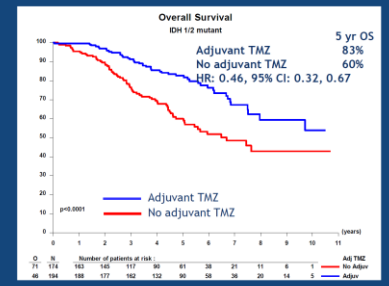
The future of cancer therapy

Adjuvant temozolomide in IDHwt and IDHmt anaplastic astrocytoma

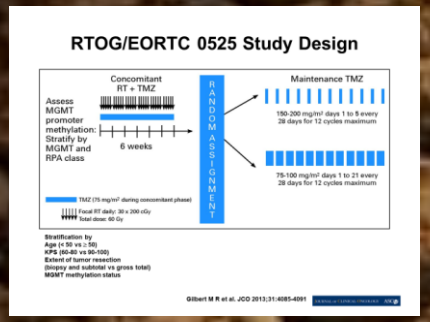
IDH wild type

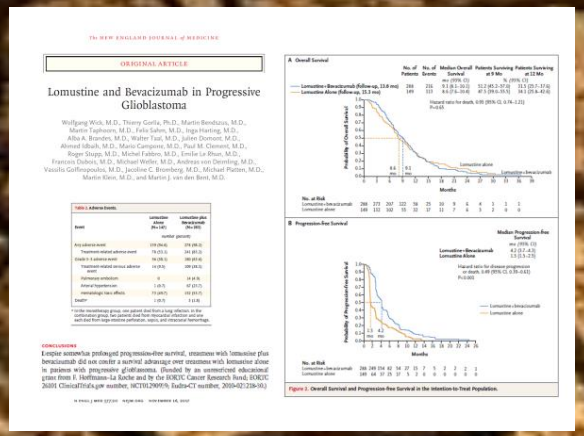


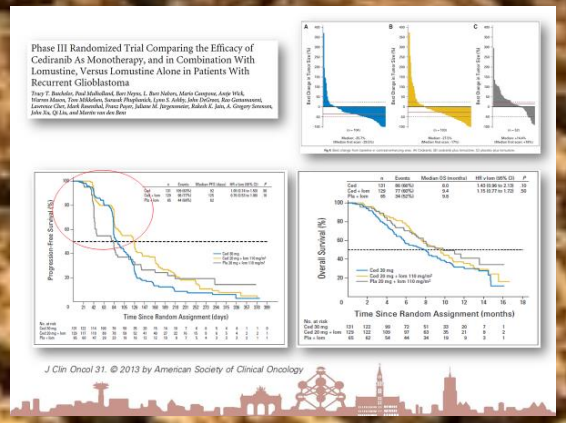
IDH mutant

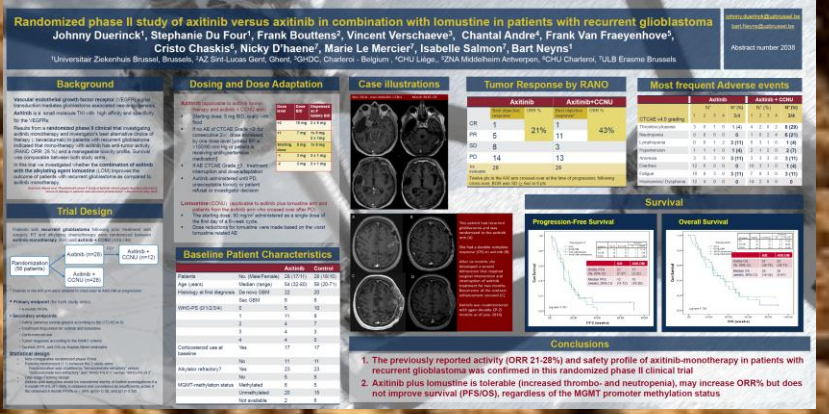


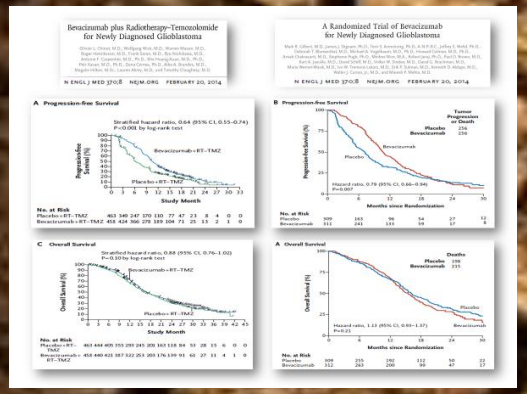
➢ Adjuvant temozolomide improves outcome in IDH mutant anaplastic astrocytoma

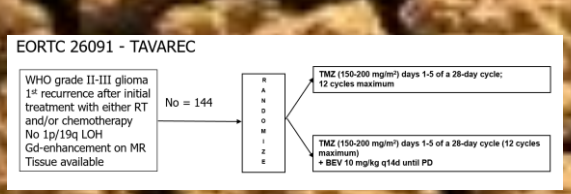


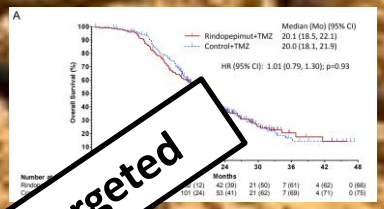






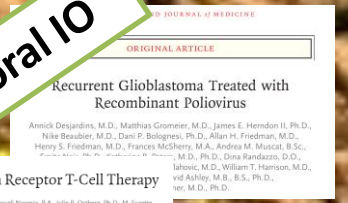


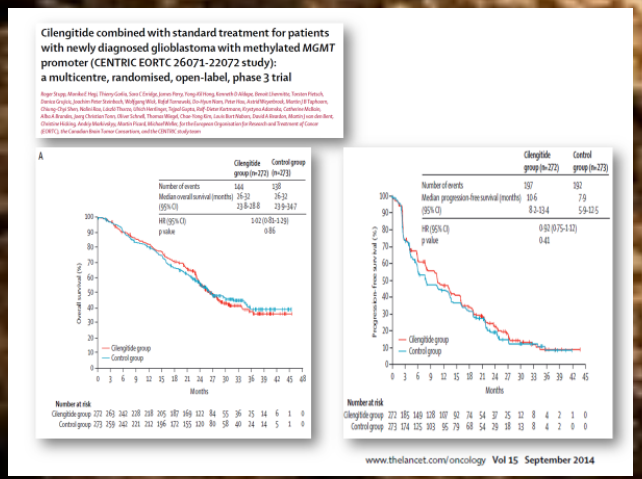


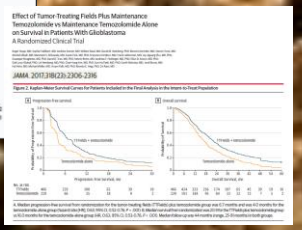


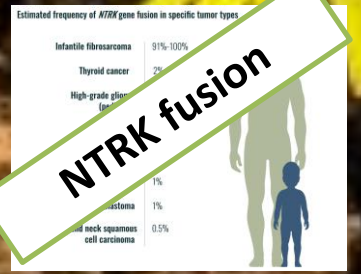
EGFR-targeted

Intratumoral IO

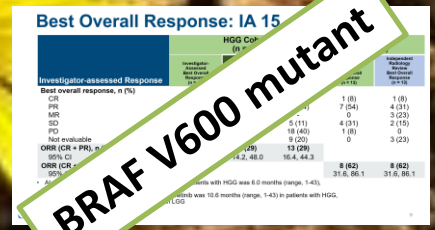








NTRK fusion



BRAF V600 mutant

Neuro-Oncology
20(5), 674–686, 2018 | doi:10.1093/neuonc/nox208 | Advance Access date 28 October 2017

Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143

Antonio Omuro,[a,d] Gordana Vlahovic,[a] Michael Lim, Solmaz Sahebjam, Joachim Baehring, Timothy Cloughesy, Alfredo Voloschin, Shakti H. Ramkissoon, Keith L. Ligon, Robert Latek,[b] Ricardo Zwirtes, Lewis Strauss, Prashni Paliwal, Christopher T. Harbison, David A. Reardon,[c] and John H. Sampson,[c]

Table 2 Continued

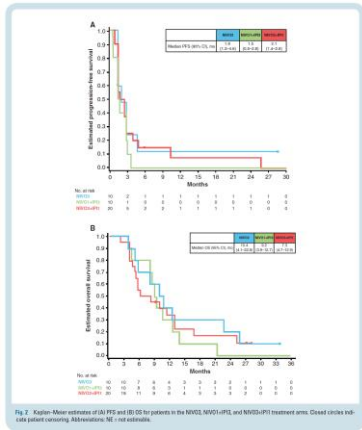
Treatment-Related Adverse Events	NIVO3 (*n* = 10)		NIVO1+IPI3 (*n* = 10)		NIVO3+IPI1 (*n* = 20)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Gastrointestinal disorders						
Colitis	0	0	2 (20)	2 (20)	1 (5)	1 (5)
Diarrhea	0	0	2 (20)	2 (20)	1 (5)	1 (5)
Pancreatitis	0	0	1 (10)	1 (10)	0	0
Vomiting	0	0	0	0	1 (5)	0
Investigations						
ALT increased	0	0	2 (20)	2 (20)	1 (5)	1 (5)
AST increased	0	0	1 (10)	1 (10)	1 (5)	1 (5)
Lipase increased	0	0	1 (10)	1 (10)	0	0
Bilirubin increased	0	0	1 (10)	0	0	0
Metabolism and nutrition disorders						
Appetite decreased	0	0	1 (10)	1 (10)	0	0
Diabetic ketoacidosis	0	0	1 (10)	1 (10)	0	0
Hyperglycemia	0	0	1 (10)	1 (10)	0	0
Hypocalcemia	0	0	1 (10)	1 (10)	0	0
Hypomagnesemia	0	0	1 (10)	0	0	0
Endocrine disorders						
Hypothyroidism	1 (10)	0	1 (10)	0	0	0
Autoimmune thyroiditis	0	0	0	0	1 (5)	0
Hyperthyroidism	0	0	1 (10)	0	0	0
General disorders and administration-site conditions						
Chest pain	1 (10)	0	0	0	0	0
Hepatobiliary disorders						
Cholecystitis	0	0	1 (10)	1 (10)	0	0
Infections and infestations						
Sepsis	0	0	1 (10)	1 (10)	0	0
Psychiatric disorders						
Confusional state	0	0	1 (10)	1 (10)	0	0
Renal and urinary disorders						
Acute kidney injury	0	0	1 (10)	1 (10)	0	0
Respiratory, thoracic, and mediastinal disorders						
Pneumonitis	1 (10)	0	0	0	1 (5)	0
Skin and subcutaneous tissue disorders						
Dermatitis bullous	0	0	1 (10)	0	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIVO3, nivolumab 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; NIVO3+IPI1, nivolumab 3 mg/kg + ipilimumab 1 mg/kg; TRAE; treatment-related adverse event; TRSAE, treatment-related serious adverse event. [a]Adverse events were reported during treatment and for ≥100 days following study drug discontinuation and were evaluated according to the CommonTerminology Criteria for Adverse Events v4.0. Adverse events were sorted based on the Medical Dictionary for Regulatory Activities (MedDRA) groupings.

Table 3 Investigator-assessed best overall response and objective response rate

Response	NIVO3 (*n* = 9)	NIVO1+IPI3 (*n* = 10)	NIVO3+IPI1 (*n* = 20)
Best overall response, *n* (%)[a]			
Complete response	0	0	0
Partial response	1 (11)	0	2 (10)
Stable disease	4 (44)	3 (30)	9 (45)
≥12 wk	2 (22)	2 (20)	4 (20)
Progressive disease	4 (44)	7 (70)	9 (45)
Objective response rate, *n* (%)[b]	1 (11)	0	2 (10)
95% CI	0.3–48.2	0–30.8	1.2–31.7

Abbreviations: NIVO3, nivolumab 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; NIVO3+IPI1, nivolumab 3 mg/kg + ipilimumab 1 mg/kg. [a]Best overall response was assessed in response-evaluable patients per RANO criteria.[30] [b]Rate of confirmed complete and partial responses.



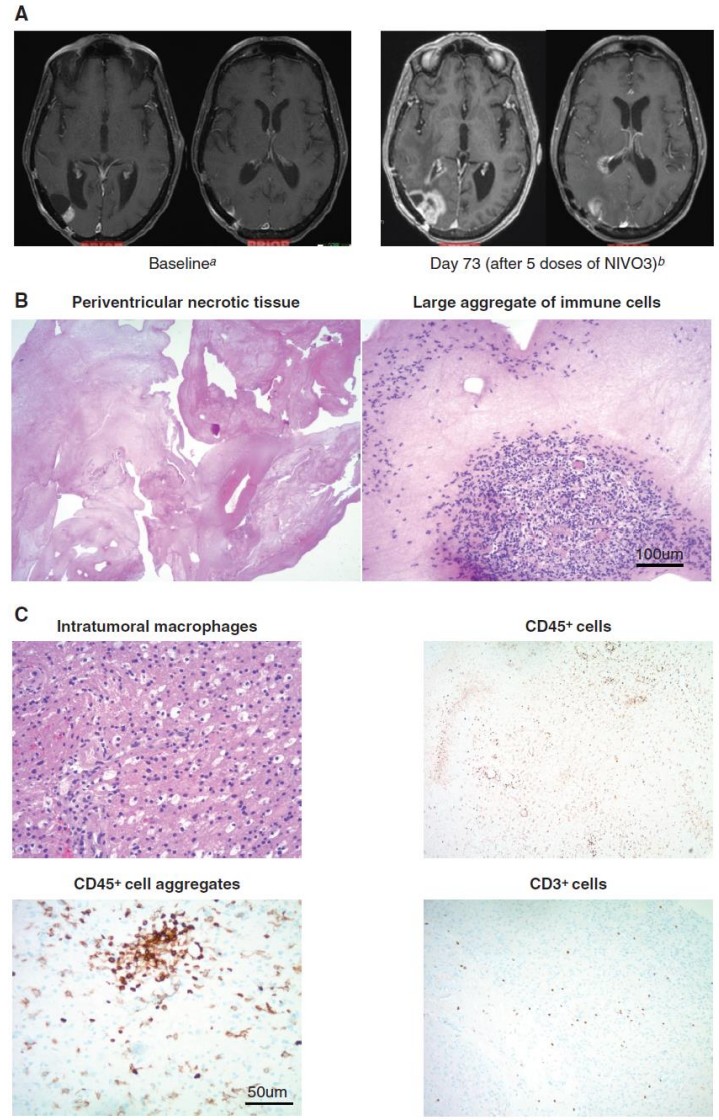
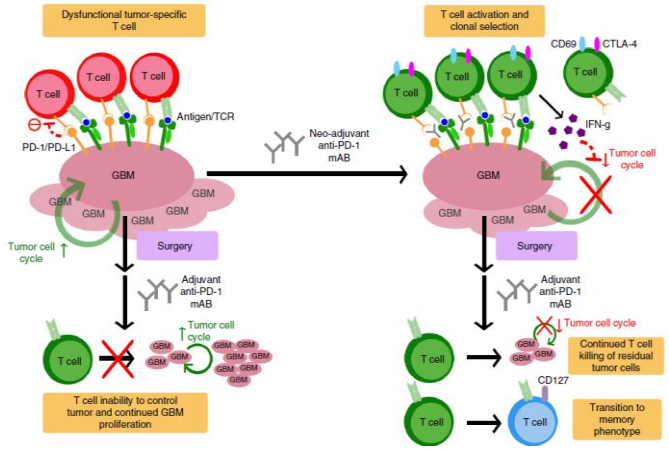


