Istituto Oncologico del Mediterraneo s.p.a.

Innovazioni in Neuro-Oncologia

Dr.ssa Marzia Mare

Istituto Oncologico del Mediterraneo
Viagrande (CT)

Congresso Regionale SIN Sicilia

Catania 15 Febbraio 2019

Sessione VB : innovazioni tecnologiche e scientifiche

Le mie disclosures

- Advisory boards from: Amgen, Italfarmaco, Merck-Serono, Roche, Sanofi, Servier

I Glioblastomi (GBM) sono i tumori primitivi dell'encefalo piu' frequenti nell'adulto.
Hanno una prognosi infausta con una sopravvivenza mediana di 14,6 mesi ,una sopravvivenza a 5 anni del 10% e più di un 90% di recidive dopo interventi standard.

NEOPLASIE CEREBRALI

LINEE GUIDA 2018

AIOM

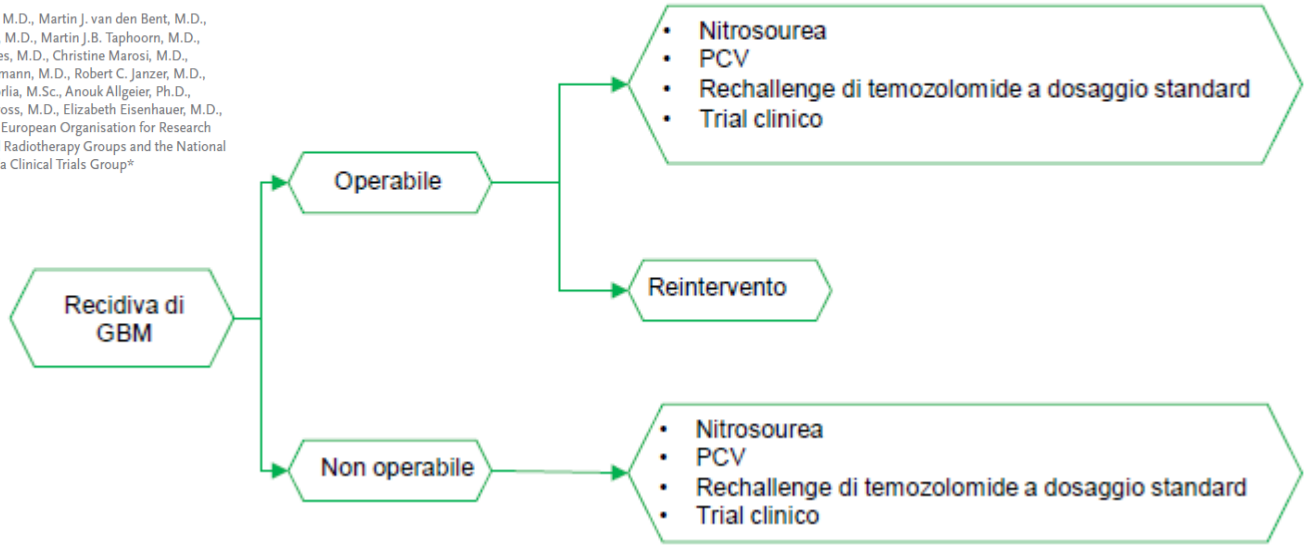
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

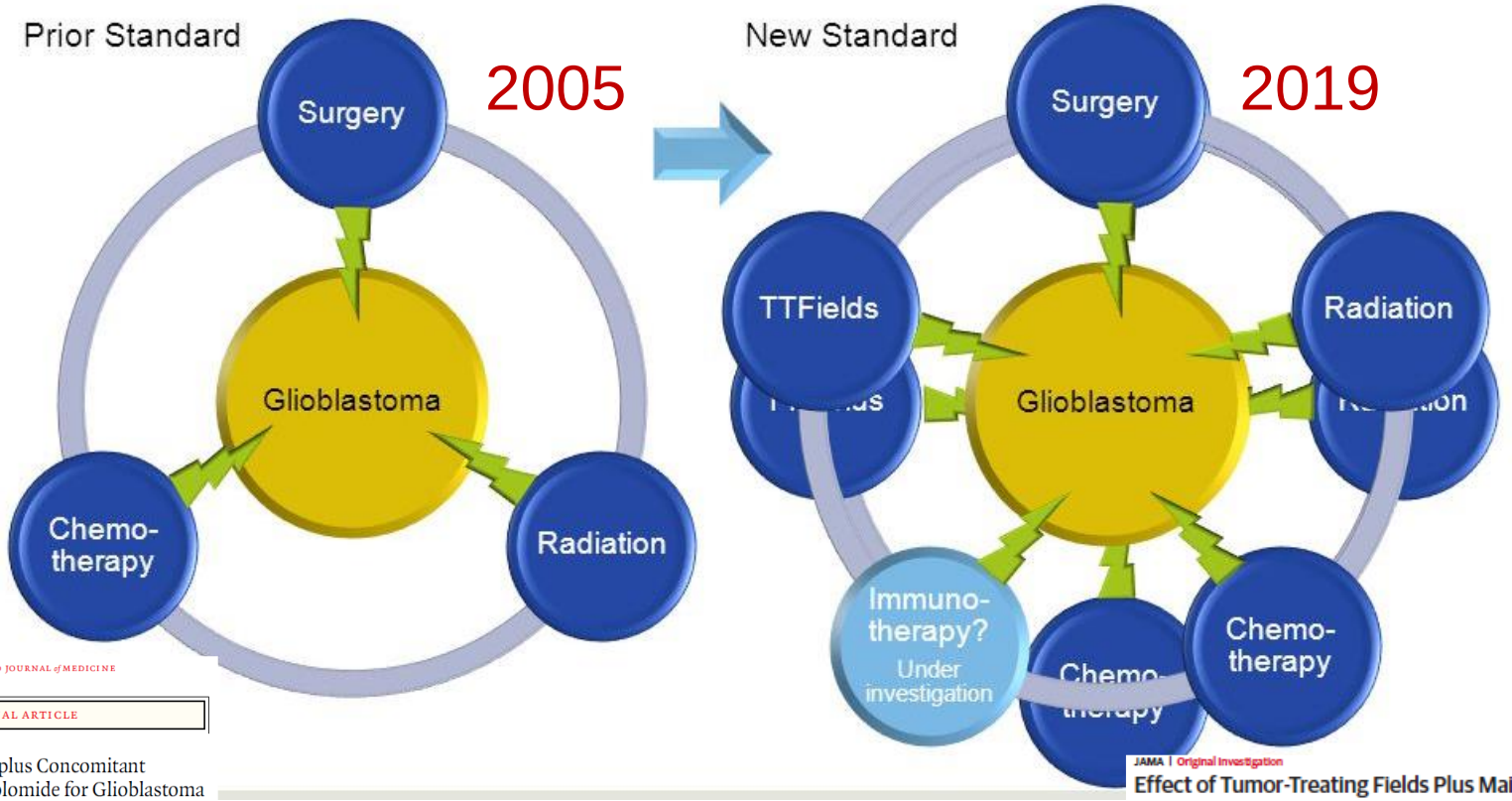
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

FIGURA 3: Recidiva di glioblastoma



New Treatment Paradigm: From Triple to Quadruple Modality



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JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew Kanner, MD; William Read, MD; David M. Steinberg, PhD; Benoit Lhermitte, MD; Steven Toms, MD; Ahmed Idbaih, MD; Mahmoot S. Ahluwalia, MD; Karen Fink, MD, PhD; Francesco Di Meco, MD; Frank Lieberman, MD; Jay-Jiguang Zhu, MD, PhD; Giuseppe Stragliotto, MD, PhD; David D. Tran, MD, PhD; Steven Brem, MD; Andreas F. Hottinger, MD, PhD; Ellon D. Kirson, MD, PhD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Chae-Yong Kim, MD, PhD; Sun-Ha Paek, MD, PhD; Garth Nicholas, MD; Jordi Bruna, MD; Hal Hirte, MD; Michael Weller, MD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

Trattamenti innovativi nel GB

Agenda:

1) Anti VEGF (Bevacizumab AVASTIN)

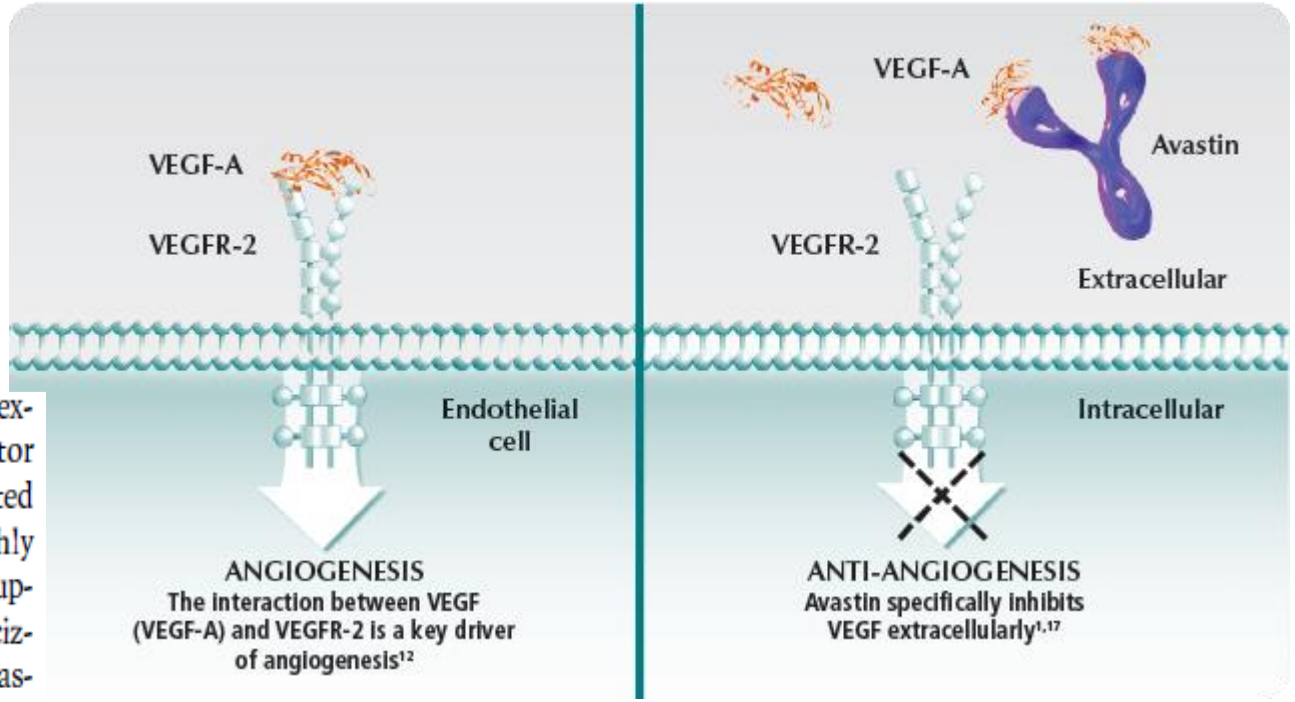
2) TTFields (Tumor-treating field therapy)

