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Summary

CCC: Molecular targeted therapies

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UEG Week Berlin 2025 | Presentation

Digestive Oncology | Hepatobiliary | Mechanisms & Personalised Medicine | Radiology & Imaging

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The speaker reviewed targeted therapies for cholangiocarcinoma, emphasizing the importance of early comprehensive molecular profiling to identify actionable alterations present in approximately 40% of intrahepatic cases, with multiple approved therapies now available for FGFR2 fusions, IDH1 mutations, HER2 overexpression, and BRAF mutations.

KEY POINTS

- The speaker stated that immunotherapy-based combinations are the established first-line treatment with modest benefit confirmed in two phase 3 studies with pembrolizumab, though biomarkers for patient selection are not yet available.
- For FGFR2 fusions, detected in around 10% of intrahepatic cholangiocarcinoma, the speaker reported consistent data from phase 2 studies showing high response rates and disease control over 80%, but progression typically occurs after 6 to 12 months due to on-target resistance mutations.
- The speaker described a sequential FGFR-targeted therapy approach starting with first-generation inhibitors like futibatinib or pemigatinib followed by newer-generation agents, with a randomized phase 3 study now evaluating this strategy versus physician's choice in the second-line setting.
- For HER2, the speaker emphasized that only HER2 3-plus patients benefit from treatment, citing zanidatamab data showing response rates of 50% versus 5% and median overall survival of 15 months versus 5 months for 3-plus versus 2-plus expression, and recommended both immunohistochemistry and NGS testing.
- The speaker noted that KRAS G12D mutations occur in up to 14% of extrahepatic cholangiocarcinoma and stated that emerging pan-RAS and G12D inhibitors should be investigated in this disease, while G12C mutations remain extremely rare at around 1%.

– The speaker strongly recommended discussion in a molecular tumor board once profiling is complete, noting that median overall survival remains around one year and that the rapidly evolving treatment landscape requires timely identification of available options including clinical trials.

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