RISULTATI DELLO STUDIO DI FASE 2, IN APERTO, RANDOMIZZATO, DI RADIOTERAPIA (RT) CON NIMOTUZUMAB E VINORELBINA IN CONCOMITANZA E RE-IRRADIAZIONE ALLA RECIDIVA, RISPETTO A MULTIPLI CICLI ELETTIVI DI RADIOTERAPIA CON VINORELBINA E NIMOTUZUMAB IN CONCOMITANZA, NEI BAMBINI E ADOLESCENTI CON DIAGNOSI RECENTE DI GLIOMA PONTINO INTRINSECO DIFFUSO (DIPG)

MAURA MASSIMINO, VERONICA BIASSONI, SABINA VENNARINI, ANGELA MASTRONUZZI, ELISABETTA SCHIAVELLO, FRANCESCO BARRETTA, LUCIA QUAGLIETTA, CLAUDIA MILANACCIO, EMILIA PECORI, ANTONELLA CACCHIONE, STEFANO VALLERO, ANNA MUSSANO, FRANCA FAGIOLI, VALENTINA DI RUSCIO, SILVIA CHIESA, GIUSEPPE SCIMONE, SALVINA BARRA, LUCIA DE MARTINO, ANTONIA RAMAGLIA, STEFANIA PICARELLO, ANTONIO VERRICO, ARIANNA TROVÒ, MARTA PODDA, GIUSEPPE CINALLI, MANILA ANTONELLI, PIERGIORGIO MODENA, CHIARA DOSSENA, LORIS DE CECCO

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI, PEDIATRICS, MILANO, BAMBINO GESÙ CHILDREN'S HOSPITAL, IRCCS, NEURO-ONCOLOGY UNIT, DEPARTMENT OF PEDIATRIC HEMATOLOGY AND ONCOLOGY, AND CELL AND GENE THERAPY, ROME, ITALY, OSPEDALE SANTOBONO-PAUSILIPON, NAPOLI, ITALY, OSPEDALE GIANNINA GASLINI, GENOVA, ITALY, AZIENDA OSPEDALIERA CITTÀ DELLA SALUTE E DELLA SCIENZA DI TORINO, FONDAZIONE POLICLINICO UNIVERSITARIO AGOSTINO GEMELLI, RADIOTERAPIA ONCOLOGICA, ROMA, ITALY, OSPEDALE SAN GIOVANNI DI DIO E RUGGI D'ARAGONA, SALERNO, ITALY, POLICLINICO S. MARTINO IST, GENOVA, ITALY, UNIVERSITÀ LA SAPIENZA, ROMA, ITALY, OSPEDALE S ANNA, COMO, ITALY

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ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

CONGRESSO NAZIONALE AIEOP
ROMA, 22-24 Settembre 2025
CENTRO CONGRESSI
UNIVERSITÀ CATTOLICA
DEL SACRO CUORE

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Oncoscience			x				

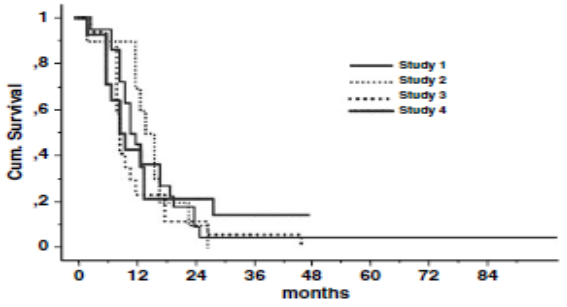
How we came to the nimotuzumab-vinorelbine study through other experiences

J Neurooncol (2008) 87:355–361
DOI 10.1007/s11060-008-9525-5

CLINICAL-PATIENT STUDY

Diffuse pontine gliomas in children: changing strategies, changing results? A mono-institutional 20-year experience

Maura Massimino · Filippo Spreafico · Veronica Biassoni · Fabio Simonetti · Daria Riva · Giovanna Trecate · Sergio Giombini · Geraldina Poggi · Emilia Pecori · Emanuele Pignoli · Michela Casanova · Andrea Ferrari · Cristina Meazza · Roberto Luksch · Monica Terenziani · Graziella Cefalo · Marta Podda · Daniela Polastri · Carlo A. Clerici · Franca Fossati-Bellani · Lorenza Gandola

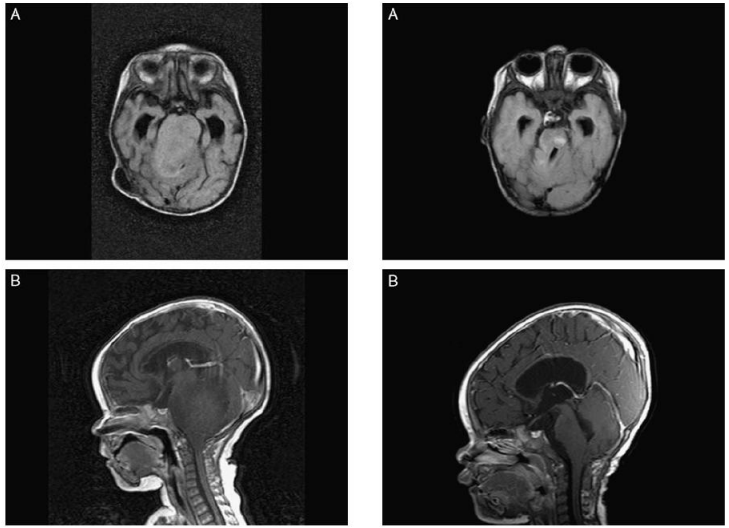


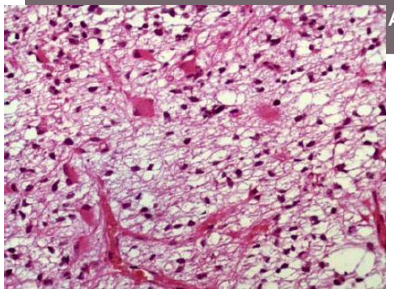
Vinorelbine, Used together radiation in our previous series (2002-2006) of 12 children with DIPG, it resulted in a median PFS of 6 months and median OS of 10 months with one survivor over 10 years

Diffuse Intrinsic Brainstem Tumor in an Infant: A Case of Therapeutic Efficacy With Vinorelbine

Andrea Maria Cappellano, MD, Eric Bouffet,† Sergio Cavalheiro, MD,‡ Maria T. Seixas,§ and Nasjla Saba da Silva, MD**

J Pediatr Hematol Oncol • Volume 33, Number 2, March 2011

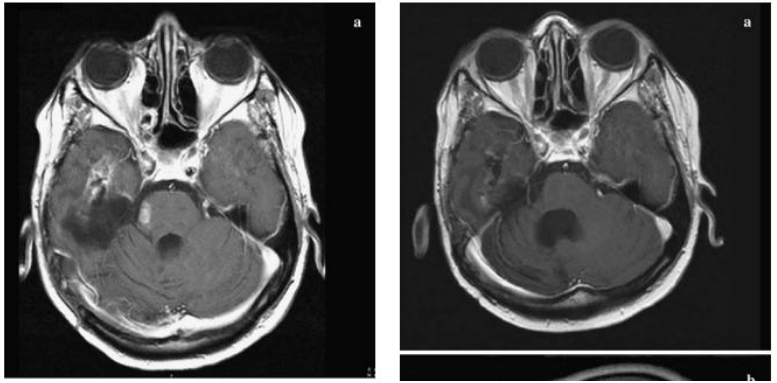




J Neurooncol (2006) 80:195–201
DOI 10.1007/s11060-006-9176-3

A case of relapsing glioblastoma multiforme responding to vinorelbine

V. Biassoni · M. Casanova · F. Spreafico · L. Gandola · M. Massimino



Why nimotuzumab

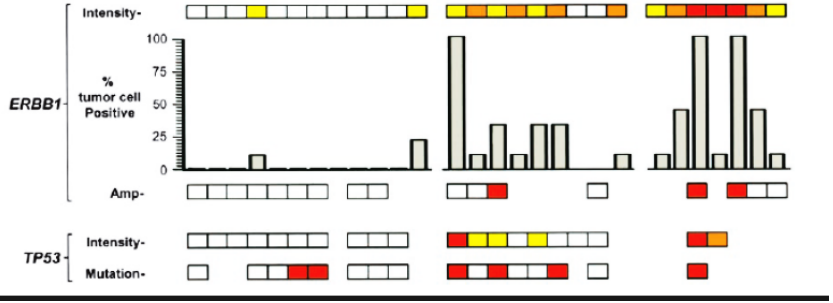
- **Among the few studies providing biological information on DIPG, Gilbertson's group demonstrated a significant increase in EGFR expression (Gilberston R 2003)**

