Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Endoscopic radiofrequency ablation combined with gemcitabine, cisplatin, and durvalumab in unresectable biliary tract cancer: a multicenter, prospective, phase II trial

Yasunobu Yamashita
Wakayama Medical University
Tadahisa Inoue
Aichi Medical University
Akiya Nakahata
Wakayama Medical University
Reiko Ahida
Wakayama Medical University
Rena Kitano
Aichi Medical University
Tomoya Kitada
Aichi Medical University
Hirohito Minami
Tokyo Medical University
Ko Tomishima
Juntendo University
Yuichiro Tozuka
Kanagawa Cancer Center
Satoshi Kobayashi
Kanagawa Cancer Center
Atsushi Okuda
Osaka Medical and Pharmaceutical University Hospital
Takeshi Ogura
Osaka Medical and Pharmaceutical University Hospital
Yuri Sakamoto
National Cancer Center Hospital
Susumu Hijioka
National Cancer Center Hospital
Yuki Fujii
Okayama University Hospital

Kazuyuki Matsumoto
Okayama University Hospital
Satoshi Fukuchi
Almeida Memorial Hospital
Ryouta Sagami
Oita University Faculty of Medicine
Noriyuki Hirakawa
Tokyo Medical University Hachioji Medical Center
Katsuya Kitamura
Tokyo Medical University Hachioji Medical Center
Mamoru Takenaka
Kindai University - Faculty of Medicine
Hideyuki Shiomi
Hyogo Medical University
Yuki Tanisaka
Saitama Medical University International Medical Center
Reiko Yamada
Mie University - Graduate School of Medicine
Shinsuke Koshita
Public Interest Incorporated Foundation Sendai City Medical Center
Ryunosuke Hakuta
Tokyo Women's Medical University
Takafumi Mie
Cancer Institute Hospital
Arata Sakai
Kobe University Graduate School of Medicine
Keisuke Hanada
Wakayama Medical University Hospital,
Toshio Shimokawa
Wakayama Medical University Hospital
Shomei Ryozawa
Saitama Medical University International Medical Center
Hiroyuki Isayama
Juntendo University
Takao Itoi
Tokyo Medical University
Masayuki Kitano
kitano@wakayama-med.ac.jp

Wakayama Medical University https://orcid.org/0000-0001-6885-9223

Research Article

Keywords: Immunochemotherapy, endoscopic radiofrequency ablation, malignant biliary tract cancer, safety, efficacy

Posted Date: November 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11755932/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Endoscopic radiofrequency ablation combined with gemcitabine, cisplatin, and durvalumab in unresectable biliary tract cancer: a multicenter, prospective, phase II trial

Yasunobu Yamashita[1], Tadahisa Inoue[2], Akiya Nakahata[1], Reiko Ahida[1], Rena Kitano[2], Tomoya Kitada[2], Hirohito Minami[3], Ko Tomishima[4], Yuichiro Tozuka[5], Satoshi Kobayashi[5], Atsushi Okuda[6], Takeshi Ogura[6], Yuri Sakamoto[7], Susumu Hijioka[7], Yuki Fujii[8], Kazuyuki Matsumoto[8], Satoshi Fukuchi[9], Ryouta Sagami[10], Noriyuki Hirakawa[11], Katsuya Kitamura[11], Mamoru Takenaka[12], Hideyuki Shiomi[13], Yuki Tanisaka[14], Reiko Yamada[15], Shinsuke Koshita[16], Ryunosuke Hakuta[17], Takafumi Mie[18], Arata Sakai[19], Keisuke Hanada[20], Toshio Shimokawa[16], Shomei Ryozawa[14], Hiroyuki Isayama[4], Takao Itoi[3], Masayuki Kitano[1]

1. Second Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan

2. Department of Gastroenterology, Aichi Medical University, Nagakute, Japan

3. Department of Gastroenterology and Hepatology, Tokyo Medical University, Shinjuku-ku, Tokyo, Japan

4. Department of Gastroenterology, Graduate School of Medicine, Juntendo University, Bunkyo-ku, Tokyo, Japan

5. Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Kanagawa, Japan

6. Pancreatobiliary Advanced Medical Center, Osaka Medical and Pharmaceutical University Hospital, Takatsuki, Osaka, Japan

7. Department of Hepatobiliary and Pancreatic Oncology, NCCH - National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

8. Department of Endoscopy, Okayama University Hospital, Okayama, Japan

9. Department of Gastroenterology, Almeida Memorial Hospital, Oita, Japan

10. Department of Advanced Gastrointestinal Cancer Medicine, Oita University Faculty of Medicine, Oita, Japan

11. Department of Gastroenterology and Hepatology, Tokyo Medical University Hachioji Medical Center, Hachioji, Tokyo, Japan

12. Department of Gastroenterology and Hepatology, Kindai University - Faculty of Medicine, Sakai, Osaka, Japan

13. Division of Hepatobiliary and Pancreatic Diseases, School of Medicine, Hyogo Medical University, Nishinomiya, Hyogo, Japan

14. Department of Gastroenterology and Hepatology, Saitama Medical University International Medical Center, Saitama, Japan

15. Department of Gastroenterology, Mie University - Graduate School of Medicine, Tsu, Mie, Japan

16. Department of Gastroenterology, Public Interest Incorporated Foundation Sendai City Medical Center, Sendai, Miyagi, Japan

17. Department of Internal Medicine, Institute of Gastroenterology, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan

18. Department of Hepato-Biliary-Pancreatic Medicine, Cancer Institute Hospital, Koto-ku, Tokyo, Japan

19. Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

20. Clinical Study Support Center, Wakayama Medical University Hospital, Wakayama, Japan

Address for correspondence: Masayuki Kitano, MD PhD

Second Department of Internal Medicine, Wakayama Medical University

811-1, Kimiidera, Wakayama City, Wakayama 641-0012, Japan

Phone: (+81)-73-4472300; Fax: (+81)-73-4453616

Email: kitano@wakayama-med.ac.jp

Running title: Immunochemotherapy with endoscopic RFA for BTC

ABSTRACT

Background Immune checkpoint inhibitors (ICIs) combined with chemotherapy have improved patient outcomes for advanced biliary tract cancer (BTC). Moreover, endoscopic radiofrequency ablation (RFA) may augment antitumor immunity with ICIs via an abscopal effect. We conducted a phase II trial to evaluate the safety, feasibility, and efficacy of endoscopic RFA combined with gemcitabine, cisplatin, and durvalumab (GCD) in unresectable BTC.

