

SPECIAL ARTICLE

ESMO Clinical Practice Guideline interim update on the management of biliary tract cancer

A. Vogel^{1,2,3} & M. Ducreux^{4,5}, on behalf of the ESMO Guidelines Committee*

¹Department of Gastroenterology, Hepatology and Endocrinology, Medical School of Hannover, Hannover, Germany; ²Division of Gastroenterology and Hepatology, Toronto General Hospital, Toronto; ³Division of Medical Oncology, Princess Margaret Cancer Center, Toronto, Canada; ⁴INSERM U1279, Université Paris-Saclay, Villejuif; ⁵Department of Cancer Medicine, Gustave Roussy, Villejuif, France



Available online 17 December 2024

Key words: biliary tract cancer (BTC), guideline, molecular diagnostics, treatment

INTRODUCTION

This interim update provides new recommendations for the following ESMO Clinical Practice Guideline (CPG): Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up.¹

View the original CPG here: <https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/clinical-practice-guideline-biliary-tract-cancer>.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Molecular diagnostics

Biliary tract cancer (BTC), particularly intrahepatic cholangiocarcinomas (CCAs) displaying small duct histology, are enriched for actionable targets [see ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) for further details; also see [Supplementary Table S1](https://doi.org/10.1016/j.esmoop.2024.104003), available at <https://doi.org/10.1016/j.esmoop.2024.104003>]. If not already carried out, molecular profiling is essential to inform treatment options in patients with advanced disease who are starting systemic therapy.

HER2 testing. HER2 alterations, comprising amplifications and mutations, as well as human epidermal growth factor receptor 2 (HER2) protein overexpression, can be found in ~5%-10% of BTC cases, with a higher prevalence observed in extrahepatic CCA and gallbladder carcinoma.^{2,3} HER2 protein overexpression and HER2 gene amplification status are routinely determined through immunohistochemistry (IHC) and FISH, respectively. Next-generation sequencing can

provide comprehensive analysis, encompassing somatic mutations and various copy number alterations (e.g. gain, amplification, loss) in the same assay. Most clinical trials focus on patients with HER2 overexpression and HER2 amplification, yet there are currently no standardised criteria for assessing HER2 status in BTC and no specific test can be recommended. Available evidence suggests that HER2 expression by IHC is best assessed using criteria applied in gastric cancer.⁴

Recommendations

- Molecular profiling is recommended when first-line systemic treatment is initiated in patients with locally advanced, advanced or metastatic disease, particularly in those at high risk of progression or recurrence [I, A].

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

Data from recent studies evaluating the management of non-metastatic BTC that is not suitable for surgery, including hepatic arterial infusion chemotherapy and selective internal radiotherapy, are summarised in [Supplementary Material Section 1](https://doi.org/10.1016/j.esmoop.2024.104003), available at <https://doi.org/10.1016/j.esmoop.2024.104003>.

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

An updated proposed algorithm for the treatment of BTC is shown in [Figure 1](#).

First-line treatment

In KEYNOTE-966, 1069 patients with previously untreated, unresectable, locally advanced or metastatic BTC were randomised to receive cisplatin–gemcitabine–pembrolizumab or cisplatin–gemcitabine–placebo.⁵ The median overall survival (OS) was 12.7 months in the pembrolizumab group versus 10.9 months in the placebo group (hazard ratio 0.83,

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

2059-7029/© 2024 The Author(s). Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