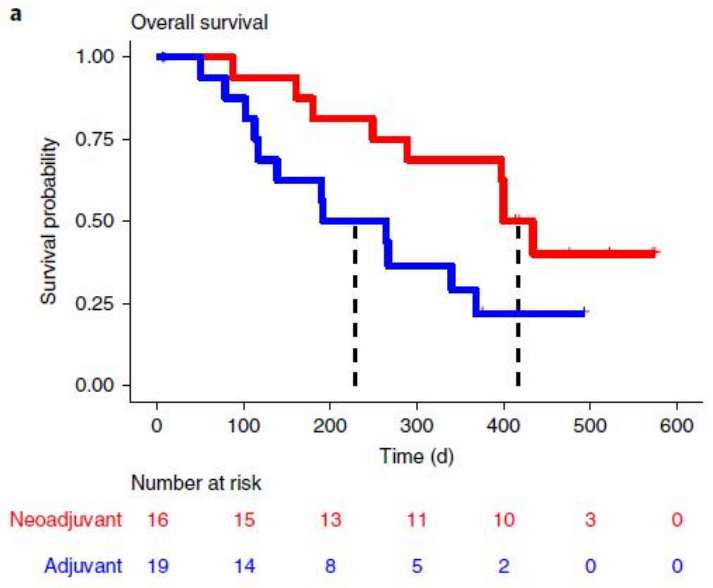
Fig. 3 A patient case depicting immune-mediated effects of therapy is presented. (A) MRI scans from a 67-year-old patient treated with NIVO3 who had suspected disease progression, with an increase in lesion size from 12 mm at baseline (left) to 40 mm at day 73 (right). MRI scans were conducted using the same parameters for each scan. (B) Resected tumor at day 81 stained with hematoxylin and eosin indicating immune-mediated changes in lesion size consistent with large aggregates of immune cells (right) and extensive tumor necrosis (left). Scale bar denotes 100 μm. (C) Immunohistochemistry of resected tumor specimens depicts infiltrating immune cell aggregates, T cells, and macrophages. Scale bar denotes 50 μm. [a]12-mm temporal lobe lesion; no corticosteroid treatment. [b]40-mm temporal lobe lesion; patient received concomitant methylprednisolone 16 mg/day.

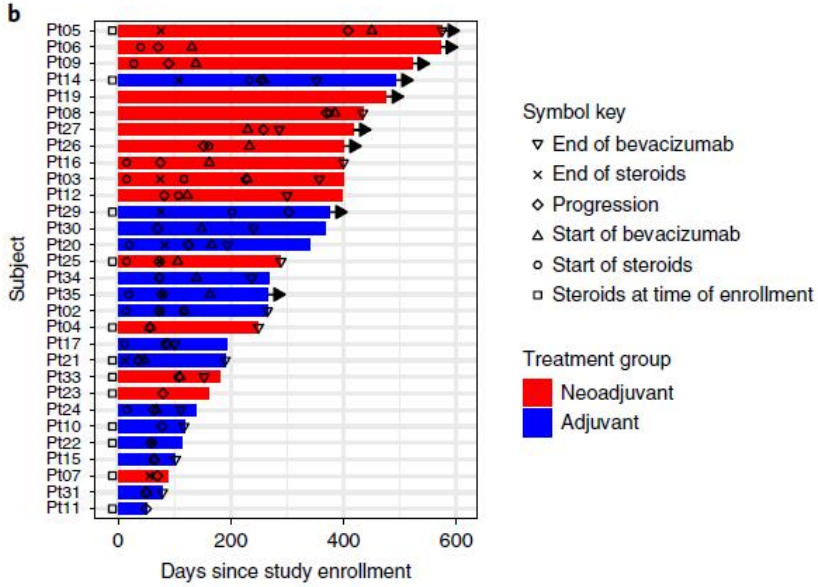
nature medicine
FOCUS | ARTICLES
https://doi.org/10.1038/s41591-018-0337-7

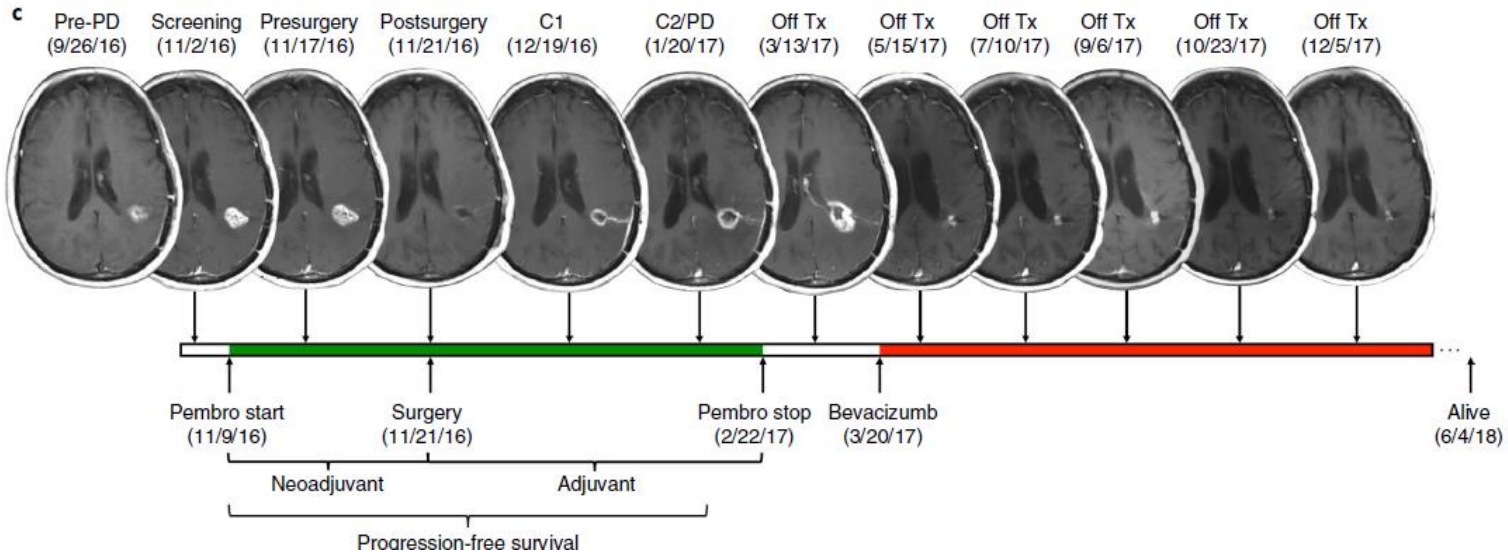
Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma

Timothy F. Cloughesy[1,2,3,18*], Aaron Y. Mochizuki[4,18], Joey R. Orpilla[5], Willy Hugo[6], Alexander H. Lee[2,5], Tom B. Davidson[3,4], Anthony C. Wang[5], Benjamin M. Ellingson[3,7], Julie A. Rytlewski[8], Catherine M. Sanders[8], Eric S. Kawaguchi[9], Lin Du[9], Gang Li[3,9], William H. Yong[10], Sarah C. Gaffey[11], Adam L. Cohen[12], Ingo K. Mellinghoff[13], Eudocia Q. Lee[11], David A. Reardon[11], Barbara J. O'Brien[14], Nicholas A. Butowski[15], Phioanh L. Nghiemphu[1], Jennifer L. Clarke[15], Isabel C. Arrillaga-Romany[16], Howard Colman[12], Thomas J. Kaley[13], John F. de Groot[14], Linda M. Liau[3,5], Patrick Y. Wen[11,19] and Robert M. Prins[2,3,5,17,19*]









Randomized Phase 3 Study Evaluating the Efficacy and Safety of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: CheckMate 143

David A. Reardon,[1,a] Antonio Omuro,[2,a] Alba A. Brandes,[3] Johannes Rieger,[4,5] Antje Wick,[6] Juan Manuel Sepulveda,[7] Surasak Phuphanich,[8] Paul de Souza,[9] Manmeet S. Ahluwalia,[10] Michael Lim,[11] Gordana Vlahovic,[12,b] John Sampson[12,b]

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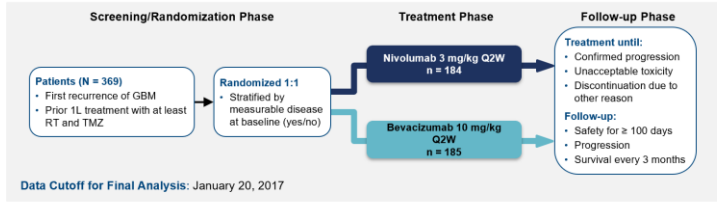
5th Quadrennial Meeting of the World Federation of Neuro-Oncology Societies
May 4-7, 2017; Zurich, Switzerland

[a] Co-first authors.
[b] Co-senior authors.