3620 *Vol. 9, 3620–3624, September 1, 2003* Clinical Cancer Research

***ERBB1* Is Amplified and Overexpressed in High-grade Diffusely Infiltrative Pediatric Brain Stem Glioma[1]**

Richard J. Gilbertson,[2] D. Ashley Hill, Roberto Hernan, Mehmet Kocak, Russell Geyer, Jim Olson, Amar Gajjar, Lisa Rush, Ronald L. Hamilton, Sydney D. Finkelstein, and Ian F. Pollack

Mixed of Biopsy/Autopsy samples



Possible TARGETED drugs

Drugable targets in DIPG.

Target	Expression/amplification	% of samples	Targeted by drugs[a]
EGFR	Protein expression	27–50%	Erlotinib, gefitinib, nimotuzumab, cetuximab, vandetanib (also VEGFR)
	Amplification	0%	
PDGFR	Protein expression	63–100%	Imatinib, dasatinib
	Amplification	36%	
VEGF(R)	NA	NA	Vandetanib (also EGFR), bevacizumab
MTOR	Protein expression	100%	Everolimus, sirolimus
	Amplification	NA	
PARP	Expression	36%	ABT-888 (study ongoing)
	Amplification	27%	
MGMT	Protein expression	0%	O6-benzylguanine
RAS	NA	NA	Lonofarnib, tipifarnib
avβ3 and avβ5	NA	NA	Cilengitide (EMD121974)
IL-13	NA	NA	IL13-PE38QQR

NA = not analyzed, EGFR = epidermal growth factor receptor, VEGF(R) = vascular endothelial growth factor (receptor), PDGFR = platelet-derived growth factor receptor, MTOR = mammilian target of rapamycin, PARP = poly (ADP-ribose) polymerase, MGMT = methylguanine methyltransferase, RAS = RAt Sarcoma, PE = pseudomonas exotoxin.

[a] The enumeration of drugs is not exhaustive.

Other:

EGFRvIII expression in 6 of 11 DIPG cases . J Neurooncol. 2012 July ; 108(3): 395–402

EGFR as target of DIPG/DMG in one arm of BIOMEDE trial (erlotinib)

EGFR overexpression in 38/118 cases (32%). Neuro Oncol. 2018 Jun; 20(Suppl 2): i52–i53

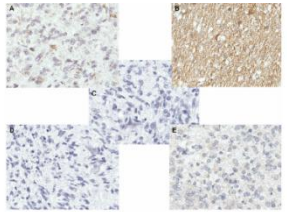


Fig. 2.
Immunohistochemistry of pediatric diffuse intrinsic pontine glioma samples reveal EGFRvIII expression. a Example of a case revealing staining in a perinuclear pattern by the EGFRvIII antibody. b Example of a case revealing a diffuse staining pattern by the EGFRvIII antibody. c A negative control example of a case being stained only by secondary antibody. d A negative control example of a case being stained by the EGFRvIII antibody after peptide competition. e Example of a tumor that did not express EGFRvIII by IHC

EGFR TKi

doi:10.1093/neuonc/noq199
NEURO-ONCOLOGY

A phase II study of gefitinib and irradiation in children with newly diagnosed brainstem gliomas: A report from the Pediatric Brain Tumor Consortium

Ian F. Pollack, Clinton F. Stewart, Mehmet Kocak, Tina Young Poussaint, Alberto Broniscer, Anu Banerjee, James G. Douglas, Larry E. Kun, James M. Boyett,

Neuro-Oncology 13(3):298–306, 2011.
doi:10.1093/neuonc/noq202
NEURO-ONCOLOGY

Phase II trial of tipifarnib and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas

Daphne A. Haas-Kogan, Anuradha Banerjee, Tina Young Poussaint, Mehmet Kocak, Michael D. Prados, J. Russell Geyer, Maryam Fouladi, Alberto Broniscer, Jane E. Minturn, Ian F. Pollack, Roger J. Packer, James M. Boyett, and Larry E. Kun

Intraarterial delivery of bevacizumab and cetuximab utilizing blood-brain barrier disruption in children with high-grade glioma and diffuse intrinsic pontine glioma: results of a phase I trial

Heather J. McCrea, MD, PhD,[1] Jana Ivanidze, MD, PhD,[2] Ashley O'Connor,[3] Eliza H. Hersh, MD,[3] John A. Boockvar, MD,[4] Y. Pierre Gobin, MD,[3] Jared Knopman, MD,[3] and Jeffrey P. Greenfield, MD, PhD[3]

Journal of Neuro-Oncology (2021) 153:263–271
https://doi.org/10.1007/s11060-021-03763-1

CLINICAL STUDY

A phase I/II study of bevacizumab, irinotecan and erlotinib in children with progressive diffuse intrinsic pontine glioma

Fatma E. El-Khouly[1,2] · Sophie E. M. Veldhuijzen van Zanten[1,2,3] · Marc H. A. Jansen[1,4] · Dewi P. Bakker[5] · Esther Sanchez Aliaga[6] · N. Harry Hendrikse[6,7] · W. Peter Vandertop[8] · Dannis G. van Vuurden[1,2] · Gertjan J. L. Kaspers[1,2]

Neuro-Oncology
doi:10.1093/neuonc/noq141
NEURO-ONCOLOGY

Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors

Birgit Geoerger, Darren Hargrave, Fabienne Thomas, Anna Ndiaye, Didier Frappaz, Felipe Andreiuolo, Pascale Varlet, Isabelle Aerts, Riccardo Riccardi, Timothy Jaspan, Etienne Chatelut, Marie-Cecile Le Deley, Xavier Paoletti, Christian Saint-Rose, Pierre Leblond, Bruce Morland, Jean-Claude Gentet, Valérie Méresse, Gilles Vassal, on behalf of the ITCC (Innovative Therapies for Children with Cancer) European Consortium

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I Study of Vandetanib During and After Radiotherapy in Children With Diffuse Intrinsic Pontine Glioma

Alberto Broniscer, Justin N. Baker, Michael Tagen, Arzu Onar-Thomas, Richard J. Gilbertson, Andrew M. Davidoff, Azmaram Pai Panandiker, Wing Leung, Thomas K. Chin, Clinton F. Stewart, Mehmet Kocak, Christopher Rowland, Thomas E. Merchant, Sue C. Kaste, and Amar Gajjar

RESEARCH ARTICLE

Repurposing Vandetanib plus Everolimus for the Treatment of *ACVR1*-Mutant Diffuse Intrinsic Pontine Glioma