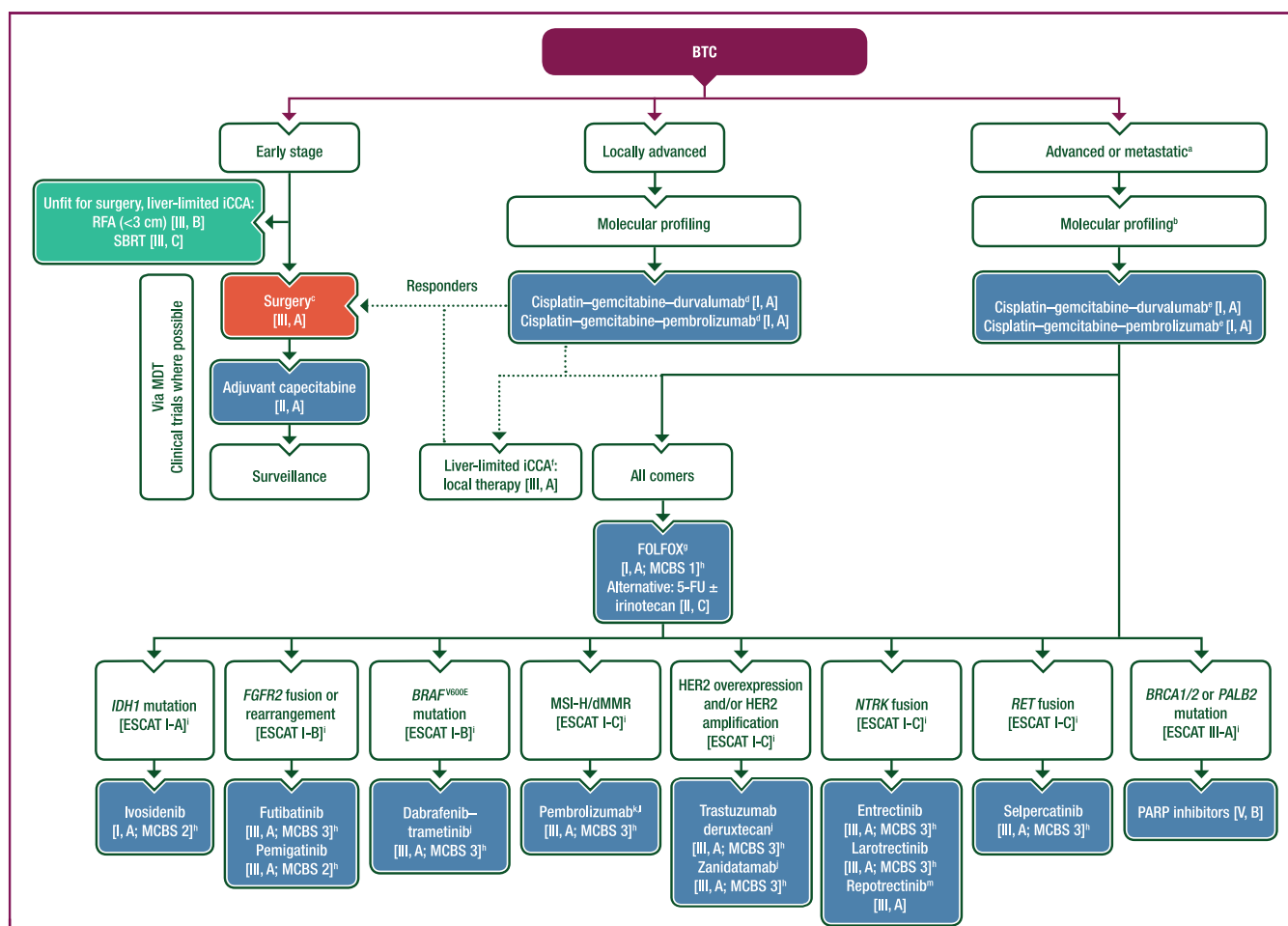


Figure 1. Management of BTC.

Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise, non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed lines: optional therapy.

5-FU, 5-fluorouracil; BTC, biliary tract cancer; CCA, cholangiocarcinoma; ChT, chemotherapy; dMMR, mismatch repair deficiency; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; FOLFOX, 5-fluorouracil–leucovorin–oxaliplatin; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MDT, multidisciplinary team; MSI-H, microsatellite instability-high; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

^aClinical trial recommended when available.

^bMolecular profiling should be carried out before or during first-line therapy. Gene panel should include *IDH1*, *FGFR2*, *BRAF*, *HER2*, *NTRK*, *RET*, *BRCA1/2* and *PALB2* to test for hotspot mutations, but may also include genes such as *c-MET*. The rapidly evolving landscape of drug targets and predictive biomarkers may necessitate larger panels in the future.

^cSpecial considerations: (i) consider need for preoperative drainage; (ii) avoid percutaneous biopsy in resectable distal or perihilar CCA; (iii) assess future liver remnant; (iv) neoadjuvant approach (selected cases); (v) completion surgery for incidental gallbladder carcinoma stage $\geq$ T1b.

^dSalvage surgery or local therapies should be considered in responding patients with initially inoperable disease.

^eConsider gemcitabine monotherapy in patients with compromised performance status or significant debility who are at risk of toxicity from platinum-containing ChT regimens.

^fReconsider surgery in the event of adequate response to treatment.

^gRegimen without a specific licensed indication in BTC.

^hESMO-MCBS v1.1²⁶ was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

ⁱESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.²⁵

^jFDA approved, not EMA approved.

^kAnti-PD-1 therapy is recommended for patients with MSI-H or dMMR who have not been treated with first-line immunotherapy.

