Patient reported abdominal pain as a surrogate of the clinical benefit of tipifarnib in pancreatic cancer patients

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BACKGROUND

The CXCL12/CXCR4 pathway mediates tumor cell homing and tolerogenesis of the immune system. Tipifarnib is a farnesyl transferase inhibitor currently in development in a registration-directed study in HRAS mutant head and neck cancer. Several lines of evidence indicate that tipifarnib is a CXCL12/CXCR4 pathway inhibitor:

- Proof of concept was achieved in a phase 2 cohort of patients (pts) with angioimmunoblastic T cell lymphoma (AITL), a tumor that overexpresses CXCL12. CXCL12 expression was associated with response: Two complete responses (CR), 3 PRs and 4 disease stabilizations (90% clinical benefit) were observed in 10 pts with relapsed/refractory AITL and other peripheral T cell lymphomas overexpressing CXCL12 in lymphoid tissues, while 1 PR and no disease stabilizations were observed in 14 pts with low CXCL12 expression (p=0.05)[a].
- Seven CRs were observed in 11 elderly/unfit acute myeloid leukemia (AML) pts expressing high levels of CXCL12 in bone marrow (Study CTEP20, pts with NRAS wt or unknown) while 1 CRs was observed in 16 pts with low bone marrow CXCL12 expression (p=0.003)[b,c].
- Ex vivo treatment of bone marrow stromal cell cultures with tipifarnib decreased secretion of CXCL12[a].

Based on these preliminary results, we have investigated other clinical settings in which activity of the CXCL12 pathway could be expected. This presentation focuses on the characterization of subsets of pancreatic cancer patients who could benefit from an inhibition of the CXCL12/CXCR4 pathway from tipifarnib treatment. CXCL12 is a known poor prognosis factor in pancreatic cancer[d].

METHODS

- **PATIENTS:** Study INT-11 was a randomized, double-blind, placebo-controlled trial of gemcitabine + tipifarnib versus gemcitabine + placebo in patients with advanced pancreatic adenocarcinoma previously untreated with systemic therapy. Tipifarnib was given at 200 mg bid orally continuously; gemcitabine was given at 1,000 mg/m(2) intravenously weekly x 7 for 8 weeks, then weekly x 3 every 4 weeks. A total of 688 patients were enrolled. The median overall survival for the experimental arm was 6.4 vs 6.1 months for the control arm (P =.75). Neutropenia and thrombocytopenia grade > 3 were observed in 40% and 15% in the experimental arm patients versus 30% and 12% in the control arm[e]. Clinical trial information: NCT00005648.
- **METHODS:** Tumor gene expression from databases in TCGA and GEO databases was investigated. The Kaplan Meier method was employed to obtain survival probabilities. Spearman rank-order correlation coefficients were determined to measure the strength of association between variables.

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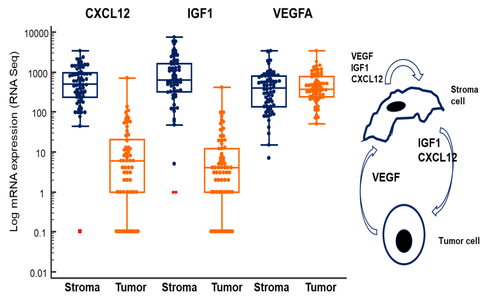
RESULTS

CXCL12 AND IGF1 ARE CO-EXPRESSED IN MANY TUMORS

INDICATION	CXCL12 / IGF1 correlation	N
Pancreatic cancer	0.873	179
Bladder cancer	0.732	408
Breast cancer	0.719	1100
Gastric cancer	0.702	415
Acute Myeloid leukemia	0.698	173
Colorectal cancer	0.693	383
Head and neck Cancer	0.685	522
Mesothelioma	0.680	87
Uveal melanoma	0.663	80
Glioblastoma	0.613	166
Adrenocortical carcinoma	0.596	75
Esophageal cancer	0.596	186
Melanoma	0.588	498
Lung adenocarcinoma	0.565	517
Prostate cancer (CXCL12 vs IGF2)	0.558	472
Lung squamous carcinoma	0.557	501
Ovarian cancer	0.536	307
Sarcoma	0.391	498
Prostate cancer	0.391	259
Diffuse B cell lymphoma	0.351	48
Kidney cancer	0.191	534
Pediatric ALL	0.175	203
Hepatocellular carcinoma	0.051	377
Cholangiocarcinoma	0.042	36