Diana M. Carvalho[1], Peter J. Richardson[2], Nagore Olaciregui[3], Reda Stankunaite[4], Cinzia Lavarino[5], Valeria Molinari[1], Elizabeth A. Corley[6], Daniel P. Smith[2], Ruth Ruddle[6], Adam Donovan[6], Akos Pal[6], Florence I. Raynaud[6], Sara Temelso[1], Alan Mackay[1], John P. Overington[7], Anne Phelan[2], David Sheppard[2], Andrew Mackinnon[2,8], Bassel Zeblan[2], Safa Al-Sarraj[10], Ashirwad Merve[11], Jeremy Pryce[12], Jacques Grill[13], Michael Hubank[4], Ofelia Cruz[14], Andres Morales La Madrid[15], Sabine Mueller[15,16], Angel M. Carcaboso[3], Fernando Carceller[6,17], and Chris Jones[1]

EGFR monoclonal antibodies

Drug Evaluation

Expert Opinion

Nimotuzumab for pediatric diffuse intrinsic pontine gliomas

Maura Massimino[1], Udo Bode, Veronica Biassoni & Gudrun Fleischhack

Neuro-Oncology 2014; **0**, 1–6, doi:10.1093/neuonc/nou091

Phase 2 study of safety and efficacy of nimotuzumab in pediatric patients with progressive diffuse intrinsic pontine glioma

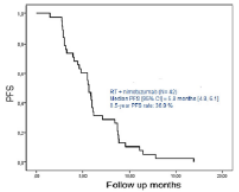
Ute Bartels, Johannes Wolff, Lia Gore, Ira Dunkel, Stephen Gilheeney, Jeffrey Allen, Stewart Goldman, Michal Yalon, Roger J. Packer, David N. Korones, Amy Smith, Kenneth Cohen, John Kuttesch, Douglas Strother, Sylvain Baruchel, Janet Gammon, Mark Kowalski, and Eric Bouffet

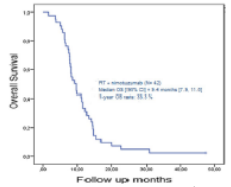
Journal of Neuro-Oncology (2019) 143:107–113
https://doi.org/10.1007/s11060-019-03140-z

CLINICAL STUDY

Nimotuzumab and radiotherapy for treatment of newly diagnosed diffuse intrinsic pontine glioma (DIPG): a phase III clinical study

G. Fleischhack[1,2] · M. Massimino[3] · M. Warmuth-Metz[4] · E. Khuhlaeva[5] · G. Janssen[6] · N. Graf[7] · S. Rutkowski[8,9] · A. Beilken[10] · I. Schmid[11] · V. Biassoni[3] · S. K. Gorelishev[5] · C. Kramm[6,12] · H. Reinhard[7,13] · P. G. Schlegel[8] · R.-D. Kortmann[14] · D. Reuter[15] · F. Bach[15] · N. E. Iznaga-Escobar[16] · U. Bode[2]





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International Journal of Radiology & Radiation Therapy

Research Article

Open Access
CrossMark

Long term survival in diffuse infiltrative brainstem gliomas in children and adolescents treated with radiotherapy and Nimotuzumab

Abstract

Background: Brainstem gliomas have a short survival time; chemotherapy has not improved outcome. We report the result obtained with the combination of Radiotherapy and the monoclonal antibody Nimotuzumab in a series of these tumors.

Volume 5 Issue 4 - 2018

Jose Alert,[1] Ivon Chon,[1] Jose Valdes,[2] Ramon Ropero,[3] Jesus Reno,[4] Migdalia Perez,[4] Mariuska Forteza,[4] Debora Garcia[4]

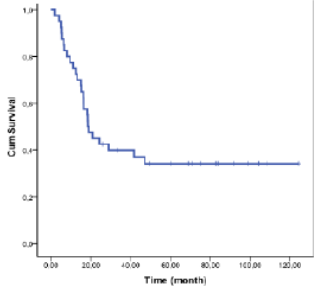


Figure 1 Overall survival function. DIPG in children and adolescents treated

The activity of nimotuzumab, was studied within a Phase II trial in 47 relapsing pediatric patients with DIPG and HGG, showing an interesting, persistent response [median overall survival was 4.4 months (0.3–25.4 months) and was significantly better for responders (median 10 months) than for non-responders (median 4.0 months)]

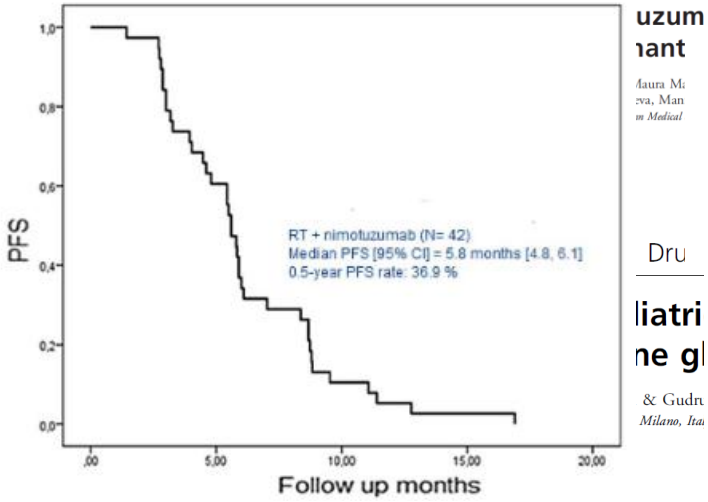
(*Journal of Clinical Oncology* 25, no. 18_suppl (June 20, 2007) 2006-2006)

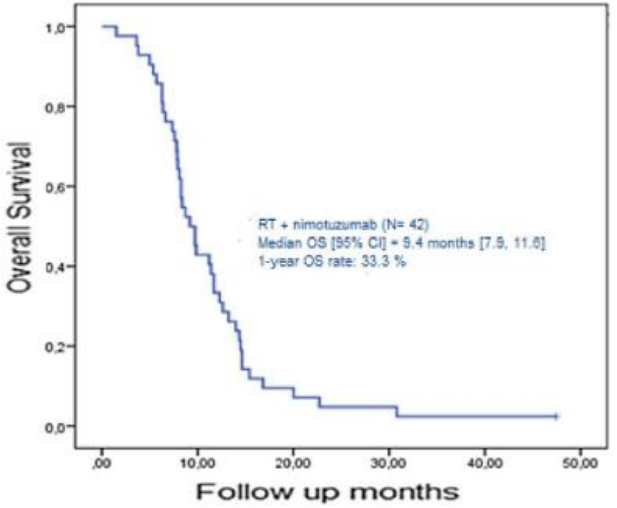
BSC05 was a multicenter exploratory study combining nimotuzumab and radiotherapy as first line treatment for DIPG → It showed disease control and an overall patient survival similar to previous experiences along with an improvement in the quality of patient survival and no severe side effects

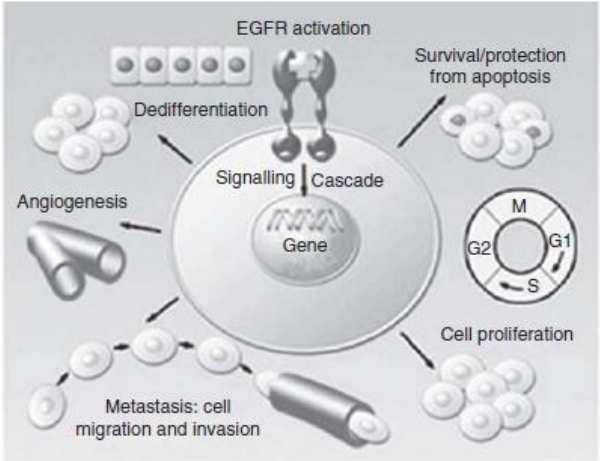
J Clin Oncol 26: 2008 (May 20 suppl; abstr 2058)