3) Immunoterapia: a) Anti PD1,Anti PD-L1 etc
   b) Vaccini
   c) CAR T

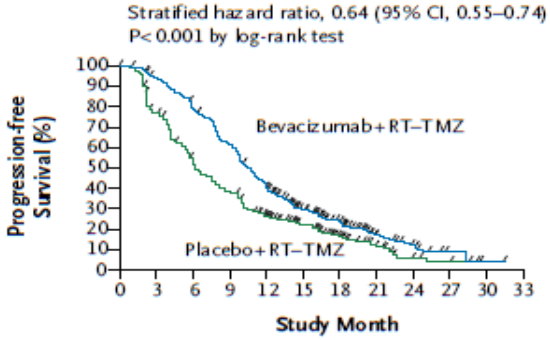
Trattamenti innovativi nel GB

Anti VEGF (Bevacizumab AVASTIN)

Glioblastomas are characterized by overexpression of vascular endothelial growth factor A (VEGF-A), a key regulator of tumor-associated angiogenesis,[12-15] and these tumors are highly vascularized.[16] The results of phase 1/2 studies support a role for the anti–VEGF-A molecule bevacizumab in recurrent and newly diagnosed glioblastoma.[17-22] We report the results of a phase 3 trial of bevacizumab plus radiotherapy–temozolomide as compared with placebo plus radiotherapy–temozolomide in patients with newly diagnosed glioblastoma.



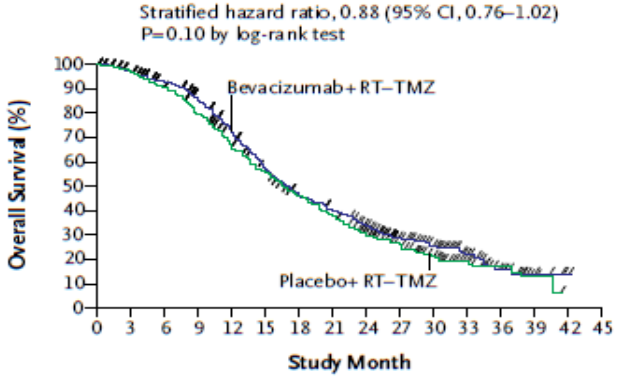
A Progression-free Survival



No. at Risk

Placebo+RT–TMZ	463	349	247	170	110	77	47	23	8	4	0	0
Bevacizumab+RT–TMZ	458	424	366	278	189	104	71	25	13	2	1	0

C Overall Survival

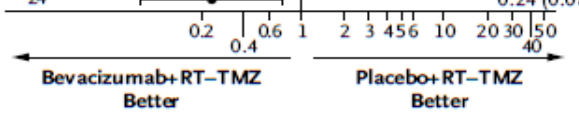


No. at Risk

Placebo+RT–TMZ	463	444	405	355	293	245	201	163	118	84	53	28	15	6	0	0
Bevacizumab+RT–TMZ	458	440	421	387	322	253	203	176	139	91	61	27	11	4	1	0

B Progression-free Survival

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	921	0.65 (0.56–0.75)
Age category I		
<65 yr	721	0.64 (0.55–0.76)
≥65 yr	200	0.68 (0.49–0.92)
Age category II		
<50 yr	229	0.64 (0.47–0.86)
50–59 yr	323	0.69 (0.54–0.88)
60–69 yr	296	0.59 (0.46–0.77)
≥70 yr	73	0.78 (0.46–1.33)
Race		
Nonwhite	89	0.65 (0.40–1.06)
White	832	0.65 (0.56–0.75)
Sex		
Male	341	0.71 (0.55–0.90)
Female	580	0.62 (0.51–0.74)
WHO performance status		
0	465	0.71 (0.58–0.88)
1–2	455	0.57 (0.46–0.69)
MGMT gene promoter status		
Methylated	237	0.76 (0.56–1.04)
Missing	223	0.61 (0.46–0.82)
Nonmethylated	461	0.56 (0.46–0.68)
RPA class		
III	151	0.64 (0.44–0.93)
IV	540	0.62 (0.51–0.74)
V	229	0.72 (0.54–0.96)
Surgical status		
Biopsy only	104	0.81 (0.53–1.26)
Partial or complete resection	817	0.62 (0.54–0.73)
MMSE score		
<27	214	0.74 (0.55–0.99)
≥27	696	0.63 (0.53–0.75)
Delay between surgery and first dose of study drug		
<4 wk	5	0.24 (0.02–2.67)
4–7 wk	873	0.66 (0.57–0.77)
>7 wk	33	0.44 (0.19–1.02)
Glioblastoma		
Primary	913	0.65 (0.57–0.76)
Secondary	8	0.45 (0.04–5.11)
Glucocorticoid use at baseline		
Missing	4	1.62 (0.14–18.31)
Off	522	0.63 (0.51–0.76)
On	395	0.69 (0.55–0.85)
EIAEDs at baseline		
No	742	0.66 (0.56–0.78)
Yes	179	0.58 (0.43–0.79)
Histologically confirmed glioblastoma		
Confirmed	875	0.66 (0.57–0.77)
Not confirmed	22	0.61 (0.23–1.60)
Missing	24	0.24 (0.08–0.75)



Trattamenti innovativi nel GB

Anti VEGF (Bevacizumab AVASTIN)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 20, 2014 VOL. 370 NO. 8

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.A., Robert Jeraj, Ph.D., Paul D. Brown, M.D., Kurt A. Jaeckle, M.D., David Schiff, M.D., Volker W. Stieber, M.D., David G. Brachman, M.D., Maria Werner-Wasik, M.D., Ivo W. Tremont-Lukats, M.D., Erik P. Sulman, M.D., Kenneth D. Aldape, M.D., Walter J. Curran, Jr., M.D., and Minesh P. Mehta, M.D.

PFS 10.7m vs 7,3m
OS 15,7m vs 16,1m

CONCLUSIONS

First-line use of bevacizumab did not improve overall survival in patients with newly diagnosed glioblastoma. Progression-free survival was prolonged but did not reach the prespecified improvement target. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00884741.)

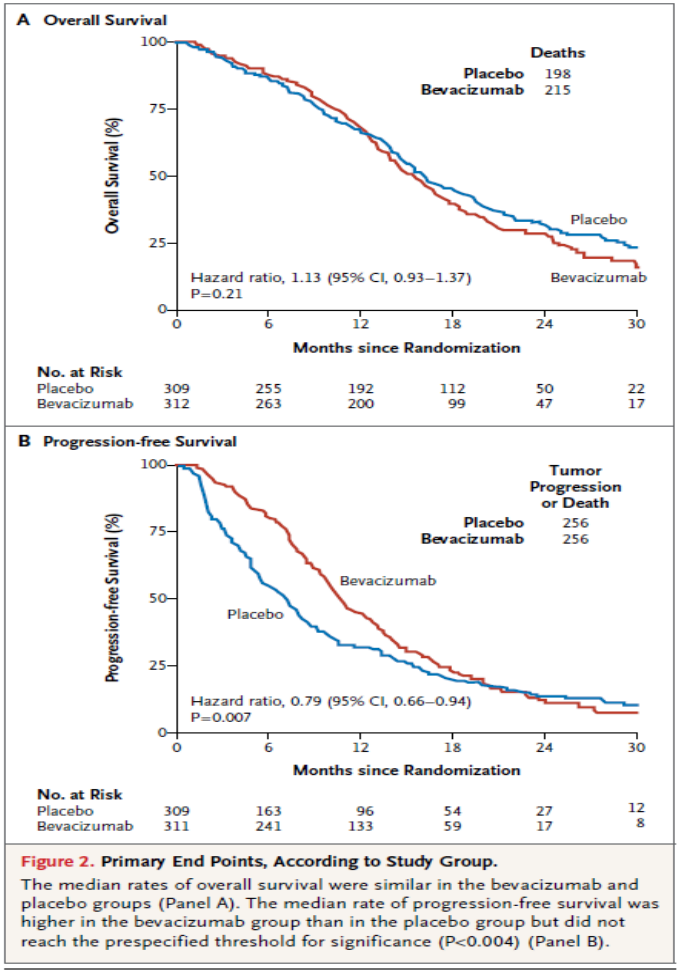


Figure 2. Primary End Points, According to Study Group.
The median rates of overall survival were similar in the bevacizumab and placebo groups (Panel A). The median rate of progression-free survival was higher in the bevacizumab group than in the placebo group but did not reach the prespecified threshold for significance (P<0.004) (Panel B).

Trattamenti innovativi nel GB

Anti VEGF (Bevacizumab AVASTIN)

Cancer Therapy: Clinical

Phase II Trial of Bevacizumab and Irinotecan in Recurrent Malignant Glioma

James J. Vredenburgh,[1,2,3] Annick Desjardins,[1,2,3] James E. Herndon II,[4] Jeannette M. Dowell,[4] David A. Reardon,[1,2,5] Jennifer A. Quinn,[1,2,3] Jeremy N. Rich,[1,2,3,6] Sith Sathornsumetee,[1,2,3] Sridharan Gururangan,[1,2,5] Melissa Wagner,[1,2] Darell D. Bigner,[1,2,7] Allan H. Friedman,[1,2] and Henry S. Friedman[1,2,3,5]

Abstract

Purpose: Recurrent grade III-IV gliomas have a dismal prognosis with minimal improvements in survival seen following currently available salvage therapy. This study was conducted to determine if the combination of a novel antiangiogenic therapy, bevacizumab, and a cytotoxic agent, irinotecan, is safe and effective for patients with recurrent grade III-IV glioma.

