Prima che la vita passi, la vita va avanti.

Negli ultimi anni la ricerca oncologica ha vissuto una fase di straordinario sviluppo, tuttavia nei paesi occidentali i tumori sono ancora la prima causa di morte.

La Fondazione Giovanni Celeghin sostiene la ricerca sulle malattie oncologiche perchè il cammino da compiere è ancora lungo e perché la terapia del paziente non si fermi all'approccio clinico-terapeutico, ma punti anche al sostegno psicologico.

Con il tuo sostegno puoi contribuire allo sviluppo di una nuova forza interiore nel paziente, fondamentale per permettergli di affrontare la malattia con serenità e consapevolezza.

Fondazione Giovanni Celeghin

FONDAZIONE GIOVANNI CELEGHIN ONLUS

MALATTIE ONCOLOGICHE: RICERCA E SOSTEGNO

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1. INFORMAZIONI GENERALI

Titolo del progetto – Role of *MGMT* methylation status at time of diagnosis and recurrence for patients with glioblastoma: exploratory analysis and clinical implications

Dipartimenti/Enti di ricerca coinvolti – Medical Oncology Department, Bellaria Hospital, Azienda USL of Bologna

Coordinatore Scientifico (Principal Investigator) – Alba Brandes, 06/02/1954

Durata del progetto – 18 months

Budget – 75000€

2. PIANO DELLA RICERCA

1. Abstract (ENGL)

• Background: Glioblastoma represents a rare and aggressive disease, and despite recent advances in treatment approaches, the prognosis of this neoplasm remains dismal. Moreover, improvements in molecular biology led to understanding better the nature of these diseases. O6-methylguanine DNA-methyltransferase (*MGMT*) promoter methylation status is a prognostic factor in newly diagnosed glioblastoma patients. However, it is not yet clear whether, and if so how, *MGMT* methylation status may change. Moreover, it is unknown whether the prognostic role of this epigenetic feature is retained during the disease course.
• Descrizione del progetto: Patients will be collected from a data warehouse of about 1000 patients with GBM. All patients were treated homogeneously and followed with similar time schedules.
We plan to assess the *MGMT* methylation status by methylation specific PCR in patients with glioblastoma and treated with temozolomide concurrent with and adjuvant to radiotherapy. The evaluations of this epigenetic feature of glioblastoma will be performed both at time of diagnosis and, when disease recurs, at time of second surgery.
• Obiettivi e risultati attesi. The project has the main object to establish the prognostic and predictive role of *MGMT* methylation status when glioblastoma recurs. Moreover, we plan to correlate the *MGMT* methylation status at diagnosis and at time of recurrence with progression-free intervals and with overall survival of the patients.

1. Abstract (ITA)

• Background: Il glioblastoma rappresenta un malattia rara ed aggressiva, e nonostante i recenti miglioramenti negli approcci terapeutici, la prognosi di questa neoplasia rimane insoddisfacente. Inoltre, i miglioramenti nella biologia molecolare hanno portato a conoscere meglio la natura di queste neoplasie. La metilazione del promotore del gene O6-metilguanina DNA-metiltransferasi (*MGMT*) è un fattore prognostico per i pazienti affetti da glioblastoma di nuova diagnosi. Tuttavia, non è ancora chiaro se e come lo stato di metilazione di *MGMT* possa modificarsi. Inoltre, non è noto se il ruolo prognostico di questa alterazione epigenetica venga mantenuto durante il decorso clinico di questa malattia.
• Descrizione del progetto: I pazienti verranno raccolti partire da un archivio di circa 1000 pazienti trattati in maniera omogenea e seguiti nel tempo con temporizzazioni simili fra loro. Abbiamo programmato di valutare lo stato di metilazione di *MGMT* con una PCR specifica per la metilazione in

pazienti affetti da glioblastoma e trattati con temozolomide concomitante alla radioterapia ed adiuvante. La valutazione di questa caratteristica epigenetica verrà eseguita sui campioni relativi alla diagnosi ed ai campioni, provenienti dagli stessi pazienti al momento della recidiva, in occasione del reintervento chirurgico.

• Obiettivi e risultati attesi. Il progetto ha l'obiettivo principale di valutare il ruolo predittivo e prognostico dello stato di metilazione di *MGMT* al momento della recidiva del glioblastoma. In particolare, abbiamo programmato di correlare lo stato di metilazione di *MGMT* alla diagnosi ed alla recidiva con gli intervalli di tempo liberi dalla progressione che con la sopravvivenza globale dei pazienti.

