The FGF/FGFR Landscape in Cancer: Clinical Implications

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FGFR 1-4

Adapted from Turner and Grose, Nature Reviews Cancer, 2010
Aberrations in Cancer

Activating Mutations

Gene amplification

Altered splicing

Translocation

Paracrine

Autocrine

Aberrant FGF

Excess FGF

Angiogenesis/stroma

Adapted from Turner and Grose, Nature Reviews Cancer, 2010
FREQUENCY AND DISTRIBUTION OF FGFR ABERRATIONS

No FGFR aberration 93%

All FGFR Aberrations 7%

FGFR1 49%

FGFR2 19%

FGFR3 26%

FGFR4 7%

> 1 FGFR aberration 5%

Frequency of FGFR Aberrations (4853 Patients)

Cases with FGFR Aberrations (343 Patients)

J Clin Oncol 32:5s, 2014 (suppl; abstr 11059)
FREQUENCY AND DISTRIBUTION OF ABERRATIONS INCLUDING LIGANDS

Frequency of FGF/FGFR aberrations (391 Patients)

- No aberration: 86%
- Any aberration: 14%

Cases with FGF/FGFR (56 Patients)

- Any ligand (FGF): 62%
  - FGF1: 20%
  - FGF2: 10%
  - FGF3: 6%
  - FGF4: 2%

Unpublished data. Not for distribution.
FREQUENCY OF LIGAND AMPLIFICATION

Ligand (FGF) Amplifications
(38 Patients)

- FGF3, FGF4, FGF19: 63%
- FGF6, FGF23: 11%
- FGF6, FGF23: 3%
- FGF23: 8%
- FGF10: 9%
- FGF14: 6%

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- **12p13**: FGF6, FGF23, CCND2

Unpublished data. Not for distribution.
FREQUENCY OF FGFR ABERRATION BY CANCER TYPE

Frequency of FGFR aberration within call cases of each cancer type (%)

- Urothelial, 126 cases: 33%
- Breast, 523 cases: 18%
- Endometrial, 81 cases: 14%
- Ovarian, 234 cases: 9%
- Adenocarcinoma unknown primary, 269 cases: 8%
- Glioma, 144 cases: 8%
- Cholangiocarcinoma, 115 cases: 7%
- Gastric, 163 cases: 7%
- Nonsmall cell lung, 677 cases: 6%
- Esophageal, 91 cases: 5%
- Pancreatic, 176 cases: 5%
- Colorectal, 294 cases: 4%
- Renal cell, 92 cases: 4%
- Neuroendocrine, 107 cases: 4%
- Sarcoma, 190 cases: 4%
- Head and neck, 215 cases: 2%
- Melanoma, 134 cases: 1%
- Leiomyosarcoma, 77 cases: 1%
FREQUENCY OF FGF/FGFR ABERRATION BY CANCER TYPE

Single Institution Experience, Total N = 391

Unpublished data. Not for distribution.
FGFR1 amplification was the most common aberration among all cancers, including significant proportions of breast cancer, ovarian cancer, urothelial cancer, esophageal cancer, gastric cancer, colorectal cancer, and adenocarcinoma of unknown primary.
APERT SYNDROME

• Craniosynostosis:
• skull deformities, facial deformities, syndactyly, normal intelligence
• Caused by: FGFR2 S252W, P253R
• Activating mutations in FGFR1-3 associated with skeletal syndromes

• Cancers harboring these mutations also include urothelial (12%), NSCLC, endometrial, renal, pancreas, colorectal, and squamous cell (lung, head and neck, skin, anal).
Clinical Associations of FGF/FGFR Aberration
Single Institution Experience, Total N = 391

- Associated with liver metastasis in univariate analysis, but not in multivariate analysis.
- No association with response to first line platinum, 5-FU/capecitabine, gemcitabine, irinotecan, taxane, or bevacizumab containing regimens.
- No association with survival:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FGF/FGFR Aberrant</th>
<th>FGF/FGFR Normal</th>
<th>Hazard Ratio (95% CI)</th>
<th>p value (log rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to metastasis (N=305)</td>
<td>27 mos (N=51)</td>
<td>17 mos (N=254)</td>
<td>1.142 (0.837 to 1.56 )</td>
<td>0.402</td>
</tr>
<tr>
<td>PFS first line therapy (N=201)</td>
<td>4.4 mos (N=33)</td>
<td>5.0 mos (N=168)</td>
<td>1.250 (0.797 to 1.96)</td>
<td>0.330</td>
</tr>
<tr>
<td>OS at 2 years (N=390)</td>
<td>73% (N=56)</td>
<td>50% (N=335)</td>
<td>1.399 (0.7151 to 2.737)</td>
<td>0.324</td>
</tr>
</tbody>
</table>

Unpublished data. Not for distribution.
FGF/FGFR Association With Cancer Treatment

Resistance to therapy:
• Increased FGFR2/FGFR3 expression and EGFR-inhibitor resistance in NSCLC (Ware, et al., PLoS ONE, 2010)
• FGF2-FGFR1 autocrine loop and gefitinib resistance in NSCLC (Ware, et al., Oncogenesis, 2013)
• FGFR1 amplification and endocrine resistance in breast cancer (Turner, et al., Cancer Research, 2010)

