Novel Strategies in the Management of Advanced GIST After the Failure of Standard Tyrosine Kinase Inhibitors

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Aberrant Signaling Pathways in GISTs

Molecular Heterogeneity in GIST

- 80 to 85% of GIST tumors involve gain-of-function KIT mutations.

- 5 to 10% involve PDGFRA mutations.

- A small minority of GIST tumors lack kinase mutations and are referred to as wild type (WT)
  → heterogeneous population that probably involves five or more distinct types of disease rather than a single type.
GIST heterogeneity: optimizing the systemic therapeutic approach based on GIST mutation genotype

- **KIT-mutant Exon 11 GISTs**, tumor response has been shown to be similar whether the IMA dose is 400 or 800 mg.

- **KIT-mutant Exon 9 GISTs** - IMA 800 mg is recommended dose

- **PDGFRA-mutant GIST** have different dosing requirements depending on their mutational status.
  - Exon 12 or 14, Exon 18 mutations that are D842V negative/IM sensitive → 400 mg dose is appropriate
  - Patients with the D842V mutation or other IMA-mutation associated with primary resistance to all of the TKIs, including IMA, sunitinib, nilotinib, and sorafenib → require higher IMA doses (generally 800 mg)
Current challenges in the standard of care for metastatic GIST

- Primary resistance in 10-20% i.e. progression within 6mths of therapy
- Secondary resistance: 50% in 2 years 80% in 7 years

Imatinib (IMA)

Sunitinib

Regorafenib

Adequate dosing and consistent compliance are essential for long term use to avoid pharmacokinetic failure

ORR: 7%
PFS: 6.8 mths

ORR: 4.5%
PFS: 4.8 mths

Primary resistant GIST

- Most common PDGFRA mutation associated with GIST, D842V, is strongly resistant to inhibition by imatinib or sunitinib
  - Crenolanib, type I mutant-specific inhibitor that preferentially binds to phosphorylated active kinases has shown efficacy in blocking the activity of D842V mutant kinases (Heinrich et al. CCR 2012) → ongoing Phase II study

- KIT-WT GIST may have any of an array of primary mutations including
  - BRAF and/or KRAS downstream of KIT,
  - increased IGF1R expression
  - Germline mutations of succinate dehydrogenase (SDH).
  - No agent in existence can adequately address all of these mutations → multiple pathways involved
Secondary resistance to Imatinib

- Due emergence of resistant clones through the development of new \textit{KIT} mutations e.g. interfere with binding of imatinib to the kinase domains

- Tend to be single amino acid substitutions in exon 17 (most common), also occur in exons 13 and 14

- Resistant patients with identifiable secondary mutations have been treated with imatinib longer than resistant patients lacking secondary mutations (median, 27 versus 14.5 months) $\rightarrow$ clonal selection of existing mutations before imatinib unlikely to explain acquired resistance.

- GISTs harboring KIT exon 11 mutations more commonly acquire secondary resistance mutations compared with KIT Exon 9–mutated GIST

Debiec-Rychter et al. 2005; Heinrich et al. 2006; Guo et al 2007
Use of smaller tyrosine kinases with broader spectra of activity than imatinib

- Sunitinib (SU), a tyrosine kinase inhibitor with antiangiogenic and antitumor effects (Demetri et al. 2006).

- Structural differences between IMA and SU that allow SU, a smaller molecule, to slip into the drug-binding pocket.

- Sunitinib proved superior to placebo with respect to median progression-free survival (PFS) [median 24.1 weeks vs 6 weeks: \( p < 0.0001 \).]
Regorafenib in resistant GIST: GRID study (Demetri et al Lancet 2013)

- Inhibits $KIT$, $PDGFRA$, $bFGFR$, $VEGFR1$-$3$, $TIE2$, $RET$, $BRAF$ and $BRAF V600E$

- In phase II study patients with wild-type GIST and $KIT$ exon 9 and 11 mutations experienced clinical benefit at comparable rates

- Phase III GRID study:
  - metastatic or unresectable disease that had failed to respond to at least two previous lines of therapy for GIST
  - PFS for regorafenib compared with the placebo arm = 4.8 versus 0.9 months, HR 0.27
  - Disease control rate was 52.6% for the regorafenib arm and 9.1% for the placebo arm ($p < 0.0001$).
Implications of GRID study

• GISTs may remain responsive to treatment targeted at oncogenic drivers, even with prior resistance to similar agents

• Broader spectrum of kinase inhibition with regorafenib
  – Targeting of multiple recognized mechanisms of resistance
  – Targeting possibly as-yet unknown escape pathways

• Extend the range of effective agents in GISTs by targeting multiple pathways
  – Combined therapeutic approaches for treatment resistant GIST
Aberrant Signaling Pathways in GISTs

P13K-AKT Pathway Inhibitors

• Regardless of the type of KIT/PDGFRA mutation in the receptor, the downstream P13K/AKT/mTOR signaling pathway is crucial for tumor cell survival of both imatinib-sensitive and imatinib-resistant GIST.

