**Disclosure Information**

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2016:

**Name of the enterprise / Nature of the interest**

<table>
<thead>
<tr>
<th>Enterprise</th>
<th>Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nothing to declare</td>
<td></td>
</tr>
</tbody>
</table>
Post Treatment Changes in GIST

Angelo Paolo Dei Tos M.D.
Department of Pathology, Treviso, ITALY
Department of Medicine, University of Padua School of Medicine

angelopaolo.deitos@aulss2.veneto.it
angelo.deitos@unipd.it
Main Issues

• Clinical relevance of pathologic response
• The case of GIST
• Insights on pathologic response to TKI
• New potential avenues
Tumor Response

• Clinical endpoint
• Main parameter in clinical studies
• Several limitations
• Mostly assessed radiologically
• Clinical use of pathologic response limited to few cancer subsets
Category I. Clinical benefit with favorable objective changes in all measurable criteria of disease.

I-A* Distinct subjective benefit with favorable objective changes in all measurable criteria for 1 month or more.

I-B* Objective regression of all palpable or measurable neoplastic disease for 1 month or more in a relatively asymptomatic patient who is able to carry on his usual activities without undue difficulty. The observed tumor regression should be unequivocal, and it is suggested that all lesions be reduced at least 50 per cent in bulk. This category applies as long as the regression persists and ends if any lesion, old or new, recurs.

I-C Complete relief of symptoms, if any, and regression of all manifestations resulting from the active disease for 1 year or more. The relation to the frequency of therapy is not relevant if the disease does not recur between courses of therapy.

Category II. Interruption or slowing in progression of disease without definite evidence of subjective or objective improvement. No criteria are presently available to classify this type of response. Statistical evidence of prolongation of survival time in specific patterns of cancer may some day be applicable.
Toxicity and response criteria of the Eastern Cooperative Oncology Group

SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors


Reporting Results of Cancer Treatment

A. B. MILLER, MB, FRCP(C), B. HOOGSTRATEN, MD, M. STAQUET, MD, AND A. WINKLER, MD*

On the initiative of the World Health Organization, two meetings on the Standardization of Reporting Results of Cancer Treatment have been held with representatives and members of several organizations. Recommendations have been developed for standardized approaches to the recording of baseline data relating to the patient, the tumor, laboratory and radiologic data, the reporting of treatment, grading of acute and subacute toxicity, reporting of response, recurrence and disease-free interval, and reporting results of therapy. These recommendations, already endorsed by a number of organizations, are proposed for international acceptance and use to make it possible for investigators to compare validly their results with those of others.

Tumor response

WHO/ECOG

RECIST

volume

50%

30%

65%
Clinical studies

Phase I

 tolerated dose!

Phase II

 ✓ MTD

active drug!

Phase III

 ✓ OR

 ✓ OS
 ✓ QoL

effective drug!

state of the art
activity (cancer outcomes)
efficacy (patient outcomes)
PRIMARY OSTEOGENIC SARCOMA
The Rationale for Preoperative Chemotherapy and Delayed Surgery

Gerald Rosen, MD,* Ralph C. Marroco, MD,† Brenda Caparros, MD,‡ Anita Nirenberg, RN,§ Cynthia Kosloff, MS,‖ and Andrew G. Huvos, MD#

Table 2. Histologic Grading of the Effect of Preoperative Chemotherapy on Primary Osteogenic Sarcoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Little or no effect identified</td>
</tr>
<tr>
<td>Grade II</td>
<td>Areas of acellular tumor osteoid, necrotic, and/or fibrotic material attributable to the effect of chemotherapy, with other areas of histologically viable tumor</td>
</tr>
<tr>
<td>Grade III</td>
<td>Predominant areas of acellular tumor osteoid, necrotic, and/or fibrotic material attributable to the effect of chemotherapy with only scattered foci of histologically viable tumor cells identified</td>
</tr>
<tr>
<td>Grade IV</td>
<td>No histologic evidence of viable tumor identified within the specimen</td>
</tr>
</tbody>
</table>

---

Cancer 1979; 43: 2163-2177
Prognostic Significance of Histopathologic Response to Chemotherapy in Nonmetastatic Ewing's Sarcoma of the Extremities

