Nuovi approcci terapeutici nei tumori cerebrali

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Glioblastoma
Glioblastoma (GMB)

- GBM represent about 17% of all primary brain tumors; approximately 5,000 new cases/year in US

- Without therapy patients with GBM die within 3 months

- Patients treated with optimal therapy have a mOS of 12 months, with fewer than 25% surviving up to 2 years and fewer than 10% up to 5 years
Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).
**NCCN Guidelines Version 2.2013**

**Anaplastic Gliomas/Glioblastoma**

### Recurrence

- **Diffuse or multiple**
  - **Recurrent disease**
    - Anaplastic oligodendroglioma
    - Anaplastic oligoastrocytoma
    - Anaplastic astrocytoma
    - Anaplastic gliomas
    - Glioblastoma

- **Resectable**
  - Resection + carmustine (BCNU) wafer
  - Resection without carmustine (BCNU) wafer

- **Local**
  - Unresectable

### Treatment

- Palliative/Best supportive care if poor performance status or systemic chemotherapy
- Surgery for symptomatic, large lesion or consider alternating electric field therapy (for glioblastoma) (category 2B)

- Palliative/Best supportive care if poor performance status or systemic chemotherapy
- Consider reirradiation (category 2B) or consider alternating electric field therapy (for glioblastoma) (category 2B)

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**CLINICAL TRIAL**

- **Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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**References:**

- See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
- See Principles of Brain Tumor Systemic Therapy (BRAIN-D).
- Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies, may impact enrollment in some adjuvant clinical trials.
- Consider MR spectroscopy, MR perfusion, or brain PET to rule out radiation necrosis.
- Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.
- Especially if long interval since prior RT and/or if there was a good response to prior RT.
Evolving Therapeutic Options for Cancer Treatment

- Surgery
- Chemotherapy
- Radiotherapy
- Immunotherapy
A historical view of immunotherapy...

- **1891**: Coley's treatment of cancer
- **1970s**: Spontaneous regressions in melanoma: immune component?
- **1980s**: 1st tumour associated antigen cloned
- **1990s**: IFN adjuvant melanoma US (1995)
- **2000s**: Provenge US
- **2010s**: 2011 Ipilimumab approved for advanced melanoma

**2014–2015**: Nivolumab, pembrolizumab
Approved in advanced melanoma and NSCLC.
Nivolumab + ipilimumab in melanoma (US)
These pathways can be activated via I-O agents to counteract tumor-mediated inhibition.

These pathways can be blocked via I-O agents to counteract tumor-mediated inhibition.

APC=antigen-presenting cell; CTLA-4=cytotoxic T-lymphocyte antigen-4; LAG-3=lymphocyte activation gene-3; MHC=major histocompatibility complex; PD-1=programmed death-1; PD-L1=PD ligand-1; PD-L2=PD ligand-2; TCR=T-cell receptor.

Immune Checkpoint Pathways

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)

CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor.
Cancer-cell directed vs immune-system directed cancer treatment: a matter of time

**Chemotherapy/target therapy**
- Tumour cell destruction

**Immunotherapy**
- Immune system activation
- Tumour cell destruction
Effect in the CNS?
Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial

Anna Maria Di Giacomo, Paolo Ascierto, Lorenzo Pilla, Mario Santinami, Pier Francesco Ferrucci, Diana Giannarelli, Antonella Marasco, Licia Rivoltini, Ester Simeone, Stefania V L Nicoletti, Ester Fonsatti, Diego Annesi, Paola Queirolo, Alessandro Testori, Ruggero Ridolfi, Giorgio Parmiani, Michele Maio
### NIBIT - M1
3-years survival update

<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
<th>Study population (N=86)</th>
<th>Patients with MBM (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS, months (95% CI)</strong></td>
<td>12.9 (7.1-18.7)</td>
<td>12.7 (2.7-22.7)</td>
</tr>
<tr>
<td><strong>3-year survival rate, % (95% CI)</strong></td>
<td>28.5 (20.1-41.3)</td>
<td>27.8 (17.2-60.6)</td>
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<tr>
<td><strong>Median ir-PFS, months (95% CI)</strong></td>
<td>4.5 (3.1-5.9)</td>
<td>3.4 (2.3-4.5)</td>
</tr>
</tbody>
</table>

Di Giacomo AM et al., Annals Oncol 2015
CheckMate 012 Arm M: Nivolumab in NSCLC Patients With Untreated CNS Metastases

