Future ONCOLOGY

Plain language summary of the TOPAZ-1 study: durvalumab and chemotherapy for advanced biliary tract cancer

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Summary

What is this summary about?

This is a summary describing the results of a **Phase III** study called TOPAZ-1. The study looked at treatment with durvalumab (a type of **immunotherapy**) and **chemotherapy** to treat participants with advanced biliary tract cancer (BTC). Advanced BTC is usually diagnosed at late stages of disease, when it cannot be cured by surgery. This study included participants with advanced BTC who had not received previous treatment, or had their cancer come back at least 6 months after receiving treatment or surgery that aimed to cure their disease. Participants received treatment with durvalumab and chemotherapy or **placebo** and chemotherapy. The aim of this study was to find out if treatment with durvalumab and chemotherapy could increase the length of time that participants with advanced BTC lived, compared with placebo and chemotherapy.

What were the results of the study?

Participants who took durvalumab and chemotherapy had a 20% lower chance of experiencing death at any point in the study compared with participants who received placebo and chemotherapy. The side effects experienced by participants were similar across treatment groups, and less than 12% of participants in either treatment group had to stop treatment due to **treatment-related side effects**.

What do the results of the study mean?

Overall, these results support durvalumab and chemotherapy as a new treatment option for people with advanced BTCs. Based on the results of this study, durvalumab is now approved for the treatment of adults with advanced BTCs in combination with chemotherapy by government organizations in Europe, the United States and several other countries.

How to say (double click sound icon to play sound)...

- **Durvalumab:** dur-VAL-yoo-mab
- **Gemcitabine:** jem-SY-tuh-been
- **Cisplatin:** sis-PLA-tin

Phase III study: A study that tests the safety, and how well a new treatment works, compared with a standard treatment.

Immunotherapy: Treatment that targets the immune system to help the body fight cancer.

Chemotherapy: A type of cancer treatment that uses drugs to kill cancer cells.

Placebo: An inactive substance that looks the same and is given in the same way as the active treatment being tested.

Treatment-related side effects: An unintended problem that is related to treatment with a drug or other therapy.

Where can I find the original article on which this summary is based?

The original article discussed in this summary, titled "Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer", was published in the *New England Journal of Medicine Evidence* in 2022. This article is available for free at: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200015.

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Who sponsored this study and summary?

The pharmaceutical company AstraZeneca (the manufacturer of durvalumab) funded and was responsible for conducting this study. AstraZeneca also funded this plain language summary.

Who should read this article?

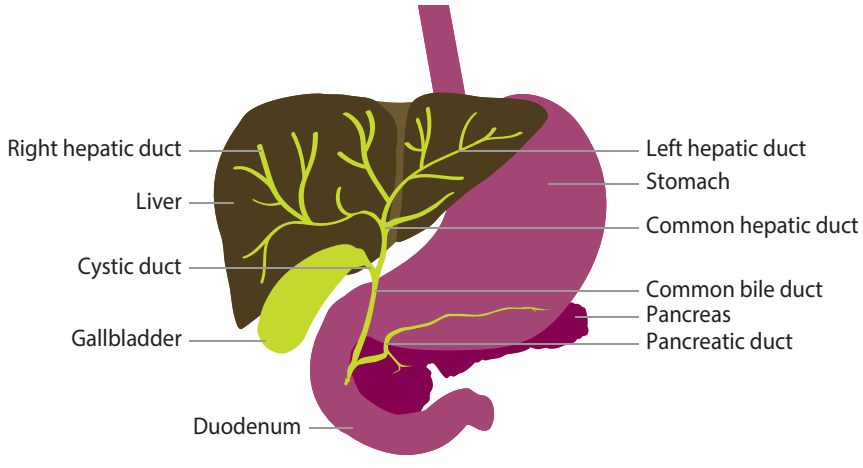
This plain language summary may be helpful for people with BTC and their caregivers, patient advocates, and healthcare professionals. This summary may also be helpful to those who are interested in learning about new treatment advances for BTCs.

What are biliary tract cancers (BTCs) and what are the treatment options?

- The biliary tract is part of the digestive system and includes the gallbladder and bile ducts
- The gallbladder stores **bile**. The bile ducts (including the left and right hepatic ducts, cystic duct, common hepatic duct and common bile duct) carry bile from the liver and gallbladder to the small intestine (duodenum)
- BTCs are a group of cancers that include those developing in the gallbladder (gallbladder cancer), the bile ducts in the liver (intrahepatic cholangiocarcinoma), or the bile ducts not in the liver (extrahepatic cholangiocarcinoma)
- Early stages of BTCs can be treated with surgery but many people are diagnosed at late stages of disease, called advanced BTC, which cannot be cured by surgery
- Historically, the **standard of care** for people with advanced BTCs has consisted of the combination of two chemotherapy drugs, gemcitabine and cisplatin. However, only around 50% of people survive longer than 1 year after treatment with chemotherapy
- New treatment options that could benefit people with advanced BTCs are needed. Immunotherapy is a new type of cancer treatment to be tested in people living with advanced BTC. Immunotherapy helps the body's own immune cells to recognize and kill cancer cells

Bile: A fluid that is made and released by the liver to help with digestion.

