

Point-by-point response to Reviewer #1.

Title: Reflects the content of the study

Abstract: Well written

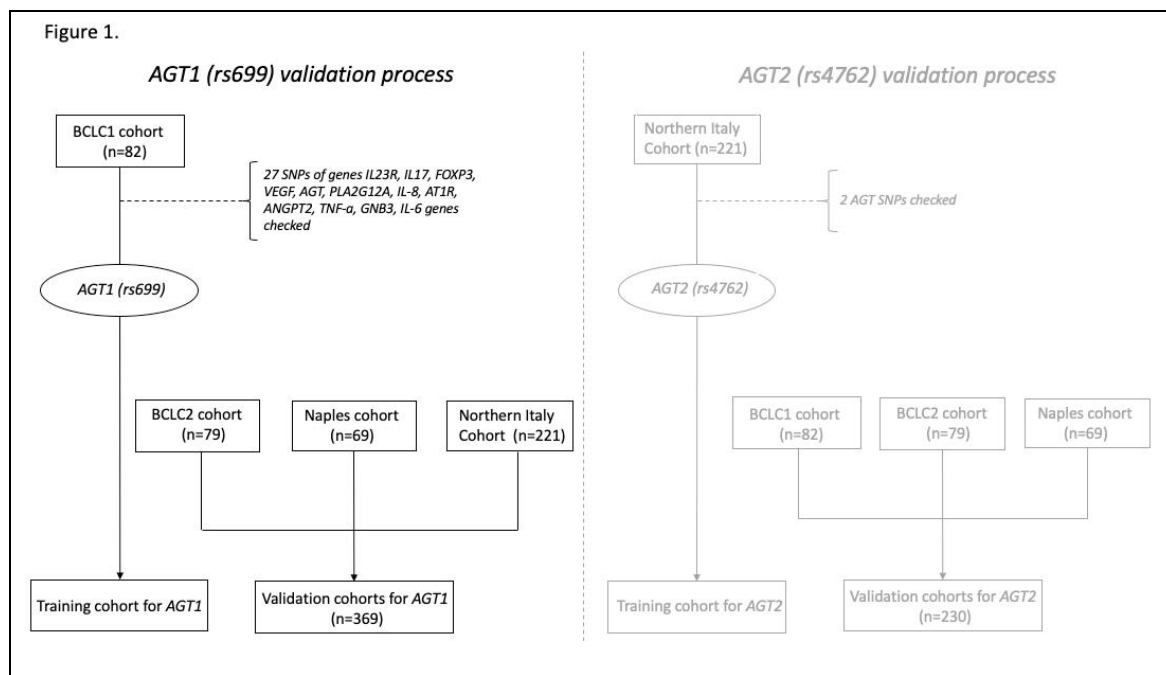
Introduction: Well written.

Response: We greatly appreciate the positive comments on Abstract and Introduction

Materials and Methods:

Very complicated. Especially a third party reader get lost while trying to figure out the study design process. I recommend a flow chart to tabulate the functions of the individual cohort

Response: Following the reviewer's suggestion, we have included a flow-chart which should clarify the role of each cohort and cohort combinations implemented in this study



Results:

Although the results seem striking, the authors show absolutely no data regarding response to therapy, recurrences, OS and DFS of the patients. Although the SNPs' that are being studied correlate with AHT and the dermatologic adverse event, the manuscript is structured around response to treatment and the reader expects these results. Furthermore, the results section is equivocally complex and very hard to understand.

Response: We respectfully appreciate the Reviewer's considerations on results regarding response to therapy, recurrence and OS. Studies that analyze associations between SNP frequencies and patients' clinical data are conditioned by the necessity of

including large numbers of patients to guarantee the reliability of the results. In our setting, the evaluation of genetic variants was in a very specific subset of individuals, patients with advanced hepatocellular carcinoma, who have homogeneous clinical and radiological baseline characteristics (preserved liver function, performance status and tumor burden) under systemic treatment.

Regarding the response to therapy assessment, the radiological assessments between the centres were not homogenous. For this reason, we decided to avoid analysis regarding radiological evaluation. We considered that it would be more appropriate to restrict our analyses to DAE development since we already demonstrated that DAE development correlates with better OS in several treatments and indications.

Table 2 includes the OS for each cohort and for each patient's genotype.

In order to clarify why we did not assess the association between radiological evaluation and genotype, we have included a short paragraph in the Discussion Section.

Discussion:

Well written.

Response: We greatly appreciate the positive comment

Tables and figures:

are sufficient.

Response: Following the Reviewer's suggestion, we have added Figure 1, a flow-chart explaining the role of each patient cohort.

Ethics:

The ethical guidelines have been followed and the manuscript is written according to the guidelines of the journal.