^lEMA approved for MSI-H or dMMR BTC; FDA approved for all MSI-H or dMMR solid tumours.

^mNot EMA or FDA approved.

95% confidence interval 0.72–0.95, $P = 0.0034$). Cisplatin–gemcitabine combined with either pembrolizumab or durvalumab is a viable option for first-line treatment. At present, there are no discernible clinical, biochemical or molecular biomarkers, nor any notable differences in efficacy or toxicity, favouring one immune checkpoint inhibitor over the other.

Intensification of chemotherapy with triplet regimens is under evaluation. In Japan, improved objective response rate (ORR) and OS were observed with cisplatin–gemcitabine–S1 versus cisplatin–gemcitabine in the phase III KHBO1401-MITSUBA trial.⁶ By contrast, modified 5-fluorouracil (5-FU)–leucovorin–irinotecan–oxaliplatin

(mFOLFIRINOX; phase II PRODIGE 38 AMEBICA study) and cisplatin–gemcitabine–nab-paclitaxel (phase III SWOG 1815 study) were not superior to cisplatin–gemcitabine in advanced BTC.^{7,8} Higher rates of treatment-related toxicity are observed with the addition of a third cytotoxic agent to gemcitabine–cisplatin in all of these regimens.

Second- and later-line treatment

FGFR2 fusions and rearrangements. Consistent with the nomination of *FGFR2* fusions and rearrangements as CCA drivers, phase II clinical trials have documented clinical efficacy of fibroblast growth factor receptor inhibitors in patients with *FGFR2* fusion-positive CCA, reporting ORRs of ~21%–42%, median progression-free survival (PFS) of ~7–9 months and median OS of ~17–21 months.^{9–13} In the FIGHT-202 study, pemigatinib achieved an ORR of 37.0%, median PFS of 7.0 months and median OS of 17.5 months.⁹ In the FOENIX study, futibatinib achieved an ORR of 42%, median PFS of 9.0 months and median OS of 21.7 months.¹⁰ These findings led to both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approval of pemigatinib and futibatinib.

HER2. In the phase II MyPathway basket trial, pertuzumab–trastuzumab achieved an ORR of 23%, median PFS of 4.7 months and median OS of 12.9 months.¹⁴ The combination of 5-FU–leucovorin–oxaliplatin with trastuzumab as a second- or third-line treatment for HER2-positive BTC was evaluated in the phase II Korean KCSG-HB19-14 trial; ORR was 29.4%, median PFS was 5.1 months and median OS was 10.7 months.¹⁵ In the phase II HERIZON-BTC-01 trial, zanidatamab achieved an ORR of 41.3% with a median PFS of 5.5 months and a 9-month OS rate of 69.9%.¹⁶ In the phase II DESTINY-PanTumor02 trial, trastuzumab deruxtecan was associated with an investigator-assessed ORR of 56.3% in patients with centrally confirmed IHC 3+ HER2 positivity, with a median PFS of 4.6 months.¹⁷ In the phase II SGNTUC-019 basket trial, tucatinib–trastuzumab achieved an ORR of 46.7%, median PFS of 5.5 months and 12-month OS rate of 53.6%.¹⁸ In the phase II SUMMIT basket study, neratinib was evaluated in *HER2*-mutated advanced BTC; ORR was 16% and median PFS was 2.8 months,¹⁹ suggesting responses may be higher in *HER2*-amplified versus *HER2*-mutated CCA. Zanidatamab is now FDA approved for previously treated, unresectable or metastatic HER2-positive BTC. Trastuzumab deruxtecan has an FDA tumour-agnostic indication in adult patients with unresectable or metastatic HER2-positive solid tumours who have received prior systemic treatment.

Other targetable alterations. *NTRK* fusions occur in <0.1% of BTC cases.^{2,20} They are targetable with specific inhibitors such as larotrectinib,²¹ entrectinib²² and repotrectinib.²³ *RET* fusions can be targeted with selpercatinib.²⁴ Because of the very low prevalence of these alterations, the respective inhibitors have only been evaluated in basket trials.

Recommendations

First-line treatment

- Cisplatin–gemcitabine–durvalumab and cisplatin–gemcitabine–pembrolizumab are recommended as first-line therapy [I, A].