Standard of care: A treatment that is accepted and widely used by healthcare professionals for a certain type of disease.



What is durvalumab?

- The medication being assessed in this study is a type of immunotherapy called durvalumab. Participants received durvalumab treatment directly into their vein at a dose of 1500 mg once every 3 weeks in combination with chemotherapy, and then durvalumab alone once every 4 weeks
- Programmed cell death-1 (PD-1) is a protein found on the surface of T cells (immune cells) that interacts with programmed cell death ligand-1 (PD-L1), another protein found on cancer cells or immune cells. This interaction between PD-1 and PD-L1 proteins reduces the activity of T cells and can prevent the immune system from attacking cancer cells
- Durvalumab is a drug that blocks the interaction of PD-1 and PD-L1 proteins by attaching to PD-L1, leading to activation of T cells and the immune system. Activation of the immune system by durvalumab may result in the death of cancer cells
- At the time of this study, durvalumab was approved in many countries, including the United States (Food and Drug Administration), European Union (European Commission), and Japan (Ministry of Health, Labour, and Welfare) for the treatment of non-small cell and small cell lung cancer. It was also under investigation for the treatment of several other cancer types, including liver, bladder, gastric, and esopheageal cancers
- Previous research has suggested that durvalumab may work for the treatment of BTCs when it is given in combination with chemotherapy

Where was the TOPAZ-1 study carried out?

TOPAZ-1 is a Phase III study that included participants with advanced BTCs from all over the world.

Who was eligible to participate in the study?

- Adults aged 18 years or more with BTC, including those with cholangiocarcinoma (cancer of the bile ducts) or gallbladder cancer not suitable for surgery
- Adults with BTC were included if they had not received previous treatment for advanced BTC or if their disease had come back at least 6 months after surgery was performed to cure their disease
- Adults with BTC did not need to have any specific gene mutation to participate in the study
- Adults with BTC had to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 to be included in the study

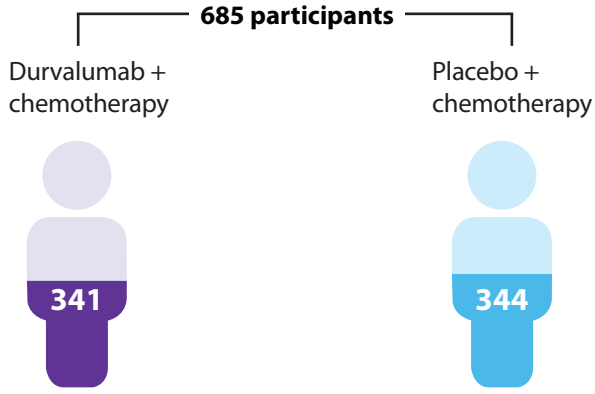
ECOG performance score is a measurement of how the disease impacts a person's daily living ability. A score of 0 means that the person is fully active and able to carry out the same activities as before their disease, and a score of 1 means that the person is restricted in physically strenuous activity but able to carry out light work.

- Adults did not participate in the study if they had cancer of the ampulla of Vater, the junction where the common bile duct meets the pancreatic duct
- Adults with BTC who had active, or a history of, illnesses or conditions where the immune system is already over activated, or a known allergy to any of the treatments given in the study, were not able to participate in the study

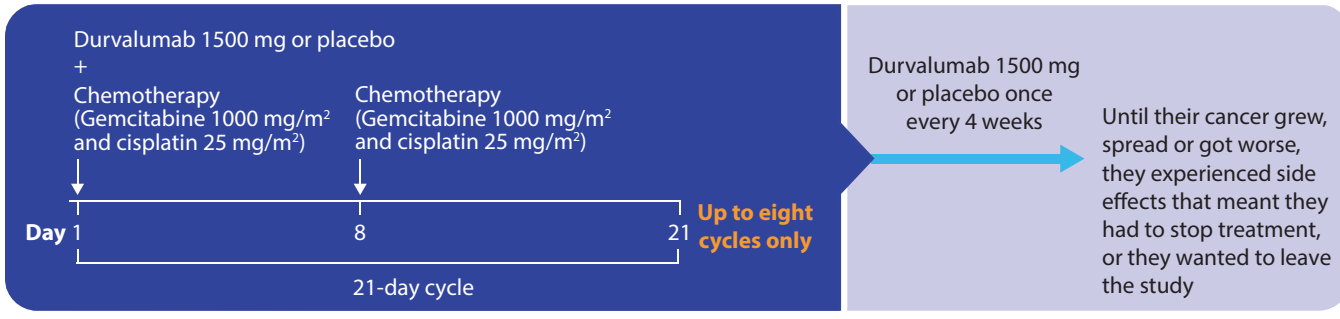
What treatment did participants receive?

