GIST: Future research directions – Highlights from recent Phase I trials and future directions

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Phase I Clinical Trials

• First in human –
  • Determine the optimal dose
  • Determine the side effects

• Evaluating new combinations of drugs that have previously been studied

• Expansion cohorts – to further look for signals of benefit
Phase I trials have led to drug approvals in GIST

• Avapritinib – Potent activity against PDGFRα D842V mutant GIST

Several Dose levels (17pts <300 mg per day)

Cumulative and largest experience
With this unique molecular subgroup
Of GIST (n=56)

Phase I trial –
first in human experience with this drug
(n=250)

Phase I trials have led to signals in GIST: Ripretinib

**Janku et al., J Clin Oncol. 2020 Oct 1; 38(28): 3294–3303**

**INTRIGUE:**
ONGOING PHASE III TRIAL EVALUATING RIPRETINIB VS SUNITINIB

**INVICTUS:**
Phase III trial of ripretinib vs placebo
LED TO MULTINATIONAL APPROVAL OF RIPRETINIB IN GIST 4TH LINE OR LATER

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**Dana-Farber Cancer Institute**
Rationale Drug Development

The right drug to the right target in the right population
In addition to the primary question, many trials ask secondary questions that provide important information:

• Does remaining on ripretinib following progression, benefit patients?

• How do drug levels in patients vary with dose changes?
Phase I trial of ripretinib allowed dose escalation from 150mg once per day, to 150mg TWICE per day.

Ripretinib
PFS1  5.5 months
PFS2  4.6 months

S. George et al. / European Journal of Cancer 155 (2021) 236-244
All currently approved treatments for GIST are inhibitors of KIT

• First line: Imatinib
• Second line: Sunitinib
• Third line: Regorafenib
• Fourth line: Ripretinib
• PDGFRα D842V: Avapritinib

• Is there a way to build on the benefit seen with KIT inhibitors by combining drugs with other mechanisms of action
Phase Ib trial ASCO 2021: Imatinib plus selinexor in patients with GIST who had previously progressed on at least imatinib – Serano et al

Median PFS 3.5 months 95% CI 1.7 – 7.3
Additional Phase I trials are exploring novel combination therapy in GIST based on strong pre-clinical rationale.

KIT inhibitor in combination with MEKi

Imatinib in combination with binimetinib
GIST patients with no prior therapy

- Phase I/II Combination of binimetinib plus ripretinib in GIST
- ClinicalTrials.gov Identifier: NCT05080621

Chi et al, ASCO 2020 virtual meeting
GPR20 is a novel protein expressed on GIST cells

- DS-6157a

- Antibody-drug conjugate is being studies to see if this new finding can be used to control GIST

DS6157a is being studied in Phase I trial

Iida et al, Cancer Discov. 2021 Jun;11(6):1508-1523
Phase I trials in GIST

• Translation from bench to bedside

• Flexible study designs to allow expansion cohorts when exploring safety and efficacy signals in rare tumor populations or subpopulations

• Future trials are focusing on combinations of KIT inhibitors and novel agents with non-KIT targets, as well as novel KIT inhibitors

• Ultimately, clinical trial participation is a choice that needs to feel right to the trial participant
THANK YOU