Second- and later-line treatment

- Futibatinib [ESMO-Magnitude of Clinical Benefit (MCBS) v1.1 score: 3] and pemigatinib (ESMO-MCBS v1.1 score: 2) are recommended in patients with *FGFR2* fusions or rearrangements who have progressed after one or more prior lines of systemic therapy [III, A; ESCAT score: I-B].
- Trastuzumab deruxtecan should be considered in patients with HER2 overexpression and/or *HER2* amplification who have progressed on or are intolerant to prior treatment [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C; FDA approved, not EMA approved].
- Zanidatamab is recommended in patients with previously treated HER2-positive disease [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C; FDA approved, not EMA approved].
- Entrectinib (ESMO-MCBS v1.1 score: 3), larotrectinib (ESMO-MCBS v1.1 score: 3) and repotrectinib (not EMA or FDA approved) are recommended in patients with *NTRK* fusions who have progressed on or are intolerant to prior treatment [III, A; ESCAT score: I-C].
- Selpercatinib should be considered in patients with *RET* fusions who have progressed on or are intolerant to prior treatment [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C].

METHODOLOGY

This eUpdate was developed in accordance with the ESMO standard operating procedures for CPG eUpdate development (<http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>). The relevant literature has been selected by the expert authors. A table of ESCAT scores is included in [Supplementary Table S1](https://doi.org/10.1016/j.esmoop.2024.104003), available at <https://doi.org/10.1016/j.esmoop.2024.104003>. ESCAT scores have been defined by the authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.²⁵ A table of ESMO-MCBS scores is included in [Supplementary Table S2](https://doi.org/10.1016/j.esmoop.2024.104003), available at <https://doi.org/10.1016/j.esmoop.2024.104003>. ESMO-MCBS v1.1²⁶ was used to calculate scores for new therapies/indications approved by the EMA or FDA (<https://www.esmo.org/Guidelines/ESMO-MCBS>). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this eUpdate. Levels of evidence and grades of recommendation have been applied using the system shown in [Supplementary Table S3](https://doi.org/10.1016/j.esmoop.2024.104003), available at <https://doi.org/10.1016/j.esmoop.2024.104003>.²⁷ Statements without grading were considered justified standard clinical practice by the authors. For future updates to the

BTC CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: <https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/clinical-practice-guideline-biliary-tract-cancer>.

ACKNOWLEDGEMENTS

J. Bridgewater, J. Edeline, R. K. Kelley, H. J. Klumpen, D. Malka, J. N. Primrose, L. Rimassa, A. Stenzinger and J. W. Valle reviewed the eUpdate and provided valuable input. Manuscript editing support was provided by Ioanna Ntai (ESMO Guidelines staff) and Angela Corstorphine and Sian-Marie Lucas of Kstorfin Medical Communications Ltd (KMC); this support was funded by ESMO. Nathan Cherny, member of the ESMO-MCBS Working Group, and Urania Dafni, Giota Zygoura, Georgia Dimopoulou and Tereza Dellaporta of Frontier Science Foundation Hellas provided a review and validation of the ESMO-MCBS scores. Nicola Latino and Francesca Chiovaro (ESMO Scientific Affairs staff) provided coordination and support of the ESMO-MCBS scoring and Angela Corstorphine and Sian-Marie Lucas of KMC provided medical writing and editing support in the preparation of the ESMO-MCBS table; this support was funded by ESMO. Dr Benedikt Westphalen (ESMO Translational Research and Precision Medicine Working Group) provided validation support for ESCAT scores. Dr Svetlana Jezdic (ESMO Medical Affairs staff) provided coordination and support of the ESCAT scoring.

FUNDING

No external funding has been received for the preparation of this guideline. Production costs have been covered by ESMO from central funds.

DISCLOSURE

AV reports personal fees for advisory board membership from AbbVie, Amgen, AstraZeneca, Boehringer Mannheim, Eisai, Incyte, Ipsen, MSD, Roche, Servier, Taiho and Tyra; personal fees as an invited speaker from AstraZeneca, Bristol Myers Squibb, Eisai, Ipsen, MSD and Roche; and personal fees as a steering committee member from MSD and Roche. MD reports personal fees for advisory board membership from ABCELY, AstraZeneca, Basilea, Bayer, BeiGene, Boehringer, Daiichi Sankyo, GSK, HalioDx, Ipsen, Lilly, MSD, Pierre Fabre, Rafael, Roche, Scandion, Servier and Zymeworks; personal fees as an invited speaker from Amgen, Bayer, BeiGene, Lilly, Merck KGaA, MSD, Pfizer, Pierre Fabre, Roche and Servier; personal stocks in ABCELY; past membership of the Board of Directors for Scandion (resigned 1 July 2024); institutional fees for advisory board membership from AstraZeneca; institutional funding as local principal investigator from Amgen and Rafael; institutional funding from Bayer, Keocyt and Roche; and spouse employment at Sandoz France.