CheckMate 143 Cohort 2 Study Design

Nivolumab vs Bevacizumab in Recurrent GBM



Data Cutoff for Final Analysis: January 20, 2017

Endpoints:
- **Primary:** OS in all randomized patients
- **Secondary:** investigator-assessed ORR and PFS (RANO); 12-month OS rate
- **Other key endpoints:** safety; biomarkers

Assessments:
- **Tumor:** contrast-enhanced MRI Q6W until week 13, then Q8W (RANO)
- **Safety:** CTCAE v4.0

1L, first line; CTCAE, Common Terminology Criteria for Adverse Events; MRI, magnetic resonance imaging; ORR; objective response rate; PFS, progression-free survival; Q2W, every 2 weeks; Q6W, every 6 weeks; Q8W, every 8 weeks; RANO, Radiologic Assessment in Neuro-Oncology criteria.

Response per Investigator Assessment (RANO)

Nivolumab vs Bevacizumab in Recurrent GBM

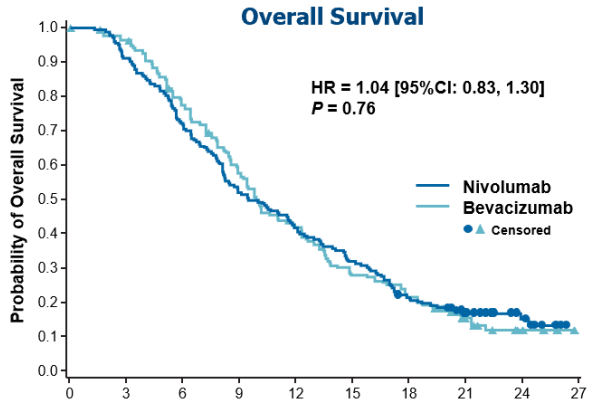
	Nivolumab n = 153[a]	Bevacizumab n = 156[a]
ORR, n (%) [95% CI]	12 (7.8) [4.1, 13.3]	36 (23.1) [16.7, 30.5]
BOR, n (%)		
CR	2 (1.3)	4 (2.6)
PR	10 (6.5)	32 (20.5)
SD	33 (21.6)	73 (46.8)
PD	107 (69.9)	26 (16.7)
Unable to determine	1 (0.7)	21 (13.5)
Not treated	1 (0.7)	16 (10.3)
Discontinued early due to toxicity	0	3 (1.9)
Other	0	2 (1.3)
Median TTR (range), months	3.0 (1.4–12.0)	1.5 (1.2–6.5)
Median DOR (range), months	11.1 (0.6–18.7)	5.3 (3.1–24.9)
PFS rate [95% CI], %		
6-months	15.7 [10.8, 21.5]	29.6 [22.7, 36.9]
12-months	10.5 [6.5, 15.5]	17.4 [11.9, 23.7]

BOR, best overall response; CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.
[a]Patients evaluable for response.

Overall Survival and Progression-Free Survival

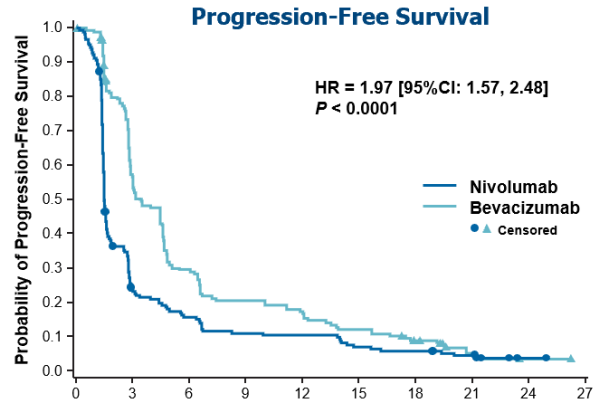
Nivolumab vs Bevacizumab in Recurrent GBM

	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], months
Nivolumab	154	9.8 [8.2, 11.8]	41.8 [34.7, 48.8]
Bevacizumab	147	10.0 [9.0, 11.8]	42.0 [34.6, 49.3]



No. at Risk										
Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], months
Nivolumab	171	1.5 [1.5, 1.6]	10.5 [6.5, 15.5]
Bevacizumab	146	3.5 [2.9, 4.6]	17.4 [11.9, 23.7]



No. at Risk										
Nivolumab	184	41	27	19	18	12	10	7	1	0
Bevacizumab	185	88	46	32	27	19	12	3	1	0

Bristol-Myers Squibb

Press Release

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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

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced the Phase 3 CheckMate -498 trial evaluating *Opdivo* (nivolumab) plus radiation versus temozolomide plus radiation in patients with newly diagnosed O6-methylguanine-DNA methyltransferase (MGMT)-unmethylated glioblastoma multiforme (GBM) did not meet its primary endpoint of overall survival (OS) at final analysis. The safety profile of *Opdivo* was consistent with previously reported studies in solid tumors. The Company will complete a full evaluation of the data from CheckMate -498 and work with investigators on the future presentation and publication of the results.

Bristol-Myers Squibb

Press Release

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Bristol-Myers Squibb Provides Update on Phase 3 Opdivo (nivolumab) CheckMate -548 Trial in Patients with Newly Diagnosed MGMT-Methylated Glioblastoma Multiforme

CATEGORY: CORPORATE/FINANCIAL NEWS

THURSDAY, SEPTEMBER 5, 2019 6:59 AM EDT

$BMY provides update on Phase 3 #GBM trial

Tweet this

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced that the Phase 3 CheckMate -548 trial evaluating the addition of *Opdivo* (nivolumab) to the current standard of care (temozolomide and radiation therapy) versus the standard of care alone did not meet one of its primary endpoints, progression-free survival (PFS), in patients with newly diagnosed glioblastoma multiforme (GBM) that is O6-methylguanine-DNA methyltransferase (MGMT)-methylated. The data monitoring committee recommended that the trial continue as planned to allow the other primary endpoint, overall survival (OS), to mature. The company remains blinded to all study data.

GLIAVAX: A STRATIFIED PHASE II CLINICAL TRIAL OF AVELUMAB AND AXITINIB IN PATIENTS WITH RECURRENT GLIOBLASTOMA

Neyns B[1], Ben Salama L[1], Awada G[1], De Cremer J[2], Schwarze JK[1], Seynaeve L[3], Du Four S[4], Fischbuch L[1], Vanbinst A[5], Everaert H[6], Michotte A[3,7], Rogiers A[8], Theuns P[2], Duerinck J[4]

1. Department of Medical Oncology, Universitair Ziekenhuis Brussel; 2. Department of Psychology, Vrije Universiteit Brussel; 3. Department of Neurology, UZ Brussel; 4. Department of Neurosurgery, UZ Brussel; 5. Department of Radiology, UZ Brussel; 6. Department of Nuclear Medicine, UZ Brussel; 7. Department of Pathology, UZ Brussel; 8. Department of Psychiatry, Universitair Verplegingscentrum Brugmann

INTRODUCTION

- Patients (pts) with recurrent glioblastoma (rGB) have a poor prognosis. No treatment has shown to improve survival.
- Axitinib (AXI), an oral VEGFR 1-3 inhibitor, has demonstrated single-agent activity in rGB and reduces the need for cortico-steroids (CS) by its anti-edematous action.
- Avelumab (AVE), a programmed cell death ligand 1 (PD-L1) IgG1 blocking antibody, has demonstrated activity in several tumor types. AXI + AVE is approved for the treatment of metastatic renal cell carcinoma.
- The combination of AXI and AVE may improve the outcome of patients with rGB.