PI3K inhibition with LY294002 resulted in substantial apoptosis in the imatinib-resistant GISTs

Combination of PI3K inhibition and imatinib

- Profound tumor regression in combination of pictilisib+IMA, superior to either treatment alone in
  - KIT exon 13 p.K642E mutation (GIST882 and GIST882Ly)
  - KIT exon 9 (GIST-BOE), KIT exon 11 (GISTPSW and GIST-DFR)
- PTEN status correlated with response in GIST treated with the combination

A randomized phase II study of perifosine (P) plus imatinib in imatinib-resistant GIST

- Akt and PI3K inhibitor
- PR rate was 4/36 (11%) by Choi (4 PR, 9 SD)
- CBR was 16/36 (44%) by RECIST
- Median PFS and OS for 40 pts were 2.2 months and 18.3 months.

Ongoing studies focused on PI3K/AKT pathway inhibition

- A Dose-finding Study of a Combination of Imatinib and Alpelisib (BYL-719) in the Treatment of 3rd Line GIST Patients
- A Dose-finding Study of a Combination of Imatinib and BKM120 in the Treatment of 3rd Line GIST Patients
Phase II studies of everolimus + imatinib

- **Phase 2 study:** everolimus 2.5 mg/day with imatinib 600 mg/day achieved 2% PR and 43% SD for 4 months or greater in patients previously progressed on imatinib and sunitinib (Stratum 2).

| Efficacy | Phase I | Imatinib 600 mg/day | Everolimus 20 mg/week (n = 13) | Everolimus 2.5 mg/day (n = 13) | Everolimus 5 mg/day (n = 5) | Phase II | Imatinib 600 mg/day + everolimus 2.5 mg/day
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<tbody>
<tr>
<td>4-month PFS rate—PP population</td>
<td>4/23 (17) [5.0–38.8]</td>
<td>13/35 (37) [21.5–55.1]</td>
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<td>Survival (Kaplan–Meier method)—ITT population</td>
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<td>Median PFS, months [CI]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.9 [1.6–3.7]</td>
<td>3.5 [1.9–5.2]</td>
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<tr>
<td>4-month PFS rate, % [CI]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>21 [4.7–37.6]</td>
<td>40 [24.6–55.9]</td>
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<td>6-month PFS rate, % [CI]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>13 [0–26.1]</td>
<td>20 [7.0–33.3]</td>
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<td>Activity/response, n (%)—ITT population</td>
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<tr>
<td>PR, CI</td>
<td>0 [0.2–35.0]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2) [0.1–11.3]</td>
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<tr>
<td>SD</td>
<td>7 (54)</td>
<td>6 (46)</td>
<td>4 (80)</td>
<td>6 (55)</td>
<td>10 (36)</td>
<td>20 (43)</td>
<td></td>
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<tr>
<td>PD</td>
<td>4 (31)</td>
<td>6 (46)</td>
<td>0</td>
<td>1 (9)</td>
<td>15 (54)</td>
<td>15 (32)</td>
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<tr>
<td>Unknown</td>
<td>2 (15)</td>
<td>0</td>
<td>1 (20)</td>
<td>4 (36)</td>
<td>3 (11)</td>
<td>11 (23)</td>
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- **In another phase II study of the combination 33% achieved SD as the best response at 4 months.**

Aberrant Signaling Pathways in GISTs

ETV1 (ETS variant 1): A Lineage specific factor in GIST

P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)
ETV1 is required for GIST survival and growth

P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)
ETV1 and KIT forms a positive feedback circuit in GIST

P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)
Synergy of combined MAPK and KIT inhibition

P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)
Phase Ib MEK162 (binimetinib) in combination with imatinib in patients with GIST

P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)
Mutation status of patients with prolonged disease stabilization

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**Graph:**
- **Median PFS:** 8 weeks
- **95% CI:** 7 to 56 weeks

**Table:**

<table>
<thead>
<tr>
<th>Dose Escalation Cohort</th>
<th>Pt #</th>
<th>Prior Therapies</th>
<th>Mutational Status</th>
<th>Duration (wks)</th>
<th>Best RR (RECIST)</th>
<th>Best RR (CHOI)</th>
</tr>
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<tbody>
<tr>
<td>Imatinib 400mg QD + MEK162 45mg BID</td>
<td>4</td>
<td>Imatinib, Sunitinib, Lin sitsitinib trial</td>
<td>SDHA R31X;SDHB loss by IHC</td>
<td>&gt;66 (active)</td>
<td>SD (-20%)</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Imatinib, Sunitinib, Sorafenib</td>
<td>KIT exon11, L576P</td>
<td>55</td>
<td>SD (-16%)</td>
<td>PR</td>
</tr>
</tbody>
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P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)
Targeting FGFR

- FGF/FGFR pathway
  - Receptors: 4 FGFRs
  - Ligands: 22 FGFs
  - Each FGFR has specificity for particular FGFs

- Context dependent signalling through various intracellular pathways

- Regulates normal biological processes
  - Protein synthesis
  - Cell growth and proliferation
  - Cell motility, migration, invasion
  - Cell differentiation
  - Resistance to cell death
  - Angiogenesis

Turner et al. Nature Reviews Cancer 2010
Targeting FGFR

- Gene expression data has revealed that FGF2 and FGFR1 are highly expressed in all primary GIST samples
- Preclinical studies combining imatinib with an FGFR inhibitor showed increased growth inhibition in imatinib-sensitive GIST cell lines
- Crosstalk between KIT and FGFR3 Promotes Gastrointestinal Stromal Tumor Cell Growth and Drug Resistance

Phase II study of FGFR inhibition

Dovitinib was administered at 500 mg orally once daily for 5 consecutive days, followed by a 2-day rest, with each cycle consisting of 28 days.