Methods Patients with unresectable BTC and biliary stricture were prospectively enrolled from 19 centers between October 2023 and June 2025. Patients received immunochemotherapy (GCD) and endoscopic RFA treatment. The primary endpoint was safety, and the secondary endpoints were progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and disease control rate (DCR).

Results Thirty five patients were analyzed. Serious adverse events (SAEs) occurred in 37.1% (90% CI, 21.5%-55.1%) of the enrolled patients, which indicated that endoscopic RFA combined with GCD was safe because the lower limit of the 90% CI for SAEs was below 48% (margin, 15%) in GCD of previous BTC international clinical trial (TOPAZ-1). Median PFS and OS were 250 (95% CI: 120–392) and 313 (95% CI, 253–450) days, respectively. The ORR and DCR were 22.9% and 77.1%, respectively. The restricted mean survival time (RMST) at 182 days of the present study (182.0 days) for OS was significantly longer than that of GCD in TOPAZ-1 (163.3 days) ($P < 0.0001$).

Conclusions Endoscopic RFA with immunochemotherapy appears safe and feasible, and thus may be promising treatment for unresectable BTC in the future development.

Keywords: Immunochemotherapy, endoscopic radiofrequency ablation, malignant biliary tract cancer, safety, efficacy

Trial registration Japan Registry of Clinical Trials (jRCTs051230119)

Introduction

Biliary tract cancer (BTC), which refers to cancers that arise in the biliary tract, is classified into intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder carcinoma, and ampullary carcinoma. BTC often presents with few symptoms, making diagnosis difficult, and as a result, about 70%–80% of patients with BTC are diagnosed at an advanced, unresectable stage [1].

Chemotherapy with gemcitabine plus cisplatin (GC) has been the standard treatment for unresectable BTC. Recently, a phase III international multicenter clinical trial (TOPAZ-1) was conducted to evaluate the efficacy of adding an immune checkpoint inhibitor (ICI) with durvalumab (D) to GC for unresectable BTC. The results showed that in the G, C, and D (GCD) group, overall survival (OS) was 12.8 months and progression-free survival (PFS) was 7.2 months, whereas in the GC group, OS was 11.5 months and PFS was 5.7 months, demonstrating significantly superior outcomes in the D combination group [2]. Based on these findings, GCD became the first-line regimen for unresectable BTC.

Furthermore, because biliary obstruction occurs as the cancer progresses in BTC, obstructive jaundice is observed in patients with advanced BTC. Therefore, biliary drainage is performed as the first-line treatment to relieve jaundice prior to chemotherapy. Furthermore, a meta-analysis of nine randomized controlled trials [3] and other studies [4–6] reported that OS was significantly longer in patients with BTC treated with stenting combined with endoscopic radiofrequency ablation (RFA) compared with stenting alone. Moreover, adding endoscopic RFA to GC chemotherapy (GCR) has been reported to prolong survival significantly compared with conventional GC chemotherapy [7]. Therefore, endoscopic RFA is expected to be useful in the treatment of

unresectable BTC. However, to our knowledge, no studies have examined endoscopic RFA combined with immunochemotherapy for BTC. Therefore, we designed the present study based on the hypothesis that a treatment regimen combining endoscopic RFA with GCD (GCDR) would be beneficial for patients with unresectable BTC and obstructive jaundice who have undergone biliary drainage. Thus, the aim of the present phase II trial was to evaluate the safety, feasibility, and efficacy of GCDR for unresectable BTC via a comparison with the GCD results in TOPAZ-1.

Patients and Methods

Study design and ethics statement

This open-label, single-arm, multicenter, phase II trial was approved by the Ethics Committee of Wakayama Medical University (W-58) and registered at the Japan Registry of Clinical Trials (jRCTs051230119). The trial was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patient eligibility

Eligibility criteria were based on the TOPAZ-1 trial. The inclusion and exclusion criteria were shown in Supplemental File 1.

Procedures and treatment

Endoscopic RFA

Endoscopic RFA was performed for BTC with either of two types of catheters (Habib EndoHPB; Boston Scientific, Marlborough, MA, USA, and ELRA RF probe; STARmed, Goyang, Korea). The selection of the RFA device was at the discretion of the endoscopist. Endoscopic RFA is performed twice. First endoscopic RFA is performed before GCD administration and second endoscopic RFA is performed on 84 days after the first endoscopic RFA (allowance: –14 to +21 days).

GCD

The date of the first endoscopic RFA was defined as Day 0. Confirmation that the following “Chemotherapy Criteria” were met by Day 14 of the first endoscopic RFA was required before initiating chemotherapy with the

investigational drug (GCD) was administered. If a patient temporarily failed to meet the "Chemotherapy Initiation Criteria" but wished to continue the study treatment, the "Chemotherapy Initiation Criteria" was reevaluated until Day 28 after the first endoscopic RFA, and continuation of the study treatment was permitted if the patient was eligible.

Endpoints

The primary endpoint was incidence of serious adverse events (SAEs), and the secondary endpoints were OS, PFS, overall response rate (ORR), disease control rate (DCR), time to recurrent biliary obstruction (TRBO), and incidence of GCD- and RFA-related AEs (CTCAE v5.0 Grade 3 or higher).

Statistical analysis

The incidence of SAEs was calculated in the efficacy analysis set, together with an exact 90% confidence interval (CI) using the Clopper–Pearson method. The expected SAE incidence was set at 48%, based on the incidence reported in the TOPAZ-1 study of GCD. Safety was considered of concern if the lower limit of the exact 90% CI exceeded 48%. The OS, PFS, and TRBO were estimated using the Kaplan–Meier method. Median survival times and median TRBO were estimated with 95% confidence intervals using the Brookmeyer–Crowley method. Survival probabilities at prespecified time points were estimated with 95% CIs using the delta method with a complementary log–log transformation. The ORR was defined as the proportion of patients with complete or partial response, and DCR as the proportion with complete response, partial response, or stable disease; exact 95% CIs were calculated using the Clopper–Pearson method. AEs related to GCD and RFA-related complications were summarized by frequency and proportion in the safety analysis set, overall and by

CTCAE version 5.0 grade where applicable. As sensitivity analyses, restricted mean survival times (RMSTs) for OS and PFS at 182 and 365 days were estimated with 95% CIs, and RMST differences between the present study and the GCD arm of TOPAZ-1 were calculated. These analyses were repeated among patients who received both endoscopic RFA and GCD. PD-L1 expression was summarized among patients with evaluable immunohistochemical staining, and OS and PFS were descriptively summarized according to PD-L1 expression status using a cutoff of 1%. All statistical analyses were performed using R version 4.4.3 (Integrated Development for R; RStudio, Inc., Boston, MA, USA).