2.Background e razionale

Alkylating agents, which are highly reactive molecules, cause cell death by binding to DNA (1). The most frequent site of alkylation in DNA is the O6 position of guanine, where alkylation forms cross-links between adjacent strands of DNA; this explains how the nitrosoureas, temozolomide, and procarbazine kill cells. The cross-linking of double-stranded DNA by alkylating agents is inhibited by the cellular DNA-repair protein MGMT, also known as O6-alkylguanine-DNA alkyltransferase. The MGMT protein rapidly reverses alkylation at the O6 position of guanine (2, 3), thereby averting the formation of lethal cross-links. Through this mechanism, MGMT causes resistance to alkylating drugs (2, 3). Approximately 30% of gliomas lack MGMT (4, 5); this deficiency may increase the sensitivity of brain tumors to alkylating agents (6-8). Because the *MGMT* gene is not commonly mutated or deleted, a lack of MGMT enzyme may be caused by changes that do not alter the genetic information of the cell.

Methylation of the CpG island in the *MGMT* gene prevents transcription, and in cell lines that cannot repair alkylation of O6-methylguanine, the *MGMT* promoter is methylated (9-11). Furthermore, *in vitro* treatment with demethylating drugs restores *MGMT* gene expression in these cells (1, 9, 12). The DNA-repair enzyme MGMT is a key factor in resistance to alkylating agents, because the transfer of alkyl groups to MGMT prevents the formation of lethal cross-links in DNA (2, 3). Esteller et al. have demonstrated that *MGMT* promoter methylation is associated with responsiveness to carmustine and an increase in overall survival and time to disease progression. Moreover, these authors found that the methylation status of the promoter is more predictive of the outcome of carmustine treatment than the patient's tumor grade, Karnofsky performance status or age (1).

Thanks to the discovery that the *MGMT* promoter is unmethylated in normal tissues, its determination has rapidly been integrated into routine diagnostics. Methylation-specific PCR (MSP), now widely used to identify epigenetic silencing of genes, is employed in particular for testing *MGMT* promoter methylation in glioma (13).

It has repeatedly been demonstrated that *MGMT* is of predictive value in determining benefit from alkylating agent chemotherapy, whether this be a nitrosourea or temozolomide (1, 8, 14). The randomized phase III EORTC 22981/26981 – NCIC CE.3 study comparing TMZ administered concomitantly with (75 mg/m2 daily), and after RT (150-200 mg/m2, for 5 days every 4 weeks), versus RT alone has demonstrated that this approach significantly improves the median survival (from 12.1 to 14.6 months) and, more importantly, leads to an improvement in the 2-year survival (10% to 26%) (15).

In a companion translational research study, *MGMT* methylation status was determined in more than one third of the patients included in the randomized trial; 45% of the cases analyzed had tumors with a

methylated *MGMT* promoter. RT/TMZ treated patients with methylated *MGMT* promoter had a median survival of 22 months and a 2-year survival rate of 46%, whereas those treated with initial RT alone had a median survival time of 15 months and a 2-year survival rate of 23%. RT/TMZ treated patients with an unmethylated promoter had a median survival time of 13 months and a 2-year survival rate of 14%, and those treated solely with RT, a median survival time of only 12 months and a 2-year survival rate <2%. The overall survival advantage of RT/TMZ treatment was statistically significant for *MGMT* methylated (p=0.007) (13) and *MGMT* unmethylated patients (p=0.035) (16). Furthermore, the interaction test for evaluating the magnitude of the effect of the addition of TMZ to RT did not provide statistically significant findings (p=0.29). In particular, despite a small difference in median survival time, the curves diverge and, potentially, long survivors may be achieved by adding TMZ to RT even in unmethylated patients, suggesting underlying mechanisms other than *MGMT* in killing glioma cells. However, due to the absolute small number of *MGMT* unmethylated patients alive at 3, 4 and 5 years no definitive conclusions can be drawn. Remarkably, the findings from this retrospective analysis were recently confirmed by those reported in a prospective analysis on 103 patients (17).
However, there are still many open questions concerning the role of this prognostic factor, and it has yet to be established, in particular, whether *MGMT* methylation status assessed during the course of the disease, rather than at the diagnosis, as done in the EORTC/NCIC trial, has an equally valuable role in predicting clinical outcome.
Therefore, we plan to evaluate the rate of *MGMT* changes between surgery at time of diagnosis and at time of disease recurrence in patients that received two surgical resections, and to correlate these findings with clinical outcomes.