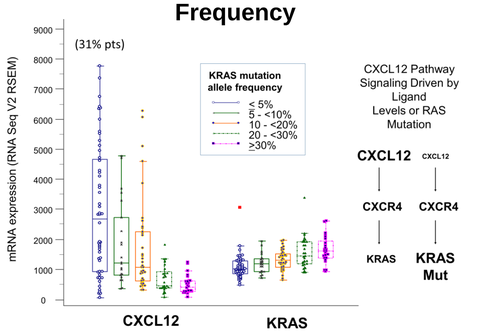
- Analysis of gene expression in 24 databases from TCGA, Provisional[f], with over 8000 pt samples indicated that CXCL12 and IGF1 are highly co-expressed, suggesting a conserved functional interaction between these genes.
- Notably, the highest IGF1/CXCL12 co-expression was observed in indications in which responses to tipifarnib as monotherapy have been previously reported such as breast cancer, bladder cancer or acute myeloid leukemia[g,h,i].

CXCL12, IGF1 expression in pancreatic cancer is from stromal origin



Gene expression data from GSE93326 and Ref n.

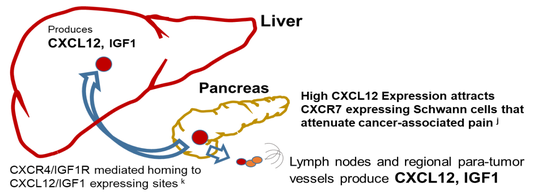
High CXCL12 Expression in Pancreatic Tumors with ≤ 5% KRAS Mutant Allele Frequency



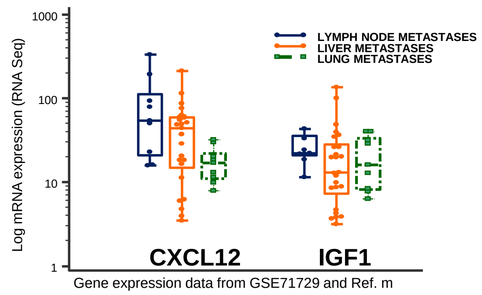
Gene Expression data from TCGA, Provisional

DISEASE MODEL FOR CXCL12 EXPRESSING SITES

CXCL12/IGF1 mediate tumor homing to liver and lymph nodes



Higher CXCL12 Expression in Lymph Node and Liver Metastases than in Lung Metastases



Gene expression data from GSE71729 and Ref. m

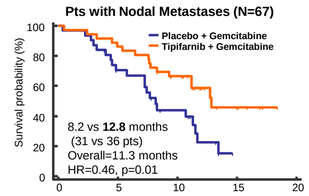
INT-11 DEMOGRAPHICS

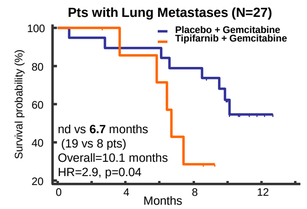
	All GT	All GP	Liver Mets Only – GT [1]	Liver Mets Only- GP [1]	No Abd. Pain - GT	No Abd. Pain - GP
N	341	347	108	125	81	74
Median Age	61	62	60	62	63	59
Female (%)	43	42	43	42	35	43
Metastatic (%)	76	77	100	100	64	70
ECOG 0-1(%)	84	87	90	90	89	90
6-mo weight loss >10% (%)	56	56	50	53	48	39
6-mo jaundice (%)	38	37	34	36	51	45
Prior Whipple (%)	14	11	13	14	16	13