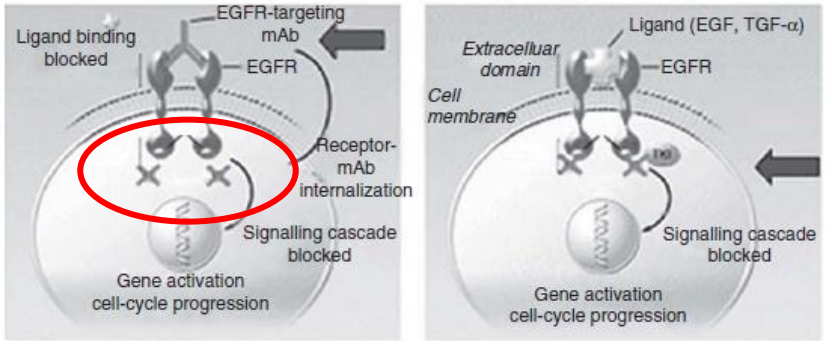
Expert Opinion on Biological Therapy
Volume 12, Issue 12, 2012

Drug Evaluation






EGFR activation
Survival/protection from apoptosis
Dedifferentiation
Signalling Cascade
Angiogenesis
Gene
M
G2
G1
S
Cell proliferation
Metastasis: cell migration and invasion


EGFR-targeting mAb
Ligand binding blocked
EGFR
Receptor-mAb internalization
Signalling cascade blocked
Gene activation cell-cycle progression
Ligand (EGF, TGF-α)
Extracelluar domain
EGFR
Cell membrane
Signalling cascade blocked
Gene activation cell-cycle progression

Why Vinorelbine and anti-EGFR

- It reportedly may have an enhanced activity in non-small cell lung cancers that are EGFR-FISH positive
- and may alter receptor binding of EGF in human breast cancer cells

Effects of vinorelbine on epidermal growth factor-receptor binding of human breast cancer cell lines in vivo

H. Depenbrock, A. Steward, J. Hanauer and A.-R. Hanauske

Gefitinib Enhances Cytotoxicities of Antimicrotubule Agents in Non-Small-Cell Lung Cancer Cells Exhibiting No Sensitizing Epidermal Growth Factor Receptor Mutation

J Thorac Oncol. 2012;7:1218–1227

In conclusion, our preclinical study demonstrated that combining gefitinib with AMTAs showed synergism in NSCLC cells harboring no sensitizing EGFR mutations. Gefitinib could enhance AMTA effects through mechanisms

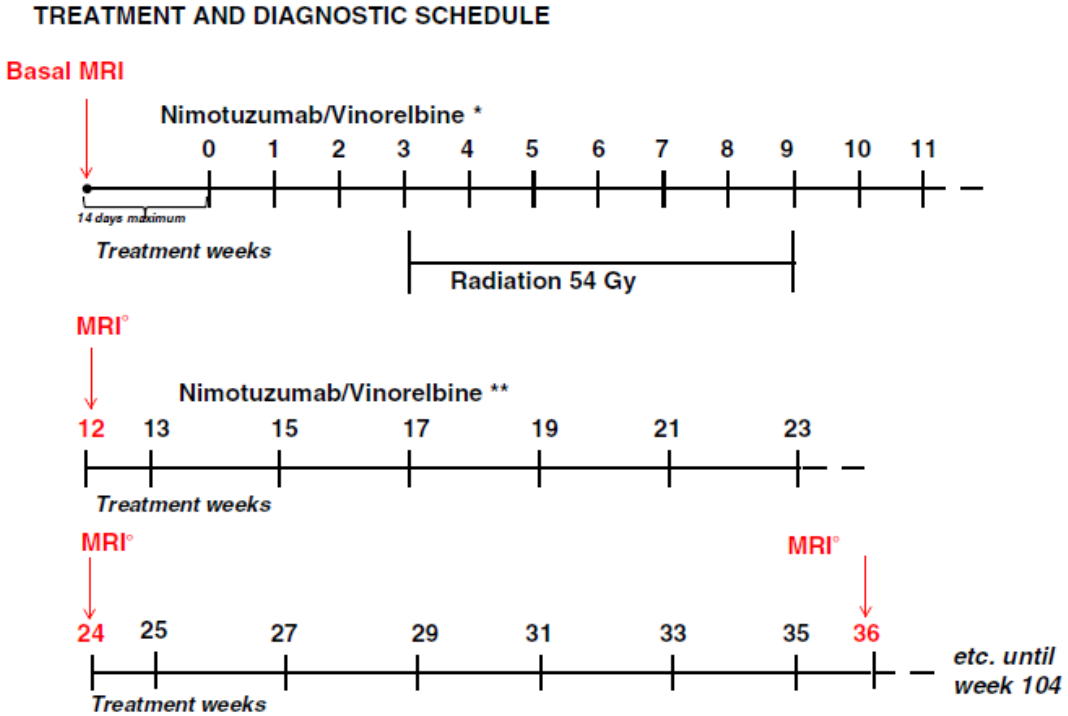
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Gefitinib Versus Vinorelbine in Chemotherapy-Naive Elderly Patients With Advanced Non–Small-Cell Lung Cancer (INVITE): A Randomized, Phase II Study

Conclusion

There was no statistical difference between gefitinib and vinorelbine in efficacy in chemotherapy-naive, unselected elderly patients with advanced NSCLC, but there was better tolerability with gefitinib. Individuals who were EGFR FISH-positive benefited more from vinorelbine than from gefitinib; this unexpected finding requires further study.

Strategy from August 2009



* Nimotuzumab 150 mg/m² - Vinorelbine 20 mg/m²
** Nimotuzumab 150 mg/m² - Vinorelbine 25 mg/m²
° MRI after 12 week induction and every 6 be- weekly infusions in the following phases

JULY 2011 → RE-IRRADIATION OF RELAPSING PATIENTS

Lost at relapse?
Local reirradiation

11 pts, 19.8 Gy, 11 Fractions

No unexpected side effects

No neurological worsening

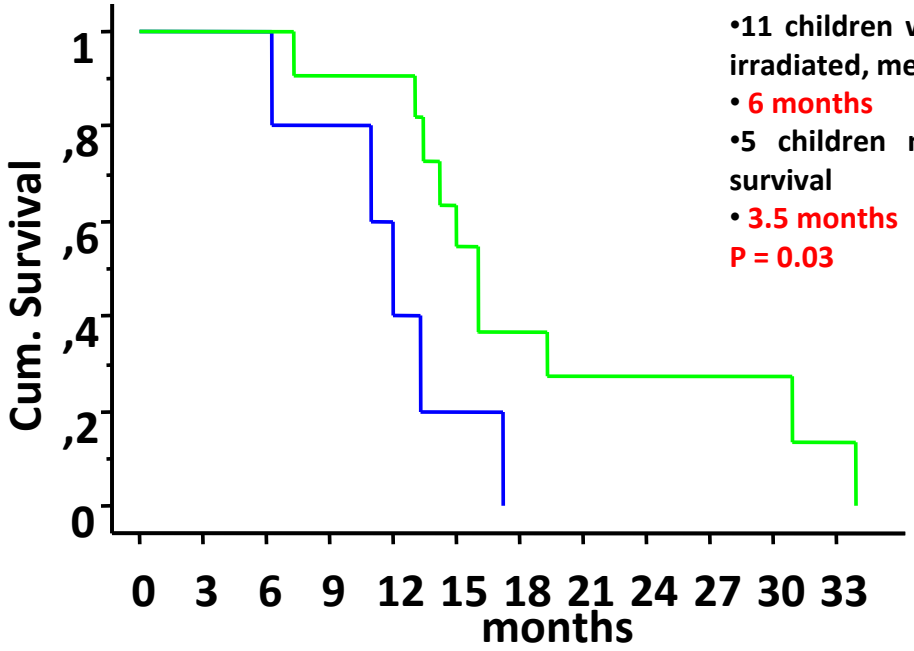
7 volume shrinkage

10 neurological improvement → steroid suspension

10 concomitant nimo/vino treatment

Survival after Re-RT: median 6.6 months (6 weeks-14 months)