By P. Picci, B.T. Rougraff, G. Bacci, J.R. Neff, L. Sangiorgi, A. Cazzola, N. Baldini, S. Ferrari, M. Mercuri, P. Ruggieri, P. Caldora, M.S. Benassi, N. Fabbri, C. Monti, and M. Campanacci

Fig 1. (A) Characteristic example of a patient who demonstrated grade I necrosis. Microscopic nodules completely fill a 10x magnification field. (B) Example of grade II necrosis. Microscopic nodules are so small that even the total sum of their individual areas would not fill a 10x magnification field. (C) Example of complete necrosis or grade III. No viable tumor cells are identifiable.
Musculoskeletal Imaging

High-Grade Soft-Tissue Sarcomas: Tumor Response Assessment—Pilot Study to Assess the Correlation between Radiologic and Pathologic Response by Using RECIST and Choi Criteria

Silvia Stacchiotti, MD, Paola Collini, MD, Antonella Massina, MD, Carlo Morosini, MD, Marta Briantella, MD, Rosella Bartali, MD, Claudio Percessan, MD, Palma Dileo, MD, Valter Torri, MD, Alessandro Grunelli, MD, and Paolo Giovanni Casali, MD
The Case of GIST

- KIT/PDGFRA/RAF driven neoplasm
  - Sensitivity to TKI related to molecular status
  - Primary (D842V) and secondary resistance
- SDH deficient subsets
  - Resistant to TKI
- Quadruple negative GIST
  - NF1 related
  - NTRK driven
Identification of KIT Gain-of-Function Mutations

Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshiro Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuisa Shinomura, Yukihiho Kitamura†

279:577-580, 1998

• KIT staining was positive in 46 of 49 GIST (94%)
• 5 of 6 GIST had mutations in KIT gene
• Mutant forms of KIT are constitutively active

Brief Report

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

Figure 1. Transaxial Gadolinium-Enhanced T1-Weighted MRI Studies of the Upper Abdomen. Before STI571 therapy (Panel A), multiple metastatic lesions were present in the liver. Contrast enhancement of the metastases was highly heterogeneous, with strong enhancement at the periphery. Enhancement was less intense in the central parts of the metastases, suggesting necrosis. After four weeks of treatment with STI571 (Panel B), the metastases had a cyst-like appearance. After eight months of treatment (Panel C), the metastases were smaller, and some had disappeared.
Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

George D. Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaspal Verwaaij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo Bello, Xin Huang, Charles M Baum, Paola G Casali

Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

George D Demetri, Peter Reichardt, Yoon-Koo Kang, Jean-Yves Blay, Piotr Rutkowski, Hans Gelderblom, Peter Hohenberger, Michael Leahy, Margaret von Mehren, Heikki Joensuu, Giuseppe Badalamenti, Martin Blackstein, Axel Le Cesne, Patrick Schoffski, Robert G Maki, Sebastian Bauer, Binh Bui Nguyen, Jianming Xu, Toshiro Nishida, John Chung, Christian Kappeler, Iris Kuss, Dirk Laurent, Paola G Casali, on behalf of all GRID study investigators*
Transcriptome sequencing identifies ETV6–NTRK3 as a gene fusion involved in GIST

Monica Brenna,* Sabrina Rossi,* Maurizio Polano,† Daniela Gasparotto,† Lucia Zanatta,† Dominga Racanelli,† Laura Valori,† Stefano Lamon,† Angelo Paolo Dei Tos* and Roberta Maestrelli***
TRKing Down an Old Oncogene in a New Era of Targeted Therapy

Aria Vaishnavi, Anh T. Le, and Robert C. Doebele

ABSTRACT
The use of high-throughput next-generation sequencing techniques in multiple tumor types during the last few years has identified NTRK1, 2, and 3 gene rearrangements encoding novel oncogenic fusions in 19 different tumor types to date. These recent developments have led us to revisit an old oncogene, Trk (originally identified as OncD), which encodes the TPM3–NTRK1 gene fusion and was one of the first transforming chromosomal rearrangements identified 32 years ago. However, no drug has yet been approved by the FDA for cancers harboring this oncogene. This review will discuss the biology of the TRK family of receptors, their role in human cancer, the types of oncogenic alterations, and drugs that are currently in development for this family of oncogene targets.

