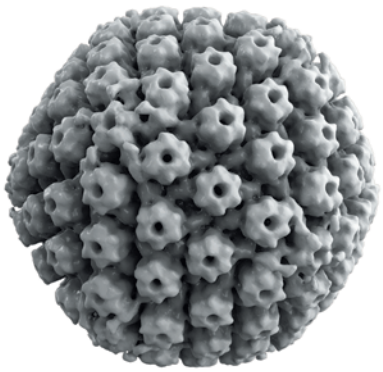


Pediatric high-grade gliomas have responded to oncolytic G207, a genetically engineered therapy using herpes simplex virus type 1 (3-D rendering above).

cancer cells and killing them, while leaving healthy neurons unscathed. A bonus: The cold-sore virus is sensitive to drugs such as acyclovir, which could mute responses should something go awry.

Between 1998 and 2008, Martuza and his collaborators—including James Markert, MD, MPH, of UAB and a cofounder of Treovir—tested G207 in adults with glioblastoma. Across three trials, the therapy proved safe and tolerable at multiple doses, as well as when paired with radiation. Yet, few patients responded to the treatment.

In children, G207 seems to have greater activity. Researchers led by Friedman, who is not affiliated with Treovir, and his colleagues administered G207 at two doses, alone or combined with a single 5-gray dose of radiation, to 12 patients ages 7 to 18. Infiltrating immune cells flooded into the cancers—with no severe toxicities—turning the immunologically "cold" tumors "hot." Eleven patients experienced a radiographic, neuropathologic, or clinical response, with a median overall survival of just over 12 months; one patient lived for more than 4 years without additional therapies. Typically, these patients survive less than 6 months.

"Further research into the mechanisms of response to virotherapy is needed" to fully understand why pediatric brain tumors were more sensitive to G207 than adult gliomas, said Friedman. However, he suggested three possible explanations.

First, younger people tend to have more robust immune systems, which could make them more responsive to virotherapy. Second, children and adolescents have had less exposure to herpes infections, which makes them less likely to harbor preexisting antibodies to HSV—an immune feature that might decrease the efficacy of G207. Finally, pediatric gliomas tend to have lower mutational burdens, a characteristic that has been linked to tumor-intrinsic inflammation and responsiveness to immunotherapy in adults.

Mechanism aside, Martuza is pleased to see the oncolytic HSV that he and his colleagues created decades ago finally making a clinical impact. But, "this is an entry-level virus," he noted, "and we and others are improving upon it." Hopefully, he said, the data will inspire others to evaluate virotherapies with greater curative potential. "This whole process is iterative."

–Elie Dolgin ■

Mechanisms of KRAS Inhibitor Resistance Revealed

As the KRAS^{G12C} inhibitors sotorasib (AMG510; Amgen) and adagrasib (MRTX849; Mirati Therapeutics) move into late-stage clinical testing, researchers have begun to investigate possible mechanisms of acquired resistance to these agents. A recent study revealed that patients with non–small cell lung cancer (NSCLC) or colorectal cancer treated with adagrasib may develop resistance in a variety of ways, including through secondary *KRAS* mutations, MAPK pathway alterations, genomic rearrangements, or histologic transformation of disease. Results were presented during the first week of the virtual American Association for Cancer Research Annual Meeting 2021, April 10–15.

KRAS^{G12C} mutations occur in about 13% of NSCLCs and 3% of colorectal cancers, and although sotorasib and adagrasib have shown antitumor activity in these malignancies, "clinical mechanisms of acquired resistance to [KRAS]^{G12C} inhibitors are unknown," said presenter Mark Awad, MD, PhD, of Dana-Farber Cancer Institute in Boston, MA. Thus, he and his team set out to characterize resistance mechanisms in patients who stop responding to the therapies.

The study included 30 patients with *KRAS*^{G12C}-mutant cancers—23 with NSCLC and seven with colorectal cancer—treated with adagrasib monotherapy. All patients experienced tumor reduction or clinical benefit followed by disease progression. Researchers performed genomic sequencing on pretreatment biopsies and/or circulating tumor DNA samples and compared them with sequenced samples taken at the time of disease progression.

The team identified a single resistance mechanism in seven patients and multiple mechanisms in five. Patients developed a range of secondary *KRAS* mutations, including G12D, G12R, G12V, G12W, G13D, H95D, H95Q, H95R, R68S, Q61H, and Y96C. Patients also developed other aberrations, including *EGFR* and *MET* amplifications; *RNAS, BRAF, MAP2K1*, and *RET* mutations; and fusions involving *RET, BRAF, RAF1*, and *FGFR*. Two patients lacking genomic resistance mechanisms had histologic transformation from lung adenocarcinoma to lung squamous cell carcinoma.

The development of multiple resistance mechanisms—particularly gene fusions—appeared to be more common in patients with colorectal cancer, although "larger datasets are needed to confirm this observation," Awad noted. Mutagenesis screens revealed that most *KRAS* resistance mutations likely result in resistance to multiple KRAS^{G12C} inhibitors, and thus sequential treatment with such agents may not be beneficial. However, some secondary mutations might offer differential sensitivity.

The findings demonstrate that "diverse mechanisms confer resistance to [KRAS]^{G12C} inhibitors," Awad said, and patients may concurrently develop resistance via multiple mechanisms. That some patients simultaneously developed secondary *KRAS* mutations, downstream *BRAF* and *MEK* alterations, and gene fusions is "a bit daunting," Awad added. "There is intense interest in understanding which combinatorial strategies will be either used at the time of acquired resistance, or moved sooner up front to hopefully delay resistance." For example, combinations that include downstream inhibitors, such as SHP2, might be effective.