Sample size calculation

In a previous international, randomized, phase III study of the GCD (TOPAZ-1), the incidence of SAEs was 47.3%. Therefore, assuming that the incidence of SAEs with GCD in combination with endoscopic RFA would be similar, the expected incidence in the present study was set at 48%. Under this assumption, the minimum sample size required for the exact confidence interval for a binomial proportion with a confidence level of 90% (corresponding to a one-sided significance level of 5%) to have a one-sided confidence width of 15% was 35 patients. Allowing for approximately 10% ineligible patients, the target sample size was set at 38 patients.

Results

A total of 39 patients with unresectable BTC and obstructive jaundice with biliary stricture were enrolled from 19 centers between October 2023 and June 2025 according to the inclusion and exclusion criteria. Of these, 35 eligible patients were analyzed; those with discontinuation before administration (n = 1), withdrawal of consent (n = 1), violation of inclusion criteria (n = 1), and violation of exclusion criteria (n = 1) were excluded (Figure 1). Baseline characteristics of present study are summarized in Table 1.

The mean age of the 35 patients (20 males and 15 females; 18 with hilar cholangiocarcinoma, 13 with distal biliary carcinomas, and 4 with gallbladder carcinomas) was 71.9 ± 9.7 years (Table 1). SAEs occurred in 37.1% (13/35) of the patients (acute cholangitis, n = 13; stent occlusion, n = 9; cholecystitis, n = 2; febrile neutropenia, n = 2; hypopituitarism, n = 1; liver abscess, n = 1; obstructive jaundice, n = 1; thrombocytopenia, n = 1; neutropenia, n = 1; atrial fibrillation, n = 1; sepsis, n = 1; fever, n = 1; pancreatitis, n = 1, with some overlap; 90% CI: 21.5%–55.1%). Grade 3 or 4 AEs for GCD and RFA occurred in 62.9% (23/35) (Grade 3, n = 16; Grade 4, n = 7) and 25.6% (9/35), respectively. There were no deaths due to GCDR related AEs and no treatment discontinuation of immunochemotherapy due to AEs after RFA.

The median follow-up period in the present study was 247 days (range, 45–600). At the end of the follow-up period, 13 patients (13/35, 37.1%) were still receiving the study treatment (GCDR), and 12 (12/35, 34.5%) had died. The median PFS and OS were 250 (95% CI: 120–392) and 313 (95% CI: 253–450) days, respectively (Figure 2A, B). The ORR and DCR were 22.9% (8/35) (complete response, n = 0; partial response [PR], n = 8) and 77.1% (27/35) (PR, n =8; stable disease, n = 19), respectively (Figure 3).

The RMST at 365 days in the present study and GCD in TOPAZ-1 were 304.0 and 283.4 days for OS and 237.1 and 206.0 days for PFS, respectively, with no significant differences between the two groups ($P = 0.16$ and $P = 0.20$, respectively) (Table 2A). RMST at 182 days in the present study and GCD in TOPAZ-1 were 182.0 and 163.3 days for OS and 147.0 and 144.9 days for PFS, respectively. While no significant difference for PFS between the two groups (P = 0.83), the RMST at 182 days in the present study (182.0 days) for OS was significantly longer than that for GCD in TOPAZ-1 (163.3 days) (P < 0.0001) (Table 2B).

Median time to TRBO before the second endoscopic RFA was 98 days (95% CI: 92–NA days). RBO was confirmed in 11 cases (11/35, 31.4%) by the time of the second endoscopic RFA with 35 plastic stents including nine inside-stents. Median TRBO was 101 days (95%CI: 59-152 days) after the second endoscopic RFA was performed. RBO was confirmed in 23 cases (23/31, 74.2%) after the second endoscopic RFA with 20 plastic stents including four inside-stents and three self-expandable metallic stents. Total RBO after first and second endoscopic RFA was confirmed in 26 cases (26/35, 74.3%).

The PD-L1 expression rate for 23 patients was < 1% (n = 11), 1%–10% (n = 8), 10%–50% (n = 2), and > 50% (n = 1), respectively. Median PFS and OS were 392 days (95% CI: 84–NA) and 458 days (95% CI: 247–NA) for PD-L1 expression (≥ 1%), and 243 (95% CI: 14–NA) and 323 days (95% CI: 202–587) for PD-L1 expression (< 1%), respectively.

Discussion

To the best of our knowledge, this exploratory phase II trial is the first study to evaluate the safety and feasibility of endoscopic RFA combined with immunochemotherapy (GCDR) in unresectable BTC. The present study adopted the same eligibility criteria of GCD in TOPAZ-1 as benchmark and compared the safety, feasibility, and efficacy of GCD treatment with (present study) and without (GCD in TOPAZ-1 as benchmark) additional endoscopic RFA. The results of the primary analysis indicated the feasibility of GCDR. Median PFS in the present study was numerically better to that of GCD in TOPAZ-1. RMST analysis of median OS at 182 days revealed that GCDR was significantly superior to GCD in TOPAZ-1. Therefore, GCDR therapy may be promising treatment for unresectable BTC in the future development.