Significance: Precision oncology approaches have accelerated recently due to advancements in our ability to detect oncogenic mutations in tumor samples. Oncogenic alterations, most commonly gene fusions, have now been detected for the genes encoding the TRKA, TRKB, and TRKC receptor tyrosine kinases across multiple tumor types. The scientific rationale for the targeting of the TRK oncogene family will be discussed here. Cancer Discov; 5(1): 25–34. ©2014 AACR.
Response to TKI inhibitors is different from cytotoxics
non-dimensional tumor response
We Should Desist Using RECIST, at Least in GIST

Robert S. Benjamin, Haesoo Choi, Homer A. Macapinlac, Michael A. Burgess, Shreyas Kumar R. Patel, Lei L. Chen, Donald A. Povoloff, and Chuslip Charnavongvej

Choi’s RECIST
GIST cells never die
Interval progression
Sunitinib: interval progression
50 mg/day, 4 weeks on, 2 weeks off
Van den Abbeele AD et al, ECCO Ann meet 2005
Brief Report

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Terahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.
Complicated response to Imatinib
Complicated response to Suntinib
Dedifferentiation in Gastrointestinal Stromal Tumor to an Anaplastic KIT-negative Phenotype: A Diagnostic Pitfall

Morphologic and Molecular Characterization of 8 Cases Occurring Either De Novo or After Imatinib Therapy

Cristina R. Antonescu, MD,* Salvatore Romeo, MD,† Lei Zhang, MD,* Khedoudja Nafa, PhD,* Jason L. Hornick, MD, PhD,‡ Gunnlaugur Petur Nielsen, MD,§ Mari Mino-Kenudson, MD,§ Hsuan-Ying Huang, MD,‖ Juan-Miguel Mosquera, MD,* Paolo A. Dei Tos, MD,† and Christopher D.M. Fletcher, MD‡

In summary, dedifferentiation in GIST may occur either de novo or after chronic imatinib exposure and can represent a diagnostic pitfall. This phenomenon is not related to additional KIT mutations, but might be secondary to genetic instability, either represented by loss of heterozygosity or low level of KIT amplification.
• Female of 75
• Rectal GIST
• KIT exon 11
• Dimensional response
• Surgical resection
Mechanism of Response/Resistance to Imatinib

- Programmed cell death Type I (apoptosis)
  - Mostly seen in cell lines
  - Never reported in post treatment GIST surgical specimens
  - Lead to cell death

- Programmed cell death Type II (autophagy)
  - Dynamic process
  - Segregation of portion of cytoplasm within autophagosome
  - Low level of autophagy promotes cell survival
Case History

• 67 Year old man
• Gastric GIST
• Exon 11 KIT mutations
• 14 years on imatinib with dimensional and densitometric response
• Suspension of Imatinib
• Progression two months since suspension
Is Autophagy Rather Than Apoptosis the Regression Driver in Imatinib-Treated Gastrointestinal Stromal Tumors?  

Francesca Miselli*,2, Tiziana Negri*,2, Alessandro Gronchi†, Marco Losa*, Elena Conca*, Silvia Brich*, Elena Fumagalli†, Marco Fiore*, Paolo G. Casali†, Marco A. Pierotti†, Elena Tamborini*2 and Silvana Pilotti*2

*Experimental Molecular Pathology Unit, Department of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; †Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ‡Department of Clinical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; §Scientific Direction, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Our descriptive results support the idea that GISTs activate autophagy rather than apoptosis in response to imatinib treatment and that their molecular makeup includes fingerprints of autophagy.
**Autophagy**

A

- 105 kDa
- 60 kDa
- 26 kDa
- 42 kDa

- PI3KII
- beclin1
- bcl2
- actin

B

- 16 kDa
- 14 kDa
- 42 kDa

- LC3-I
- LC3-II
- actin

C

- 105 kDa
- 60 kDa
- 26 kDa

- PI3KII
- beclin1
- bcl2

**Apoptosis**

- 35 kDa → full-length caspase 3
- 17 kDa → cleaved caspase 3
- 20 kDa → cleaved caspase 7
- 70 kDa → full-length lamin A/C
- 28 kDa → cleaved lamin A/C
- 42 kDa → actin
Autophagy inhibition and antimalarials promote cell death in gastrointestinal stromal tumor (GIST)