"This is one of the first big cohort analyses on the mechanisms of acquired resistance to the KRAS^{G12C} inhibitors," said Kwok-Kin Wong, MD, PhD, of the Laura and Isaac Perlmutter Cancer Center at NYU Langone Medical Center in New York, NY, who was not involved in the study. He considers the results exciting, although secondary *KRAS* mutations and activating mutations in the signal transduction pathway are not necessarily surprising. Histologic transformation, he said, is an unexpected mechanism that merits additional investigation.

For Wong, the study highlights the numerous escape mechanisms that make treating *KRAS*^{G12C}-mutant lung cancer with a single agent difficult, pointing to a need for combination strategies.

David Hong, MD, of The University of Texas MD Anderson Cancer Center in Houston, who was not involved in the research either, agreed. "Although the numbers here are relatively small, the results show us that … resistance is complicated and varied," he said. "Unfortunately, likely there will not be a one-size-fits-all path toward KRAS^{G12C} resistance." –*Catherine Caruso* ■

TCR Bispecific Boosts Survival in Uveal Melanoma

A bispecific fusion protein designed to redirect T cells toward a melanoma-associated antigen nearly halved the risk of death among patients with an aggressive form of eye cancer, researchers reported during the first session of the virtual American Association for Cancer Research (AACR) Annual Meeting 2021, being held April 10–15.

In a phase III randomized trial of 378 patients with untreated metastatic uveal melanoma, 73% of those who received the bispecific protein therapy, known as tebentafusp (Immunocore), were alive 1 year later. In comparison, 58% of those prescribed a checkpoint inhibitor or chemotherapeutic agent of the investigator's choice met that same benchmark. The disease-control rate was greater in the tebentafusp-treated cohort as well—45% versus 28%.

Adverse events associated with tebentafusp treatment were predictable and manageable, noted Jessica Hassel, MD, of the University Hospital Heidelberg in Germany, who presented the findings. The rate of treatment discontinuation was lower in the tebentafusp arm compared with the investigator's choice arm—2% versus 4.5%, respectively.

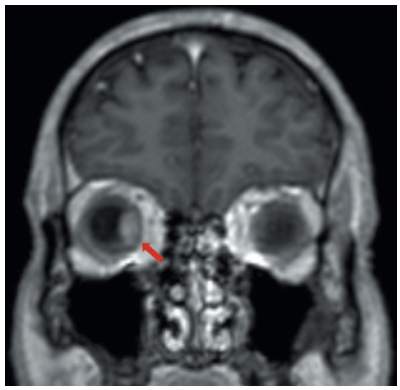
If approved, tebentafusp would represent the first major pharmacologic advance for the treatment of metastatic uveal melanoma, a rare disease for which no other therapy has been shown to improve overall survival. "It's going to become the standard of care for these patients," said site investigator Jose Lutzky, MD, of the University of Miami Miller School of Medicine in Florida.

Yet, the drug—which pairs an anti-CD3 immune effector cell-binding domain with a high-affinity gp100-directed T-cell receptor (TCR)—won't be an option for everyone with advanced uveal melanoma. Because the immune-mobilizing TCR part of tebentafusp recognizes gp100 peptides presented exclusively on HLA-A*02:01 molecules, the therapy's reach is limited to the 40% of individuals globally, mainly Caucasians of European descent, who harbor that HLA polymorphism.

According to David Berman, MD, PhD, head of R&D at Immunocore, the company hopes to extend the reach of its various TCR bispecifics in development by advancing products built around either other common HLA subtypes or "non-classical" MHC molecules that might allow for universal TCR-based products.

As for tebentafusp, Immunocore plans to file for regulatory approval later this year. Trials involving patients with nonmetastatic uveal melanoma could follow. "We do believe this is a platform that can be used in the adjuvant setting," Berman said.

At the AACR meeting, trial investigators also detailed exploratory analyses from a phase I/II trial of tebentafusp in 127 patients with previously treated metastatic uveal melanoma. In one presentation, the researchers highlighted several tumor and circulating biomarkers—including a specific ratio of macrophages to T cells found in pretreatment biopsies and levels of IL6 in the blood—that were predictive of favorable clinical outcomes. In another, they showed



Uveal melanoma.

that tebentafusp triggered transient increases in assorted inflammatory cytokines and chemokines in the blood. The drug also changed the tumor microenvironment to promote cytotoxic CD8+ T-cell infiltration.

"We can redirect T cells and convert immune deserts into very active immune environments," Berman said.

Despite those beneficial immune effects, very few patients experienced radiographic responses in any of the trials—just 5% in the second-line study and 9% in the pivotal first-line one. Many more patients achieved stable disease. Even among those for whom disease progression was the best outcome, a landmark analysis 100 days post-treatment revealed a pronounced survival benefit with tebentafusp, with the risk of death down 60% compared with patients who received other therapies.

The bottom line: "The response rate is not particularly high," Lutzky said, "but the survival data are really amazing." –*Elie Dolgin* ■

Engineering a Next-Gen IL2 Therapy

Aldesleukin, a recombinant form of the cytokine IL2, has been approved by the FDA for metastatic melanoma and renal cell carcinoma since the 1990s. However, its early promise has been hampered by substantial toxicity and suboptimal efficacy, prompting the development of next-generation IL2-based treatments intended to circumvent side effects and enhance antitumor activity.

"During the last two to three decades, people have tried to improve