Experimental Design: We conducted a phase II trial of bevacizumab and irinotecan in adults with recurrent grade III-IV glioma. Patients with evidence of intracranial hemorrhage on initial brain magnetic resonance imaging were excluded. Patients were scheduled to receive bevacizumab and irinotecan i.v. every 2 weeks of a 6-week cycle. Bevacizumab was administered at 10 mg/kg. The dose of irinotecan was determined based on antiepileptic use: patients taking enzyme-inducing antiepileptic drugs received 340 mg/m^2, whereas patients not taking enzyme-inducing antiepileptic drugs received 125 mg/m^2. Toxicity and response were assessed.

Results: Thirty-two patients were assessed (23 with grade IV glioma and 9 with grade III glioma). Radiographic responses were noted in 63% (20 of 32) of patients (14 of 23 grade IV patients and 6 of 9 grade III patients). The median progression-free survival was 23 weeks for all patients (95% confidence interval, 15-30 weeks; 20 weeks for grade IV patients and 30 weeks for grade III patients). The 6-month progression-free survival probability was 38% and the 6-month overall survival probability was 72%. No central nervous system hemorrhages occurred, but three patients developed deep venous thromboses or pulmonary emboli, and one patient had an arterial ischemic stroke.

Conclusions: The combination of bevacizumab and irinotecan is an active regimen for recurrent grade III-IV glioma with acceptable toxicity.

Trattamenti innovativi nel GB

Anti VEGF (Bevacizumab AVASTIN)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Central Nervous System Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Consider Clinical Trial (Preferred for Eligible Patients)

Adult Low-Grade Infiltrative Supratentorial Astrocytoma/ Oligodendroglioma (excluding pilocytic astrocytoma)

- Adjuvant Treatment: For low-risk patients:
  - PCV (procarbazine + lomustine + vincristine)[1]
  - Temozolomide[2-4]
- Adjuvant Treatment: For high-risk patients:
  - RT + adjuvant PCV (category 1)
  - RT + adjuvant temozolomide[2-4] (category 2B)
  - RT + concurrent and adjuvant temozolomide (category 2B)
- Recurrence or Progressive, Low-Grade Disease:
  - RT + adjuvant PCV
  - RT + adjuvant temozolomide
  - RT+ concurrent and adjuvant temozolomide
  - Temozolomide[3-5,a]
  - Lomustine or carmustine
  - PCV[6]
  - Platinum-based regimens[7-9,g]

Anaplastic Gliomas

- Adjuvant Treatment
  - Anaplastic oligodendroglioma (1p19q co-deleted) (KPS ≥60)
    - RT with neoadjuvant PCV[10,b]
    - RT with adjuvant PCV[11,b]
    - RT with concurrent TMZ and adjuvant TMZ
  - Anaplastic astrocytoma/anaplastic oligoastrocytoma, NOS[c] (KPS ≥60)
    - RT followed by adjuvant TMZ (12 cycles)[12]
    - RT with concurrent TMZ and adjuvant TMZ
    - RT with neoadjuvant PCV[b]
    - RT with adjuvant PCV[b]
  - Anaplastic gliomas (KPS <60):
    - Temozolomide (category 2B)
- Recurrence Therapy[d]
  - Temozolomide[4,5,13,14]
  - Lomustine or carmustine[15]
  - PCV
  - Bevacizumab[16-18,e]
  - Bevacizumab + chemotherapy[f] (irinotecan,[19,20] carmustine/lomustine,[21] temozolomide, carboplatin [category 2B for carboplatin][22,23])
  - Irinotecan[24,25]
  - Cyclophosphamide (category 2B)[26,27]
  - Platinum-based regimens[g]
  - Etoposide[28]

Trattamenti innovativi nel GB

3) TTFields (Tumor-treating field therapy):
E’ un trattamento antimitotico che agisce selettivamente sulle cellule di GBM in divisione emettendo campi elettrici alternati a media frequenza (200kHz) e bassa intensità. erogati mediante trasduttori applicati sullo scalpo per 18 ore al giorno

TTFields: FDA Approvals

- The initial approval of TTFields, in 2011, was as monotherapy for adult patients (ages 22 years and older) with recurrent glioblastoma multiforme who had received chemotherapy and shown signs of progressive disease
- On October 5, 2015, this indication was expanded to include patients with newly diagnosed glioblastoma who have undergone surgical biopsy or resection and have completed radiation therapy with concomitant temozolomide

FDA, US Food and Drug Administration.

Trattamenti innovativi nel GB

2) TTFields (Tumor-treating field therapy)

Phase III Study 695 pz
Standard treatment (ST)+TTF vs ST
mPFS 6,7m vs 4m p<0.01 HR 0.63
mOS 20.9m vs 16m p<0.01 HR 0.63
Nei pz con metil.MTMG mOS 31m
Tox cutanea G3 2%

JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma
A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew Kanner, MD; William Read, MD; David M. Steinberg, PhD; Benoit Lhermitte, MD; Steven Torres, MD; Ahmed Idbaih, MD; Manmeet S. Ahluwalia, MD; Karen Fink, MD, PhD; Francesco Di Meco, MD; Frank Lieberman, MD; Jay-Jiguang Zhu, MD, PhD; Giuseppe Stragliotto, MD, PhD; David D. Tran, MD, PhD; Steven Brem, MD; Andreas F. Hottinger, MD, PhD; Ellen D. Kirson, MD, PhD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Chae-Yong Kim, MD, PhD; Sun-Ha Paek, MD, PhD; Garth Nicholas, MD; Jordi Bruna, MD; Hal Hirte, MD; Michael Weller, MD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

IMPORTANCE Tumor-treating fields (TTFields) is an antimitotic treatment modality that interferes with glioblastoma cell division and organelle assembly by delivering low-intensity alternating electric fields to the tumor.

OBJECTIVE To investigate whether TTFields improves progression-free and overall survival of patients with glioblastoma, a fatal disease that commonly recurs at the initial tumor site or in the central nervous system.

DESIGN, SETTING, AND PARTICIPANTS In this randomized, open-label trial, 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) were enrolled at 83 centers (July 2009-2014) and followed up through December 2016. A preliminary report from this trial was published in 2015; this report describes the final analysis.

INTERVENTIONS Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy (n = 466) or temozolomide alone (n = 229). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered (≥ 18 hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups (150-200 mg/m^2) for 5 days per 28-day cycle (6-12 cycles).

MAIN OUTCOMES AND MEASURES Progression-free survival (tested at α = .046). The secondary end point was overall survival (tested hierarchically at α = .048). Analyses were performed for the intent-to-treat population. Adverse events were compared by group.

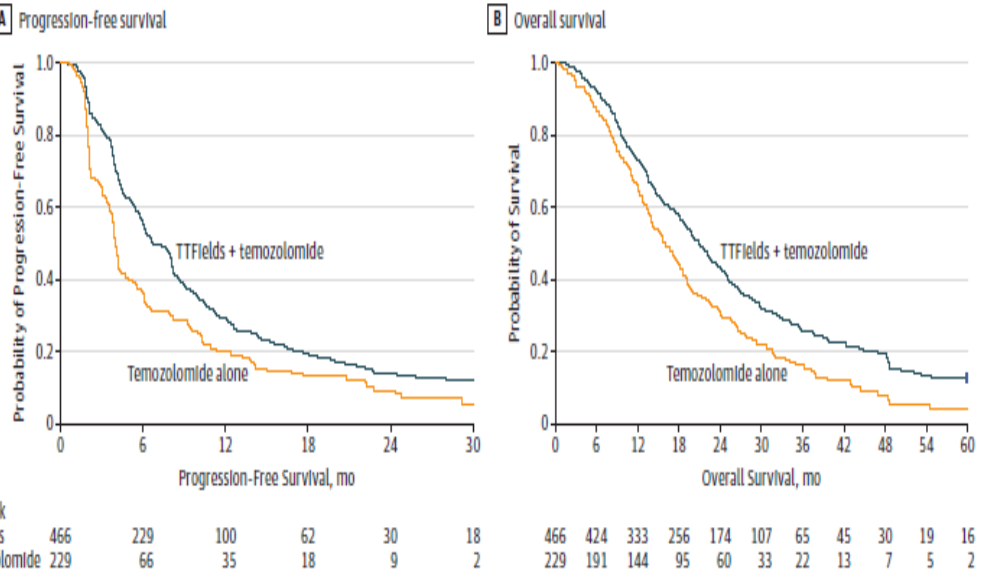
RESULTS Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76; *P* < .001). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; *P* < .001). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide vs no patients who received temozolomide alone.

CONCLUSIONS AND RELEVANCE In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718
Corrected on March 21, 2018.

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76; *P* < .001). B, Median survival from randomization was 20.9 for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; *P* < .001). Median follow up was 44 months (range, 25-91 months) in both groups.

Trattamenti innovativi nel GB

2) TTFields (Tumor-treating field therapy)

JAMA Oncology | Original Investigation

Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma

A Secondary Analysis of a Randomized Clinical Trial

Martin J. B. Taphoorn, MD; Linda Dirven, PhD; Andrew A. Kanner, MD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Sophie Taillibert, MD; Steven A. Toms, MD; Jerome Honnorat, MD, PhD; Thomas C. Chen, MD, PhD; Jan Sroubek, MD; Carlos David, MD; Ahmed Idbaih, MD, PhD; Jacob C. Easaw, MD, PhD; Chae-Yong Kim, MD, PhD; Jordi Bruna, MD, PhD; Andreas F. Hottinger, MD, PhD; Yvonne Kew, MD, PhD; Patrick Roth, MD; Rajiv Desai, MD; John L. Villano, MD, PhD; Eilon D. Kirson, MD, PhD; Zvi Ram, MD; Roger Stupp, MD

IMPORTANCE Tumor-treating fields (TTFields) therapy improves both progression-free and overall survival in patients with glioblastoma. There is a need to assess the influence of TTFields on patients' health-related quality of life (HRQoL).

OBJECTIVE To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of EF-14, a phase 3 randomized clinical trial, compares TTFields and temozolomide or temozolomide alone in 695 patients with glioblastoma after completion of radiochemotherapy. Patients with glioblastoma were randomized 2:1 to combined treatment with TTFields and temozolomide or temozolomide alone. The study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

INTERVENTIONS Temozolomide, 150 to 200 mg/m^2/d, was given for 5 days during each 28-day cycle. TTFields were delivered continuously via 4 transducer arrays placed on the shaved scalp of patients and were connected to a portable medical device.