CheckMate 012 Arm M (N = 12)
• Stage IV NSCLC (any histology), ECOG PS 0–1
• ≥1 asymptomatic CNS metastasis, with no prior local therapy

Nivolumab 3 mg/kg Q2W until progression

Endpoints analyzed:
• Baseline characteristics and prior treatment
• Disposition
• Safety: nervous system AEs
• Efficacy: OS, PFS, intracranial best overall response

2/12 pts (16.7%) achieved intracranial responses, including one CR long-lasting (>10.5 mo)
The NIBIT-M2 study design

Screening/Baseline Randomization

Arm A
Induction Phase
Fotemustine: 100mg/m² iv q1 week for 3 doses

Maintenance Phase
Fotemustine: 100mg/m² q3 weeks from week 9 for 6 doses

Arm B
Induction Phase
Fotemustine: 100mg/m² iv q1 week for 3 doses and then from week 9 for 6 doses
Ipilimumab: 10 mg/kg iv q3 weeks for 4 doses

Maintenance Phase
Ipilimumab: 10 mg/kg iv q12 weeks from week 24

Arm C
Induction Phase
Nivolumab 1mg/kg iv + ipilimumab 3mg/kg iv q3 for 4 doses

Maintenance Phase
Nivolumab 3mg/kg iv q2 weeks

Follow-up phase
Treatment until PD or excessive to toxicity or patient’s refusal
<table>
<thead>
<tr>
<th>Ongoing Clinical Trials</th>
<th>NCT</th>
<th>Phase</th>
<th>Status</th>
<th>Treatment(s)</th>
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</thead>
<tbody>
<tr>
<td>Anti-PD 1 Brain Collaboration for Patients With Melanoma Brain (ABC)</td>
<td>NCT02374242</td>
<td>II</td>
<td>Recruiting</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Nivolumab in Symptomatic Brain Metastases (CA209-322)</td>
<td>NCT02621515</td>
<td>II</td>
<td>Recruiting</td>
<td>Nivolumab</td>
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<td>A randomized, Phase III study of Fotemustine versus the Combination of Fotemustine and</td>
<td>NCT02460068</td>
<td>III</td>
<td>Recruiting</td>
<td>Ipilimumab+Fotemustine</td>
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<tr>
<td>Ipilimumab in Patients with Metastatic Melanoma with brain metastasis (NIBIT-M2 Study)</td>
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<td></td>
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<td>Ipilimumab+Nivolumab</td>
</tr>
<tr>
<td>GEM STUDY: Radiation and Yervoy in pts with melanoma and brain mts (GRAY-B)</td>
<td>NCT021151390</td>
<td>II</td>
<td>Recruiting</td>
<td>Ipilimumab+WBRT</td>
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<tr>
<td>SRS plus Ipilimumab</td>
<td>NCT01950195</td>
<td>I</td>
<td>Recruiting</td>
<td>Ipilimumab+SRS</td>
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<tr>
<td>A Multi-Center Phase 2 Open-Label Study to Evaluate Safety, Efficacy in Subjects</td>
<td>NCT02320058</td>
<td>II</td>
<td>Recruiting</td>
<td>Ipilimumab+Nivolumab</td>
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<tr>
<td>With MM to the Brain Treated With Nivolumab in Combination With Ipilimumab Followed by Nivolumab (CheckMate 204)</td>
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<tr>
<td>MK-3475 in Melanoma and NSCLC Patients With Brain Metastases</td>
<td>NCT02085070</td>
<td>II</td>
<td>Recruiting</td>
<td>Nivolumab</td>
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</tbody>
</table>
Glioblastoma
Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency


ABSTRACT

Purpose
Recurrent glioblastoma multiforme (GBM) is incurable with current therapies. Biallelic mismatch repair deficiency (bMMRD) is a highly penetrant childhood cancer syndrome often resulting in GBM characterized by a high mutational burden. Evidence suggests that high mutation and neoantigen loads are associated with response to immune checkpoint inhibition.
GBM from germline biallelic Mismatch Repair Deficiency (bMMRD) have higher mutational load and neoantigen

Case report: Two siblings with recurrent multifocal GBM treated with anti-PD1 nivolumab showing clinically significant durable responses.

