Mismatch-repair deficiency is a well-established biomarker of improved overall survival after treatment with immune checkpoint inhibitors, and pol-d status may also predict benefit from immune checkpoint inhibitors. We observed that other than patients with these two genetic subtypes, the only patients with hypermutated tumors who benefited from immune checkpoint inhibitors had cancers strongly associated with environmental carcinogens — chronic exposure to ultraviolet radiation or tobacco.

The current FDA approval granted on the basis of tumor mutational burden may be too broad, and immune checkpoint inhibitors should be considered in the context of the cause of the high tumor mutational burden and not based solely on an absolute threshold. This approval, given purely on the basis of response rate, also neglects more meaningful clinical end points, including survival and quality of life, and slows the development of more effective therapies for this patient population.

To the Editor:

The ACTIV-3/TICO LY-CoV555 Study Group (Dec. 22) hypothesized that low penetration of the antibody into the infected lungs might explain the lack of benefit of bamlanivimab (LY-CoV555) in hospitalized patients with coronavirus disease 2019 (Covid-19). However, we previously measured transudation of human immunodeficiency virus type 1 (HIV-1) into the lungs...
Correspondence

Monoclonal antibodies (VRC07-523 and PGT121) into tissues of 1-month-old rhesus macaques as part of a study to assess the effectiveness of monoclonal antibodies as postexposure prophylaxis.\(^2\) We detected high concentrations of passively transferred antibodies in the lungs of the two macaques (250 ng per milliliter in one and 285 ng per milliliter in the other) after subcutaneous administration of 10 mg per kilogram of body weight of monoclonal antibody cocktail. The concentration of antibody in the lungs was higher than the mean concentration detected in 26 other tissues (184 ng per milliliter); monoclonal antibody biodistribution was not affected by the virus in challenged animals.

Our observations suggest that the rapid selection of neutralization-resistant variants, rather than biodistribution, might have undermined the efficacy of bamlanivimab in this trial. This hypothesis is supported by recent data provided by Regeneron about the preliminary efficacy of the combination of casirivimab and imdevimab in reducing the risk of death or mechanical ventilation in hospitalized patients with Covid-19.\(^3\)

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Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas

To the Editor: In reviewing articles about drug-coated balloons that are used in vascular-access maintenance in patients undergoing dialysis, I found four articles that describe studies with similar outcomes: one by Trerotola et al.,\(^1\) two by Swinnen et al.,\(^2,3\) and one by Lookstein et al.

The Authors Reply: Many factors dictate monoclonal antibody distribution.\(^1\) Although we appreciate the data from Jaworski on the distribution of an HIV-1 monoclonal antibody in infant monkeys, other studies in different systems have yielded different results. For example, in cynomolgus monkeys, dose-dependent increases in concentrations of mepolizumab, an IgG1 antibody (the same subclass as LY-CoV555 and VRC07-523), were observed in bronchoalveolar lavage fluid, and the resulting concentrations were reported to be approximately 500 to 1000 times lower than the steady-state plasma concentrations of the antibody.\(^2\) The Regeneron press release\(^3\) noted a hazard ratio of 0.78 for progression to death or mechanical ventilation in hospitalized patients, with an 80% confidence interval of 0.51 to 1.2; thus, these data are still inconclusive.

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Since publication of their article, the authors report no further potential conflict of interest.

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