MAIN OUTCOMES AND MEASURES Primary study end point was progression-free survival; HRQoL was a predefined secondary end point, measured with questionnaires at baseline and every 3 months thereafter. Mean changes from baseline scores were evaluated, as well as scores over time. Deterioration-free survival and time to deterioration were assessed for each of 9 preselected scales and items.

RESULTS Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months; $P < .01$); physical (5.1 vs 3.7 months; $P < .01$) and emotional functioning (5.3 vs 3.9 months; $P < .01$); pain (5.6 vs 3.6 months; $P < .01$); and leg weakness (5.6 vs 3.9 months; $P < .01$), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months; $P < .001$) and pain (TTFields improved; 13.4 vs 12.1 months; $P < .01$). Role, social, and physical functioning were not affected by TTFields.

CONCLUSIONS AND RELEVANCE The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

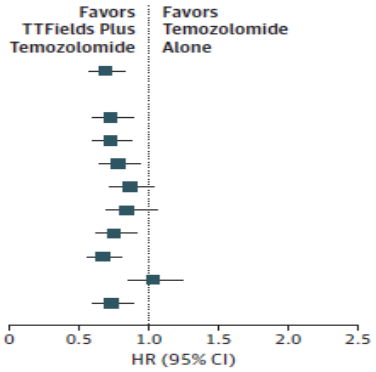
TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

JAMA Oncol. 2018;4(4):495-504. doi:10.1001/jamaoncol.2017.5082
Published online February 1, 2018.

Figure 3. Deterioration-Free Survival and Time to Deterioration

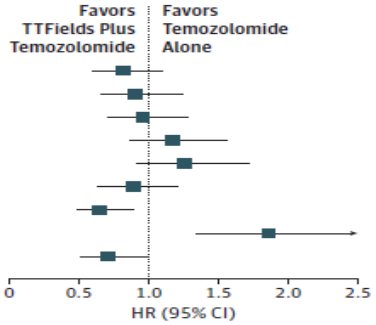
A Deterioration-free survival

Source	Median, mo: TTFields Plus Temozolomide	Median, mo: Temozolomide Alone	HR (95% CI)
Progression-free survival	6.7	4.0	0.69 (0.57-0.83)
Deterioration-free survival			
Global health status	4.8	3.3	0.73 (0.60-0.88)
Physical functioning	5.1	3.7	0.73 (0.60-0.88)
Cognitive functioning	4.4	3.6	0.78 (0.64-0.94)
Role functioning	4.3	3.8	0.86 (0.71-1.02)
Social functioning	4.5	3.9	0.84 (0.70-1.06)
Emotional functioning	5.3	3.9	0.75 (0.62-0.91)
Pain	5.6	3.6	0.67 (0.56-0.81)
Itchy skin	3.9	4.0	1.03 (0.85-1.25)
Weakness of legs	5.6	3.9	0.74 (0.61-0.89)



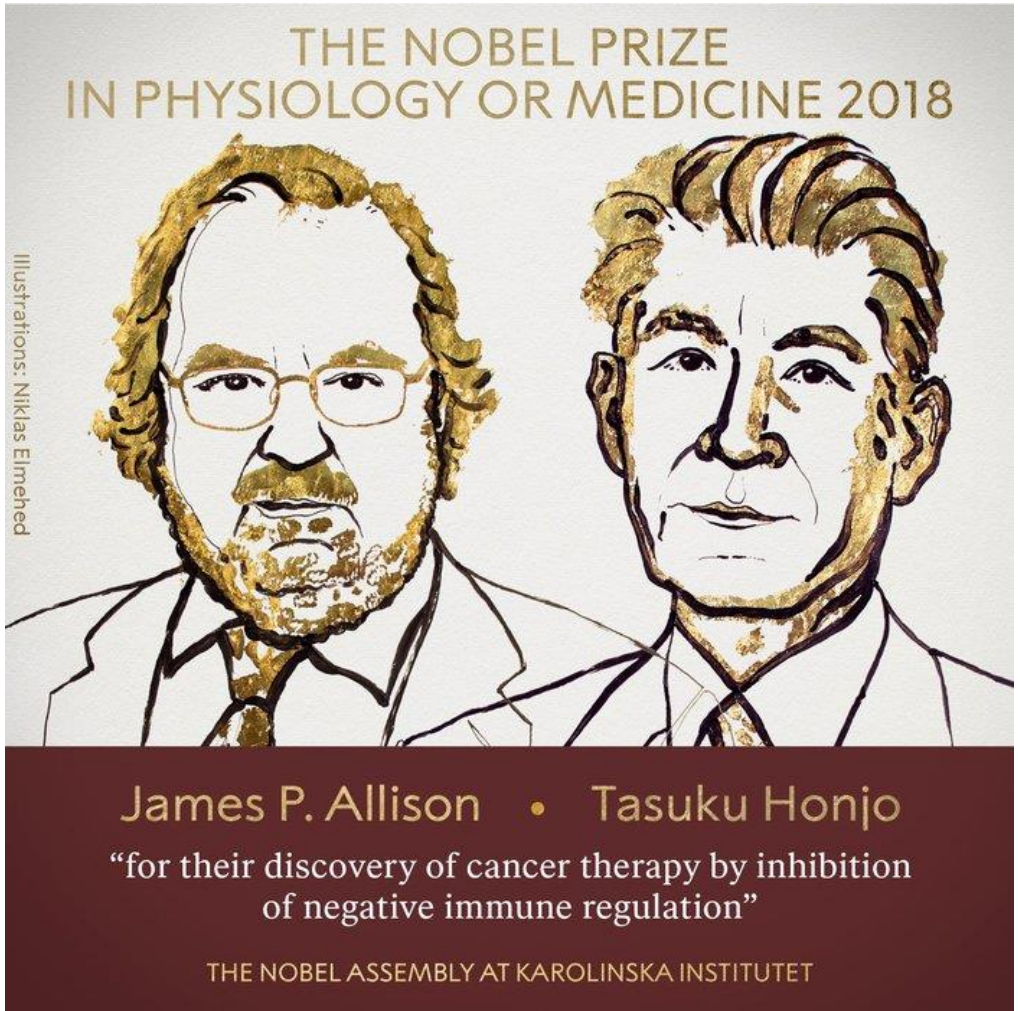
B Time to deterioration

Source	Median, mo: TTFields Plus Temozolomide	Median, mo: Temozolomide Alone	HR (95% CI)
Global health status	14.130	9.63	0.81 (0.60-1.10)
Physical functioning	14.170	13.97	0.90 (0.66-1.24)
Cognitive functioning	10.270	13.97	0.95 (0.71-1.28)
Role functioning	9.20	13.97	1.16 (0.86-1.56)
Social functioning	10.60	13.97	1.25 (0.91-1.72)
Emotional functioning	13.430	14.03	0.88 (0.64-1.21)
Pain	13.370	12.13	0.65 (0.48-0.89)
Itchy skin	8.167	14.40	1.85 (1.33-2.57)
Weakness of legs	14.170	14.03	0.71 (0.51-0.99)



