recurrent kyklonic events were seen in 45%, 28%, and 46% of samples harboring mutated ecDNA, respectively.

The main culprit causing kyklonas, an enzyme family called APOBEC3, "normally modulates innate immunity by restricting viruses, many of which have circular genomes," Bergstrom explains. "Our theory is that APOBEC3 may regard ecDNA as a similar foreign body that needs to be cut up."

"We saw repeated APOBEC3 attacks on ecDNA circles after they formed; it wasn't a one-off occurrence," Alexandrov adds. "This isn't unlike what's been seen on viral genomes in HPV [human papillomavirus]-driven cancers. That's why we think APOBEC3 is mistaking ecDNA for a virus, creating kyklonas along the way and, because ecDNA often carries oncogenes, inadvertently accelerating cancer development."

Roel Verhaak, PhD, of The Jackson Laboratory for Genomic Medicine in Farmington, CT, observes that "ecDNA has of late been revitalized as an important topic." Not involved in this study, he was most intrigued by the hypothesis as to why kyklonas occurs. "It suggests a targeted, proactive role for APOBEC3 in trying to prevent the genesis of ecDNA," he says. "I thought this was quite provocative, and I always appreciate it when authors go out on a limb in their study discussion."

"There's still much to unpack with our data," Alexandrov says, including validating kyklonas as a novel mode of cancer evolution. Meanwhile, he and Bergstrom are further exploring survival differences seen with clustered mutations and their clinical utility.

"More patients are undergoing routine genomic testing, and the information—whether or not mutations are clustered—is already in the results," Alexandrov notes. "It just hasn't been used to predict outcomes, but that's readily implementable. As well, are there particular therapies to which a patient with clustered mutations responds, and vice versa? It's another question to pursue to better understand the prognostic power of our findings." *–Alissa Poh* ■

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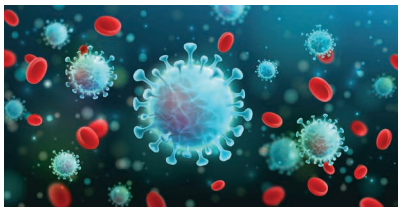
Top COVID-19 Prognostic Factors Identified



Researchers have identified more than a dozen factors that may increase COVID-19's severity. But for patients with thoracic malignancies, seven variables predict the likelihood of dying, according to a recent study that analyzed data from the international TERAVOLT registry (J Thorac Oncol 2022 Feb 1 [Epub ahead of print]). The study also demonstrates that creating real-time databases like TERAVOLT is feasible—and that they capture valuable information.

The registry, which was launched in March 2020 and now houses data from 92 centers in 19 countries, was designed to track the effect of COVID-19 on patients with thoracic malignancies. Clinicians entered patients' demographics, comorbidities, cancer treatments, and cancer lab test results. In a preliminary analysis of the first 200 patients, researchers reported a mortality rate of 33% and identified several variables that correlated with the risk of death, including age, smoking status, and comorbidities (Lancet Oncol 2020;21:914–22).

The goal of the recent study was to help clinicians determine which patients might need greater monitoring or changes in care, says coauthor Jennifer Whisenant, PhD, of Vanderbilt University Medical Center in Nashville, TN. She and her colleagues analyzed data from 1,491 patients in the TERAVOLT registry hospitalized between March 2020 and April 2021. They assessed whether any of 73 variables—such as body mass index, smoking status, age, gender, and the number and type of cancer therapies received—correlated with mortality risk during an average follow-up of 42 days. Given this short period, deaths likely resulted from COVID-19, not cancer.

At 24.2%, the overall mortality rate was lower than in the initial study. Eastern Cooperative Oncology Group (ECOG) performance status had the greatest influence on the risk of death, followed by neutrophil count, which other studies have linked to the immune overreaction that appears to kill some patients with COVID-19. The rest of the seven mortality risk factors were serum procalcitonin levels, development of pneumonia, C-reactive protein levels, tumor stage, and age.

The researchers provide a predictive nomogram that accounts for each of the seven factors.

Notably, the cutoff date for the study was April 15, 2021, before many patients were vaccinated. However, Whisenant and coauthor Alessio Cortellini, MD, of Imperial College London, UK, say that the results remain relevant because of the prevalence of vaccine hesitancy and because patients with thoracic malignancies may have weak responses to SARS-CoV-2 vaccination. They add that the TERAVOLT researchers are planning studies to examine the severity of the SARS-CoV-2 omicron strain on mortality, the effect of hospital crowding, and other factors.

"The study is addressing an important issue," says Robert Cerfolio, MD, of NYU Langone Health in New York, who wasn't connected to the research. The message, he says, is that most patients with cancer can continue their treatment.

Daniel Boffa, MD, of Yale School of Medicine in New Haven, CT, who wasn't connected to the research either, says so much has changed since the study's cutoff date—including the increased availability of vaccination, development of new viral variants, and approval of additional COVID therapies—that the findings probably won't alter treatment for most patients. However, he says, TERAVOLT is significant because it shows "a first-in-history level of connectivity among the global cancer community." TERAVOLT's rapid collection and sharing of data makes an analysis like the one the authors performed "possible in an almost real-time manner."

