

# Emergence of SARS-CoV-2 Spike Escape Mutation Q493R After Bamlanivimab/Etesevimab Treatment for COVID-19

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## Case Report

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# Abstract

We report here the first *in vivo* selection of a Spike mutation (Q493R) conferring simultaneous full resistance to both bamlanivimab and etesivimab.

## Main Text

Accelerated SARS-CoV-2 evolution occurs under selective pressure by therapeutic interventions with neutralizing antibodies<sup>1</sup>. Bamlanivimab has been recently withdrawn from the vendor as a monotherapy because of failure against E484K SARS-CoV-2 variants. Emergency use remains authorized for the bamlanivimab/etesevimab cocktail<sup>2</sup>, for which no completely resistant variant has been reported to date *in vivo*.

A 73-years old male was diagnosed on February 2021 with cholangiocarcinoma: while waiting for chemotherapy, he developed sepsis and was admitted to Varese hospital on Apr 12 for steroid and antimicrobial treatment. Nasopharyngeal swab (NPS) for SARS CoV-2 RT-PCR was negative on admission, but positive on Apr 24. Given he had recovered from sepsis, on Apr 25 he was moved to the COVID unit of the hospital. Falling within one of the frail patient categories for emergency use of anti-Spike monoclonal antibodies approved by the Italian Drug Agency and being seronegative for anti-S1/S2 IgG (Diasorin, Italy), on Apr 26 the patient received an i.v. infusion of bamlanivimab 700 mg/etesevimab 1400 mg at the hospital. RT-PCR performed on the NPS collected before infusion was positive for SARS-CoV-2, with a cycle threshold (Ct) of 12 (Alinity, Abbott). Follow-up NPS remained positive on Apr 28 (Ct 15) and May 3 (Ct 24); a chest CT scan on Apr 30 showed progression to interstitial pneumonia, and the patient was placed in noninvasive ventilation.

SARS CoV-2 RT-PCR on nasopharyngeal swab (NPS) was performed with Alinity platform (Abbott), and anti-S1/S2 IgG were measured using a chemiluminescent immunoassay (Diasorin). Sanger sequencing of Spike gene on the Apr 24 NPS revealed a PANGOLIN clade B.1.1.7 (NextStrain clade 20I/501Y.V1, GenBank sequence MZ157261), which was 94% prevalent in Italy at that time: since May 3 we observed a secondary A1478G peak in the S gene, corresponding to Q493R amino acid mutation, which became predominant as soon as May 8 (Ct 18; GenBank sequence MZ157275) (Fig. 1).

E484, F490, Q493, and S494 are the 4 amino acid residues within the Spike receptor-binding motif (RBM) that are known to be critical for bamlanivimab binding. Q493 is also among the many more RBM residues crucial for interactions with etesivimab. Q493R/K (which can be selected *in vitro* by bamlanivimab<sup>3</sup>) is to date the only mutation that causes resistance to both bamlanivimab and etesivimab. In pseudoviral neutralization assays Q493R reduces susceptibility to bamlanivimab by >6,666 folds, to etesevimab by 232 folds, and to the combination of both by >100 folds<sup>2</sup>; accordingly, in a flow cytometry competitive assay, Q493R reduces IC<sub>50</sub> of >100 folds for bamlanivimab and 42 folds for etesivimab<sup>3,4</sup>.

Q493 mutations increase binding affinity to ACE2 <sup>5</sup>, but further studies are needed to clarify whether such escape mutants are fit enough to spread and persist in humans.

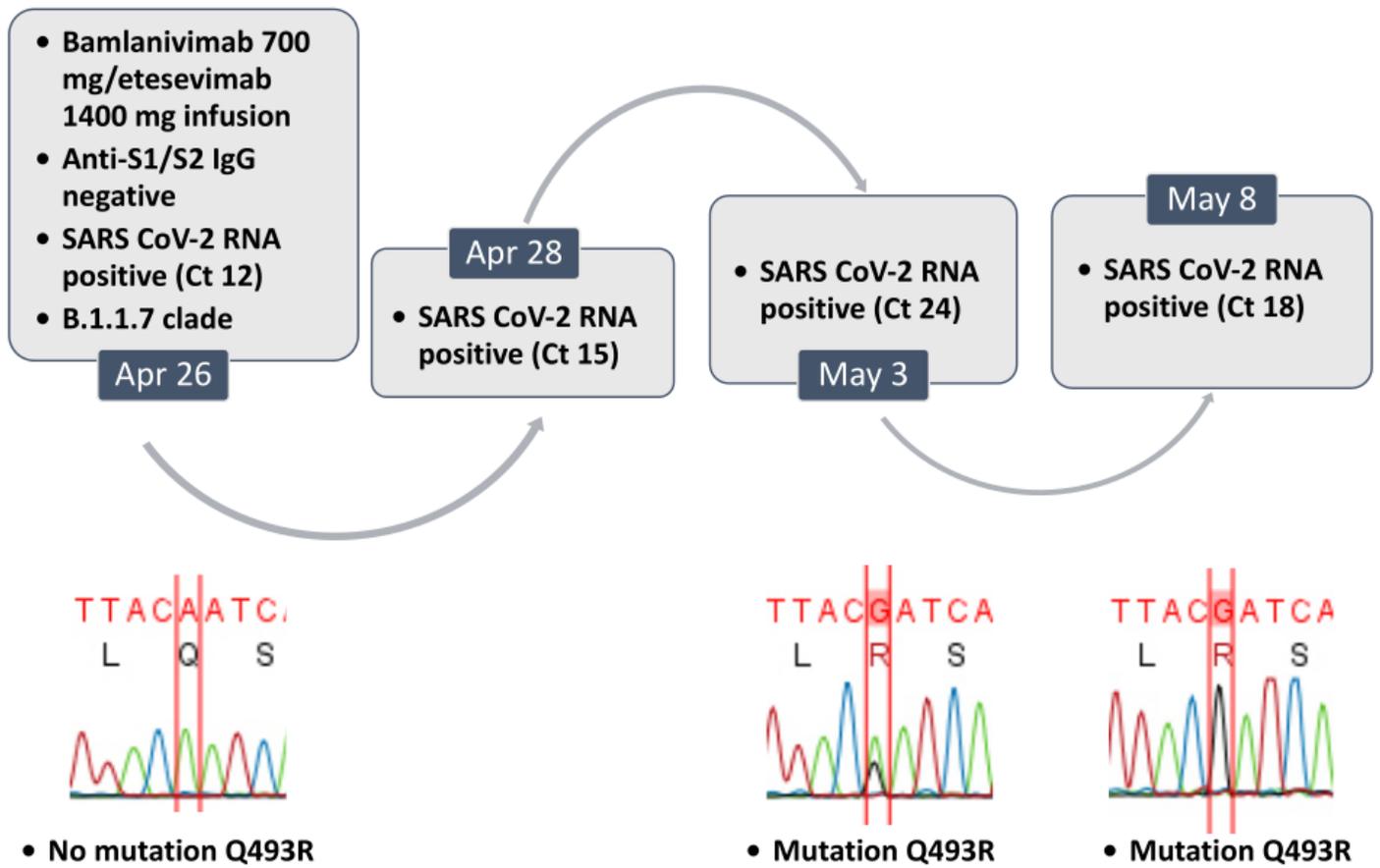
## Declarations

We declare we have no conflict of interest related to this manuscript.

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## Figures



**Figure 1**

Evolution of SARS-CoV-2 variants in time after treatment with bamlanivimab-etesivimab.