Trattamenti innovativi nel GB

3) Immunoterapia



Remove the breakes
and
Step on the gas

Trattamenti innovativi nel GB

3) Immunoterapia

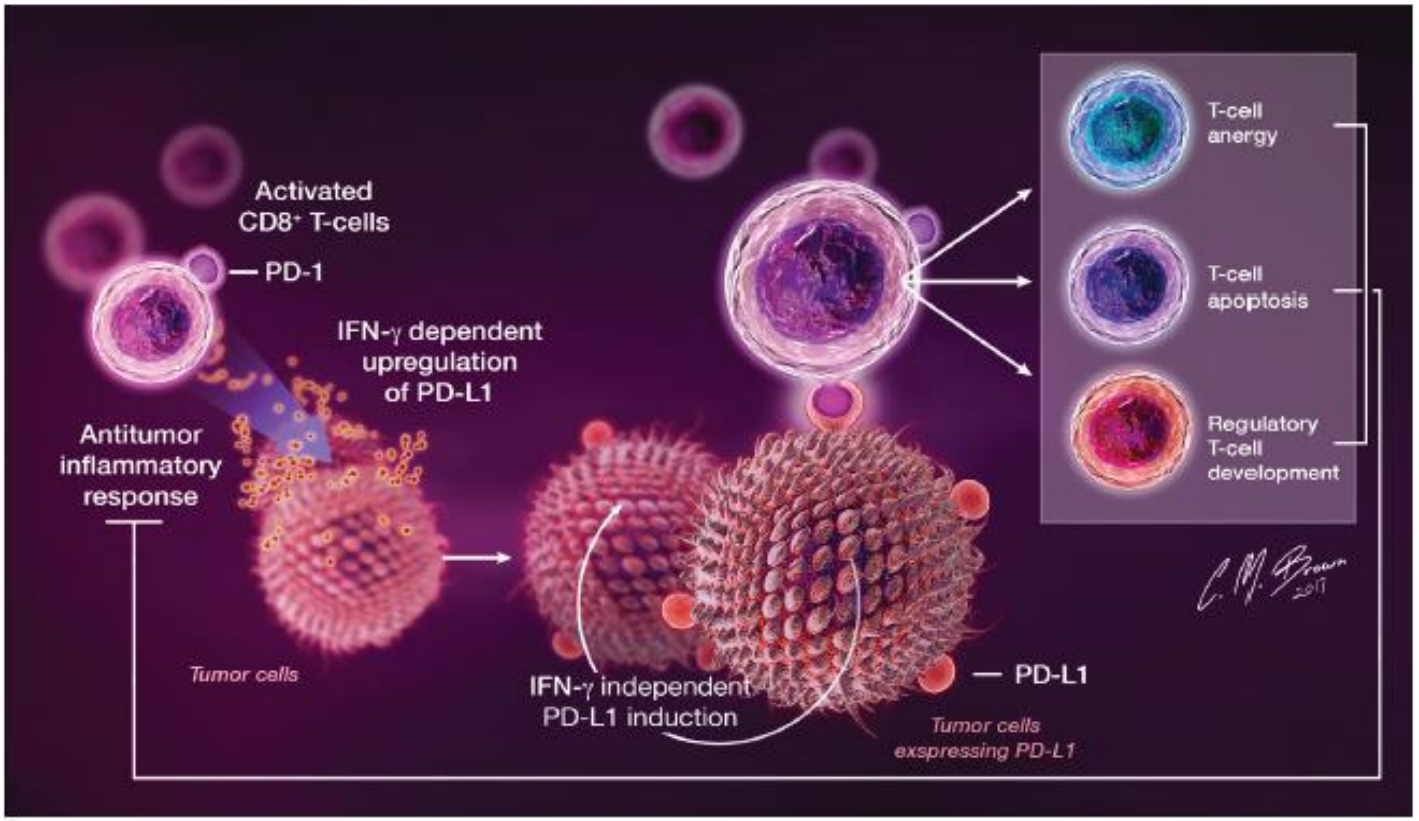
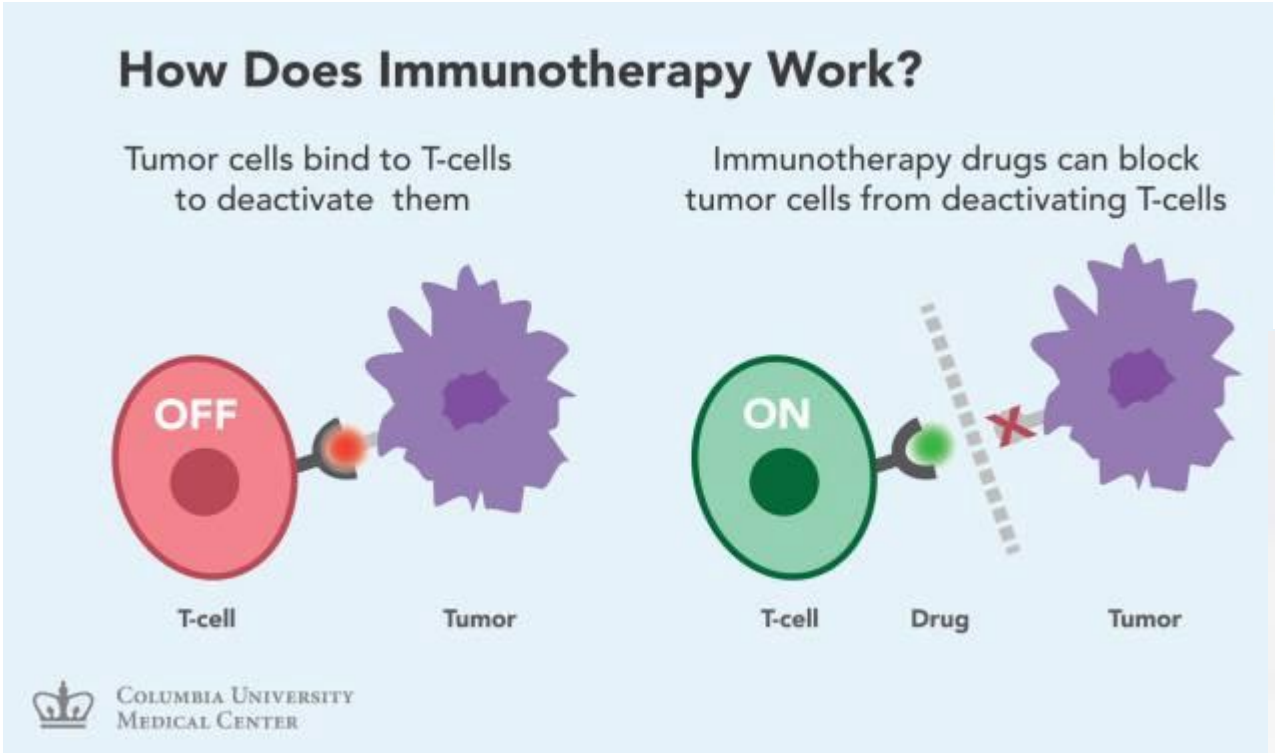


Figure 3: In the setting of cancer, PD-L1 is upregulated on tumor cells in response to IFN-γ released by infiltrating immune cells during antitumor immune responses, as well as through tumor-specific IFN-γ-independent mechanisms. PD-L1 serves as a receptor on cancer cells that, through interactions with PD-1expressing TIL, induces an intrinsic resistance to CTL killing and suppresses antitumor immune responses.

Trattamenti innovativi nel GB

3) immunoterapia: Anti PD1 Nivolumab e Pembrolizumab



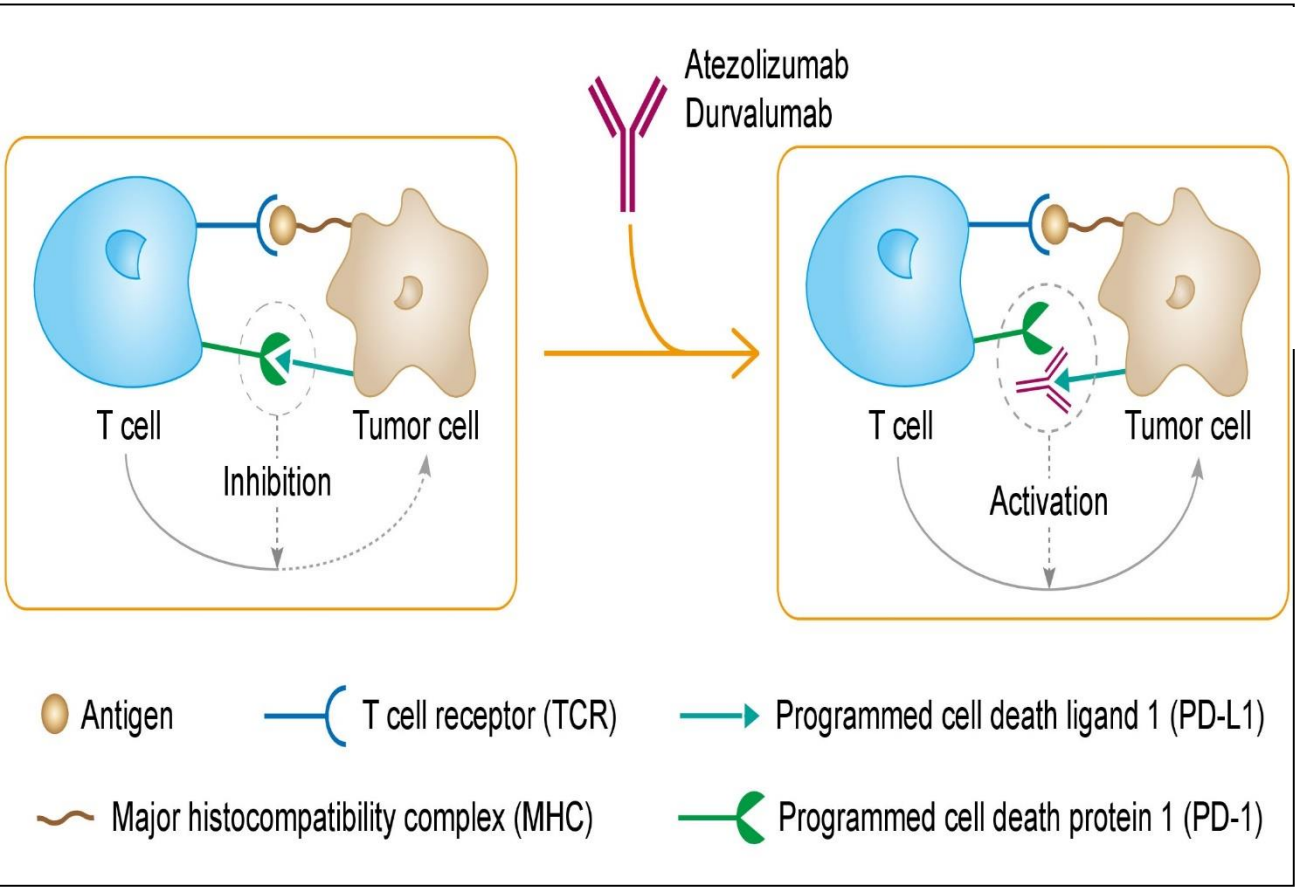
OS10.3 RANDOMIZED PHASE 3 STUDY EVALUATING THE EFFICACY AND SAFETY OF NIVOLUMAB VS BEVACIZUMAB IN PATIENTS WITH RECURRENT GLIOBLASTOMA: CHECKMATE 143

D. A. Reardon[1a], A. Omuro[2a], A. A. Brandes[3], J. Rieger[4,5], A. Wick[6], J. Sepulveda[7], S. Phuphanich[8], P. de Souza[9], M. S. Ahluwalia[10], M. Lim[11], G. Vlahovic[12b], J. Sampson[12b]; [1]Dana-Farber Cancer Institute and Harvard University School of Medicine, Boston, MA, United States, [2]Memorial Sloan-Kettering Cancer Center, New York, NY, United States, [3]AUSL-IRCCS Institute of Neurological Sciences, Bologna, Italy, [4]Klinikum der Goethe-Universität, Frankfurt, Germany, [5]University of Tübingen, Tübingen, Germany, [6]Neurology Clinic, University of Heidelberg, National Center for Tumor Diseases, Heidelberg, Germany, [7]Hospital Universitario 12 De Octubre, Madrid, Spain, [8]Cedars-Sinai Medical Center, Los Angeles, CA, United States, [9]University of Western Sydney School of Medicine, Liverpool, Australia, [10]Cleveland Clinic, Cleveland, OH, United States, [11]The Johns Hopkins Hospital, Baltimore, MD, United States, [12]Duke University Medical Center, Durham, NC, United States.