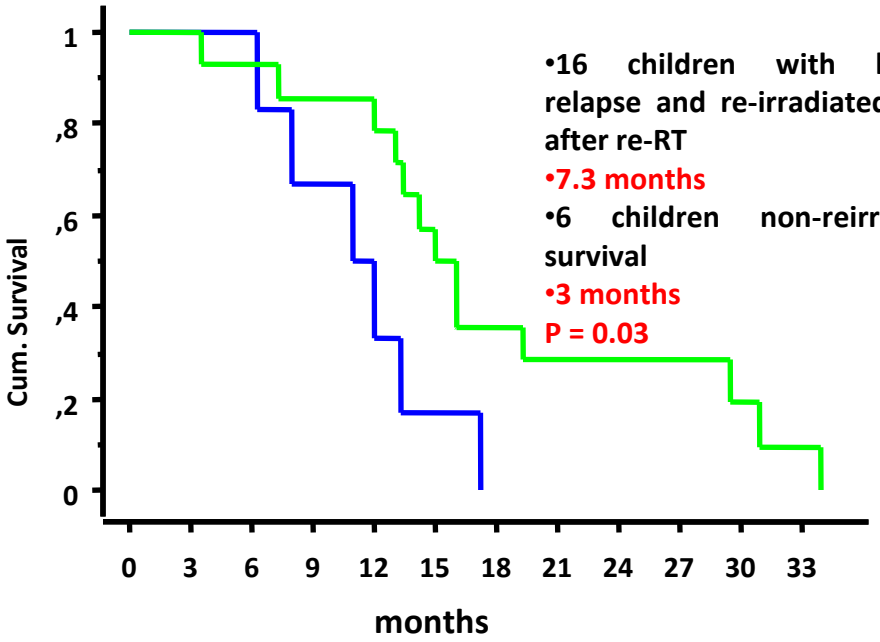
Local reirradiation and survival significance



- 11 children with local relapse and re-irradiated, median survival after re-RT
- 6 months
- 5 children non-reirradiated, median survival
- 3.5 months

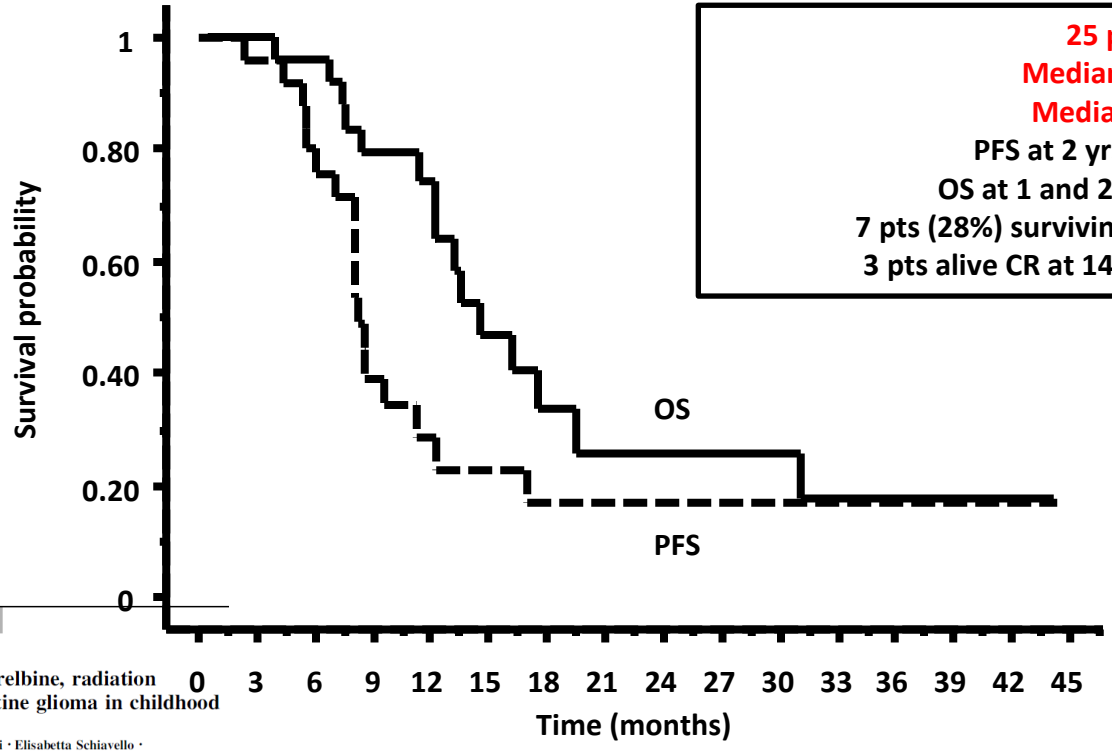
P = 0.03

Any (!) reirradiation and survival significance



- 16 children with local/disseminated relapse and re-irradiated, median survival after re-RT
- 7.3 months
- 6 children non-reirradiated, median survival
- 3 months
- P = 0.03

Results



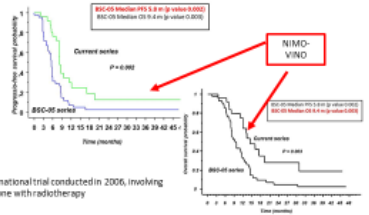
25 patients
Median PFS 8.5 m
Median OS 16 m
PFS at 2 yrs 26% and 13%
OS at 1 and 2 yrs 76% and 29%
7 pts (28%) surviving more than 24 months
3 pts alive CR at 144, 176 and 180 months

J Neurooncol (2014) 118:305–312
DOI 10.1007/s11060-014-1428-z

CLINICAL STUDY

Results of nimotuzumab and vinorelbine, radiation and re-irradiation for diffuse pontine glioma in childhood

Maura Massimino · Veronica Biassoni · Rosalba Miceli · Elisabetta Schiavello · Monika Warmuth-Metz · Piergiorgio Modena · Michela Casanova · Emilia Pecori · Felice Giangaspero · Manila Antonelli · Francesca Romana Buttarelli · Paolo Potepan · Bianca Pollo · Raffaele Nunziata · Filippo Spreafico · Marta Podda · Andrea Anichini · Carlo Alfredo Clerici · Iacopo Sardi · Loris De Cecco · Udo Bode · Ferdinand Bach · Lorenza Gandola



PED BSC-05 international trial conducted in 2006, involving nimotuzumab alone with radiotherapy

Conclusions

- The nimotuzumab/vinorelbine combination was very well tolerated, with no acute side-effects, allowing treatment on an outpatient basis
- This combination had significant differences with previous institutional and literature reported experiences
- Re-irradiation was a valuable opportunity to be further studied

Other similar experiences

Child's Nervous System (2024) 40:1671–1680
https://doi.org/10.1007/s00381-024-06329-4

RESEARCH

Nimotuzumab-vinorelbine combination therapy versus other regimens in the treatment of pediatric diffuse intrinsic pontine glioma