METHODS

- Phase 2 open-label, single-center, dual-stratum clinical trial (Universitair Ziekenhuis Brussel)
- Inclusion criteria:
  - rGB following prior surgery, radiation therapy and temozolomide chemotherapy
  - Not amenable for surgery
- Stratification according to baseline use of corticosteroids:
  - Cohort-1: ≤ daily physiologic dose
  - Cohort-2: > daily physiologic dose
- Intervention:
  - Cohort-1: start with AXI 5 mg BID + AVE 10 mg/kg Q2W
  - Cohort-2: start with AXI 5 mg BID; addition of AVE 10 mg/kg Q2W after 6 weeks (wks) if CS tapered to ≤ daily physiologic dose
- Treatment until progressive disease (by immunotherapy Response Assessment for Neuro-Oncology [iRANO] criteria), unacceptable toxicity or withdrawal of consent
- Primary endpoint:
  - 6-month-progression-free survival rate (6-m-PFS, %)
- Secondary endpoints:
  - Objective response rate (ORR)
  - Overall survival (OS)
  - Safety graded by CTCAE version 4
  - Evolution of neurocognitive function
- Sample size: 26 pts according to Fleming one-stage design (prespecified 6-m-PFS of ≥ 50%; alpha 0.10; beta 0.20)
- Drug supply by Pfizer/Merck Serono
- ClinicalTrials.gov Identifier: NCT03291314

Corresponding author:
Bart Neyns, MD, PhD - Bart.Neyns@uzbrussel.be

RESULTS

TABLE 1. BASELINE CHARACTERISTICS*

	Overall (n=54)	Cohort-1 (n=27)	Cohort-2 (n=27)
Gender (n [%])			
Male	34 (63.0)	14 (25.9)	20 (37.0)
Female	20 (37.0)	13 (24.1)	7 (13.0)
Median age (range)	55 (19-75)	57 (20-70)	47 (19-75)
WHO Performance Status (n [%])			
0	27 (50.0)	20 (37.0)	7 (13.0)
1	22 (40.7)	6 (11.1)	16 (29.6)
2	5 (9.3)	1 (1.9)	4 (7.4)
Diagnosis			
De novo GB	35 (64.8)	18 (33.3)	17 (31.5)
Secondary GB	19 (35.2)	9 (16.7)	10 (18.5)

*Two extra pts were included, one in each cohort.

TABLE 2. OBJECTIVE RESPONSE AND DISEASE CONTROL RATE

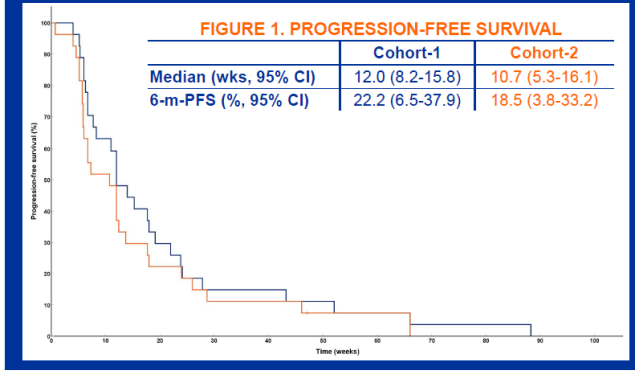
	Overall (n=54)	Cohort-1 (n=27)	Cohort-2 (n=27)
Confirmed ORR (n [%])	15 (27.8)	9 (33.3)	6 (22.2)
CR	2 (3.7)	1 (3.7)	1 (3.7)
PR	13 (24.1)	8 (29.6)	5 (18.5)
SD	15 (27.8)	8 (29.6)	7 (25.9)
PD	24 (44.4)	10 (37.0)	14 (51.9)
Disease control rate (n [%])	30 (55.6)	17 (63.0)	13 (48.1)
Median duration of response (wks)	18.0	17.9	19.0

TABLE 3. ADVERSE EVENTS (AE) IN PTS WHO RECEIVED AT LEAST ONE DOSE OF STUDY DRUGS

AE (in 10% or more of pts)	All-grade (n [%])	Grade 3-4 (n [%])
Dysphonia	36 (66.7)	0 (0)
Lymphopenia	27 (50.0)	2 (3.7)
Hypertension	26 (48.1)	4 (7.4)
Diarrhea	26 (48.1)	2 (3.7)
Fatigue	25 (46.3)	4 (7.4)
Thrombocytopenia	25 (46.3)	1 (1.9)
Erythrocytosis	18 (33.3)	0 (0)
TSH increase	16 (29.6)	1 (1.9)
ALT increase	14 (25.9)	1 (1.9)
Mucositis/aphtosis	13 (24.1)	0 (0)
GGT increase	9 (16.7)	5 (9.3)
AST increase	9 (16.7)	1 (1.9)
Neutrophilia	9 (16.7)	0 (0)
Anorexia	8 (14.8)	1 (1.9)
Headache	6 (11.1)	0 (0)
Chills-acute infusion reaction	6 (11.1)	0 (0)
AP increase	6 (11.1)	0 (0)
AE OF SPECIAL INTEREST	**All-grade (n [%])**	**Grade 3-4 (n [%])**
Papulopustular rash	4 (7.4)	0 (0)
Rash NOS	3 (5.6)	0 (0)
Pulmonary embolism	3 (5.6)	3 (5.6)
Hepatitis*	2 (3.7)	1 (1.9)
Seborrheic rash	2 (3.7)	0 (0)
Pneumonitis*	1 (1.9)	1 (1.9)
Psoriasiform rash	1 (1.9)	1 (1.9)
Microscopic colitis	1 (1.9)	0 (0)

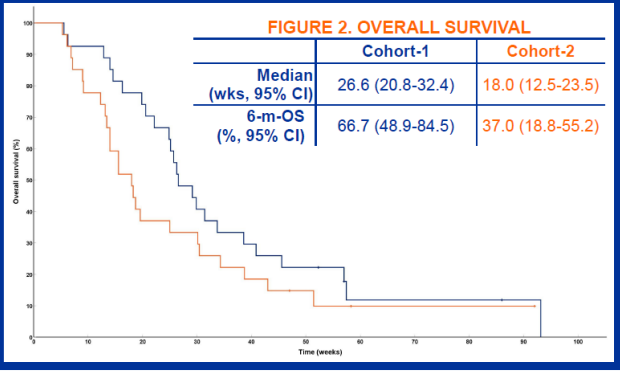
* One pt with both pneumonitis and hepatitis

FIGURE 1. PROGRESSION-FREE SURVIVAL



	Cohort-1	Cohort-2
Median (wks, 95% CI)	12.0 (8.2-15.8)	10.7 (5.3-16.1)
6-m-PFS (%, 95% CI)	22.2 (6.5-37.9)	18.5 (3.8-33.2)

FIGURE 2. OVERALL SURVIVAL



	Cohort-1	Cohort-2
Median (wks, 95% CI)	26.6 (20.8-32.4)	18.0 (12.5-23.5)
6-m-OS (%, 95% CI)	66.7 (48.9-84.5)	37.0 (18.8-55.2)

FIGURE 3. SWIMMER PLOTS: TIME ON AXI MONOTHERAPY, PFS and OS

Color legenda: light blue: PFS on AXI monotherapy (cohort-2 only); dark blue: PFS on AXI + AVE; orange: OS; black block: death; arrow: pt on treatment.