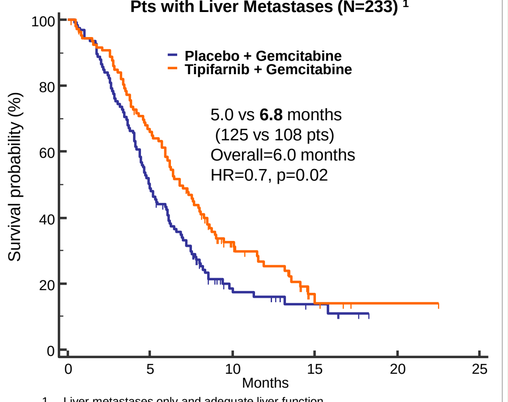
1. Only liver metastases and AP at study entry < 3x ULN

CLINICAL BENEFIT FROM TIPIFARNIB

Nodal and Liver Metastasis Associated with Clinical Benefit from Tipifarnib



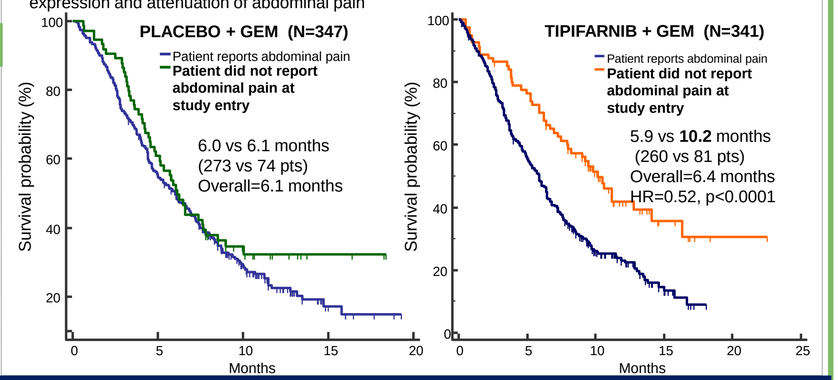




1. Liver metastases only and adequate liver function defined by AP < 3x ULN

Absence of Abdominal Pain Associated with Clinical Benefit from Tipifarnib

Subset analysis of study INT-11 survival based on expected association between high CXCL12 expression and attenuation of abdominal pain



CONCLUSIONS

- **Tipifarnib downregulates CXCL12 and may provide clinical benefit to subsets of pancreatic cancer pts.**
- **Patients with disease limited to lymph nodes or liver metastases, and those with no abdominal pain appear more likely to benefit from tipifarnib.**
- **Low KRAS mutant allele frequency (< 5%, ~30% pancreatic cancer pts) could help identify subjects with tumors overexpressing CXCL12.**
- **The effects of a crosstalk between the IGF1 and CXCL12 pathways are being further investigated.**

References: [a]Witzig et al., 2018. ASH 2018. Abstract 2937, [b]Gualberto et al., 2017. ASH 2017. Abstract 3957, [c]GEO GSE8970, [d]Samarendra et al., 2017. Br J Cancer 117, 124–135, [e]Van Cutsem et al., 2004. J Clin Oncol. 15:1430-8, [f]Cerami et al., 2012. Cancer Discov. 2:401-4, [g]Johnston et al., 2003. J Clin Oncol. 21:2492-9, [h]Lancet et al. 2007. Blood 109:1387-94, [i]Rosenberg et al., 2006. Cancer 103:2035-41, [j]Demir et al., 2017. PNAS USA 114:E85-E94, [k]Akekawatchai et al., 2005. J Biol Chem. 280:39701-8, [l]Renz et al., 2018. Cancer Cell 33: 75–90, [m]Moffitt et al., 2015. Nat Genet. 47:1168-78