Ayşe Özkan[1] · Begül Yağcı Küpeli[2] · Serhan Küpeli[1] · Gülay Sezgin[1] · İbrahim Bayram[1]

Received: 5 September 2023 / Accepted: 21 February 2024 / Published online: 13 March 2024

frontiers in Oncology

ORIGINAL RESEARCH
published: 10 January 2020
doi: 10.3389/fonc.2019.01436

Personalized Treatment of H3K27M-Mutant Pediatric Diffuse Gliomas Provides Improved Therapeutic Opportunities

Johannes Gojo[1,2], Zdenek Pavelka[3], Danica Zapletalova[3,4], Maria T. Schmook[5], Lisa Mayr[1,2], Sibylle Madlener[1,2], Michal Kyr[3,4], Klara Vejmelkova[3,4], Martin Smrcka[6], Thomas Czech[2,7], Christian Dorfer[2,7], Jarmila Skotakova[6], Amedeo A. Azizi[1,2], Monika Chocholous[1,2], Dominik Reisinger[1,2], David Lastovicka[6], Dalibor Valik[9], Christine Haberler[10], Andreas Peyrl[1,2], Hana Noskova[11], Karol Pál[12], Marta Jezova[13], Renata Veselska[11], Sarka Kozakova[9], Ondrej Slaby[12,13], Irene Slavc[1,2†] and Jaroslav Sterba[3,4,9†]*

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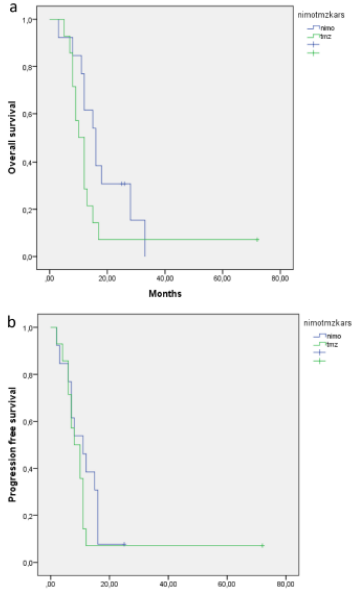
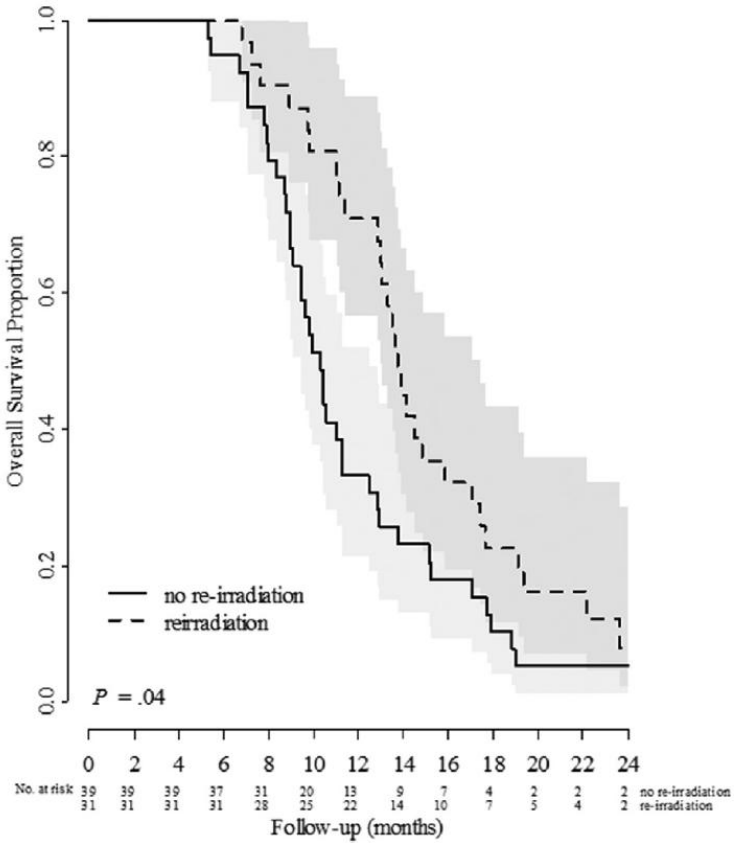
Edited by:
Hatem E. Sabaawy,
Rutgers, The State University of New Jersey, United States

Fig. 1 a Overall survival and b progression free survival in patients receiving first-line nimotuzumab and vinorelbine combination chemotherapy compared with those receiving temozolomide-based chemotherapies





European Journal of Cancer 73 (2017) 38–47

Available online at www.sciencedirect.com

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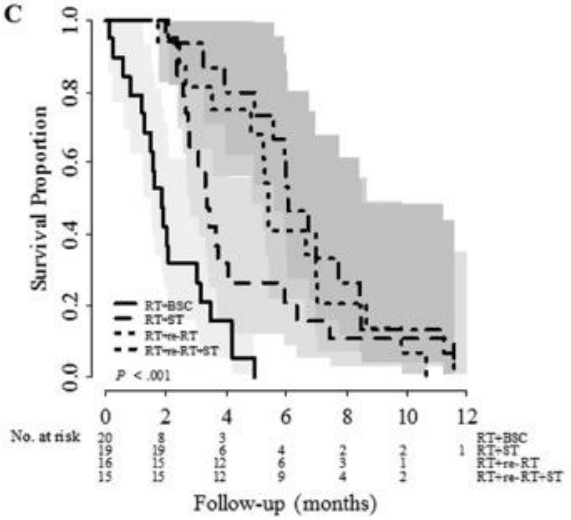
journal homepage: www.ejcancer.com

Original Research

Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: A matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group☆

Geert O. Janssens [a,*], Lorenza Gandola [b], Stephanie Bolle [c], Henry Mandeville [d], Monica Ramos-Albiac [e], Karen van Beek [f], Helen Benghiat [g], Bianca Hoeben [h], Andres Morales La Madrid [i], Rolf-Dieter Kortmann [j], Darren Hargrave [k], Johan Menten [l], Emilia Pecori [b], Veronica Biassoni [l], Andre O. von Bueren [m,n], Dannis G. van Vuurden [o], Maura Massimino [l], Dominik Sturm [p], Max Peters [a], Christof M. Kramm [n]



LT survivors

VOLUME 36 · NUMBER 19 · JULY 1, 2018
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries

Lindsey M. Hoffman, Sophie E.M. Veldhuijzen van Zanten, Niclas Colditz, Joshua Baugh, Brooklyn Chaney, Marion Hoffmann, Adam Lane, Christine Fuller, Lili Miles, Cynthia Hawkins, Ute Bartels, Eric Bouffet, Stewart Goldman, Sarah Leary, Nicholas K. Foreman, Roger Packer, Katherine E. Warren, Alberto Broniscer, Mark W. Kieran, Jane Minturn, Melanie Comito, Emmett Broxson, Chie-Schin Shih, Soumen Khatua, Murali Chintagumpala, Anne Sophie Carret, Nancy Yanez Escorza, Timothy Hassall, David S. Ziegler, Nicholas Gottardo, Hetal Dholaria, Renee Doughman, Martin Benesch, Rachid Drissi, Javad Nazarian, Nada Jabado, Nathalie Boddaert, Pascale Varlet, Géraldine Giraud, David Castel, Stephanie Puget, Chris Jones, Esther Hulleman, Piergiorgio Modena, Marzia Giagnacovo, Manila Antonelli, Torsten Pietsch, Gerrit H. Gielen, David T.W. Jones, Dominik Sturm, Stefan M. Pfister, Nicolas U. Gerber, Michael A. Grotzer, Elke Pfaff, André O. von Bueren, Darren Hargrave, Guirish A. Solanki, Filip Jadrijevic Cvrlje, Gertjan J.L. Kaspers, William P. Vandertop, Jacques Grill, Simon Bailey, Veronica Biassoni, Maura Massimino, Raphaël Calmon, Esther Sanchez, Brigitte Bison, Monika Warmuth-Metz, James Leach, Blaise Jones, Dannis G. van Vuurden, Christof M. Kramm, and Maryam Fouladi

