Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-23-767

Review Comments (Round 1)

Reviewer A

This is an interesting case report. I have only minor comments.

Comment 1: I suggest writing the gene names in italics.

Reply 1: The proper convention is to use italics when referring to DNA/RNA sequences for a gene and normal font when referring to the protein. We have attempted to use this consistently throughout the manuscript. BRAF V600E most clearly refers to the protein, so we use normal font for this usage. Likewise, dabrafenib inhibits BRAF protein not *BRAF* DNA so we use normal font when referring to kinase inhibitors. In instances where we could be referring to either the protein or the gene we have used normal font.

Changes in the text: please see complete text for italicized genes

Comment 2: p. 3, line 92; p. 4, line 162: Provide a reference for 0.8% of GISTs harboring BRAF V600E.

Reply 2: We have provided source data from cBioPortal and also from a recent review of the literature.

Changes in the text: Line 98

Comment 3: p. 5, line 178: spell out PFS and OS.

Reply 2: abbreviations have been spelled out

Changes in the text: p. 5, line 178; see changes to text

Comment 4: p. 5, lines 210-211: It is not clear from the case report (p. 3, lines 109-111) how long the patient received adjuvant imatinib or whether imatinib was indeed toxic and not beneficial.

Reply 2: only treated for six months

Changes in the text: line 125

Reviewer B

Generally, well written and important report, some corrections required.

Comment 1: Line 51 GIST can arise anywhere in the gut, usually stomach and small but also large bowel. Suggest " ..mesenchymal tumor arising in the gut, most commonly stomach or small bowel"

Reply 2: changed text to address comment

Changes in the text: Line 51

Comment 2: Line 52 Suggest "The most common driver mutations are in KIT or PDGFRA (italics for gene names). Most tumors with KIT mutations respond to treatment with imatinib but only a minority with PDGFRA mutations, the commonest D842V mutation causing resistance to all currently available agents other than avapritinib."

Reply 2: Changed text to address the difference in treatment between KIT and PDGFRA mutations

Changes in the text: See line 52-53

Comment 3: Lines 53, 54 and elsewhere – italics for gene names

Reply 2: text changed to reflect comment

Changes in the text: Lines 53,54

Comment 4: Lines 59,60 The abstract needs to follow the narrative in the case report. "She was initially treated with adjuvant imatinib, which was discontinued when molecular analysis showed an absence of KIT and PDGFRA mutations. When her disease progressed she was started on sunitinib, which was ineffective and poorly tolerated. Regorafenib was also poorly tolerated. Additional mutational analysis revealed a BRAF V600E mutation and she was started on dabrafenib which resulted in a partial response"

Reply 2: abstract case description re-worded to fit narrative of case report

Changes in the text: See lines 58-63

Comment 5: Line 89 – same comment as above – suggest after PDGFRA mutations insert "although these latter are rare, the majority being imatinib-resistant"

Reply 2: changed text to address comment

Changes in the text: See line 92-93

Reviewer C

Comment 1: This case report adds important clinical data to the literature for the treatment of rare BRAF p.(V600E) mutated GIST. However, the authors should add more information on the histological and molecular evaluation of this tumor. How sure are the authors this is truly a GIST? There is no information on the immunohistochemical stainings (KIT? DOG1? CD34?),

morphological details (cell type: epithelioid, spindle) nor specific molecular evidence (methylation profiling or copy number alterations). BRAF p.(V600E) mutations are frequent in a large variety of tumor types. Also add information on the molecular test used. Were other mutations detected apart from the BRAF mutation?. Please also add references to support BRAF+ GIST incidence.

Reply 1: Immunohistochemical staining and morphological details added to manuscript. Methylation profiling and copy number alterations were not done.

Changes in the text: Please see lines 112-118

Reviewer D

Thois is an interesting case report on the efficacy of dabrafenib alone and in combination with trametinib in a patient with advanced non-resectable c-kit wild type

BRAF-mutated GIST.After a complete resposnse a suspected progression induced the introduction of the second TKI until fatal tumor progression occurred.

Comment:

Comment 1: In the introduction it should be mentioned that BRAF-mutated colorectal cancers are not responsive to dabrafenib as stated in the article published in Nature Medicine 2023;29(5):1103-1112.