BACKGROUND: Despite available treatment options for patients (pts) with recurrent glioblastoma (GBM), < 5% of pts survive 5 years beyond initial diagnosis, and no single-agent therapy has demonstrated a survival benefit in the second-line setting, including bevacizumab (bev), which is approved for the treatment of recurrent disease. Nivolumab (nivo), a fully human IgG4 monoclonal antibody that inhibits the programmed death 1 receptor, has provided clinical benefit in multiple cancer types. In cohort 2 of the open-label, phase 3 CheckMate 143 study (NCT02017717), the efficacy and safety of nivo was compared with that of bev in pts with GBM experiencing their first recurrence after prior radiotherapy (RT) and temozolomide (TMZ). METHODS: Pts with no prior VEGF therapy were randomized 1:1 to receive nivo 3 mg/kg Q2W or bev 10 mg/kg Q2W until confirmed disease progression; pts were stratified by the presence/absence of measurable disease. The primary endpoint was overall survival (OS); secondary endpoints were 12-mo OS rate and investigator-assessed progression-free survival (PFS) and objective response rate (ORR) per Response Assessment in Neuro-Oncology criteria. RESULTS: At the time of final analyses (Jan 20, 2017), 369 pts were randomized to the nivo (n = 184) or bev (n = 185) treatment arms; of these pts, 182 received nivo and 165 received bev. At baseline, most pts in the nivo (83%) and bev (84%) arms had measurable disease, and 40% (nivo) and 43% (bev) of pts required corticosteroids, with 14% (nivo) and 15% (bev) receiving ≥ 4 mg/day. Deaths were reported in 154 (nivo) and 147 (bev) pts; median OS was 9.8 mo with nivo and 10.0 mo with bev, and the 12-mo OS rate was 42% in both arms. PFS medians were 1.5 mo (nivo) and 3.5 mo (bev). Among evaluable pts treated with nivo (n = 153) or bev (n = 156), ORRs were 8% (nivo) and 23% (bev); duration of response medians were 11.1 mo (nivo) and 5.3 mo (bev). Treatment-related AEs (TRAEs) occurred in 57% (nivo) and 58% (bev) of pts; the most common TRAEs (≥ 10% of pts in either arm; nivo vs bev) were fatigue (21% vs 14%) and hypertension (1% vs 22%). Grade 3–4 TRAEs were reported in 18% (nivo) and 15% (bev) of pts. Serious AEs (all causality) were reported in 46% (nivo) and 35% (bev) of pts; seizure (8% vs 6%) and malignant neoplasm progression (11% vs 7%) were the only serious AEs reported in ≥ 5% of pts in either arm. AEs leading to discontinuation occurred in 10% (nivo) and 15% (bev) of pts. CONCLUSIONS: Nivo did not demonstrate an improved OS compared with bev in pts with recurrent GBM. The ORR was lower with nivo than bev; however, responses with nivo were more durable. The safety profile of nivo was consistent with that observed in other tumor types. Studies of nivo in combination with RT ± TMZ in pts with newly diagnosed GBM are ongoing.

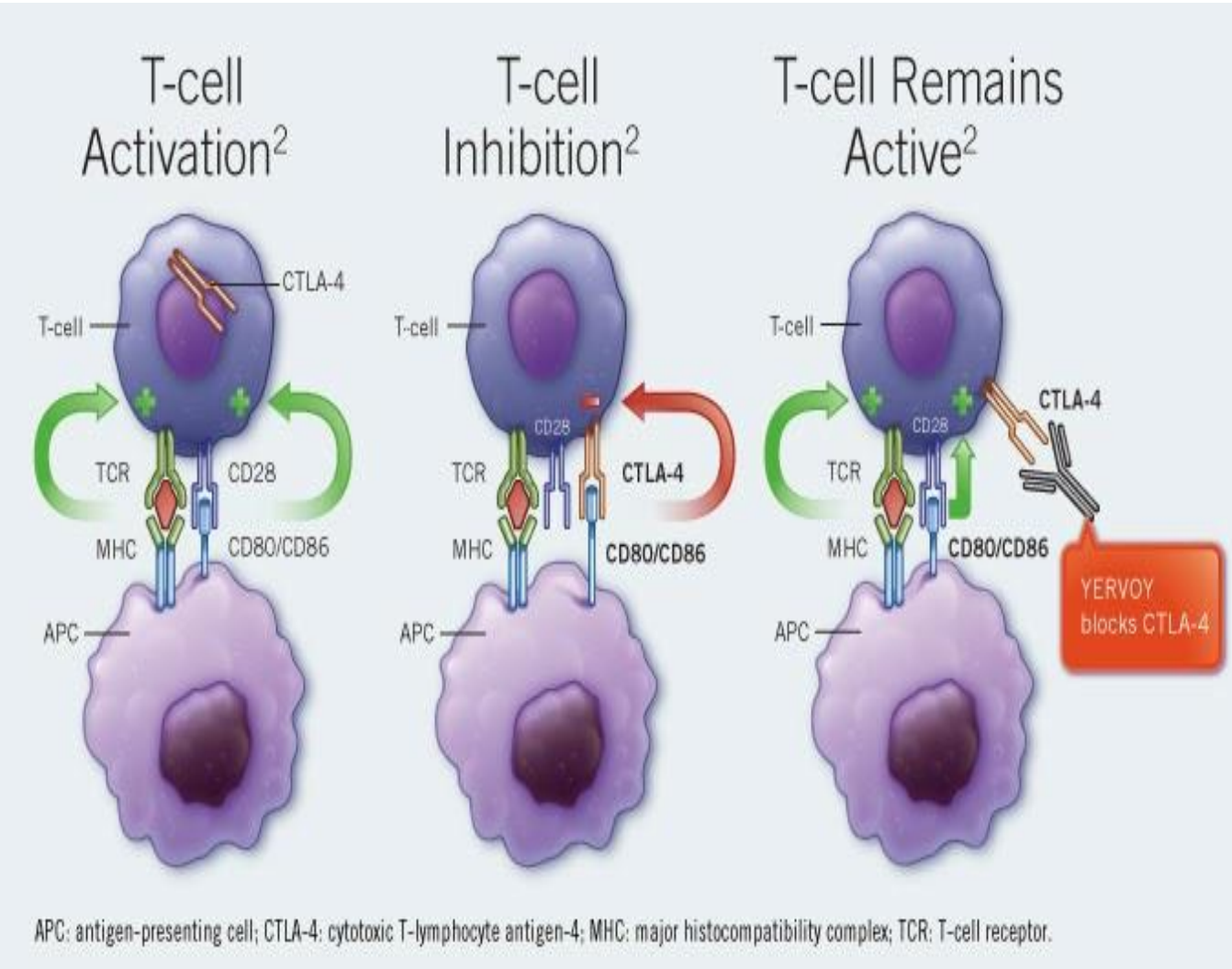
Trattamenti innovativi nel GB

3) Immunoterapia :a) Anti PD-L1 Atezolizumab, Durvalumab



Trattamenti innovativi nel GB

3) Immunoterapia : a) Anti CTLA-4 Ipilimumab



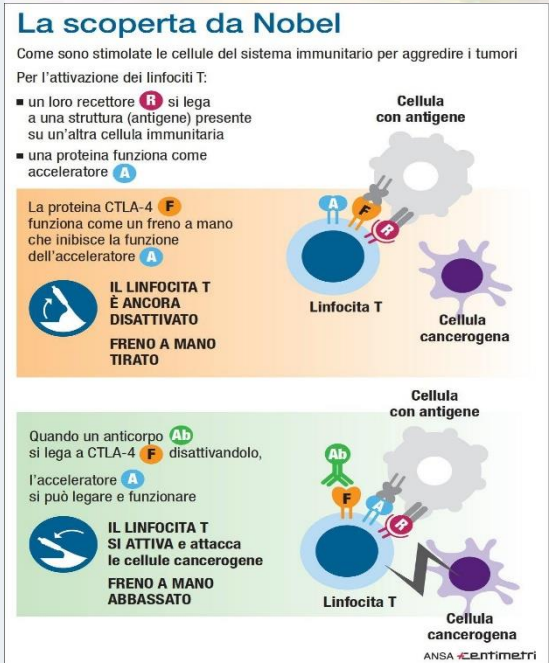
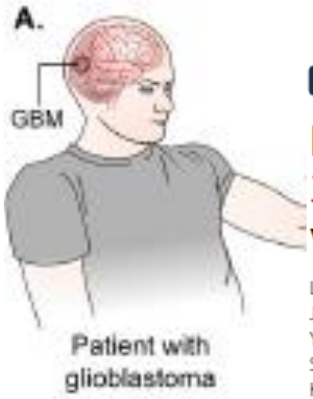


Table 1: Clinical trials with PD-1/PD-L1 blockade in malignant glioma

Malignancy	Phase	N	Name of trial	Therapeutic compounds	Clinical trial identifier	Status	R
Recurrent High Grade Glioma	I	26*	Hypofractionated Stereotactic Irradiation With Nivolumab in Patients With Recurrent High Grade Gliomas	Nivolumab, hfSRT	NCT02829931	Recruiting	
Recurrent Malignant Glioma	I	46*	Hypofractionated Stereotactic Irradiation (HFSRT) With Pembrolizumab and Bevacizumab for Recurrent High Grade Gliomas	Pembrolizumab, bevacizumab, hfSRT	NCT02313272	Recruiting	
Malignant Glioma	I	66*	Nivolumab With DC Vaccines for Recurrent Brain Tumors (AVERT)	Nivolumab, DC vaccine	NCT02529072	Recruiting	
Glioblastoma, Gliosarcoma	II	48*	Combination Adenovirus + Pembrolizumab to Trigger Immune Virus Effects (CAPTIVE)	DNX-2401, pembrolizumab	NCT02798406	Recruiting	
Glioblastoma	I/II	60*	A Phase 1/2 Safety Study of Intratumorally Dosed INT230-6 (IT-01)	INT230-6, anti-PD-1 antibody	NCT03058289	Recruiting	
Glioblastoma	II	205*	A Dose Escalation and Cohort Expansion Study of Anti-CD27 (Varlilumab) and Anti-PD-1 (Nivolumab) in Advanced Refractory Solid Tumors	Varlilumab, nivolumab	NCT02335918	Recruiting	
Recurrent/ Progressive Glioblastoma	Pilot	30*	A Pilot Surgical Trial To Evaluate Early Immunologic Pharmacodynamic Parameters For The PD-1 Checkpoint Inhibitor, Pembrolizumab (MK-3475), In Patients With Surgically Accessible Recurrent/Progressive Glioblastoma	Pembrolizumab	NCT02852655	Recruiting	
Glioblastoma Multiforme	I	20*	Pilot Study of Autologous Chimeric Switch Receptor Modified T Cells in Recurrent Glioblastoma Multiforme	Anti-PD-L1 CSR T cells, cyclophosphamide, fludarabine	NCT02937844	Recruiting	
Glioblastoma	I/II	62*	A Study Evaluating the Association of Hypofractionated Stereotactic Radiation Therapy and Durvalumab for Patients With Recurrent Glioblastoma (STERIMGLI)	Durvalumab, hfSRT	NCT02866747	Recruiting	
Glioblastoma	II	159	Phase 2 Study of MEDI4736 in Patients With Glioblastoma	MEDI4736, radiotherapy, bevacizumab	NCT02336165	Active, Not Recruiting	
Recurrent Glioblastoma	II	82	Pembrolizumab +/- Bevacizumab for Recurrent GBM	Pembrolizumab, bevacizumab	NCT02337491	Active, Not Recruiting	
Recurrent Glioblastoma	II	30*	Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen Vaccine and Nivolumab in Treating Patients With Recurrent Glioblastoma	Autologous DCs pulsed with tumor lysate antigen vaccine, nivolumab	NCT03014804	Not Yet Recruiting	
Glioblastoma Multiforme	II	29	Neoadjuvant Nivolumab in Glioblastoma (Neo-nivo)	Nivolumab	NCT02550249	Completed	
Recurrent High-Grade Gliomas		20	OS09.5 Synergistic effect of reirradiation and PD-1 inhibitors in recurrent high-grade gliomas	PD-1 Inhibitors, reirradiation			