- **101/1008 patients from these registries survived beyond 2 years**
- **Overall survival was 42.3% at 1 year, 9.6% at two years and 2.2% at 5 years**
- **Prognostically favorable:**
  - **Age <3 and> 10 years**
  - **Prolonged duration of symptoms**
  - **Absence of cranial nerve palsy, areas of necrosis, ring enhancement and extra-Pontine extension**
  - **Use of systemic therapy, in particular anti-EGFR**
- **H3.1 mutation better than H3.3**
- *38 non-treatment patients survived 1 month on average*

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

PHASE 2 OPEN LABEL RANDOMIZED STUDY OF RADIOTHERAPY, CONCOMITANT NIMOTUZUMAB AND VINORELBINE AND RE-IRRADIATION AT RELAPSE VERSUS RADIOTHERAPY AND MULTIPLE ELECTIVE RADIOTHERAPY COURSES WITH CONCOMITANT VINORELBINE AND NIMOTUZUMAB FOR NEWLY DIAGNOSED CHILDHOOD AND ADOLESCENCE DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) AND AN OBSERVATIONAL STUDY FOR DIFFUSE MIDLINE GLIOMA WITH K27 MUTATION

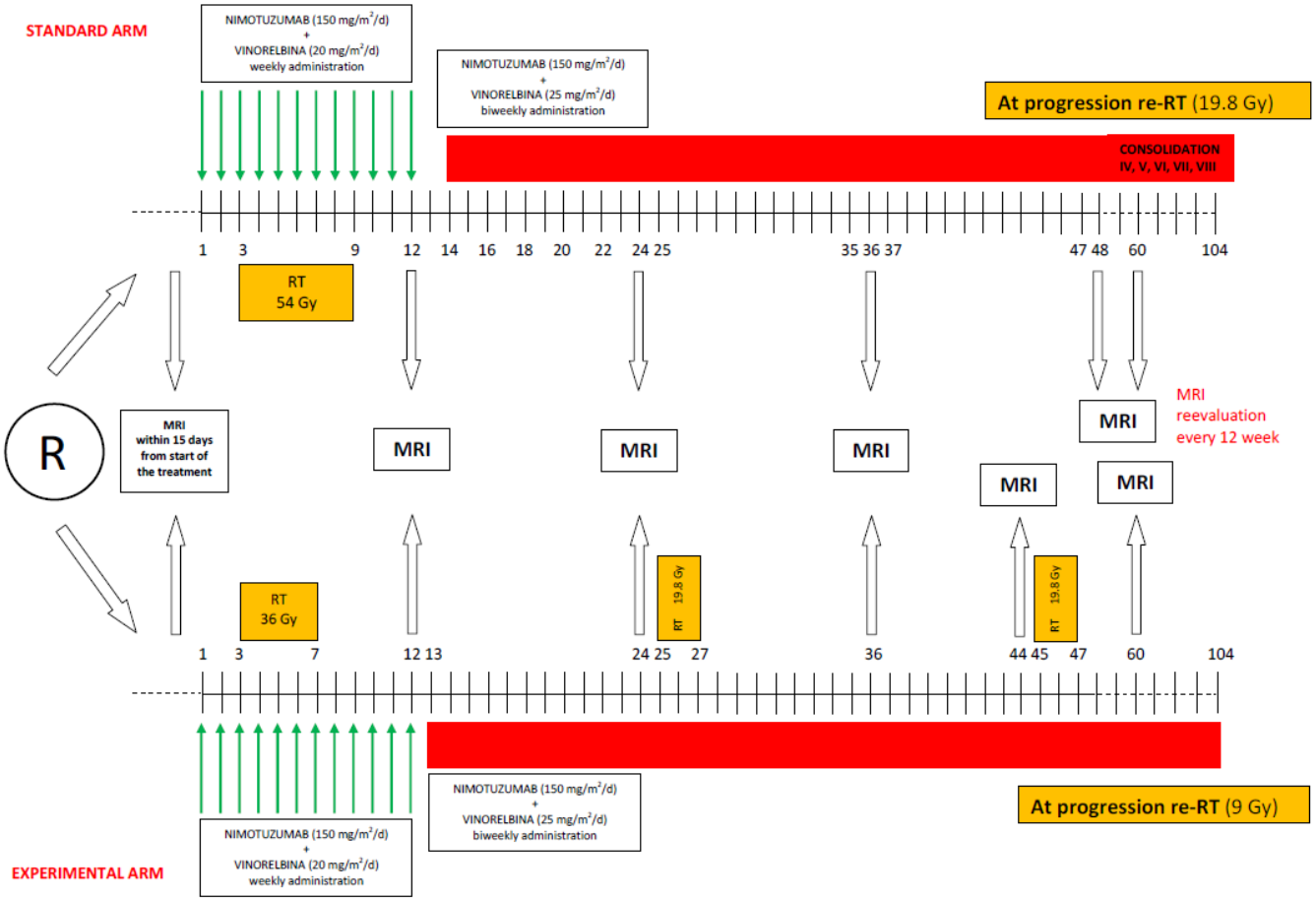
INT – DIPG

Sponsor: Fondazione IRCCS Istituto Nazionale dei Tumori
EudraCT Number: 2015-002185-23

Protocol version 3.0
2018, April 23

Purpose

- The purposes of this trial were to evaluate the feasibility, response, PFS/OS of a randomized study comparing two different RT schedules for DIPG while administering the same systemic treatment


STANDARD ARM
NIMOTUZUMAB (150 mg/m²/d) + VINORELBINA (20 mg/m²/d) weekly administration
NIMOTUZUMAB (150 mg/m²/d) + VINORELBINA (25 mg/m²/d) biweekly administration
At progression re-RT (19.8 Gy)
CONSOLIDATION IV, V, VI, VII, VIII
1 3 9 12 14 16 18 20 22 24 25 35 36 37 47 48 60 104
RT 54 Gy
R
MRI within 15 days from start of the treatment
MRI
MRI reevaluation every 12 week
RT 36 Gy
RT 19,8 Gy
1 3 7 12 13 24 25 27 36 44 45 47 60 104
NIMOTUZUMAB (150 mg/m²/d) + VINORELBINA (25 mg/m²/d) biweekly administration
At progression re-RT (9 Gy)
NIMOTUZUMAB (150 mg/m²/d) + VINORELBINA (20 mg/m²/d) weekly administration
EXPERIMENTAL ARM

- Vinorelbine 20 mg/m2 + nimotuzumab 150 mg/m2 administered weekly for 12 weeks
  - thereafter every other week until tumor progression or for up to 2 years
- Standard (ST) arm: focal RT at total dose of 54 Gy (1.8 Gy/day);
  - for local progression re-irradiation at 19.8 Gy
  - in case of dissemination craniospinal irradiation (CSI) at 36 Gy
- Experimental (SP) arm included **three elective courses of RT** at defined timepoints at 36 Gy, 19.8 Gy and 19.8 Gy
  - possible reirradiation for relapse at 9 Gy

Results

- 57 pts were screened and **55 included**
  - **From 5 AIEOP centers**,
- 29 males, median age 7.1 years (range 3.1-17.6)
  - One patient was excluded for screening failure and one for withdrawal after two months for parents decision
- The latest observed censoring time was 54.3 months