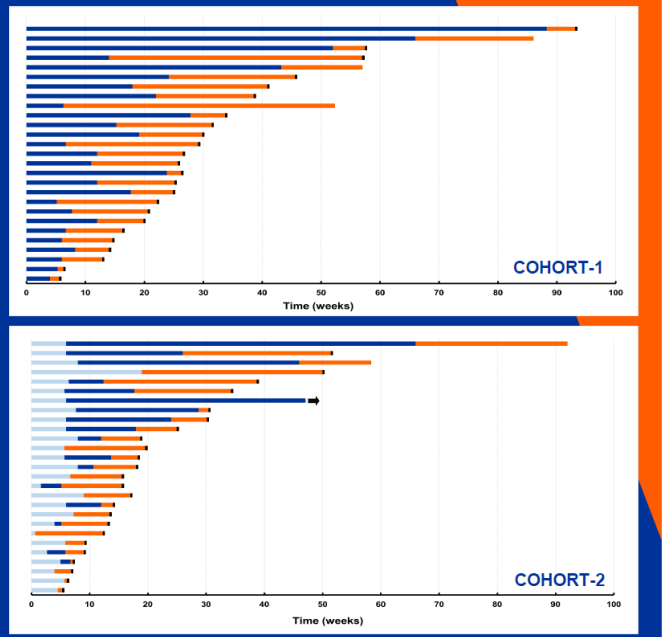
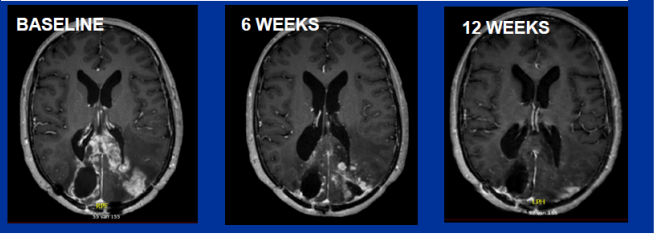


FIGURE 4. GADOLINIUM-ENHANCED T1 MAGNETIC RESONANCE IMAGES OF A STUDY PATIENT TREATED WITH AXI + AVE (COHORT-1)

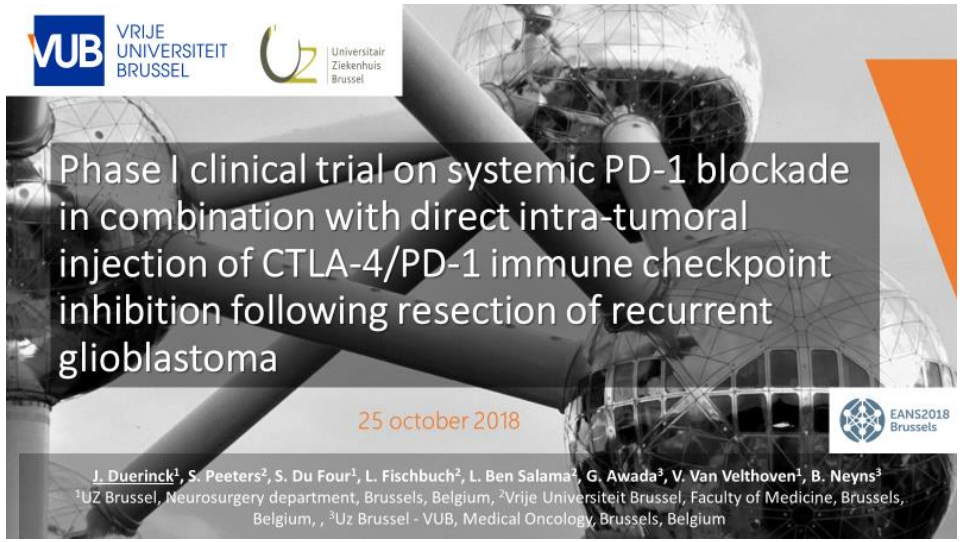


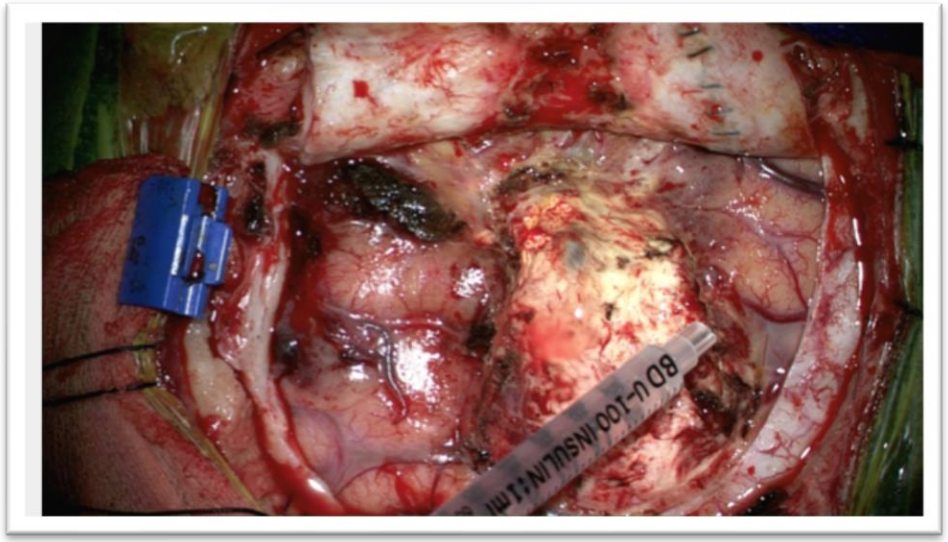
CONCLUSION

The combination of AXI + AVE is well tolerated but did not meet the threshold for activity justifying further investigation in an unselected population of patients with rGB.