REFERENCES

1. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(2):127-140.
2. Kendre G, Murugesan K, Brummer T, et al. Charting co-mutation patterns associated with actionable drivers in intrahepatic cholangiocarcinoma. *J Hepatol*. 2023;78(3):614-626.
3. Galdy S, Lamarca A, McNamara MG, et al. HER2/HER3 pathway in biliary tract malignancies; systematic review and meta-analysis: a potential therapeutic target? *Cancer Metastasis Rev*. 2017;36(1):141-157.
4. Haffner I, Schierle K, Raimúndez E, et al. HER2 expression, test deviations, and their impact on survival in metastatic gastric cancer: results from the prospective multicenter VARIANZ study. *J Clin Oncol*. 2021;39(13):1468-1478.
5. Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10391):1853-1865.
6. Ioka T, Kanai M, Kobayashi S, et al. Randomized phase III study of gemcitabine, cisplatin plus S-1 versus gemcitabine, cisplatin for advanced biliary tract cancer (KHBO1401- MITSUBA). *J Hepatobiliary Pancreat Sci*. 2023;30(1):102-110.
7. Shroff RT, Guthrie KA, Scott AJ, et al. SWOG 1815: a phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. *J Clin Oncol*. 2023;41(suppl 4):LBA490.
8. Phelip JM, Desrame J, Edeline J, et al. Modified FOLFIRINOX versus CISGEM chemotherapy for patients with advanced biliary tract cancer (PRODIGE 38 AMEBICA): a randomized phase II study. *J Clin Oncol*. 2022;40(3):262-271.
9. Vogel A, Sahai V, Hollebecque A, et al. An open-label study of pemetinib in cholangiocarcinoma: final results from FIGHT-202. *ESMO Open*. 2024;9(6):103488.
10. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. *N Engl J Med*. 2023;388(3):228-239.
11. Pant S, Schuler M, Iyer G, et al. Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): an international, single-arm, phase 2 study. *Lancet Oncol*. 2023;24(8):925-935.
12. Borad M, Javle M, Shaib WL, et al. Efficacy of derazantinib in intrahepatic cholangiocarcinoma (iCCA) patients with FGFR2 fusions, mutations or amplifications. *Ann Oncol*. 2022;33(suppl 7):S567-S568.
13. Javle MM, Abou-Alfa GK, Macarulla T, et al. Efficacy of derazantinib in intrahepatic cholangiocarcinoma patients with FGFR2 mutations or amplifications: interim results from the phase 2 study FIDES-01. *J Clin Oncol*. 2022;40(suppl 4):427.
14. Javle M, Borad MJ, Azad NS, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2021;22(9):1290-1300.
15. Lee CK, Chon HJ, Cheon J, et al. Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14). *Lancet Gastroenterol Hepatol*. 2023;8(1):56-65.
16. Harding JJ, Fan J, Oh DY, et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. *Lancet Oncol*. 2023;24(7):772-782.
17. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol*. 2024;42(1):47-58.
18. Nakamura Y, Mizuno N, Sunakawa Y, et al. Tucatinib and trastuzumab for previously treated human epidermal growth factor receptor 2-positive metastatic biliary tract cancer (SGNTUC-019): a phase II basket study. *J Clin Oncol*. 2023;41(36):5569-5578.

19. Harding JJ, Piha-Paul SA, Shah RH, et al. Antitumour activity of neratinib in patients with HER2-mutant advanced biliary tract cancers. *Nat Commun.* 2023;14(1):630.
20. Westphalen CB, Preinfalk A, Kruger S, et al. Neurotrophic tropomyosin receptor kinase (NTRK) and nerve growth factor (NGF) are not expressed in Caucasian patients with biliary tract cancers: pooled data from three independent cohorts. *Clin Transl Oncol.* 2019;21(8):1108-1111.
21. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol.* 2020;21(4):531-540.
22. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol.* 2020;21(2):271-282.
23. Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: update from the phase I/II TRIDENT-1 trial. *Ann Oncol.* 2023;34(suppl 2):S787-S788.
24. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol.* 2022;23(10):1261-1273.
25. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol.* 2018;29(9):1895-1902.
26. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of clinical benefit scale version 1.1. *Ann Oncol.* 2017;28(10):2340-2366.
27. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2001;33(2):139-144 [adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis.* 1994;18(3):421].