3.Risultati preliminari

In previous analysis on a limited number of GBM patients (n=44) Brandes et al. (18) evaluated data from tumor specimens obtained during first and second surgery. *MGMT* methylation status was determined in both specimens, and all patients who underwent second surgery had undergone RT followed by TMZ or concurrent RT/TMZ in the time interval between first and second surgery.
Concordance between *MGMT* methylation status at the time of first surgery and second surgery was relatively low (63%). Moreover, the authors found that *MGMT* status changed more frequently in patients with *MGMT* methylated (61.5%) than in patients with *MGMT* unmethylated (24%) status at first surgery (P= 0.03), and that patients treated with concurrent chemotherapy-RT were characterized by a substantially high percentage of *MGMT* shifts from *MGMT* methylated status at the time of first surgery to unmethylated status at the time of second surgery (P=0.03). These data were not confirmed by another study (19) that showed a lower incidence (11%) of changes in *MGMT* methylation status between diagnosis and disease recurrence. Interestingly, in this study the survival after disease progression was significantly correlated with *MGMT* status determined at second surgery.

4.Obiettivi specifici e risultati attesi

The principal aim of this project is to establish if *MGMT* methylation status can change during the clinical course in patients with glioblastoma.
This evaluation will be correlated with:

- Age of patients
- Time to progression after first surgery
- Time between the surgical procedures (at diagnosis and at time of recurrence)
- Treatments received between the two surgical procedures

- Overall survival
- Post-progression survival
- Progression-free survival after recurrence and treatment after recurrence

In this way, we plan to assess the *MGMT* methylation status concordance between assessment at time of diagnosis and disease progression; the prognostic role of *MGMT* at recurrence, as well as the prognosis value of the change of *MGMT* status at time of disease progression
Moreover, we plan to evaluate the role of *MGMT* methylation status to predict the effectiveness of alkylating agents after disease progression.

5.Personale coinvolto nel progetto

	Affiliation	Role	Scientific Background	Time on the project
Alba A Brandes	Medical Oncology department, Bellaria-Maggiore Hospitals, Azienda USL, Bologna	Principal Investigator - Medical Oncologist	Dr. Brandes has been the Principal Investigator of 20 national and international research protocols on brain tumors and other solid tumors, and National Coordinator of more than 40 research protocols. Author or co-author of more than 180 peer-reviewed articles. Author of over 300 abstracts and book chapters. Coordinator of the European Guidelines for the treatment of Glioblastoma and Medulloblastoma Member of the restricted panel of the European Society of Medical Oncology (ESMO) for brain tumors Coordinator of the National Guidelines for the Italian Association in Medical Oncology (AIOM) for Brain Tumours.	15%
Luca Morandi	Pathology Department – Bellaria-Maggiore Hospitals, Azienda USL, Bologna	Sub-investigator – Biologist	Wide experience in quantitative competitive PCR, PCR-RFLP, PCR-DGGE, Western Blotting, methylation sensitive PCR; quantitative methylation sensitive Real Time PCR by Molecular	20%

			beacon, Massive parallel Sequencing, microRNA expression	
Enrico Franceschi	Medical Oncology department, Bellaria-Maggiore Hospitals, Azienda USL, Bologna	Sub-investigator – Medical Oncologist	Co-investigator in several EORTC clinical trials. From October 2008 is a Young Oncologist for EORTC Brain Tumor Group. From 2012 is a founding member of the Early Career Investigator EORTC Platform. Clinical research areas include tumors of the brain, breast, lung and colorectal. He has been the author or co-author of more than 50 peer-reviewed articles on tumors of the brain, breast and lung, and has also written over 70 abstracts and book chapters.	25%
Stefania Bartolini	Medical Oncology department, Bellaria-Maggiore Hospitals, Azienda USL, Bologna	Sub-investigator – Biologist/Data manger	Co-investigator in several EORTC clinical trials	25%

6.Metodo

Patients will be collected from a data warehouse of about 1000 patients with GBM.
All the patients were treated homogeneously by the same physician (Dr. Brandes) and clinical and neuroradiological evaluations were performed every 2 to 3 months. Macdonald's Criteria were used to assess disease response to treatments (20).
This project will be submitted to the Local Ethical Committee

Timeline
0-6 months: patients' identification from data warehouse, inclusion into the study and database
6-12 months : *MGMT* assessment (pair-wise testing for *MGMT* at diagnosis and recurrence of GBM) with methylation specific PCR
12-18 months: correlations between *MGMT* methylation findings and clinical outcomes.

