New Drugs in Oncology

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The 2024 American Society of Clinical Oncology (ASCO) Annual Meeting showcased groundbreaking advancements in oncology, with notable sessions led by renowned experts in the field. The Meeting showcased sessions on new drugs that are transforming the landscape of cancer therapy, offering new hope to patients worldwide.

NIROGACESTAT IN DESMOID TUMORS

Mrinal Gounder, Memorial Sloan Kettering Cancer Center, New York, USA, presented nirogacestat as a newly FDA-approved treatment for desmoid tumors in November 2023. Desmoid tumors are non-cancerous but locally aggressive connective tissue growths, often occurring in the abdomen, arms, and legs, affecting about 2–4 individuals per million annually. They can cause pain, immobility, and complications like bowel obstruction, but do not metastasize and rarely cause mortality.

Gounder noted: "In the last 5–6 years, surgery is no longer the primary treatment for desmoid tumors, due to causing more adverse effects and mortality than the disease itself." However, only about 20% of desmoid tumors can spontaneously regress/resolve in a select few patients. Gounder continued by quoting findings from a study by Colombo et al.,[1] which assessed the behavior of primary sporadic desmoid fibromatosis managed by active surveillance. The primary endpoint was progression-free survival (PFS) at 3 years, with treatment-free survival (TFS) also analyzed. Results showed that 39% of patients experienced disease progression, while spontaneous regression was observed in 25% initially, and in 31% after progression. PFS at 36 months was 54.5%, and TFS was 65.9%. Larger tumor size, extremity location, and *S45F* mutation were associated with shorter TFS, suggesting that active surveillance is viable but requires careful monitoring of certain risk factors.[1]

> **In the last 5–6 years, surgery is no longer the primary treatment for desmoid tumors**

Gounder continued by describing the mechanism of action of the drug, highlighting one of his own studies that compared the efficacy, safety, and tolerability of nirogacestat versus placebo in patients with progressing desmoid tumors. Nirogacestat is a gamma secretase inhibitor that disrupts the dysregulated Notch signaling in desmoid tumors. In the Phase III trial, nirogacestat significantly improved PFS and quality of life (QoL) compared to placebo, with a hazard ratio of 0.29. At 2 years, 76% of nirogacestat patients were event-free compared to 44% for placebo. The drug also demonstrated higher response rates and symptom relief across various subgroups, including those with prior chemotherapy or tyrosine kinase inhibitor treatment.[2]

Common side effects include diarrhea, nausea, rash, and fatigue, with unique

concerns such as ovarian toxicity in women. Gounder recommended regular monitoring of hormone levels and potential fertility preservation for female patients. Other side effects like nasal congestion, skin rash, and diarrhea can be managed with dose adjustments and supportive care.

Nirogacestat is the only FDA-approved drug for the treatment of desmoid tumors and is effective in first or subsequent lines of therapy. The drug offers a significant advancement in the treatment of desmoid tumors, emphasizing improved QoL and symptom management.

FRUQUINTINIB IN METASTATIC COLORECTAL CANCER

Cathy Eng, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, USA, presented fruquintinib, a selective oral inhibitor of vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3, as a new treatment for colorectal cancer (CRC), approved by the FDA in November 2023. This approval followed previous treatments with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapy, anti-VEGF therapy, and, for *RAS* wild-type metastatic CRC, anti-EGFR therapy. Indicated for third-line or later settings in unresectable metastatic colorectal carcinoma, fruquintinib's approval is based on improved overall survival (OS). The current 5-year survival rate for metastatic colorectal carcinoma patients is 15%.

Eng highlighted fruquintinib's mechanism, which inhibits VEGFR to impact angiogenesis, proliferation, and survival. The current FDA indication is based on two prior Phase III trials. The first one was the FRESCO study, conducted in China, which demonstrated a median OS increase from 6.6 to 9.3 months;[3] while another FRESCO-2 study showed a median OS improvement from 4.8 to 7.4 months, confirming significant survival benefits in heavily pre-treated patients.[4] She also highlighted the health-related QoL findings from FRESCO-2, showing that fruquintinib did not negatively impact health-related QoL and improved the time to deterioration in health utility.

To highlight the potential clinical utilization of fruquitinib, Eng described a case study of one of a 56-year-old woman who presented with a history of unresectable, microsatellite-stable, *RAS* mutant tumor type metastatic CRC, who had previously received FOLFOX+ bevacizumab, with residual Grade 2 neuropathy and FOLFRI+ bevacizumab, and who was seeking new treatment options. Her Eastern Cooperative Oncology Group (ECOG) performance status was 1, and laboratory tests were within normal limits. After consulting with the patient and advising her of different treatments and associated side effects, the patient opted for treatment with fruquitinib at 5 mg daily. However, after 3 months of treatment, the patient reported increased discomfort of her left thumb and her right heel during cycle three of Week 2. She was started on emollients and proceeded with a 1-week treatment delay. The patient is currently on cycle four and reports no residual hand-foot skin reactions. The patient decided not to decrease her dose as symptoms resided and opted to continue therapy.

BELZUTIFAN FOR ADVANCED RENAL CELL CARCINOMA

Eric Jonasch, Department of Genitourinary Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, presented belzutifan as a new treatment for advanced renal cell carcinoma (RCC). Belzutifan is an oral inhibitor of hypoxia-inducible factor 2 alpha approved for the treatment of von Hippel-Lindau disease and RCC following prior treatment with immune checkpoint inhibitors and tyrosine kinase inhibitors.

Jonash described a case study of a 64-year-old woman with metastatic clear cell RCC who underwent nephrectomy for T3a Grade 3 clear cell carcinoma but developed new pulmonary nodules 18 months later. She was initially treated with ipilimumab and nivolumab. However, post-treatment she experienced regrowth of lung nodules and mediastinal adenopathy after 15 months. Cabozantinib was administered as a second-line treatment, which worked initially, but after 9 months she experienced progression in the lung once again. Jonash identified belzutifan as a further treatment option for this patient. He mentioned results from the Phase III LITESPARK-005 study by Albiges et al.,[5] which showed that belzutifan demonstrated significant antitumor activity in advanced clear cell renal cell carcinoma, and significantly improved PFS and objective response rate compared to everolimus, with more patients remaining progression-free at 12 and 18 months. The study showed complete responses in 3.5% of the belzutifan group versus none in the everolimus group. Additionally, belzutifan presented with a better safety profile, with fewer discontinuations in the belzutifan group versus everolimus.[5]

> **Fruquintinib did not negatively impact health-related QoL and improved the time to deterioration in health utility**

Jonash went on to describe some notable adverse effects of belzutifan and everolimus, such as anemia and fatigue, which are an expected side effect of the drug; however, he also pointed out that hypoxia is a side effect that physicians need to be aware of.

To further underline this, he described another clinical case where the patient began treatment with belzutifan at 120 mg daily and was instructed to monitor their oxygen saturation. One week after treatment initiation, the patient noticed changes in their oxygen saturation; Oxygen saturation at rest dropped from a baseline of 95% to 87%, but rose above 90% with physical activity. After a short break from belzutifan, and subsequent dose reduction to 80 mg daily, the patient's oxygen saturation returned to above 90%.

CONCLUSION

This insightful session showcased how emerging drugs like nirogacestat, fruquintinib, and belzutifan can advance treatments in oncology, offering improved PFS and QoL, and effective management of side effects for various cancers. Nirogacestat provides a novel approach in the treatment of desmoid tumors, fruquintinib extends survival in patients with metastatic CRC, and belzutifan offers a promising option for advanced RCC.

References

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