POSTER PRESENTED AT THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING, 31ST MAY - 4TH JUNE 2019, CHICAGO, IL

Glitipni





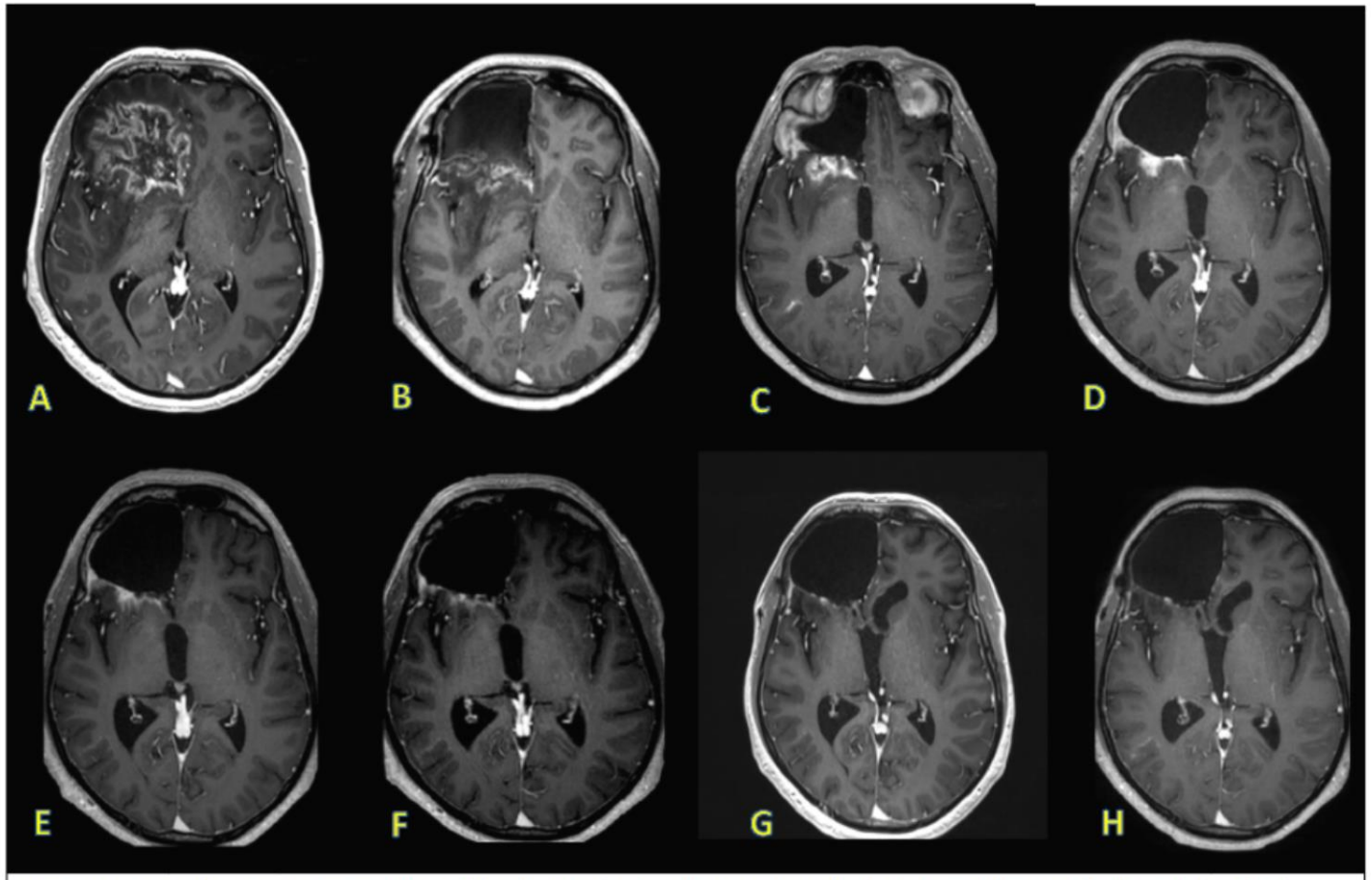


Figure 1: Case report from a patient in COHORT -2 of the Glitipni study. This patient was treated with intra-tumoral injecton of ipilimumab (5 mg) and nivolumab (10 mg) plus intravenous nivolumab (10 mg) every two weeks. He is now off study treatment, stable and still alive after 56 weeks from baseline.

Image A shows the baseline status on MRI before resection of the glioblastoma. Image B is one day post-op. The following images (C, D, E, F, G, H) are made with a 6 weeks interval. Post-operative captation of contrast at the margins of the resection cavity decreases through time. This suggests an inflammatory origin of the captation of contrast, rather than recurrent tumor tissue.

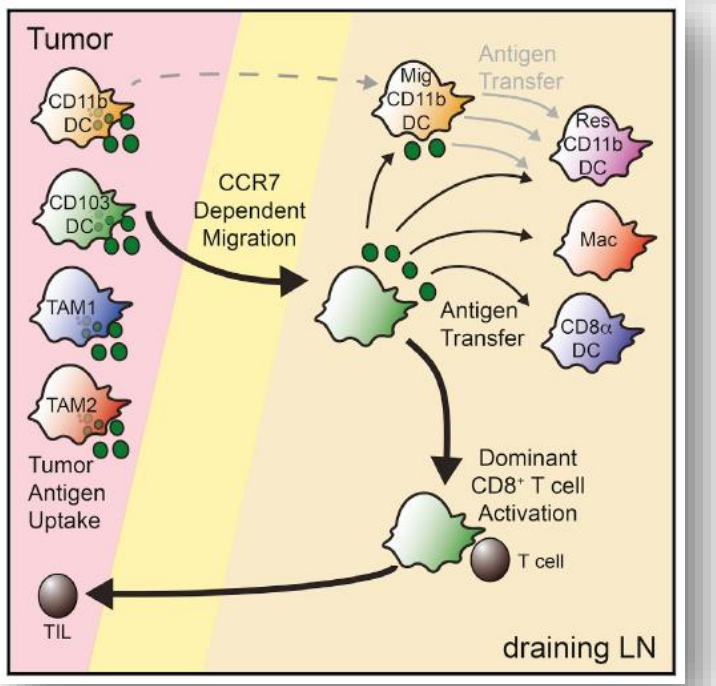
Cancer Cell
Article
Cancer Cell 26, 1–15, November 10, 2014

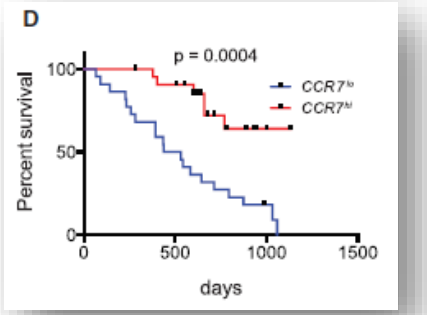
Dissecting the Tumor Myeloid Compartment Reveals Rare Activating Antigen-Presenting Cells Critical for T Cell Immunity

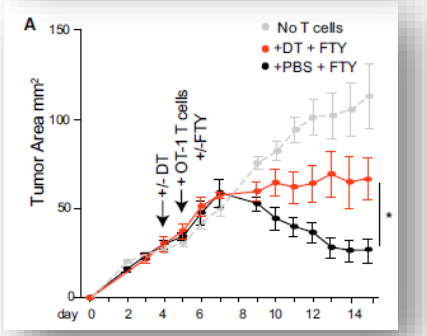
Miranda L. Broz,[1] Mikhail Binnewies,[1] Bijan Boldajipour,[1] Amanda E. Nelson,[1] Joshua L. Pollack,[2] David J. Erle,[2] Andrea Barczak,[2] Michael D. Rosenblum,[3] Adil Daud,[4] Diane L. Barber,[5] Sebastian Amigorena,[7] Laura J. van't Veer,[6] Anne I. Sperling,[8] Denise M. Wolf,[6] and Matthew F. Krummel[1,*]

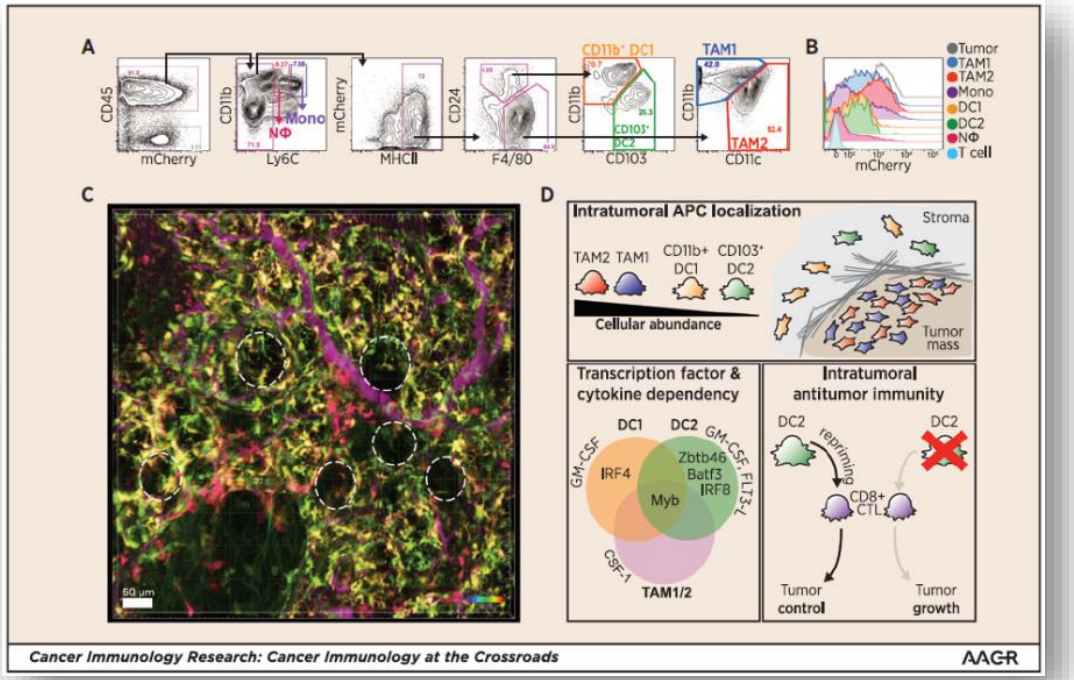
Cancer Cell
Article
Cancer Cell 30, 324–336, August 8, 2016 © 2016