3. BUDGET PREVISTO

Costs	**Budget**	**Motivation**
Supplies	12000€	Reagents for methylation specific PCR for

		MGMT methylation status determination
Researches (non-staff) salary	35000€	Identification of patients, evaluation of inclusion criteria, evaluation of clinical outcomes PERSON TO BE DEFINED
Subcontracts (data manager salary)	18000€	Database creation and management PERSON TO BE DEFINED
Travel expenses:	3000€	International meetings and fees
Other expenses	7000€	Statistic analysis, posters and papers publication costs
TOTAL	**75000€**	

4. INFORMAZIONI SUL COORDINATORE SCIENTIFICO E SUL TEAM

P.I.: Alba Brandes M.D.

PERSONAL INFORMATION

Name	**ALBA BRANDES**
Address	**CALLE CHINOTTO 11 – 30132 VENEZIA SANT'ELENA - VE**
Telephone	**+39 51 6225697 - +39 51 6225697**
Fax	**+39 51 6225057**
E-mail	**alba.brandes@yahoo.it**
Nationality	Italian
Date of birth	06 FEB 1954

EDUCATION AND TRAINING

• Dates (from – to)	27 July 1981
• Name and type of organisation providing education and training	Padova University
• Principal subjects/occupational skills covered	Degree in Medical and Surgery
• Title of qualification awarded	M. D.
• Dates (from – to)	10 July 1984
• Name and type of organisation providing education and training	Padova University
• Principal subjects/occupational	Specializing in Medical Oncology

skills covered	
• Dates (from – to)	14 December 1987
• Name and type of organisation providing education and training	Padova University
• Principal subjects/occupational skills covered	Specializing in Allergology and Clinical Immunology

WORK EXPERIENCE

• Dates (from – to)	From april 2006
• Name and address of employer	Bellaria – Maggiore Hospitals
• Type of business or sector	AUSL Bologna
• Occupation or position held	**Chief of Medical Oncology Dept.**
• Dates (from – to)	*From 2004 since 2006*
• Name and address of employer	Azienda Ospedale-Università di Padova
• Occupation or position held	**Chief of Neuroncology Unit**
• Dates (from – to)	**From 1999 to 2000**
• Name and address of employer	Centro Oncologico Regionale del Veneto - **Regione Veneto**
• Occupation or position held	Member of the Scientific and Technical Comittee of the Veneto Regional Cancer Center and Research Manager of *Regione Veneto* : "*Studio dei bisogni di una popolazione selezionata di pazienti che afferiscono a un Day Hospital Oncologico per ottimizzarne l'organizzazione*"
• Dates (from – to)	*1989*
• Name and address of employer	Medical Oncology
• Type of business or sector	**Padova University Hospital**
• Occupation or position held	**Associate Medical Oncology Dept**

• Dates (from – to)	*1987-1989*
• Name and address of employer	Medical Oncology
• Type of business or sector	**Medical Oncology (Venice)**
• Occupation or position held	**Medical Assistant**
• Dates (from – to)	*1987*
• Type of business or sector	**USLL 16 Venezia**
• Occupation or position held	**E. R. Medical Assistant**
• Dates (from – to)	*1985*
• Type of business or sector	**San Donà Hospital**
• Occupation or position held	**E.R. Medical Assistant**
• Dates (from – to)	*From 1982 to 1988*
• Type of business or sector	**ULSS 16 Venezia**
• Occupation or position held	**Physician in General Medicine**

PERSONAL SKILLS AND COMPETENCES

MOTHER TONGUE	**ITALIAN**
OTHER LANGUAGES	
	ENGLISH
• Reading skills	EXCELLENT
• Writing skills	EXCELLENT
• Verbal skills	EXCELLENT

ADDITIONAL INFORMATION

2 June 2001: Knighted with the title of **Cavaliere della Repubblica** by the President of the Republic of Italy for her activities in oncology research.