To our knowledge, only one report has evaluated whether endoscopic RFA combined with chemotherapy (GC) leads to more AEs than chemotherapy alone [7]. That report found no significant difference in safety between the two groups. On the other hand, no studies have been conducted on the safety of endoscopic RFA combined with immunochemotherapy (GCD). Therefore, in the present study, we evaluated safety as the primary endpoint. To allow using AEs with GCD in TOPAZ-1as benchmark, the present study used the same eligibility criteria of the TOPAZ-1 study. In the present study, SAEs occurred in 37.1% (13/35) (90% CI: 21.5%–55.1%) of the enrolled patients. Since TOPAZ-1's SAE is 48% and its margin is set at 15%, adding 15% to TOPAZ-1's SAE (48%) results in a 63% upper limit of the 90% confidence interval. Since the current upper limit (55.1%) falls within this range, safety has been confirmed. Because the lower limit of the 90% CI for SAEs was < 48% in GCD in TOPAZ-1 [2], this result indicated that GCDR does not increase the incidence of SAEs

compared with GCD in TOPAZ-1. No deaths due to GCDR related AEs occurred, and no patients discontinued immunochemotherapy due to AEs after RFA. Therefore, the present results demonstrated the safety of the combination of immunochemotherapy and endoscopic RFA.

Meta-analyses have demonstrated that adding endoscopic RFA to stent placement improves OS in patients with BTC in comparison of stent alone [3, 8]. It has also been reported that endoscopic RFA combined with chemotherapy (GC) improves OS and PFS in comparison of chemotherapy alone (GC). Therefore, endoscopic RFA treatment may improve the prognosis of patients with unresectable BTC. However, there have been no reports on the combination of immunochemotherapy and endoscopic RFA. The present study showed median PFS and OS were 250 (95% CI: 120–392) and 313 (95% CI: 253–450) days, respectively. Regarding GCD in TOPAZ-1, median PFS and OS were 216 (95% CI: 201–222) and 384 (95% CI: 333–420) days, respectively [2]. The median PFS in the present study (GCDR) was longer than that for GCD in TOPAZ-1. RMST analysis at 182 days was performed. The RMST in present study (182.0 days) for OS was significantly longer than that for GCD in TOPAZ-1 (163.3 days) ($P < 0.0001$). Therefore, adding endoscopic RFA to GCD therapy (GCDR) may contribute to an improved prognosis in patients with unresectable BTC. Regarding this point, a phase III trial needs to be conducted to compare efficacy between immunochemotherapy with and without endoscopic RFA. By combining chemotherapy plus ICIs with RFA treatment for BTC, we hypothesized that antigen presentation was enhanced by combining the antigen presentation from tumor cells necrotized by chemotherapy with that from RFA. We further hypothesized that adding ICI therapy would induce stronger immune activity against the tumor, leading to more effective treatment of unresectable BTC at not only the ablation site, but also

the distant metastases through an abscopal effect (Figure 4). The following reports from other fields support our hypothesis. With regard to the relation between the immune system and RFA, the following data have been reported in studies on hepatocellular carcinoma (HCC) [9, 10] and liver metastasis [11]. RFA is an effective treatment for HCC and can also exert an “adjuvant” effect on spontaneous antitumor T-cell responses, as suggested by human and animal studies. The adjuvant effect is thought to depend on the huge amount of necrotic tumor antigen made available to the immune system by HCC thermal ablation. In addition, radiofrequency thermal ablation may result in the release of local stimuli responsible for the activation and maturation of antigen-presenting cells. Therefore, the combination of ICIs and RFA in HCC results in a significant reduction in tumor size compared with either RFA or ICI alone. On the other hand, in terms of combination therapy with radiation and ICIs in lung cancer, efficacy has been observed not only at the site of radiation therapy, but also in distant metastases (abscopal effect) [12, 13].

The present study has several limitations. Fist, the data include only Grade 3 or higher events and SAEs; not all AEs were compiled. Second, in terms of efficacy, a comparison with GCD in TOPAZ-1 was conducted using RMST analysis, but this was not a direct comparison with a randomized controlled trial. The results require further validation in a randomized phase III trial.

In conclusion, endoscopic RFA with immunochemotherapy appears safe and feasible, and may be promising treatment for unresectable BTC in the future development. In the future, we plan to conduct a phase III trial to compare GC with and without endoscopic RFA.

Data Availability Statement

Complete anonymized data, analysis methods, and research materials will be made available to other researchers at the time of publication for 5 years upon reasonable request.

Acknowledgements

None.

Conflict of Interest

M.K is Associate Editor of International Journal of Clinical Oncology. S.K has received honoraria from AstraZeneca K.K and MSD K.K. S.H has received honoraria from AstraZeneca K.K, MSD K.K, Boston scientific Japan K.K, Kaneka medics K.K, and J-MIT K.K. The other authors declare no conflicts of interest regarding the publication of this study.

Funding

This study was funded by AstraZeneca K.K (no grant number). The funder had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; in the preparation, review, and approval of the manuscript; or in the decision to submit the manuscript for publication.

Author contributions

Yasunobu Yamashita and Masayuki Kitano: drafting of the article, conception and design; Yasunobu Yamashita, Keisuke Hanada and Toshio Shimokawa: analysis and interpretation of the data; Tadahisa Inoue, Akiya Nakahata, Reiko Ahida, Rena Kitano, Tomoya Kitada, Hirohito Minami, Ko Tomishima, Yuichiro Tozuka, Satoshi Kobayashi, Atsushi Okuda, Takeshi Ogura, Yuri Sakamoto, Susumu Hijioka, Yuki Fujii, Kazuyuki Matsumoto, Satoshi Fukuchi, Ryouta Sagami, Noriyuki Hirakawa, Katsuya Kitamura, Mamoru Takenaka, Hideyuki Shiomi, Yuki Tanisaka, Reiko Yamada: Data collection; Shinsuke Koshita, Ryunosuke Hakuta, Takafumi Mie, Arata Sakai, Shomei Ryozawa, Hiroyuki Isayama, and Takao Itoi: critical revision of the article for important intellectual content; Masayuki Kitano: final approval of the article.

Ethics Statement

This study was approved by the ethics committee of Wakayama Medical University (W-58) and performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from all patients in this study. This study was registered at the Japan Registry of Clinical Trials (jRCTs051230119).