Response to therapy:
• FGF3/FGF4 amplification and HCC lung metastasis response to sorafenib (Arao, et al., Hepatology, 2013)
• FGF/FGFR inhibitors
HOMOLOGY OF TYROSINE KINASE RECEPTORS

Adapted from DeBacco, et al., Cancer Therapy Vol 2, 317-328, 2004
FGF/FGFR Inhibitors

Non-Selective
- Dovitinib
- Lenvatinib
- Lucitanib
- Nintedanib
- Brivanib
- Ponatinib
- Oratinib
- ENMD-2076

Selective
- BJG398
- AZD4547
- Debio 1347
- Ly287445
- ARQ087
- JNJ-42756493
- TAS120

Ab and Ligand Trap
- MGFR1877S (RG744)
- FP-1039 (GSK3052230)

Adapted from Soria Presentation at TAT conference 2014
Dovitinib (TKI258) in Breast Cancer

† FGFR1+/FGF3+ patient with 3.4 copies of FGFR1 by qPCR
‡ FGFR1+/FGFR2+ patients
§ FGFR1+/FGFR3+ patients.
Lucitanib in FGF-aberrant Breast Cancer Phase I/Ila Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients, N (%)</th>
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<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>0 (0%)</td>
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<tr>
<td>Partial Response (PR)</td>
<td>6 (50%)</td>
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<tr>
<td>Stable Disease (SD)</td>
<td>6 (50%)</td>
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<tr>
<td>Objective Response Rate (CR+PR)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Disease Control Rate (CR+PR+SD)</td>
<td>12 (100%)</td>
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<tr>
<td>Median Progression Free Survival (PFS), months</td>
<td>9.6</td>
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<tr>
<td>Median Duration of Response, months</td>
<td>11.5</td>
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<tr>
<td>Median Time to First Response, months</td>
<td>1.8</td>
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BGJ398 (selective FGFR1-3 inhibitor)  
Phase I, N = 94

• Tumors with any FGFR aberration
• Preliminary response data:
  • 4/5 patients with urothelial tumors with FGFR3-activating mutations
  • 2 patients with FGFR1-amplified squamous cell lung cancers
  • 1 patient with FGFR2 fusion in cholangiocarcinoma
  • 1 patient with FGFR1-amplified breast cancer

Sequist, et al., AACR Annual Meeting 2014
A phase 3, multicenter, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with 131I-refractory differentiated thyroid cancer (SELECT).

**Primary Endpoint: Kaplan-Meier Estimate of PFS**

- **Median PFS, months (95% CI):**
  - Lenvatinib: 18.3 (15.1-NR)
  - Placebo: 3.6 (2.2-3.7)
- **HR (99% CI):** 0.21 (0.14-0.31)
- **Log-rank test:** $P < 0.0001

**Number of subjects at risk:**

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<tr>
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<th>Lenvatinib</th>
<th>Placebo</th>
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<tr>
<td>261</td>
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<td>131</td>
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**Abbreviations:** CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

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SUMMARY

- FGF/FGFR signaling plays an important role in both normal and neoplastic processes
- FGF/FGFR aberrations are common in human cancers
- Many aberrations are thought to be activating and many are promising candidates as “drivers” of neoplastic behavior
- Several FGF/FGFR inhibitors are in development
- They show early evidence for response in FGF/FGFR aberrant cancers
- We propose a histology independent trial to evaluate lenvatinib in solid tumors with FGF/FGFR aberrations
Advanced cancer with FGF/FGFR aberration (determined prior to study entry)

Start Lenvatinib 24 mg/day
Restage every 8 weeks

- SD, PR, CR
  - Continue Lenvatinib

- PD, toxicity
  - Off study

SD = Stable Disease, PR = Partial Response, CR = Complete Response, PD = Progressive Disease
# KEY INCLUSION CRITERIA

1. Pathologically confirmed advanced or metastatic malignancy characterized by one or more of the following:
   - A. Patient is intolerant of standard therapy
   - B. Patient refuses standard therapy
   - C. Malignancy is refractory to standard therapy
   - D. Malignancy relapsed after standard therapy
   - E. Malignancy for which there is no standard therapy that improves survival by at least 3 months.

2. Evaluable tumor(s) with documented alteration(s) in FGF/FGFR-related gene(s). The FGF/FGFR aberration(s) can be identified at any point in the subject’s cancer course.

3. Laboratory function within specified parameters

4. Adequately controlled blood pressure (BP): BP ≤ 150/90 mm Hg at screening (may be repeated and may be controlled with anti-hypertensive medication).

5. Adequate performance status: ECOG PS 0-2

6. Subjects must be off other anti-tumor agents for at least 5 half lives of the agent or 4 weeks from the last day of treatment, whichever is shorter. Endocrine therapies (e.g., for breast or prostate cancer) and anti-Her2 therapies (for example, trastuzumab or lapatinib) are allowed to continue while on this study.

7. Ability to understand and willingness to sign a written consent document.
SAMPLE SIZE

1. Start enrolling into exploratory cohort:
   a. includes all cancer types
   b. includes all FGF/FGFR aberrations
   c. Up to 35 subjects

2. If an individual patient with any cancer type or aberration has CR, PR, or SD ≥ 6 months, create expansion cohort of that cancer type or aberration.

3. Expansion cohorts enroll concurrently with exploratory cohort

4. Expansion cohorts have standard Simon two stage stopping rules

5. Up to five expansion cohorts allowed

6. **Sample size 35-185**
THANK YOU