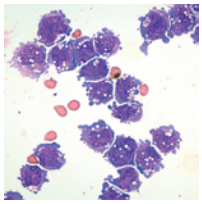
Lymphoma

Major Finding: LMO2 expression correlated with increased response to olaparib and olaparib with R-CHOP.

Mechanism: LMO2-mediated homologous recombination defects increased DNA double-strand breaks in highly LMO2-expressing cells.

Impact: Clinical trials of PARP inhibitors in patients with highly LMO2-expressing cancers are warranted.

HIGH LMO2 EXPRESSION CONFERS SENSITIVITY TO PARP INHIBITION IN DLBCL



High expression of LIM-domain only 2 (LMO2) is one of the strongest biomarkers predicting longer survival in diffuse large B-cell lymphomas (DLBCL), but the biological significance of LMO2 expression is not known. Parvin, Ramirez-Labrada, and colleagues found that patient-derived DLBCLs and DLBCL lines that highly express LMO2 protein had increased DNA double-strand breaks (DSB). Induction of high LMO2 expression in DLBCL lines with low LMO2 expression led to an increase in DNA DSBs, whereas LMO2 knockdown in lines with higher LMO2 expression caused a decrease in DNA DSBs. LMO2 protein expression caused deficiencies in homologous recombination (HR)–based DSB repair mechanisms; for example, LMO2 protein expression reduced BRCA1- and RAD51-associated DNA-damage foci. LMO2 appeared to form a complex with the HR inhibitor 53BP1 at sites of HR-mediated DNA DSB repair, and 53BP1 was required for LMO2's inhibition of HR. Treatment with the PARP inhibitor olaparib, which stalls replication-fork progression and triggers a DNA-damage response, led to a decrease in proliferation and an increase in apoptosis in DLBCL lines that highly expressed LMO2. This result was also noted in T-cell acute lymphoblastic leukemia (T-ALL) cell lines, hinting at the potential broader relevance of the finding. The reduced proliferation of highly LMO2-expressing DLBCL lines observed with olaparib was increased when the drug was given in combination with doxorubicin, and this was also the case in patient-derived DLBCL, follicular lymphoma, and T-ALL cells, consistent with the idea that high LMO2 levels inhibit HR-mediated DNA DSB repair. In mouse models of DLBCL using cell lines and patient-derived xenografts, response to treatment with olaparib was greatly increased in mice with tumors with high expression of LMO2, and response to treatment with olaparib combined with standard R-CHOP immunochemotherapy was greater than the response to either agent alone. Collectively, these results suggest that clinical trials of PARP inhibitors in highly LMO2-expressing cancers—which are not limited to DLBCL and include some breast and prostate cancers—may be fruitful. ■

Parvin S, Ramirez-Labrada A, Aumann S, Lu X, Weich N, Santiago G, et al. LMO2 confers synthetic lethality to PARP inhibition in DLBCL. Cancer Cell 2019 Aug 22 [Epub ahead of print].

Clinical Trials

Major Finding: A phase I trial of the FGFR inhibitor rogaratinib showed safety and efficacy in advanced cancers.

Concept: Tumor overexpression of *FGFR* mRNA correlated with enhanced treatment response.

Impact: This trial and others on rogaratinib are ongoing; *FGFR* expression may be a useful biomarker.

SAFETY AND PRELIMINARY EVIDENCE OF EFFICACY SHOWN FOR ROGARATINIB

Inhibitors of the fibroblast growth factor receptors (FGFR) have shown promise in several cancers, but their effectiveness appears limited to cases with rare genetic *FGFR* aberrations. Schuler and colleagues report findings from an ongoing first-in-human phase I dose-escalation and dose-expansion study of the pan-FGFR inhibitor rogaratinib in 126 adults (91 [72%] male; 35 [28%] female) with advanced cancers. The dose-escalation phase involved 23 patients, and the dose-expansion phase involved 103 patients with tumors that overexpressed *FGFR* mRNA; these patients had urothelial carcinoma (52 patients), head and neck squamous cell carcinoma (8 patients), non–small cell lung cancer (20 patients), and other solid tumor types (23 patients). The primary endpoints were determination of safety and tolerability, maximum tolerated dose and dose-related toxicities, and recommended dose for a phase II trial. Fifteen of 100 evaluable patients (15%) had objective responses, as did 10 of 15 patients (67%) with *FGFR*-overexpressing tumors without any apparent genetic *FGFR* aberrations. Dose-limiting toxicities were not detected and the maximum tolerated dose was not reached. The most common adverse effects among all 126 patients were hyperphosphatemia (71 patients; 61%), diarrhea (65 patients; 52%), and decreased appetite (48 patients; 38%). Fatigue (11 patients; 9%) and asymptomatic increased lipase (10 patients; 8%) were the most common grade 3–4 adverse effects. Five patients exhibited severe adverse effects, including decreased appetite with diarrhea, acute kidney injury, hypoglycemia, retinopathy, and vomiting; six patients (all in the dose-expansion phase) permanently discontinued study treatment due to adverse effects. Of the 22 patients who died during the study or within 30 days of treatment discontinuation, no deaths were determined to be due to treatment. These results indicate that rogaratinib is safe, tolerable, and exhibits preliminary evidence of efficacy in a variety of cancer subtypes and suggest that *FGFR* mRNA expression level, in addition to *FGFR* mutation status, may be a useful biomarker for selecting patients for FGFR-inhibitor therapy. ■

Schuler M, Cho BC, Sayehli CM, Navarro A, Soo RA, Richly H, et al. Rogaratinib in patients with advanced cancers selected by FGFR mRNA expression: a phase 1 dose-escalation and dose-expansion study. Lancet Oncol 2019 Aug 9 [Epub ahead of print].