Trattamenti innovativi nel GB

3) Immunoterapia : b) Vaccini – Dcvax (Dendritic Cell Vaccines)



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Journal of
Translational Medicine

RESEARCH Open Access

First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma

Linda M. Liau[1*], Keyoumars Ashkan[2], David D. Tran[3], Jian L. Campian[4], John E. Trusheim[5], Charles S. Cobbs[6], Jason A. Heth[7], Michael Salacz[8], Sarah Taylor[8], Stacy D. D'Andre[9], Fabio M. Iwamoto[10], Edward J. Dropcho[11], Yaron A. Moshel[12], Kevin A. Walter[13], Clement P. Pillainayagam[14], Robert Aiken[15], Rekha Chaudhary[16], Samuel A. Goldlust[17], Daniela A. Bota[18], Paul Duic[19], Jai Grewal[59], Heinrich Elinzano[20], Steven A. Toms[20], Kevin O. Lillehei[21], Tom Mikkelsen[22], Tobias Walbert[22], Steven R. Abram[23], Andrew J. Brenner[24], Steven Brem[25], Matthew G. Ewend[26], Simon Khagi[26], Jana Portnow[27], Lyndon J. Kim[28], William G. Loudon[29], Reid C. Thompson[30], David E. Avigan[31], Karen L. Fink[32], Francois J. Geoffroy[33], Scott Lindhorst[34], Jose Lutzky[35], Andrew E. Sloan[36], Gabriele Schackert[37], Dietmar Krex[37], Hans-Jorg Meisel[38], Julian Wu[39], Raphael P. Davis[40], Christopher Duma[41], Arnold B. Etame[42], David Mathieu[43], Santosh Kesari[44], David Piccioni[44], Manfred Westphal[45], David S. Baskin[46], Pamela Z. New[46], Michel Lacroix[47], Sven-Axel May[48], Timothy J. Pluard[49], Victor Tse[50], Richard M. Green[51], John L. Villano[52], Michael Pearlman[53], Kevin Petrecca[54], Michael Schulder[55], Lynne P. Taylor[56], Anthony E. Maida[58], Robert M. Prins[1], Timothy F. Cloughesy[1], Paul Mulholland[57] and Marnix L. Bosch[58*]

Abstract

Background: Standard therapy for glioblastoma includes surgery, radiotherapy, and temozolomide. This Phase 3 trial evaluates the addition of an autologous tumor lysate-pulsed dendritic cell vaccine (DCVax®-L) to standard therapy for newly diagnosed glioblastoma.

Methods: After surgery and chemoradiotherapy, patients were randomized (2:1) to receive temozolomide plus DCVax-L (n = 232) or temozolomide and placebo (n = 99). Following recurrence, all patients were allowed to receive DCVax-L, without unblinding. The primary endpoint was progression free survival (PFS); the secondary endpoint was overall survival (OS).

Results: For the intent-to-treat (ITT) population (n = 331), median OS (mOS) was 23.1 months from surgery. Because of the cross-over trial design, nearly 90% of the ITT population received DCVax-L. For patients with methylated MGMT (n = 131), mOS was 34.7 months from surgery, with a 3-year survival of 46.4%. As of this analysis, 223 patients are ≥ 30 months past their surgery date; 67 of these (30.0%) have lived ≥ 30 months and have a Kaplan-Meier (KM)-derived mOS of 46.5 months. 182 patients are ≥ 36 months past surgery; 44 of these (24.2%) have lived ≥ 36 months and have a KM-derived mOS of 88.2 months. A population of extended survivors (n = 100) with mOS of 40.5 months, not explained by known prognostic factors, will be analyzed further. Only 2.1% of ITT patients (n = 7) had a grade 3

Trattamenti innovativi nel GB

3) Immunoterapia : b) Vaccini Peptidici (EGFRvIII Rindopepimut)

Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial

*Michael Weller, Nicholas Butowski, David D Tran, Lawrence D Recht, Michael Lim, Hal Hirte, Lynn Ashby, Laszlo Mechtler, Samuel A Goldlust, Fabio Iwamoto, Jan Drappatz, Donald M O'Rourke, Mark Wong, Mark G Hamilton, Gaetano Finocchiaro, James Perry, Wolfgang Wick, Jennifer Green, Yi He, Christopher D Turner, Michael J Yellin, Tibor Keler, Thomas A Davis, Roger Stupp, and John H Sampson, for the ACT IV trial investigators**

Summary

Background Rindopepimut (also known as CDX-110), a vaccine targeting the *EGFR* deletion mutation EGFRvIII, consists of an EGFRvIII-specific peptide conjugated to keyhole limpet haemocyanin. In the ACT IV study, we aimed to assess whether or not the addition of rindopepimut to standard chemotherapy is able to improve survival in patients with EGFRvIII-positive glioblastoma.

Methods In this randomised, double-blind, phase 3 trial, we recruited patients aged 18 years and older with glioblastoma from 165 hospitals in 22 countries. Eligible patients had newly diagnosed glioblastoma confirmed to express EGFRvIII by central analysis, and had undergone maximal surgical resection and completion of standard chemoradiation without progression. Patients were stratified by European Organisation for Research and Treatment of Cancer recursive partitioning analysis class, *MGMT* promoter methylation, and geographical region, and randomly assigned (1:1) with a prespecified randomisation sequence (block size of four) to receive rindopepimut (500 µg admixed with 150 µg GM-CSF) or control (100 µg keyhole limpet haemocyanin) via monthly intradermal injection until progression or intolerance, concurrent with standard oral temozolomide (150–200 mg/m² for 5 of 28 days) for 6–12 cycles or longer. Patients, investigators, and the trial funder were masked to treatment allocation. The primary endpoint was overall survival in patients with minimal residual disease (MRD; enhancing tumour <2 cm² post-chemoradiation by central review), analysed by modified intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01480479.

Findings Between April 12, 2012, and Dec 15, 2014, 745 patients were enrolled (405 with MRD, 338 with significant residual disease [SRD], and two unevaluable) and randomly assigned to rindopepimut and temozolomide (n=371) or control and temozolomide (n=374). The study was terminated for futility after a preplanned interim analysis. At final analysis, there was no significant difference in overall survival for patients with MRD: median overall survival was 20·1 months (95% CI 18·5–22·1) in the rindopepimut group versus 20·0 months (18·1–21·9) in the control group (HR 1·01, 95% CI 0·79–1·30; p=0·93). The most common grade 3–4 adverse events for all 369 treated patients in the rindopepimut group versus 372 treated patients in the control group were: thrombocytopenia (32 [9%] *vs* 23 [6%]), fatigue (six [2%] *vs* 19 [5%]), brain oedema (eight [2%] *vs* 11 [3%]), seizure (nine [2%] *vs* eight [2%]), and headache (six [2%] *vs* ten [3%]). Serious adverse events included seizure (18 [5%] *vs* 22 [6%]) and brain oedema (seven [2%] *vs* 12 [3%]). 16 deaths in the study were caused by adverse events (nine [4%] in the rindopepimut group and seven [3%] in the control group), of which one—a pulmonary embolism in a 64-year-old male patient after 11 months of treatment—was assessed as potentially related to rindopepimut.

Interpretation Rindopepimut did not increase survival in patients with newly diagnosed glioblastoma. Combination approaches potentially including rindopepimut might be required to show efficacy of immunotherapy in glioblastoma.

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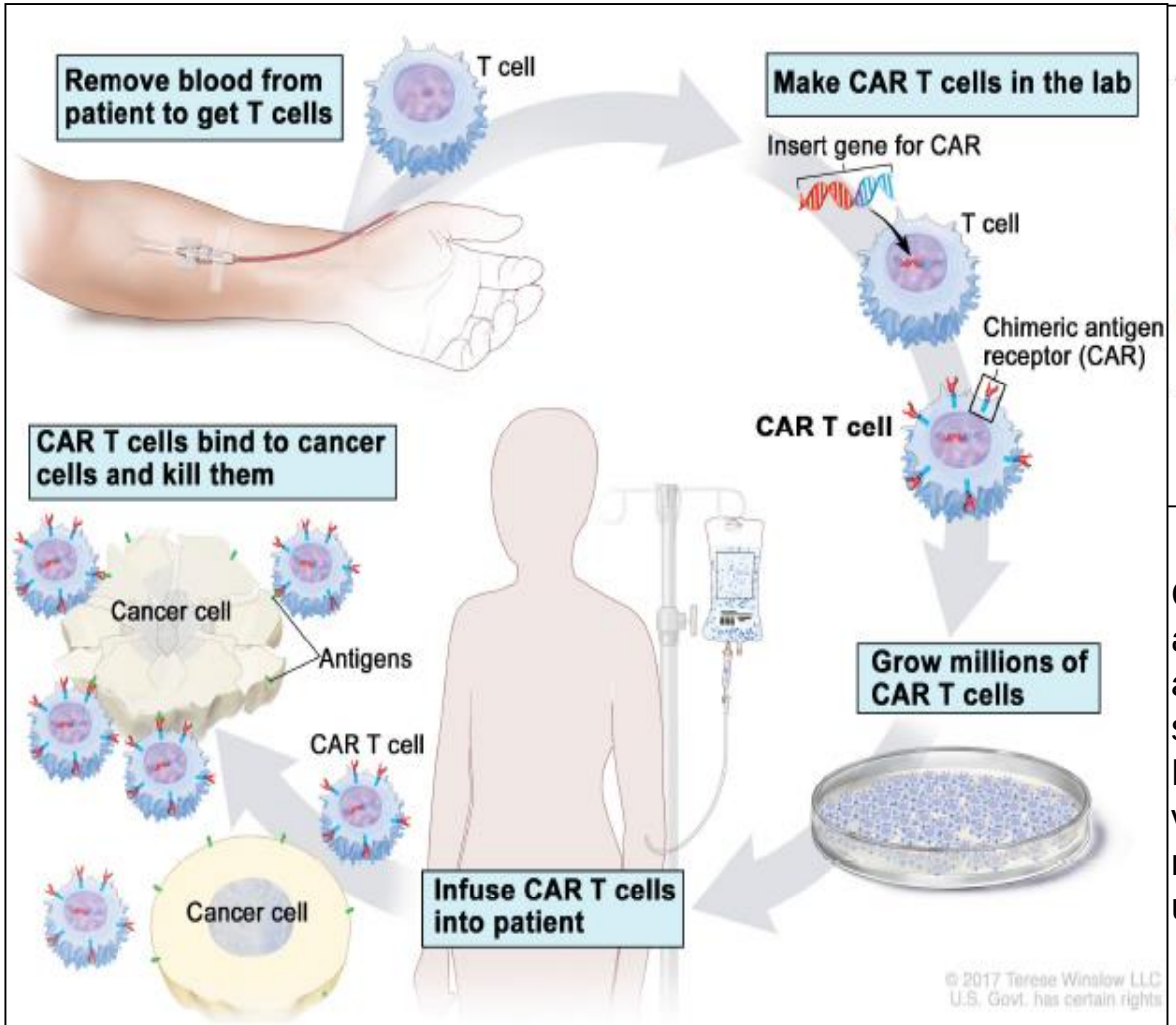
See Comment page 1294