Anu Gupta*, Srirupa Roy*, Alexander J. F. Lazar,c,d, Wei-Lien Wangc,d, John C. McAuliffef,e,f, David Reynoso,c,f, James McMahong, Takahiro Taguchih, Giuseppe Florish, Maria Debiec-Rychteri, Patrick Schöffski, Jonathan A. Trentc,f, Jayanta Debnathi, and Brian P. Rubinj,k,l

*Department of Molecular Genetics, Lerner Research Institute, cDepartment of Anatomic Pathology, and Department of Tumor Biology, Cleveland Clinic, Cleveland, OH 44195; dDepartment of Pathology and Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94143; eSarcoma Research Center and Departments of Pathology and Sarcoma Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; fMD/PhD Program, University of Texas, Houston, TX 77030; gDivision of Human Health and Medical Science, Graduate School of Kuroshio Science, Kochi University, Nankoku, Kochi 783-8505, Japan; and Departments of General Medical Oncology and aHuman Genetics, Catholic University of Leuven, 3000 Leuven, Belgium

Edited* by Brian J. Druker, Oregon Health and Science University, Portland, OR, and approved June 22, 2010 (received for review January 8, 2010)

Fig. 3. Imatinib induces autophagy in vitro and in vivo.
Autophagy inhibition and antimalarials promote cell death in gastrointestinal stromal tumor (GIST)


*Department of Molecular Genetics, Lerner Research Institute; †Department of Anatomic Pathology, and ‡Taussig Cancer Center, Cleveland Clinic, Cleveland, OH 44195; §Department of Pathology and Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94143; ††Sarcoma Research Center and Departments of ‡Pathology and ‡Sarcoma Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; ††MD/PhD Program, University of Texas; Houston, TX 77054; †Department of Human Health and Medical Science, Graduate School of Kurohio Science, Kochi University, Nankoku, Kochi 783-8505, Japan; and Departments of ‡General Medical Oncology and ‡Human Genetics, Catholic University of Leuven, 3000 Leuven, Belgium

Fig. 4. ATG depletion and antimalarial lysosomal inhibitors promote cell death in imatinib-treated GIST cells.
Autophagy inhibition and antimalarials promote cell death in gastrointestinal stromal tumor (GIST)

Anu Gupta*, Srirupa Roy*, Alexander J. F. Lazar*c,d, Wei-Lien Wang*c,d, John C. McAuliffe*e,f, David Reynoso*c,f, James McMahon*, Takahiro Taguchi*, Giuseppe Floris*, Maria Debiec-Rychter*, Patrick Schöffski*, Jonathan A. Trent*c,f, Jayanta Debnath* and Brian P. Rubin*.*

*Department of Molecular Genetics, Lerner Research Institute; †Department of Anatomic Pathology, and ‡Tausig Cancer Center, Cleveland Clinic, Cleveland, OH 44195; †Department of Pathology and Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94143; ‡Sarcoma Research Center and Departments of †Pathology and ‡Sarcoma Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030; †MD/PhD Program, University of Texas, Houston, TX 77030; ‡Division of Human Health and Medical Science, Graduate School of Kuroshio Science, Kochi University, Nankoku, Kochi 783-8505, Japan; and Departments of †General Medical Oncology and ‡Human Genetics, Catholic University of Leuven, 3000 Leuven, Belgium.

Edited* by Brian J. Druker, Oregon Health and Science University, Portland, OR, and approved June 22, 2010 (received for review January 8, 2010)

Fig. 5. Antimalarials attenuate the outgrowth of imatinib-resistant GIST cells in vitro.
Imatinib induces autophagy via upregulating XIAP in GIST882 cells

Qingqing Xie a, Qi Lin a, Dezhi Li a, Jianming Chen b, *

a School of Life Sciences, Xiamen University, Xiamen 36102, Fujian, China
b Key Laboratory of Marine Genetic Resources, Fujian Collaborative Innovation Center for Exploitation and Utilization of Marine Biological Resources, Third Institute of Oceanography, Xiamen, Fujian 361005, China
Absence of Progression as Assessed by Response Evaluation Criteria in Solid Tumors Predicts Survival in Advanced GI Stromal Tumors Treated With Imatinib Mesylate: The Intergroup EORTC-ISG-AGITG Phase III Trial

Conclusions

• Tumor pathologic response may represents a better clinical parameter
• TKI is not a cytotoxic therapy
• Inhibition of autophagy at max response should be explored
• Cytotoxics or Immunotherapy