Reply 2: Text updated to address comment and citation

Changes in the text: See line 107

Comment 2: It is only an hypothesis that the BRAF-mutation is a driver in the presented case.

Reply 2: While it was initially a hypothesis, based on the patients resistance to standard GIST therapy and tumor regression with dabrafenib treatment I think it can be surmised that at least initially, the BRAF mutation was a driver mutation in this case. There were also no other known driver mutations noted in molecular analysis. Also, two separate groups have reported that transgenic mice with BRAF V600E mutation targeted to GIST precursor cells develop GI stromal tumors (Kondo et al.. Journal of Pathology doi: 10.1002/path.5552; and Ran et alo. Cancer Research doi: 10.1158/0008-5472.CAN-16-3510)

Changes in the text: No changes to text. But we could add the mouse models to the paper if so desired.

Comment 3: Figure 1 shows that after 7 months dabrafenib therapy a complete response was achieved.At this time a PET-scan could have been done as it would have been helpful also at 12 months when a progress (not according to RECIST-criteria) was suspected by an,,to my opinion, unsufficient CT-scan.In fact a double contrast study (oral barium and intravenous

jodine contrast) should have been performed.Furthermore,if the assumed progression was real a compliance problem as a possible cause should be discussed before development of drug resistance is discussed. :judging from the CT-scan picture I see a complete response at 7 months of therapy.This increaseses the pressure on the clinician to follow such patients with

attention to possibly avoid reuction of compliance when such a success has been communicated to the patient .

Reply 2: Patient's adherence to medication was considered and was presumed to be overall very good although did admit to missing a couple of doses. The couple of doses that she did miss would not account for the progression of her disease.

Changes in the text: See line 139-140

Comment 4: The patient mentioned in the Nature Medicine publication had stable disease 30 months after beginn of the combination therapy (this article should be added to the literature)

Reply 2: changed text to reflect this detail

Changes in the text: See line 218-219

Review Comments (Round 2)

Comment:

I further suggest to say that the BRAF V600E-mutation "may be" responsible for development of stromal tumors in the GI-tract and say clearly that this is still a hypothesis. The two publications mentioned by the authors by no means demonstrate development of cancer from ICC. In fact in the first manuscript authors stated that introduction of Trp53-loss was necessary to achieve GIST-like tumors but chromosomal aberration-study was not performed to definitively demonstrate cancer development. In the more recent second publication the results presented were even more confusing as smooth muscle cells are suggested to be the cell of origin of GIST-like tumors. Also in this case no chromosomal analysis has been performed. I ask the authors to "critically" mention both articles in the discussion.

Reply:

It is known that BRAF mutations can act as driver mutations in GIST. Furthermore, the patient's disease course followed what would be expected of a BRAF GIST-resistance to standard GIST therapy with KIT inhibitors and notable tumor regression with treatment of a dabrafenib. Thus, I think it can be surmised that at least initially the BRAF mutation was the driver mutation in this case.

The pathology in this case was reviewed by two expert soft tissue pathology reviewers both of which determined that this was a GIST.

We have updated the discussion to include more details on the various mouse models.

Changes in text:

Line 175, 178

Line 177-180

Line 179-185

Comment:

Case reports are very important not only for scientific but also for educational purposes. I therefore ask the authors to say that they first obtained complete response (at 7 months) and then progress was detected. Although resistance development was assumed it can not be excluded that a compliance problem was responsible for the progress. In fact, the patient admitted missing " a couple of doses" a behavior which is known to clinicians.

Reply:

The text was changed to reflect that complete response was obtained at 7 months before progression. While patient did admit to missing a couple of doses, her adherence to the regimen was overall determined to be good. The couple of doses she admitted to missing would hot have accounted for the progression.

Changes in text:

Line 143

Review Comments (Round 3)

The authors introduced some important changes.

I however like to insist that in the two articles now mentioned in the discussion the Demonstration that the GIST-like Tumors were "malignant“. Therefore this adjective should be deleted and the Definition should be „GIST-like-Tumor„.

Reply: Text changed to reflect comment.

Change in text: Line 18, Line 22