



GIST Support International

www.gistsupport.org

gsi@gistsupport.org

(215) 340-9374 12 Bomaca Drive, Doylestown, PA 18901

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TO: Sandra J. Horning MD, Senior VP for Clinical Development in Oncology,
Genentech

FROM: Board Members and Science Coordinator of GIST Support International
Lee Ann Lamb, co-manager Yvonne Blixt
Marina Symcox PhD, co-manager Donna Capps
Joan Marie Hayno, Secretary Barbara Doré
Ginger Sawyer, Treasurer Julia D. Royster PhD

CC: Denise Reinke APRN BC AON, President and CEO of SARC

TOPIC: continuation and expansion of R1507 trials

GIST Support International is an all-volunteer nonprofit organization of over 1300 patients, caregivers, and professionals concerned with gastrointestinal stromal tumor (GIST). About 15% of adult patients and almost all pediatric patients have wildtype GIST (no mutations in KIT or PDGFRA). Surgery alone has been ineffective in these patients, and they have also had very limited response to therapy with tyrosine kinase inhibitors that target KIT and PDGFRA. Novel biological targets must be explored to help these patients.

Members of the GSI science committee attend the academic sessions of the Pediatric and wildtype GIST clinics hosted at the NIH. We have been extremely encouraged by the excitement shown by the scientists and clinicians at these meetings regarding the potential for clinical testing of IGF-1R antibody in patients with pediatric or wildtype GIST.

The insulin-like growth factor pathway is of immediate critical importance to pediatric GIST patients and other wildtype GIST patients. Microarray analysis of samples from pediatric GIST patients showed a 5-fold increase in IGF-I and a 10-fold increase in IGF-1R in pediatric GIST patients, compared to adults with KIT/PDGFRA mutated GIST (Agaram et al, 2008). Other investigators have confirmed over-expression of IGF-1R, possibly due to amplification of chromosomal regions (Tarn et al, 2008). Even stronger (30-fold) overexpression of IGF-1R has been found in both adult wildtype and pediatric GIST (Corless et al, 2009). Anecdotally, we are aware of one pediatric GIST patient who entered a trial for a different IGF pathway inhibitor and continues to have excellent results.

The NIH and researchers from many academic centers who collaborate in the Pediatric and wildtype GIST clinic are pursuing the IGF pathway in pediatric GIST and other childhood malignancies (Kim et al, 2009). Specific to pediatric and wildtype GIST, Dr. Margaret von Mehren and Dr. Katherine Janeway have written a protocol for a trial of R1507 to be offered to patients at various sites across the nation, including the NIH. The Sarcoma Alliance for

Research through Collaboration (SARC) will coordinate this trial, which is currently on hold pending your decision of whether to pursue studies using R1507.

Patients need this trial to find out how much this drug can help them extend their life expectancies – hopefully enough to grow up and pursue careers, get married, have children, and live normal lives. We implore Roche and Genentech to continue trials for R1507, a drug that we believe has great promise.

REFERENCES

Agaram NP, LaQuaglia MP, Ustun B, Guo T, Wong GC, Socci ND, Maki RG, DeMatteo RP, Besmer P, Antonescu CR. Molecular characterization of pediatric gastrointestinal stromal tumors. *Clin Cancer Res*. 2008 May 15;14(10):3204-15. PubMed PMID: 18483389.

Belinsky MG, Rink L, Cai KQ, Ochs MF, Eisenberg B, Huang M, von Mehren M, Godwin AK. The insulin-like growth factor system as a potential therapeutic target in gastrointestinal stromal tumors. *Cell Cycle*. 2008 Oct;7(19):2949-55. PubMed PMID: 18818517; PubMed Central PMCID: PMC2626174.

Braconi C, Bracci R, Cellerino R. Molecular targets in Gastrointestinal Stromal Tumors (GIST) therapy. *Curr Cancer Drug Targets*. 2008 Aug;8(5):359-66. PubMed PMID: 18690842.

Braconi C, Bracci R, Bearzi I, Bianchi F, Sabato S, Mandolesi A, Belvederesi L, Cascinu S, Valeri N, Cellerino R. Insulin-like growth factor (IGF) 1 and 2 help to predict disease outcome in GIST patients. *Ann Oncol*. 2008 Jul;19(7):1293-8. PubMed PMID: 18372285.

Corless CL, Beadling C, Justusson E, Heinrich MC. Evaluation of the presence of IGF1R overexpression in wild-type and kinase mutant GI stromal tumors. 2009 ASCO Annual Meeting Abstract No:10506. Citation: *J Clin Oncol* 27:15s, 2009 (suppl; abstract 10506).

Dupart JJ, Trent JC, Lee HY, Hess KR, Godwin AK, Taguchi T, Zhang W. Insulin-like growth factor binding protein-3 has dual effects on gastrointestinal stromal tumor cell viability and sensitivity to the anti-tumor effects of imatinib mesylate in vitro. *Mol Cancer*. 2009 Nov 10;8(1):99. [Epub ahead of print] PubMed PMID: 19903356.

Kim SY, Toretsky JA, Scher D, Helman LJ. The role of IGF-1R in pediatric malignancies. *Oncologist*. 2009 Jan;14(1):83-91. PubMed PMID: 19126579; PubMed Central PMCID: PMC2721475.

Pantaleo MA, Astolfi A, Di Battista M, Heinrich MC, Paterini P, Scotlandi K, Santini D, Catena F, Manara MC, Nannini M, Maleddu A, Saponara M, Lolli C, Formica S, Biasco G. Insulin-like growth factor 1 receptor expression in wild-type GISTs: a potential novel therapeutic target. *Int J Cancer*. 2009 Dec 15;125(12):2991-4. PubMed PMID: 19672856.

Rikhof B, van Doorn J, Suurmeijer AJ, Rautenberg MW, Groenen PJ, Verdijk MA, Jager PL, de Jong S, Gietema JA, van der Graaf WT. Insulin-like growth factors and insulin-like growth factor-binding proteins in relation to disease status and incidence of hypoglycaemia in patients with a gastrointestinal stromal tumour. *Ann Oncol*. 2009 Sep;20(9):1582-8. PubMed PMID: 19276395.

Steigen SE, Schaeffer DF, West RB, Nielsen TO. Expression of insulin-like growth factor 2 in mesenchymal neoplasms. *Mod Pathol*. 2009 Jul;22(7):914-21. PubMed PMID: 19407853.

Tarn C, Rink L, Merkel E, Flieder D, Pathak H, Koumbi D, Testa JR, Eisenberg B, von Mehren M, Godwin AK. Insulin-like growth factor 1 receptor is a potential therapeutic target for gastrointestinal stromal tumors. *Proc Natl Acad Sci U S A*. 2008 Jun 17;105(24):8387-92. PubMed PMID: 18550829; PubMed Central PMCID: PMC2448846.