Coordinator of the drafting of European Guidelines for the treatment of Glioblastoma and Medulloblastoma.

Principal Investigator of National and International Clinical Trials of the European Organization for Research and Treatment of Cancer (**EORTC**), National Cancer Institute of Canada (**NCIC**).

Coordinator of StartOncolgy: state – of – the – art instrument on cancer treatment

Vice-Chairman of EORTC Brain Tumor Group.

Responsible of Quality Control Assurance EORTC-BTG

Member of the European Society of Medical Oncolgy (**ESMO**) for the treatment of Brain Tumours

Deputy for EORTC - BTG in EORTC – RT Group

Member of Review Panel of National Cancer Research Institute Clinical Studies Groups – London – UK.

Referee for the research projects of the German Ministry of Education and Research

Member of RARECARE (Surveillance of Rare Cancers in Europe)

Member of the IBTA (International Brain Tumour Alliance)

Member of Provincial Drug Committee – Bologna

Member of the Oncology Committee – Emilia Romagna Italy

Member of the del Follow-up project of Breast Cancer – *Regione Emilia Romagna*

Responsible for the **subproject PERCORSI** for glioblastoma patients into the **PERNO (Progetto della Regione Emilia Romagna in Neuro Oncologia)**

Member of the Regional Center for Innovation – **IGRT project**

Referee for the Health Evaluation of Research Projects 2008 - Ministero

del Lavoro, della Salute e delle Politiche Sociali

National Expert on the Evaluation of Training Events for the ECM

President and Founder of the Cooperative Italian Group in Neuro Oncology (**GICNO**)

Coordinator of the National Guidelines for the Italian Association in Medical Oncology (**AIOM**) for Brain Tumours.

Chairman of the Medical Oncology Dept. concerning the provision of **ScholarShips** provided by the AIOM for the treatment of brain tumours.

Chairman of the Medical Oncology Dept. in agreement with Messina and Padova Universities to train specialist in Medical Oncology

CLINICAL TRIALS AND PUBLICATIONS

Clinical Research areas include sarcomas and analogous malignancies of the brain, breast, lung and ovary. I'm the author or co-author of more than 150 peer-reviewed articles on tumours of the brain, breast, lung and ovary. I have also written over 300 abstracts and book chapters.

In addition, I'm the coordinator of 20 national and international research protocols on brain tumours.

Pubblicazioni del Coordinatore Scientifico e degli altri membri del gruppo di ricerca (max 30)

Publications - Dr Alba Brandes
H-Index=40

1. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, Bernsen HJ, Frenay M, Tijssen CC, Grisold W, Sipos L, Enting RH, French PJ, Dinjens WN, Vecht CJ, Allgeier A, Lacombe D, Gorlia T, Hoang-Xuan K. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol. 2013 Jan 20;31(3):344-50.
2. Shonka N, Brandes A, De Groot JF. Adult medulloblastoma, from spongioblastoma cerebelli to the present day: a review of treatment and the integration of molecular markers. Oncology (Williston Park). 2012 Nov;26(11):1083-91.
3. Franceschi E, Stupp R, Van Den Bent MJ, Van Herpen C, Laigle Donadey F, Gorlia T, Hegi M, Lhermitte B, Strauss LC, Allgeier A, Lacombe D, Brandes AA. EORTC 26083 phase I/II trial of dasatinib in combination with CCNU in patients with recurrent glioblastoma. Neuro-oncology . 2012;14(12):1503-10.

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6. Bartolotti M, Franceschi E, Brandes AA. EGF receptor tyrosine kinase inhibitors in the treatment of brain metastases from non-small-cell lung cancer. Expert Review of Anticancer Therapy . 2012;12(11):1429-35.

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11. Brandes AA, Franceschi E, Gorlia T, Wick W, Jacobs AH, Baumert BG, Van Den Bent M, Weller M, Stupp R. Appropriate end-points for right results in the age of antiangiogenic agents: Future options for phase II trials in patients with recurrent glioblastoma. Eur J Cancer . 2012;48(6):896-903.

12. Franceschi E, Brandes AA. Brain metastases from non-small-cell lung cancer: Is there room for improvement? Expert Review of Anticancer Therapy. 2012;12(4):421-3.

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carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: The MITO-2 randomized phase III trial. Journal of Clinical Oncology . 2011;29(27):3628-35.

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