- 27 were included in the standard arm
- 28 in the experimental one
- 15 patients needed a shunt, 13 during treatment
- 23 tumors were biopsied
  - 21 according to local protocols
- 22/23 tumors had H3.3 K27 mutation
  - + 1 biopsied at relapse

- 54/55 relapsed
  - 35 locally
  - 19 with a component of dissemination

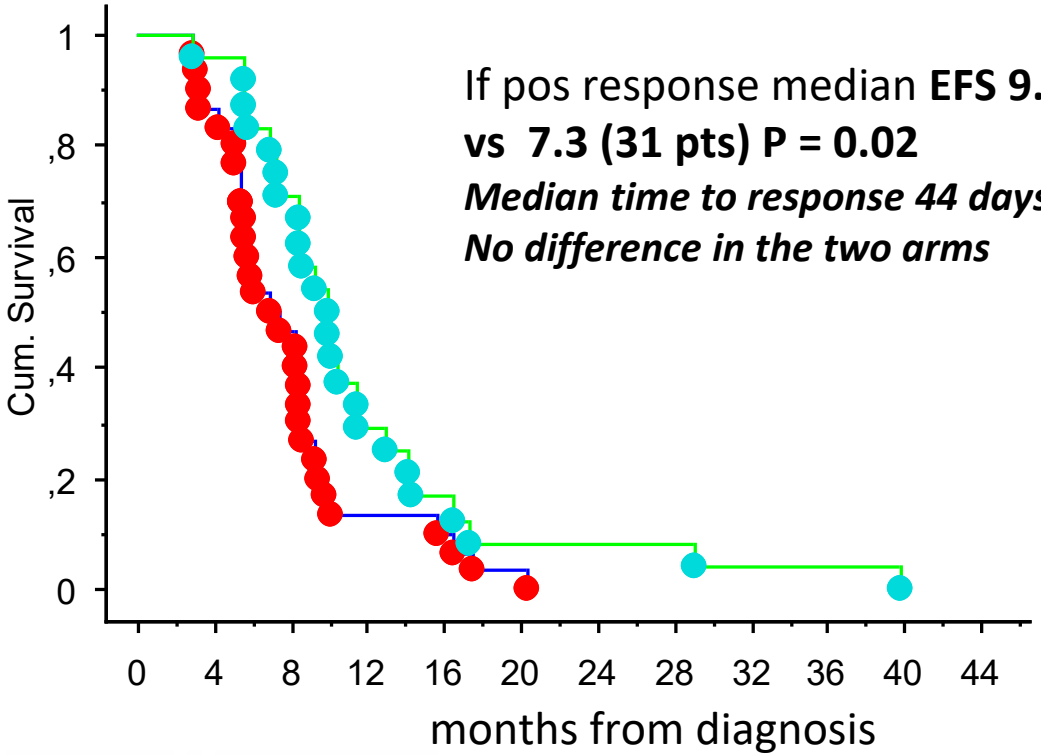
- 54 died
  - 53 for tumor progression
  - 1 for tracheotomy bleeding

- Median EFS and OS were 8.4 and 14 months, respectively
- **EFS/OS at 1 year were 20%/60%**
- **OS was 9.1% at 2 years**
- **5 pts lived longer than 24 months**
- Not significant PFS/OS differences between patients with local vs. disseminated relapses
- Patients submitted to biopsies had more dissemination (P=0.058) and less local progression (P=0.017) but not different PFS and OS

The two arms

- Median EFS/OS for standard and experimental arms were 8.4/8.4 and 14.0/13.9 months, respectively.
- **One-year** EFS/OS for standard and experimental arms was 18.5% (8.4-40.9%)/21.4% (10.5-43.6%), p=0.934 and 59.3% (43.3-81.0%)/60.7% (45.1-81.8%), p=0.663, respectively.
- **Two-year** OS for standard and experimental arms was 7.4% (2.0-28.1%)/10.7% (3.7-31.2%), p=0.663, respectively.

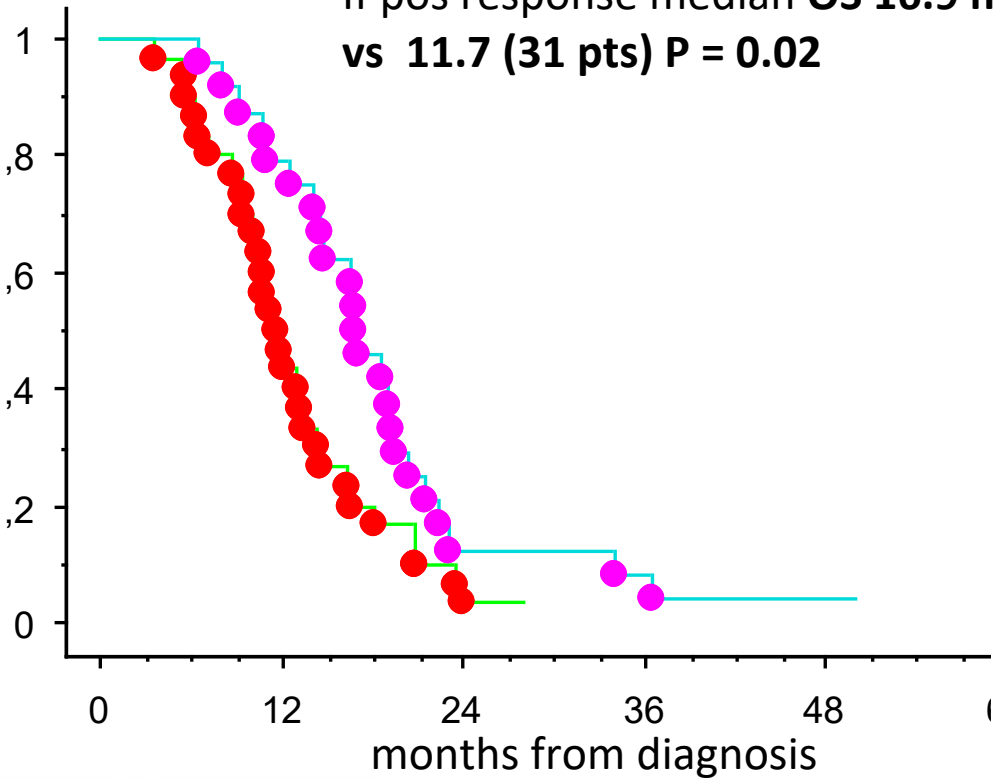
EFS according to RECIST response over 20%



If pos response median **EFS 9.9 months (23 pts)**
vs 7.3 (31 pts) P = 0.02
Median time to response 44 days
No difference in the two arms

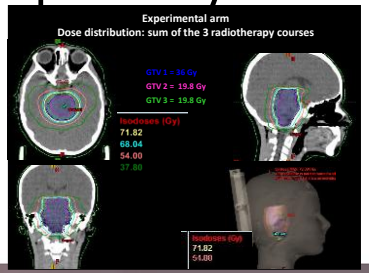
OS according to RECIST response over 20%

If pos response median **OS 16.9 months (23 pts)**
vs 11.7 (31 pts) P = 0.02



Conclusions

- Three courses of irradiation were feasible and never produced radionecrosis grade 3
- 9 patients developed pseudoprogression (1 at reirradiation with CSI after relapse);
  - *6 in st arm (P = 0.15)*
- Treatment was feasible and OS confirmed previous results obtained in a single center
- SP arm was feasible in a national ground, not differences with ST
- Smaller subgroups analyses ongoing



Grazie a
Tutte le famiglie e i pazienti
e tutti i colleghi

maura.massimino@istitutotumori.mi.it