References

[1] Goetze TO, Roderburg C, Friedrich FW, Trojan J (2024) New perspectives in biliary tract cancers. ESMO Gastrointest Oncol; 5: 100092. https://doi.org/10.1016/j.esmogo.2024.100092

[2] Oh DY, Ruth He A, Qin S, et al (2022) Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 1(8). https://doi.org/10.1056/EVIDoa2200015

[3] Tarar ZI, Farooq U, Gandhi M, et al (2023) Effect of radiofrequency ablation in addition to biliary stent on overall survival and stent patency in malignant biliary obstruction: an updated systematic review and meta-analysis. Eur J Gastroenterol Hepatol 35(6): 646–653. https://doi.org/10.1097/MEG.0000000000002568

[4] Inoue T, Ibusuki M, Kitano R, et al (2023) Endoscopic radiofrequency ablation for ingrowth occlusion after bilateral metal stent placement for malignant hilar biliary obstruction: a prospective pilot study. Gastrointest Endosc 97(2): 282–290. https://doi.org/ 10.1016/j.gie.2022.09.025

[5] Oh D, Chong J, Song TJ, et al (2022) The usefulness of endobiliary radiofrequency ablation before metal stent placement in unresectable malignant hilar obstruction. J Gastroenterol Hepatol 37(11): 2083–2090. https://doi.org/10.1111/jgh.15967

[6] Yang J, Wang J, Zhou H, et al (2018) Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. Endoscopy 50: 751–760. https://doi.org/10.1055/s-0043-124870

[7] Inoue T, Naitoh I, Kitano R, et al (2022) Endobiliary radiofrequency ablation combined with gemcitabine and cisplatin in patients with unresectable extrahepatic cholangiocarcinoma. Curr Oncol 29: 2240–2251. https://doi.org/10.3390/curroncol29040182

[8] Ramai D, Maida M, Smith ER, et al (2025) Endoluminal radiofrequency ablation with stenting versus stenting alone in patients with malignant biliary obstruction: a meta-analysis of randomized trials. Endoscopy 57: 272–281. https://doi.org/10.1055/a-2378-9533

[9] Liang J, Ma M, Feng W, et al (2025) Anti-PD-L1 blockade facilitates antitumor effects of radiofrequency ablation by improving tumor immune microenvironment in hepatocellular carcinoma. Apoptosis 30: 55–68. https://doi.org/10.1007/s10495-024-02019-3

[10] Zerbini A, Pilli M, Fagnoni F, et al (2008) Increased immunostimulatory activity conferred to antigen-presenting cells by exposure to antigen extract from hepatocellular carcinoma after radiofrequency thermal ablation. J Immunother 31(3): 271–282. https://doi.org/10.1097/CJI.0b013e318160ff1c

[11] Shi L, Chen L, Wu C, et al (2016) PD-1 blockade boosts radiofrequency ablation-elicited adaptive immune responses against tumor. Clin Cancer Res 22: 1173–1184. https://doi.org/10.1158/1078-0432.CCR-15-1352

[12] Fiorica F, Tebano U, Gabbani M, et al (2021) Beyond abscopal effect: a meta-analysis of immune checkpoint inhibitors and radiotherapy in advanced non-small cell lung cancer. Cancers (Basel) 13(10): 2352. https://doi.org/10.3390/cancers13102352

[13] Kaufmann J, Trommer M, Rühle A, et al (2026) Radiotherapy in patients with NSCLC developing progressive disease during immune checkpoint inhibition: abscopal responses and survival. Clin Transl Radiat Oncol 58: 101125. https://doi.org/10.1016/j.ctro.2026.101125

Figure legends

Figure. 1 Patient flowchart

FAS, full analysis set; SAS, safety analysis set.

Figure. 2 Survival curve after radiofrequency ablation combined with gemcitabine, cisplatin, and durvalumab

A. Progression-free survival (PFS)

B. Overall survival (OS)

Figure. 3 Waterfall plots for the response to cancer treatment

PD, progressive disease; PR, partial response; SD, stable disease.

Figure. 4 Proposed mechanism of action of radiofrequency ablation combined with immunochemotherapy

We hypothesized that antigen presentation would be enhanced by combining the antigen presentation from tumor cells necrotized by chemotherapy with that from radiofrequency ablation. Moreover, adding immune checkpoint inhibitor therapy in this situation would induce stronger immune activity against the tumor, leading to more effective treatment of unresectable biliary tract cancer at not only the ablation site, but also the distant metastases via an abscopal effect. PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Table 1 Background characteristics of the patients in the present study.

	N = 35
Age (years)	71.9 ± 9.7
Gender	
Male	20 (57.1%)
Female	15 (42.9%)
ECOG	
0	31 (88.6%)
1	4 (11.4%)
2	0 (0%)
Primary tumor site	
Hilar cholangiocarcinoma	18 (51.4%)
Distal cholangiocarcinoma	13 (37.2%)
Gallbladder carcinoma	4 (11.4%)
Disease classification	
Local advanced	20 (57.1%)
Distant metastasis	15 (42.9%)
Bismuth type	
I	4 (11.4%)
II	12 (34.3%)
IIIa	7 (20.0%)
IIIb	8 (22.9%)
Undeterminable	4 (11.4%)

PD-L1	
< 1%	11
≥ 1%	11
Non-examination	13
CEA	48.0 ± 221.1
CA19-9	2041.7 ± 8018.6

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; PD-L1, Programmed death-ligand 1