MRI of two siblings with biallelic Mismatch Repair Deficiency treated with nivolumab
Safety and Activity of Nivolumab Monotherapy and Nivolumab in Combination With Ipilimumab in Recurrent Glioblastoma: Updated Results From CheckMate 143

- David A. Reardon,1 John Sampson,2 Solmaz Sahebjam,3 Michael Lim,4 Joachim Baehring,5 Gordana Vlahovic,2 Timothy Cloughesy,6 Lewis Strauss,7 Robert Latek,7 Prashni Paliwal,7 Chris Harbison,7 Alfredo Voloschin,8 Antonio Omuro9

1Dana-Farber Cancer Institute and Harvard University School of Medicine, Boston, MA, USA; 2Duke University Medical Center, Durham, NC, USA; 3Moffitt Cancer Center, Tampa, FL, USA; 4The Johns Hopkins Hospital, Baltimore, MD, USA; 5Yale School of Medicine, New Haven, CT, USA; 6University of California, Los Angeles, Los Angeles, CA, USA; 7Bristol-Myers Squibb, Princeton, NJ, USA; 8Emory University School of Medicine, Atlanta, GA, USA; 9Memorial Sloan Kettering Cancer Center, New York, NY, USA

- ASCO 2016
CheckMate 143

Study Design

Screening and Randomization

Cohort 1
1:1 Randomization
(n = 20)

Screening
First recurrence of GBM after previous radiotherapy and temozolomide

Cohort 1b
Non-randomized
(n = 20)

Treatment

Nivolumab 3 mg/kg Q2W
(n = 10)

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W x 4 doses, then nivolumab 3 mg/kg Q2W
(n = 10)

Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W x 4 doses, then nivolumab 3 mg/kg Q2W
(n = 20)

Follow-up

• Treatment until confirmed progression or study discontinuation for any reason
• Treatment beyond progression was permitted for patients who tolerated therapy and had an investigator-assessed benefit
• Post-treatment follow-up for safety, OS, and progression

OS = overall survival; Q2W = every 2 weeks; Q3W = every 3 weeks.
Percentage of Patients with Grade 3–4 TRAEs and TRSAEs

- Nivolumab 3 mg/kg: TRAE = 0%, TRSAE = 0%
- Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg: TRAE = 90%, TRSAE = 70%
- Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg: TRAE = 25%, TRSAE = 10%
# Investigator-assessed Best Overall Response and Objective Response Rate per RANO Criteria

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab 3 mg/kg (n = 10)</td>
<td>Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n = 10)</td>
</tr>
<tr>
<td><strong>Best overall response,(^a) n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (50)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (30)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>ORR,(^b) n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>(0.3, 44.5)</td>
<td>(0.0, 30.8)</td>
</tr>
</tbody>
</table>

\(^a\)Per RANO criteria  
\(^b\)Complete response + partial response; confidence interval (CI) based on the Clopper and Pearson method
CheckMate 143

Ongoing randomized studies will address the efficacy of nivolumab versus bevacizumab in a previously treated population


**CA209-498 Study Design**

**Screening**
- Newly diagnosed histologically confirmed GBM
- approx 1200 tumors screened for MGMT
- CENTRAL LABORATORY confirmation
- UNmethylated MGMT

**Randomization**
- Treatment arm N
  - N = 275
  - **Nivo** 240 mg Q2wk x 8 + RT 60 Gy over 6wk
  - ≤3 days to start Nivo
  - ≤7 days to start RT

**Treatment**
- Treatment arm N
  - Starting with dose 9, Nivo 480 mg Q4W

- Treatment arm TMZ
  - N = 275
  - **TMZ** 75mg/m² daily + RT 60 Gy over 6wk
  - 4 week break, then TMZ 150-200 mg/m² D1-5 of 28-day cycle x 6 cycles

**Follow-Up**
- F/U visits (35 + 115 days post Rx)
  - then
  - F/U for progression (if not observed)
  - then
  - 3 monthly Survival F/U

≤ 42 days total
CheckMate
CHECKpoint pathway and
nivolumAb clinical Trial Evaluation

CA209-548 Study Design

Screening*

Histologically-
confirmed
Newly-diagnosed
GBM

CENTRAL
LABORATORY
confirmation
MGMT Methylated,
partially or
Indeterminate
(transfer from 498)

* Initially via
CA209-498 study.
Close monitoring
of accrual is
essential

RANDOMIZATION

Nivo [blinded] 240 mg
N = 160
IV Q2wk x 8 doses
+ RT 60 Gy over 6wk
+ TMZ 75mg /m² continuously
during RT