DOVIGIST: PII Dovitinib trial

- Efficacy of dovitinib demonstrated in a 2nd study
- The DCR of 52.6% compares favorably with that of other second-line treatments

<table>
<thead>
<tr>
<th>Best Response at 12 Wk, n = 38</th>
<th>n</th>
<th>%</th>
<th>90% CI</th>
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<tbody>
<tr>
<td>Partial response (PR)</td>
<td>1</td>
<td>2.6</td>
<td></td>
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<tr>
<td>Stable disease (SD)</td>
<td>19</td>
<td>50.0</td>
<td></td>
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<tr>
<td>PD</td>
<td>5</td>
<td>13.2</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>13</td>
<td>34.2</td>
<td></td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>1</td>
<td>2.6</td>
<td>0.1-11.9</td>
</tr>
<tr>
<td>DCR (≥ SD)</td>
<td>20</td>
<td>52.6</td>
<td>38.2-66.7</td>
</tr>
</tbody>
</table>

Heat Shock Protein 90 (HSP90) Inhibition

- Chaperone protein that assists other proteins to fold properly, stabilizes proteins against heat stress, and aids in protein degradation.
- Stabilizes proteins required for tumor growth
- Inhibition of HSP90 may interfere with all of the six hallmark traits of cancer

Retaspimycin hydrochloride (IPI-504)

- HSP90 inhibition causes degradation of wild-type KIT and an imatinib-resistant KIT D816V mutant.

- Phase III study of IPI-504 (retaspimycin hydrochloride) versus placebo was terminated early due to excessive treatment related death.
- These deaths were considered drug-related and included renal failure, liver failure, metabolic acidosis, and cardiopulmonary arrest.

Promising phase I data

Other HSP90 inhibitors

- **BIIB021** – PII, stable disease for 10 of 23 subjects (43%)

- **Ganetespib** – PII, stable disease for 5 of 23 subjects (22%)

- **AUY922** – PII on-going

Is there a role for immunotherapy in GIST?

• Can we combine targeted therapy and immunotherapy in GIST?

• Peginterferon a-2b with imatinib for treatment of stage III/IV GIST to induce dendritic cell and cytotoxic T-lymphocyte differentiation toward Th1 response.
  – Interim analysis of 8 patients demonstrated significant induction of IFN-γ-producing-CD8(+) , -CD4(+) , -NK cell, and IFN-γ-producing-tumor-infiltrating-lymphocytes,
  – Median follow-up of 3.6 years,
  – ORR = 100%, overall survival = 100%,
  – one patient died of unrelated illness while in remission

NCIS Developmental Therapeutics Unit
Phase I trials 2015

Ongoing

• Pan-FGFR inhibitor - FGFR1/2/3 expression levels
• AKT inhibitor (AZD5363, Astra Zeneca)
• P-TEFb inhibitor (BAY 1143572, Bayer)
• Trastuzumab + NK-cell therapy for HER2 amplified/ overexpressed tumours
• Balanced PI3Kα/β inhibitor
• Exportin 1 (XPO1) inhibitor - selective inhibitor of nuclear export (Selinexor, Karyopharm)
• PDL-1 + MEK inhibitor (Roche)
• ASLAN001: HER1/2/4 inhibitor + carboplatin and paclitaxel
• PLK1 inhibitor: Tekmira
• Wnt/Porc inhibitor: ETC/ D3
Integrated Molecular Analysis of Cancer (IMAC) at NCIS

- Screening for actionable targets using NGS/IHC and copy number analysis in tumour tissue
- All cancer types
- Establish prevalence of mutations in local patients
- Evaluate clinical impact of molecular profiling (RR/PFS/OS)

Patient with progressive disease

Consent, screening, tissue collection

FFPE or fresh tissue

Next generation sequencing using Ion Torrent PGM Sequencer with minimum requirement of 10-40ng DNA

FISH and CISH/ Gene expression profiling/ immunohistochemistry

Medical Oncologist

Interpretation and recommendation

Results reviewed by IMAC tumour board

Final Profiling Report

Matched Therapy
Conclusions

- Dual inhibition of PK13K/AKT, mTOR, MEK/ETV1, FGFR and HSP90 with KIT/PDGFR pathways +/- immunotherapeutic approaches may become a new paradigm in treatment.

- Challenges of combined targeted approaches include significant risk of overlapping/unknown toxicity which could prevent clinical application.

- The challenges, opportunities, and limitations of these approaches mean that randomized trials are needed for further evaluation.