Table 2. RMST analysis for OS and PFS

A. OS

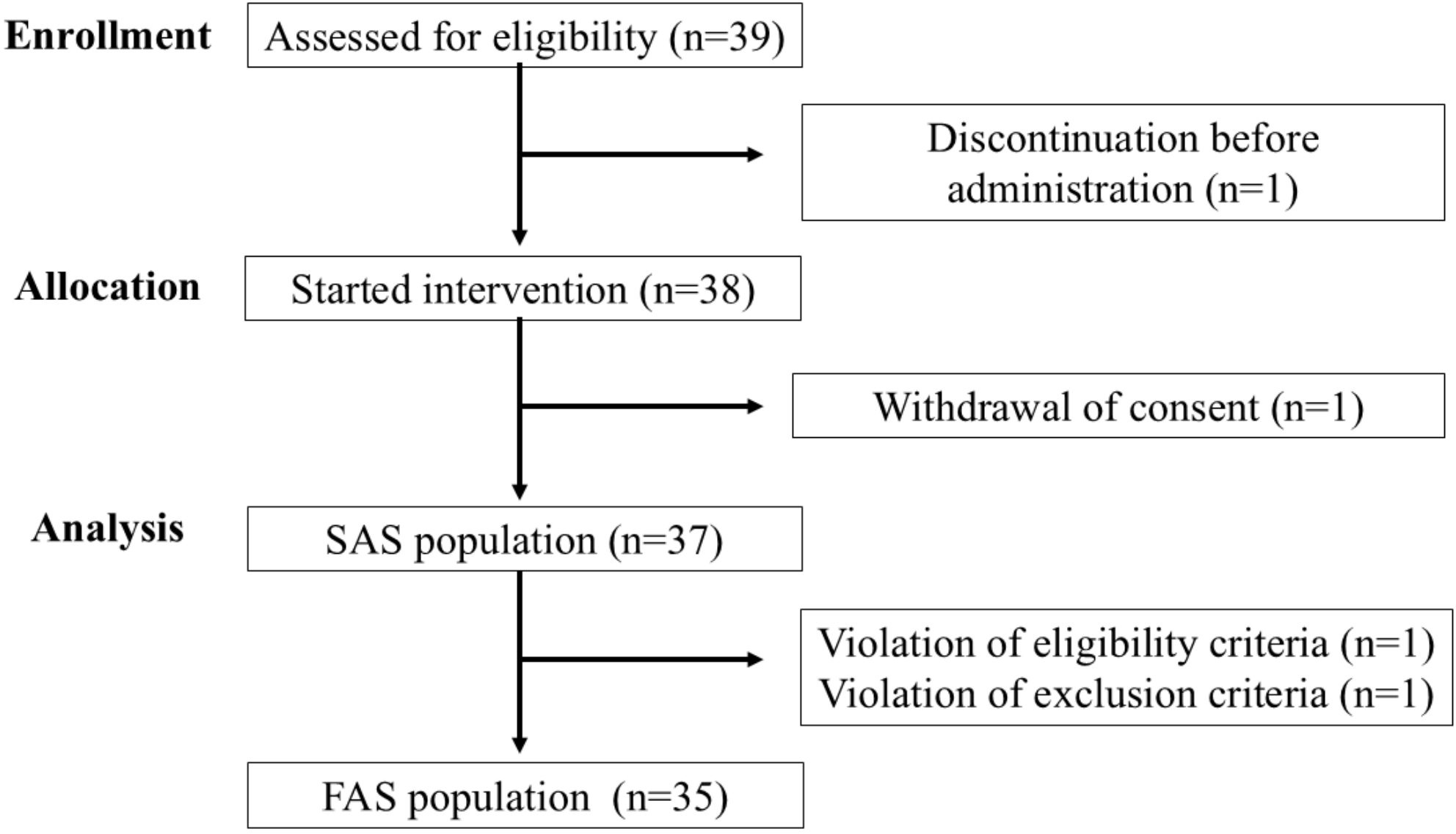
	tau	RMST	[95% CI]	P-value
GCDR	182	182.0	[182, 182]	
TOPAZ-1	182	163.3	[158.6, 168.1]	
GCDR - TOPAZ-1	182	18.7	[13.9, 23.4]	<0.0001
GCDR	365	304.0	[278.6, 329.4]	
TOPAZ-1	365	283.4	[270, 296.8]	
GCDR - TOPAZ-1	365	20.6	[–8.2, 49.3]	0.1603

RMST, restricted mean survival time; OS, overall survival; GCDR, endoscopic radiofrequency ablation (R) combined with gemcitabine (G), cisplatin (C), and durvalumab (D), tau: truncation time

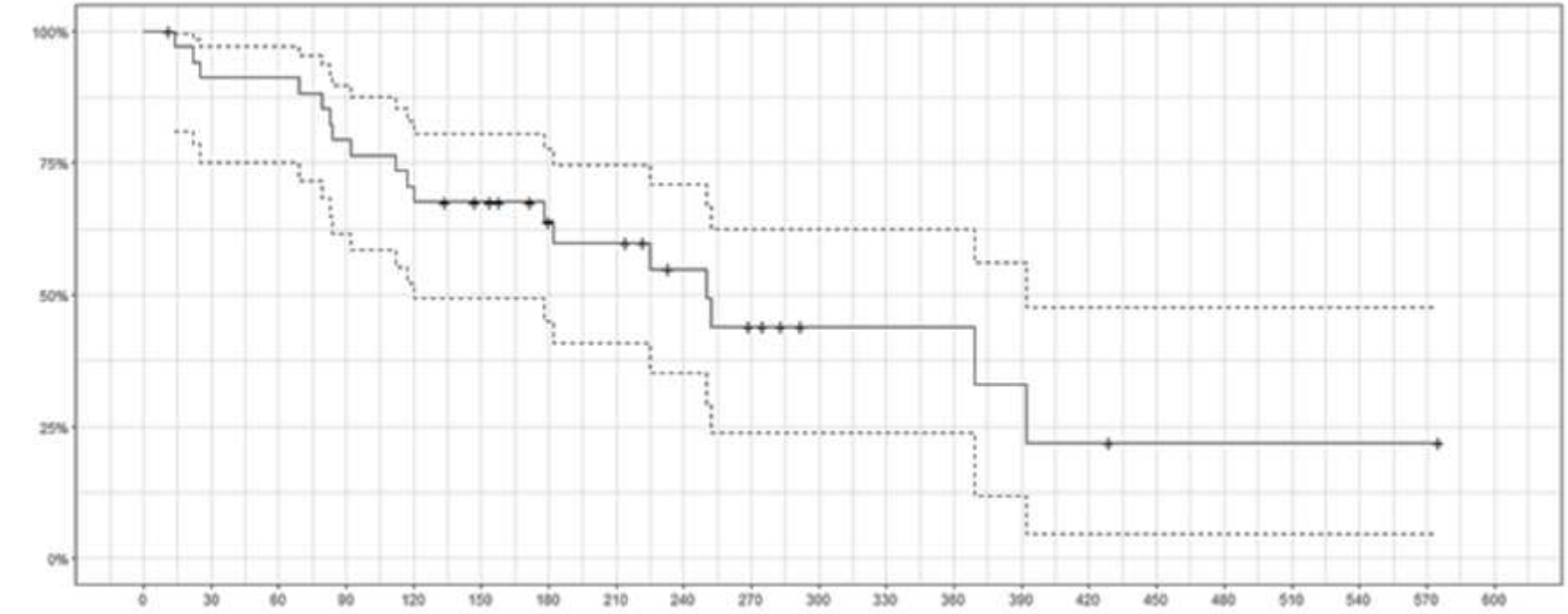
B. PFS

	tau	RMST	[95% CI]	P-value
GCDR	182	147.0	[128.7, 165.3]	
TOPAZ-1	182	144.9	[139.1, 150.7]	
GCDR - TOPAZ-1	182	2.1	[–17.1, 21.3]	0.8311
GCDR	365	237.1	[191.5, 282.7]	
TOPAZ-1	365	206.5	[194.7, 218.3]	
GCDR - TOPAZ-1	365	30.6	[–16.5, 77.7]	0.2032