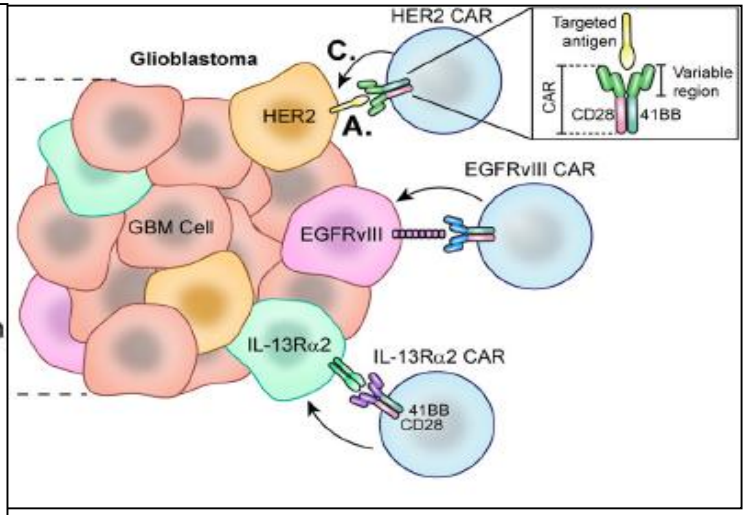
* Investigators who participated in this trial are listed in the appendix

Department of Neurology (Prof M Weller MD) and Department of Oncology (Prof R Stupp MD), University Hospital and University of Zurich, Zurich, Switzerland; Department of Neurological Surgery, University of California, San Francisco, CA, USA (N Butowski MD); Washington University, St Louis, MO, USA (D D Tran MD); Stanford University Medical Center, Palo Alto, CA, USA (L D Recht MD); The Johns Hopkins Hospital, Baltimore, MD, USA (M Lim MD); Juravinski Cancer Centre, Hamilton, ON, Canada (H Hirte MD); Barrow Neurological Institute, Phoenix, AZ, USA (L Ashby MD); DENT Neurologic Institute, Buffalo, NY, USA (L Mechtler, MD); John Theurer Cancer Center, Hackensack, NJ, USA (S A Goldlust MD); Columbia University Medical Center, New York, NY, USA (F Iwamoto M D); University of

Trattamenti innovativi nel GB

3) Immunoterapia : c) CAR T-Cell Therapy (Chimeric Antigen Receptor)





CAR sono delle proteine di fusione artificiali aventi un dominio extra –trans e intra cell. atte a riconoscere l'antigene specifico sulla cellula tumorale.(HER2,EGFRvIII,IL13R Esse vengono trasfettate mediate plasmidi o virus nei lif T ed una volta reinfusi nel pz riconoscono l'antigene tumorale e scatenano una reazione immune

Trattamenti innovativi nel GB

3) Immunoterapia : c) CAR T-Cell Therapy (Chimeric Antigen Receptor)

CAR Target | CA (nu sub | easures

IL-13 Rα2[25,45] | Firs Sec | erall survival s recurrence at esection cavity response of l and spinal ting 7.5 months

HER2 (virus-specific)[49] | Sec | erall survival s t with partial nore than

ents with dur- disease during ths of follow-up

EGFRvIII[26] | Sec | erall survival

t remains alive s post CART-cell t time of this re- e

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S., Lihong Weng, M.D., Jamie R. Wagner, B.A., Araceli Naranjo, B.A., Julie R. Ostberg, Ph.D., M. Suzette Blanchard, Ph.D., Julie Kilpatrick, M.S.N., Jennifer Simpson, B.A., Anita Kurien, M.B.S., Saul J. Priceman, Ph.D., Xiuli Wang, M.D., Ph.D., Todd L. Harshbarger, M.D., Massimo D'Apuzzo, M.D., Julie A. Ressler, M.D., Michael C. Jensen, M.D., Michael E. Barish, Ph.D., Mike Chen, M.D., Ph.D., Jana Portnow, M.D., Stephen J. Forman, M.D., and Behnam Badie, M.D.

SUMMARY

A patient with recurrent multifocal glioblastoma received chimeric antigen receptor (CAR)–engineered T cells targeting the tumor-associated antigen interleukin-13 receptor alpha 2 (IL13Rα2). Multiple infusions of CAR T cells were administered over 220 days through two intracranial delivery routes — infusions into the resected tumor cavity followed by infusions into the ventricular system. Intracranial infusions of IL13Rα2-targeted CAR T cells were not associated with any toxic effects of grade 3 or higher. After CAR T-cell treatment, regression of all intracranial and spinal tumors was observed, along with corresponding increases in levels of cytokines and immune cells in the cerebrospinal fluid. This clinical response continued for 7.5 months after the initiation of CAR T-cell therapy. (Funded by Gateway for Cancer Research and others; ClinicalTrials.gov number, NCT02208362.)

Trattamenti innovativi nel GB

3) Immunoterapia : c) CAR T-Cell Therapy (Chimeric Antigen Receptor)

NCT# and Institution	Study Name	Phase	Target	Delivery	Additional Features
NCT02844062 Beijing Sanbo Brain Hospital, China	Pilot study of autologous anti-EGFRVIII CART cells in recurrent glioblastoma multiforme	I	EGFRvIII	Intravenous	Lymphodepleting chemotherapy: Cyclophosphamide 250 mg/m^2 days 1–3 Fludarabine 25 mg/m^2 days 1–3
NCT03170141 Shenzhen Geno-immune Medical Institute, China	4SCAR-IgT against glioblastoma multiforme	I/II	EGFRvIII	Intravenous Intracavitary	Lymphodepleting chemotherapy: Cyclophosphamide 250 mg/m^2 days 1–3 Fludarabine 25 mg/m^2 days 1–3 Use PD-1/PD-L1 antibody-producingT cells (IgT) designed to address tumor microenvironment in addition to direct tumor cell killing
NCT02442297 Baylor College of Medicine	T cells expressing HER2-specific chimeric antigen receptors for patients with glioblastoma (iCAR)	I	HER2	Intracavitary	Patients must undergo surgical tumor resection
NCT01109095 Baylor College of Medicine	CMV-specific cytotoxicT lymphocytes expressing CAR targeting HER2 in patients with GBM (HERT-GBM)	I	HER2	Intravenous	First cohort of 17 patients published[49]
NCT02664363 Duke University	EGFRvIII CART cells for newly diagnosed GBM (ExCeL)	I	EGFRvIII	Intravenous	Newly diagnosed residual disease at least 2 cm Leukapheresis occurs prior to standard radiation and chemotherapy, and CART cells are administered during post-radiation temozolomide
NCT0328331 Duke University	Intracerebral EGFRVIII CART cells for recurrent GBM (INTERCEPT)	I	EGFRvIII	Intratumoral via convection enhanced delivery	CART cells are infused immediately following stereotactic radiosurgery
NCT0220937 University of Pennsylvania, University of California San Francisco	AutologousT cells redirected to EGFRvIII with a chimeric antigen receptor in patients with EGFRvIII+ glioblastoma	I	EGFRvIII	Intravenous	First cohort of 10 patients published[26]
NCT0145459 National Cancer Institute	CART-cell receptor immunotherapy targeting EGFRvIII for patients with malignant gliomas expressing EGFRvIII	I/II	EGFRvIII	Intravenous	Lymphodepleting chemotherapy: Cyclophosphamide 60 mg/kg days 1–2 Fludarabine 25 mg/m^2 days 1–5 Given with intravenous aldesleukin (IL-2)
NCT0293844 Beijing Sanbo Brain Hospital, China	Pilot study of autologous chimeric switch receptor modified T cells in recurrent glioblastoma multiforme	I	PD-L1	Intravenous	Lymphodepleting chemotherapy: Cyclophosphamide 250 mg/m^2 days 1–3 Fludarabine 25 mg/m^2 days 1–3 CAR contains the extracellular domain of PD-1
NCT02208362 City of Hope Medical Center	Genetically modifiedT cells in treating patients with recurrent or refractory malignant glioma	I	IL-13 Rα2	Intracavitary Intraventricular	First cohort of 3 patients published,[45] as well as case report of complete response[25]

Trattamenti innovativi nel GB

Conclusioni:

Ad oggi non abbiamo ancora trattamenti innovativi da poter utilizzare nella nostra pratica clinica quotidiana per questa malattia che rimane sempre a prognosi infausta

.

Sicuramente gli studi di immunoterapia in corso porteranno, a dei buoni risultati come e' successo in altre neoplasie (melanoma o il tumore del polmone)

In questi anni abbiamo imparato che:

- Multidisciplinarietà
- Centri di riferimento
- Trials clinici

GRAZIE