Critical Role for CD103$^+$/CD141$^+$ Dendritic Cells Bearing CCR7 for Tumor Antigen Trafficking and Priming of T Cell Immunity in Melanoma

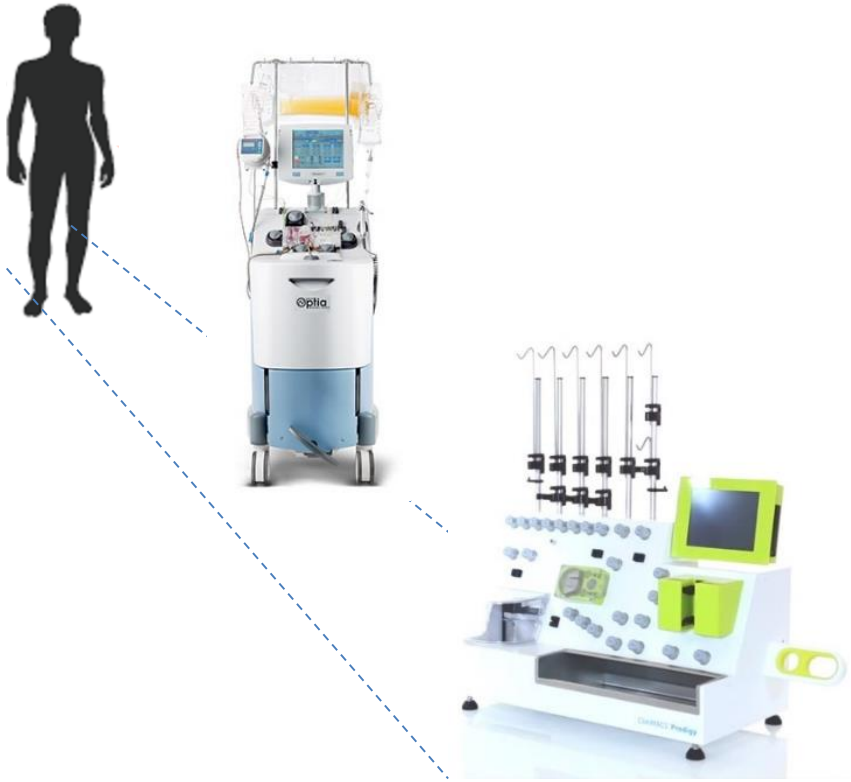








- ✓ Across multiple mouse tumor models and human tumor biopsies, intratumoral myeloid dendritic cell (DC) populations identified as distinct from macrophage populations
- ✓ Within these, CD103+ DCs are extremely sparse and yet remarkably capable CTL stimulators.
- ✓ These are uniquely dependent on IRF8, Zbtb46, and Batf3 transcription factors
- ✓ Generated by GM-CSF and FTL3L cytokines
- ✓ Regressing tumors have higher proportions of these cells
- ✓ T-cell-dependent immune clearance relies on them
- ✓ Abundance of their transcripts in human tumors correlates with clinical outcome
- ✓ This cell type presents opportunities for prognostic and therapeutic approaches across multiple cancer types.



Anti CD14

Anti BDCA-3

Anti BDCA-1

Anti BDCA-4

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 December 2017
EMA/CAT/708058/2017
Committee for Advanced Therapies (CAT)

SCIENTIFIC RECOMMENDATION ON CLASSIFICATION OF ADVANCED THERAPY MEDICINAL PRODUCTS
Article 17 – Regulation (EC) No 1394/2007

FINAL VERSION

The present scientific recommendation refers exclusively to the case as presented to the Agency without prejudice to future evaluations by the Agency.
It is stressed that the scientific recommendation on advanced therapy classification does not amount to any endorsement of the plausibility of the product, including the mode of action or therapeutic indication(s) claimed by the applicant.

1. CAT OUTCOME SUMMARY

Proposed product invented name or identifier ("the Product")	CD1c (BDCA-1)+ myeloid dendritic cells (myDC) isolated from peripheral blood mononuclear cells	
EMA product number	EMA/H0004927	
Company developing the Product (applicant)	Universitair Ziekenhuis Brussel (UZ Brussel)	
Brief description (common name or international non-proprietary name where available) of Active substance(s)	Autologous CD1c (BDCA-1)+ myeloid dendritic cells isolated from peripheral blood mononuclear cells	
Brief description of the finished Product	Autologous CD1c (BDCA-1)+ myeloid dendritic cells in a suspension for intratumoural injection	
Proposed Indication (as proposed by the applicant)	Patients with advanced, pre-treated solid tumours with injectable metastases	
Advanced therapy medicinal product classification (as agreed by the CAT)	Not ATMP	x
	Gene therapy medicinal product	
	Somatic cell therapy medicinal product	
	Tissue engineered product	
	Combined ATMP	
CAT Co-ordinator	Metoda Lipnik-Stangelj	
ITF Co-ordinator	Emil Cochino	

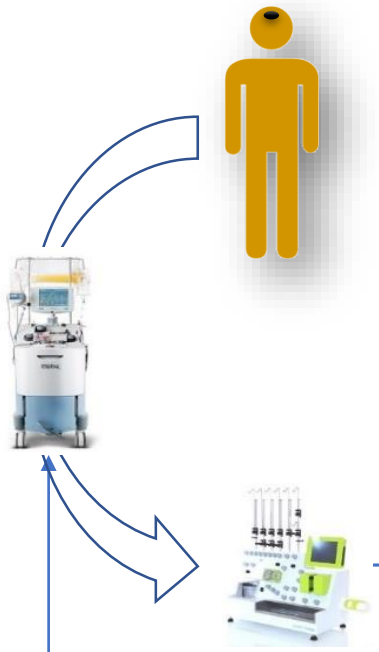
Sabado et al Cell Research (2017) 27:74-95; Schreibelt et al. Clin Cancer Res; 22(9) May 1, 2016; Jurjen *Cancer Res* 2013;73:1063-1075

Julia Katharina Schwarze et al, ESMO IO 2018 and SITC AM 2019

HLA Typing

Eligibility based on prior history
- Recurrent glioblastoma
- PD following RT and temozolomide
- No immunosuppressive co-medications (incl steroids > 8mg MP/d)
- PS 0-1, nl organ function

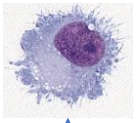
Screen
- MRI, FET-PET
- Blood analysis

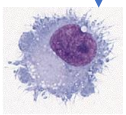


CryoPreserve

Manufacturing of moDC-Ag pulsed moDC

CD14+ mono





CD1c(BDCA-1)+ DC

CD141(BDCA-3)+ DC

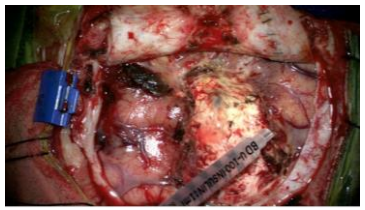
- NanoString Immune Cancer Panel
- IHC/mIF profiling (PD-L1, CD8+)
- NGS

- Protein extraction for DC loading with TA

- Elispot for preexisting T-cell responses

Procurement of tumor tissue

WBC & CSV



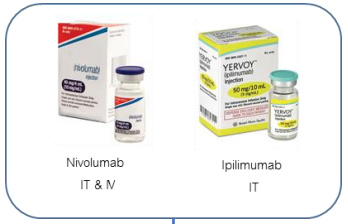
Maximal safe resection or Stereotactic biopsy/injection
+ Omaya reservoir

CD1c(BDCA-1)+ DC
CD141(BDCA-3)+ DC

IntraTumoral Injection

Q14 days x2

Start @Day14 post surgery



Procurement of 4 ml of CSV Q2w

- CSV Cytology
- Flow cytometry
- cfDNA analysis
- Elispot for Ag response
- T-Cell Analysis (collaboration with P Coulie)

Optimism is a duty. The future is open. It is not predetermined. No one can predict it, except by chance. We all contribute to determining it by what we do. We are all equally responsible for its success.

Karl Popper

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