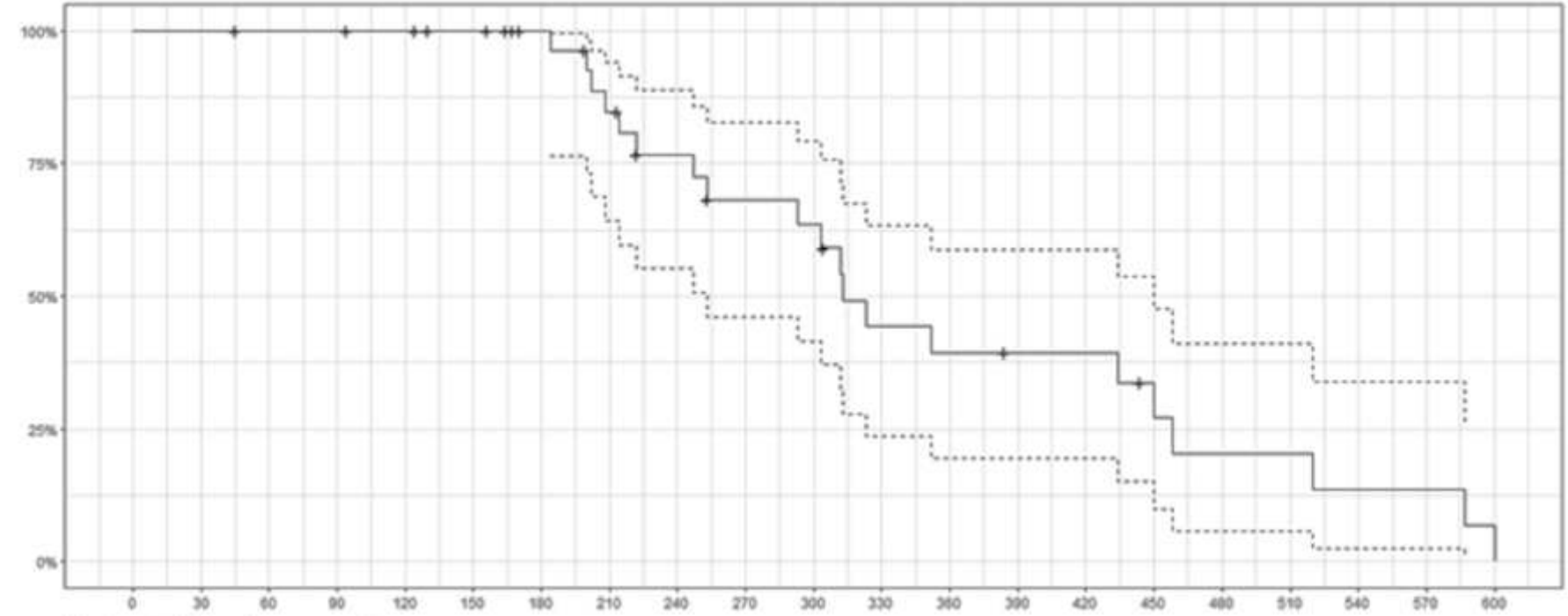
RMST, restricted mean survival time; PFS, progression free survival; GCDR, endoscopic radiofrequency ablation (R) combined with gemcitabine (G), cisplatin (C), and durvalumab (D), CI, confidence interval, tau: truncation time