≤3 days to start Nivo
≤7 days to start RT

Placebo [blinded]
N = 160
IV Q2wk x 8 doses
+ RT 60 Gy over 6wk
+ TMZ 75mg /m² continuously
during RT

Follow-Up

≥42 days total

Starting with dose 9,
Nivo 480 mg, Q4wk
+ 4 week break, then
TMZ 150-200 mg/m²
D1-5 of 28-day
cycle x 6 cycles

≥35 + 115
days post Rx
then
F/U for
progression
(if not observed)
then
3 monthly
Survival
F/U

Starting with dose 9,
Placebo, Q4wk
+ 4 week break, then
TMZ 150-200 mg/m²
D1-5 of 28-day
cycle x 6 cycles
Immune check-point(s) blockade-based combinations/sequences holding the most promise for future development

- Vaccines
- Cytokines
- Tumor microenvironment modulating agents
- Selected chemotherapeutic agents
- Targeted therapies
- Epigenetic therapies
IDO1 is a tryptophan-catabolizing enzyme that is overexpressed in many cancers and induces immune tolerance by suppressing T-cell responses.

- IDO1 is expressed in human tumors and in dendritic cells within tumor draining lymph nodes.
- IDO1 expression is associated with more rapid tumor progression and reduced survival.
- IDO1 inhibition exhibits antitumor activity through the reactivation of effector T cells and is synergistic with PD-1 blockade.
IDO1 Expression Is Associated With Poor Patient Outcome in Various Tumor Types

- IDO1 is highly expressed in multiple tumor types
  - Melanoma
  - NSCLC
  - Ovarian cancer
  - Pancreatic cancer
  - CRC
  - Glioblastoma
  - Squamous cell carcinoma
  - Endometrial carcinoma
  - DLBCL
  - RCC
  - TCC
  - TNBC

Kaplan-Meier survival curves in melanoma based on IDO1 accumulation in the lymph node


TCC=transitional cell carcinoma; TNBC=triple negative breast cancer
IDO1 Inhibition Correlates With Increases in TIL Number and Function

- IDO1 inhibition leads to increased number of TILs and decreased suppressor cells in tumors
- Enhanced IFN-γ secretion from TILs was observed following IDO1 inhibitor treatment

IFN=interferon
Koblish HK, et al. AACR 2015. Poster 1336
Inhibition of IDO1 with epacadostat enhances anti-tumor efficacy of PD-1 blockade in a syngeneic glioblastoma (GBM) model

• GL261 cells, a murine GBM tumor line derived from intracerebral methylcholanthrene implantation, were stereotactically implanted intracranially in albino syngeneic C57BL/6 mice.

• Mice were randomized (n=8/group) to receive treatment:
  • anti-PD-1;
  • epacadostat;
  • anti-PD-1 + epacadostat;
  • control

• IDO1 inhibition with epacadostat increased the eradication rate of anti-PD-1 (1% vs 50%) therapy in an orthotopic syngeneic GBM model and long term survivors rejected tumor following orthotopic re-challenge.

Melanoma
Lung cancer
CTLA-4/PD1/PDL1
CTLA-4/PD1

Combos/Sequences

Melanoma
Lung cancer
CTLA-4/PD1/PDL1
CTLA-4/PD1

Other tumors
Breast
Mesothelioma
Glioblastoma
Renal
Colorectal
Urothelial
Ovarian
Head-Neck

Novel targets
LAG-3
TIM-3
ICOS
4-1BB
CD40
OX-40
IDO
KIR
MEDICAL ONCOLOGY AND IMMUNOTHERAPY
DEPT. OF MEDICAL ONCOLOGY
UNIVERSITY HOSPITAL OF SIENA

Michele Maio and

• Maresa Altomonte
• Erika Bertocci
• Luana Calabrò
• Ornella Cutaia
• Riccardo Danielli
• Anna Maria Di Giacomo
• Carolina Fazio
• Ester Fonsatti

• Francesca Colizzi
• Sandra Coral
• Alessia Covre
• Elisabetta Fratta
• Hugues Nicolay
• Giulia Parisi
• Aurora Rizzo
• Luca Sigalotti
Save The Date
Cancer Bio-Immunotherapy in Siena
xv NIBIT Meeting

For more information, updates and useful links, please visit our website:
www.sienameeting-nibit.org

October 5-7 2017