Figure 1 (previous page). Effect of Immune Checkpoint Inhibitors on Survival in Patients with Tumors with High Tumor Mutational Burden.
Shown are Kaplan–Meier plots of overall survival in 137 patients with advanced colorectal cancer according to tumor mutational burden (TMB; Panel A) and the same cohort of patients with advanced colorectal cancer stratified according to tumor mutational burden, mismatch-repair–deficient (MMRd) and mismatch-repair–proficient (MMRp) status, and *pol*-deficient (*pol-d*) status (Panel B). A subgroup analysis (Panel C) shows hazard ratios for death according to tumor type in a separate cohort of 1661 patients with MMRp tumors treated with immune checkpoint inhibitors. Patients with various tumor types were combined into two separate models according to whether tumor mutational burden of 10 or more mutations per megabase significantly predicted benefit from immune checkpoint inhibitors when accounting for mismatch-repair–deficient and *pol-d* status. Other tumors include kidney, breast, and neuroendocrine tumors, uveal melanoma, and mucosal melanoma (see the Methods Section, Table S4 in Supplementary Appendix 2 [legend in Supplementary Appendix 1]). All hazard ratios were calculated with the use of Cox proportional-hazards univariate regression. CI denotes confidence interval, Mb megabase, NE could not be estimated, NR not reached, and NSCLC non–small-cell lung cancer.

Mismatch-repair deficiency is a well-established biomarker of improved overall survival after treatment with immune checkpoint inhibitors,[4] and *pol-d* status may also predict benefit from immune checkpoint inhibitors.[5] 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.

Benoit Rousseau, M.D.
Michael B. Foote, M.D.
Luis A. Diaz, Jr., M.D.
Memorial Sloan Kettering Cancer Center
New York, NY
ldiaz@mskcc.org
and Others

Drs. Rousseau and Foote contributed equally to this letter.

A complete list of authors is available with the full text of this letter at NEJM.org.

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Monoclonal Antibody for Patients with Covid-19

TO THE EDITOR: The ACTIV-3/TICO LY-CoV555 Study Group (Dec. 22)[1] 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)

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]

Juan P. Jaworski, D.V.M., Ph.D.

Consejo Nacional de Investigaciones Científicas y Técnicas
Buenos Aires, Argentina
jaworski.juan@inta.gob.ar

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3. Regeneron Pharmaceuticals. Regeneron announces encouraging initial data from COVID-19 antibody cocktail trial in hospitalized patients on low-flow oxygen. December 29, 2020 (https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-encouraging-initial-data-covid-19-antibody).

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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.

Jens D. Lundgren, M.D.

Rigshospitalet
Copenhagen, Denmark
jens.lundgren@regionh.dk

H. Clifford Lane, M.D.

National Institute of Allergy and Infectious Diseases
Bethesda, MD

James D. Neaton, Ph.D.

University of Minnesota
Minnesota, MN

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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.