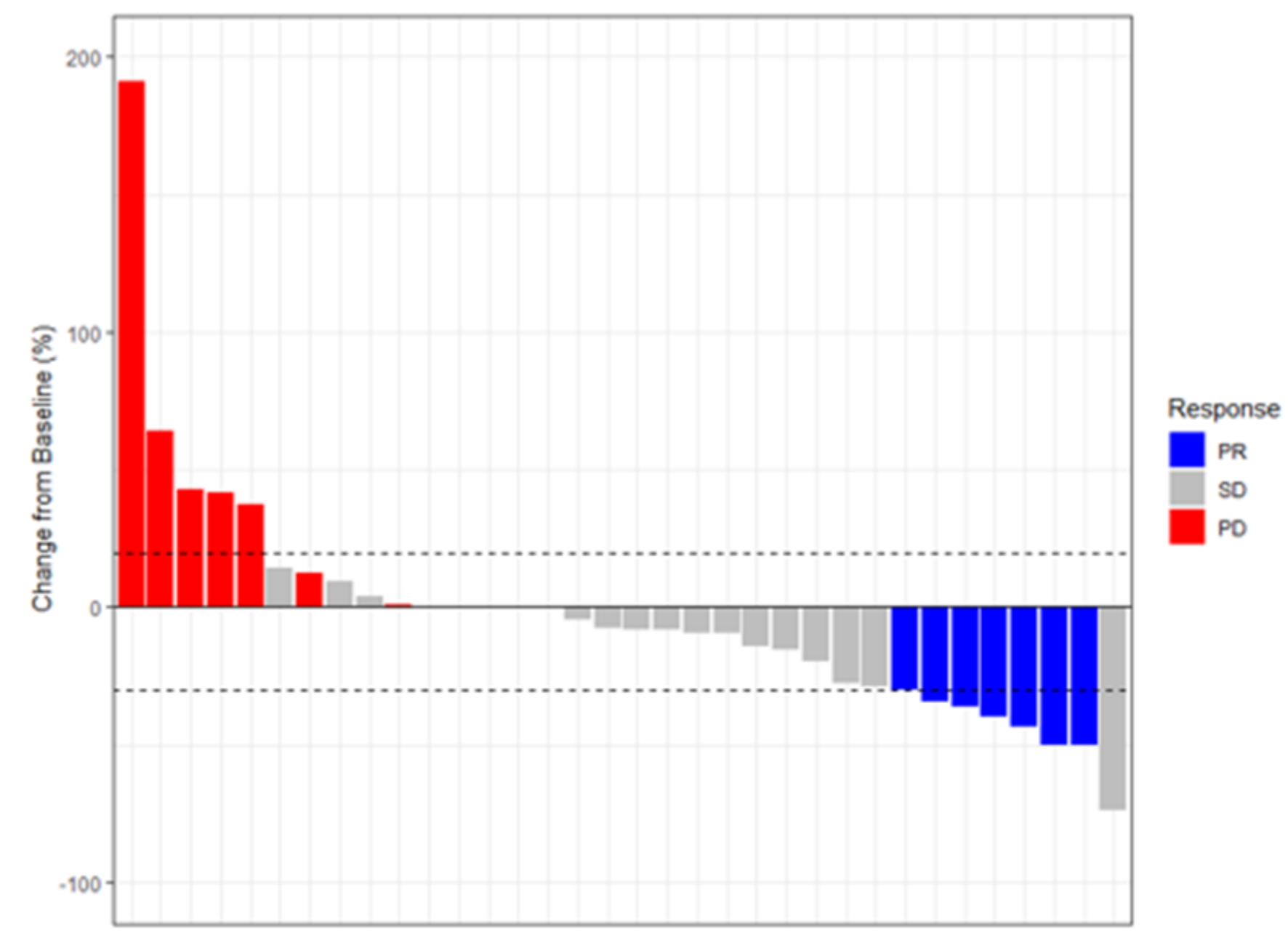

Enrollment
Assessed for eligibility (n=39)
Discontinuation before administration (n=1)
Allocation
Started intervention (n=38)
Withdrawal of consent (n=1)
Analysis
SAS population (n=37)
Violation of eligibility criteria (n=1)
Violation of exclusion criteria (n=1)
FAS population (n=35)

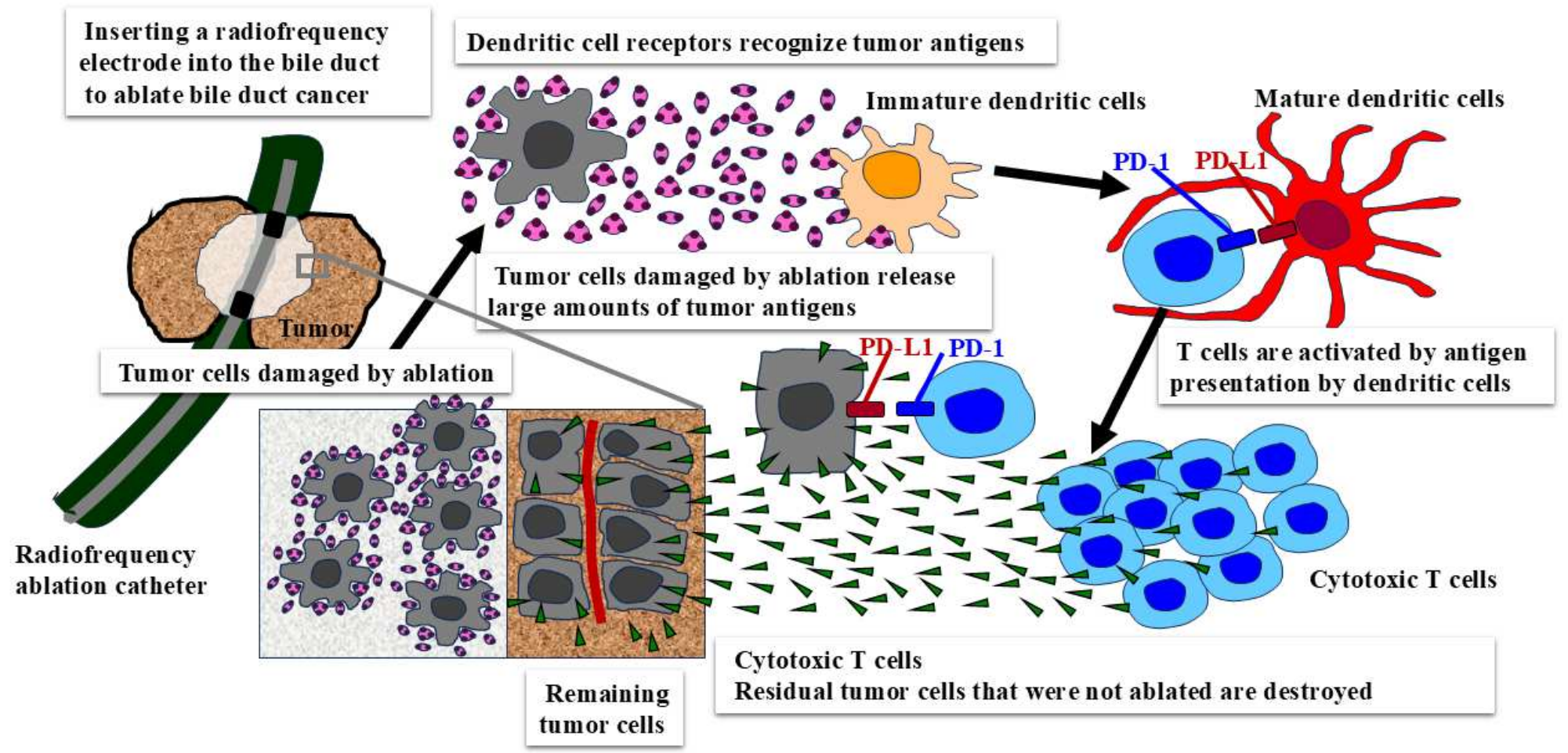
A


100%
75%
50%
25%
0%
0
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
480
510
540
570
600

B


100%
75%
50%
25%
0%
0
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
480
510
540
570
600


200
100
0
-100
Change from Baseline (%)
Response
PR
SD
PD


Inserting a radiofrequency electrode into the bile duct to ablate bile duct cancer
Dendritic cell receptors recognize tumor antigens
Immature dendritic cells
Mature dendritic cells
PD-1
PD-L1
Tumor
Tumor cells damaged by ablation release large amounts of tumor antigens
Tumor cells damaged by ablation
PD-L1
PD-1
T cells are activated by antigen presentation by dendritic cells
Radiofrequency ablation catheter
Cytotoxic T cells
Remaining tumor cells
Cytotoxic T cells
Residual tumor cells that were not ablated are destroyed