## Adagrasib Data Create Buzz at ESMO

In a phase I/II clinical trial, the KRAS$^{G12C}$ inhibitor adagrasib (MRTX849; Mirati) demonstrated encouraging clinical activity against metastatic colorectal cancer, both as a monotherapy and when combined with the EGFR inhibitor cetuximab (Erbitux; Lilly), with the drug duo yielding a disease control rate (DCR) of 100%.

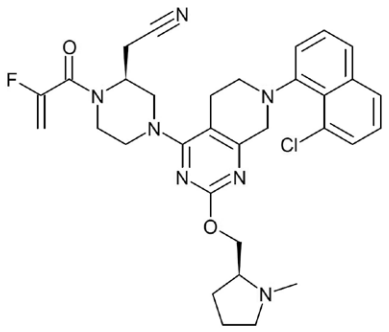
The findings were presented by Jared Weiss, MD, of the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill, at the 2021 European Society for Medical Oncology (ESMO) Congress, held September 16–21.

Like Amgen's KRAS$^{G12C}$-selective drug sotorasib (Lumakras), adagrasib irreversibly and selectively binds mutant KRAS$^{G12C}$ in its inactive, GDP-bound state. In addition, "preclinical data show that EGFR signaling is the dominant method of colorectal cancer resistance to KRAS$^{G12C}$ inhibitors," explained Weiss.

To test the hypothesis that combining adagrasib with cetuximab might enhance inhibition of KRAS-dependent signaling, researchers launched the phase I/II KRYSTAL-1 study, enrolling 46 patients with previously treated metastatic colorectal cancer and a *KRAS*$^{G12C}$ mutation who received adagrasib monotherapy. Weiss reported that after a median follow-up of 8.9 months, 10 of 45 evaluable patients had responded to adagrasib; stable disease was observed in 29 more patients, yielding a DCR of 87%. The median duration of response (DOR) was 4.2 months, and progression-free survival (PFS) was 5.6 months. At the time of data analysis, 18 of the 45 patients (40%) remained on treatment.

For 28 patients enrolled in the adagrasib plus cetuximab arm, after a median follow-up of 7 months, the response rate was 39% (11/28). Stable disease was observed in 61% of patients (17/28). The DCR was 100%. At the time of data analysis, 20 of the 28 patients (71%) were still receiving the drug combination.

Among patients given adagrasib alone, 91% experienced adverse events—with 30% experiencing grade 3 or 4 adverse events—most commonly diarrhea, nausea, fatigue, and vomiting. No patients discontinued treatment. All patients receiving the drug duo reported adverse events—with 16% experiencing grade 3 or 4 adverse events—mostly the same as with adagrasib monotherapy—in addition to skin-related problems, such as dermatitis and rash, due to EGFR inhibition. As a result, 6% of patients in this group discontinued therapy.




Structure of adagrasib.

Thus, "adagrasib is tolerable and has a manageable safety profile, both as a monotherapy and combined with cetuximab," said Weiss.

Study discussant Federica Di Nicolantonio, PhD, of the University of Torino and Candiolo Cancer Center in Italy, said Weiss presented "excellent and exciting data." However, she noted that PFS for the combination arm was not yet available.

Di Nicolantonio also related some findings from studies of sotorasib. In the CodeBreak-100 trial testing sotorasib monotherapy, researchers observed a response rate of 12%, compared with 22% for adagrasib monotherapy in KRYSTAL-1. Prior to ESMO, Amgen announced that when sotorasib was combined with its EGFR inhibitor panitumumab (Vectibix) in the CodeBreak-101 trial, the DCR was 81% in 26 patients, compared with 100% in KRYSTAL-1. However, different trial protocols and patient populations make accurate cross-trial comparisons difficult.

The studies' researchers reported no apparent associations between drug responses and molecular status, such as *EGFR* amplification or *BRAF* V600E, *TP53*, or *PIK3CA* mutations, in exploratory analyses of the monotherapies or combinations. "Additional analyses should be carried out to explore features that are relevant to the biology of metastatic CRCs [colorectal cancers]," Di Nicolantonio said. "This would include transcriptomics, methylomes, immunoscore, and maybe the presence of specific microbiota, which could affect response to KRAS$^{G12C}$ inhibitors." *–Suzanne Rose* ■

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## Trastuzumab Deruxtecan Data Impresses at ESMO

Antibody–drug conjugates (ADC) are taking center stage as second- and third-line treatments for HER2-positive metastatic breast cancer. However, a dearth of data limits direct comparisons of the safety and efficacy of ADCs—even the original HER2-targeting ADC trastuzumab emtansine (T-DM1; Kadcyla; Roche) and the newer trastuzumab deruxtecan (T-DXd; Enhertu; AstraZeneca, Daiichi Sankyo).

Early results of DESTINY-Breast03, a multinational, randomized, phase III trial comparing T-DM1 with T-DXd as a second-line treatment for patients with inoperable or metastatic HER2-positive breast cancer, were released at the 2021 European Society of Medical Oncology (ESMO) Congress, held September 16–21. The study—the first randomized trial of T-DXd, and the first to compare two ADCs in any malignancy—could change standard of care.

The two ADCs are superficially similar but exhibit several differences. Although both use the HER2 antibody trastuzumab to target malignant cells, T-DXd carries approximately eight drug molecules per antibody, whereas T-DM1 ferries about 3.5 drug molecules per antibody. Each ADC boasts a different drug, with T-DXd toting a topoisomerase I inhibitor not commonly used for breast cancer, and T-DM1 bringing an antimicrotubule agent. Additionally, the linkers connecting the drug to the antibody in T-DXd have been engineered to be cleavable by tumor cells, which can release