Similar databases could help researchers improve cancer treatment and allow rapid responses to future

pandemics, Boffa argues. "Judging the importance of TERAVOLT on the impact of a single study is short sighted. It would be akin to asking the Wright brothers after their first flight, 'Who would ever need to fly 120 feet?'" *–Mitch Leslie* ■

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Cilta-cel OK'd for Multiple Myeloma

A second chimeric antigen receptor (CAR) T-cell therapy has been added to multiple myeloma's treatment arsenal, with ciltacabtagene autoleucel, or cilta-cel (Carvykti; Janssen/Legend Biotech), receiving the FDA's nod on February 28. Like idecabtagene vicleucel, or ide-cel (Abecma; Bristol Myers Squibb)—which was greenlighted less than a year ago—cilta-cel targets BCMA and is a fifth-line option for this disease.

Having two CAR T-cell therapies available "will be great," says Adam Cohen, MD, of the University of Pennsylvania in Philadelphia, given that "bottlenecks in manufacturing ide-cel have led to long waitlists at many centers."

Cilta-cel's launch "will take a few months—just because it's approved doesn't mean we can offer it to patients immediately," adds Eric Smith, MD, PhD, of Dana-Farber Cancer Institute in Boston, MA. "Even when it gets going, I don't know that both CAR-Ts will be able to fulfill the demand out there right away."

Updated, longer-term results from the pivotal CARTITUDE-1 trial, presented during the American Society of Hematology's annual meeting in December 2021, secured cilta-cel's approval. Among 97 patients who had received multiple prior treatments—including all three mainstays, proteasome inhibitors, anti-CD38 drugs, and immunomodulatory agents—the objective response rate to cilta-cel was 98%. After 22 months, the stringent complete response rate was 83%, and median progression-free and overall survival were not reached.

"These are really exciting, encouraging data," Smith says. Before CAR T-cell therapy, one of the most recent approvals for relapsed/refractory multiple myeloma was selinexor (Xpovio; Karyopharm), a selective inhibitor of nuclear export, "which benefited a minority of these difficult-to-treat patients, and on average, only for a few months," he points out. "By contrast, cilta-cel and ide-cel are dramatic advances."

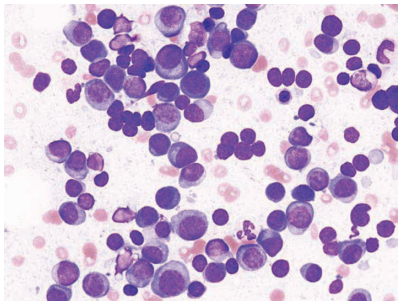
With all caveats of cross-trial comparisons duly noted, "the depth and duration of responses do seem better with cilta-cel" than ide-cel, Cohen says. However, "there could be an increased risk of late-developing neurotoxicity involving parkinsonian symptoms that we'd want to discuss with patients." One way to reduce this risk, clinicians have learned, "is to control the disease burden as much as possible—through aggressive bridging therapy, if necessary—before starting cilta-cel."

Both Cohen and Smith observed that cilta-cel doesn't stick around long—unlike ide-cel, where CAR-bearing T cells are detectable in many patients after 12 months. Interestingly, this lack of persistence doesn't appear to influence response durability, at least based on preliminary data. More analyses are underway to suss out whether persistence matters, and whether enriching for particular T-cell subsets—perhaps those with central memory or stem-like phenotypes—is important.

As well, trials of both immunotherapies are ongoing "in earlier disease settings," Cohen says, "and the hope is, ultimately, first-line CAR-T, which could benefit a subset of high-risk patients whose outcomes are consistently poor despite all the treatments we have."

Additional multiple myeloma targets, such as FcRH5 and GPRC5D, have recently emerged, Smith notes. He is interested in sending CAR T cells after the latter protein, with CC-95266 (Bristol Myers Squibb) among several products now in phase I trials stemming from his lab research. Others are pursuing T-cell–engaging bispecifics, including talquetamab (Janssen) for GPRC5D and cevostamab (Genentech) for FcRH5.

"My sense is these therapies will first be used for patients who have relapsed following BCMA CAR-T," Cohen



Multiple myeloma.

remarks. "However, once they're all on the market, we can begin testing the best sequences or, possibly, combinations. It could take years, but it's a good problem to have."

"A cure remains elusive," Smith adds, "but it's great to get patients into durable remissions and, meanwhile, find options for their next relapse. We can keep kicking the can down the road, so to speak, with new therapies becoming available each year." *–Alissa Poh* ■

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Assessing Toripalimab in NSCLC

Findings from CHOICE-01 indicate that toripalimab (Junshi Biosciences) prolongs the time to disease progression in patients with untreated non–small cell lung cancer (NSCLC) when added to chemotherapy. Data from the phase III trial were presented by Jie Wang, MD, of the Chinese Academy of Medical Sciences and Peking Union Medical College in Beijing, during the March session of the American Society of Clinical Oncology's monthly Plenary Series.

Toripalimab is one of China's domestically developed PD-1 inhibitors. Known there as Tuoyi, it is an approved second-line therapy for melanoma, urothelial cancer, and nasopharyngeal carcinoma. In the United States, it is under priority review for the latter cancer, with a decision expected in April.

CHOICE-01 enrolled 465 patients with advanced or metastatic NSCLC that lacked sensitizing *EGFR* or *ALK* mutations. They were randomly assigned 2:1 to receive toripalimab