685 participants were included in the study and were allocated to groups at random to receive either durvalumab and chemotherapy (341 participants) or placebo and chemotherapy (344 participants)

In the study, participants were given treatment with durvalumab and chemotherapy or placebo and chemotherapy for up to eight 21-day cycles, followed by treatment with durvalumab or placebo once every 4 weeks until they had to stop, as shown in the diagram below



A placebo does not contain any medicine, but it looks the same, and is given in the same way, as the treatment being tested (durvalumab).



Participants received treatment directly into a vein or veins

In some cases, participants could stay on treatment even if their cancer grew, spread, or got worse, if their doctors believed they could still benefit from the treatment

In the study, neither the participants nor their doctors knew if the participant received durvalumab or placebo with chemotherapy. This was done to make sure that any differences measured between the two groups of participants were caused by the treatment only

What was measured in the study?

The aim of this study was to find out if treatment with durvalumab and chemotherapy could increase the length of time that participants lived, compared with placebo and chemotherapy

Other outcomes measured in the study included:

- The length of time to when a participant's cancer grew, spread, or got worse
- The percentage of participants whose tumor responded to treatment. Response was defined when a participant's tumor shrank by at least 30% or disappeared after treatment
- The length of time that a participant's tumor continued to respond to treatment. Response was defined when a participant's tumor shrank by at least 30% or disappeared after treatment
- The length of time that participants with PD-L1 high tumors (defined as 1% or more of cancer and / or immune cells with PD-L1 expression) were alive after treatment compared with those with PD-L1 low tumors (defined as less than 1% of cancer and / or immune cells with PD-L1 expression)
- The impact of the treatment or disease on a participant's quality of life, which was reported directly by the participant. The quality of life results will be reported elsewhere
- The side effects of the treatments
- The results presented in this report are from a planned early analysis of these measures in the TOPAZ-1 study. This analysis was performed using data collected on 11 August 2021

PD-L1 expression was assessed by looking at tumor samples under the microscope in a laboratory. In some cancer types, durvalumab has been shown to work better for people who have PD-L1 high tumors, as durvalumab works by attaching to this receptor as described above.

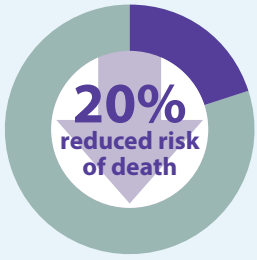
Who were the participants in the study?

	Durvalumab + chemotherapy (341 participants)	Placebo + chemotherapy (344 participants)
Female, %	50.4	48.8
Median age (range), years	64 (20–84)	64 (31–85)
Median age is the age at which half of the population is older and half of the population is younger		
Region, %		
Asia	52.2	57.0
Rest of the world	47.8	43.0
Race, %		
Asian	54.3	58.4
White	38.4	36.0
Black or African American	2.3	1.7
American Indian or Alaska Native	0.0	0.3
Other	5.0	3.5
ECOG PS 0, %	50.7	47.4
ECOG performance status is a measurement of how the disease impacts a person's daily living ability		
Primary tumor type, %		
Intrahepatic cholangiocarcinoma	55.7	56.1
Extrahepatic cholangiocarcinoma	19.4	18.9
Gallbladder cancer	24.9	25.0
Disease status, %		
Not eligible for surgery	80.4	81.1
Returned after surgery	19.6	18.6
PD-L1 expression, %		
High	57.8	59.6
Low	30.2	29.9
Missing (absent)	12.0	10.5

- Participant characteristics and their cancer were similar between the two treatment groups
- By the end of the study, the most common reason for participants stopping treatment was that their cancer grew
- Fewer patients stopped treatment because of cancer growth in the durvalumab and chemotherapy group (55.7%) than in the placebo and chemotherapy group (69.2%)
- Other reasons for participants stopping treatment included that they experienced side effects that caused them to stop treatment (5.9% with durvalumab and chemotherapy and 5.2% with placebo and chemotherapy), they decided to leave the study (3.8% with durvalumab and chemotherapy and 4.7% with placebo and chemotherapy), and they improved or recovered from their disease (0.3% with durvalumab and chemotherapy and 0.3% with placebo and chemotherapy)

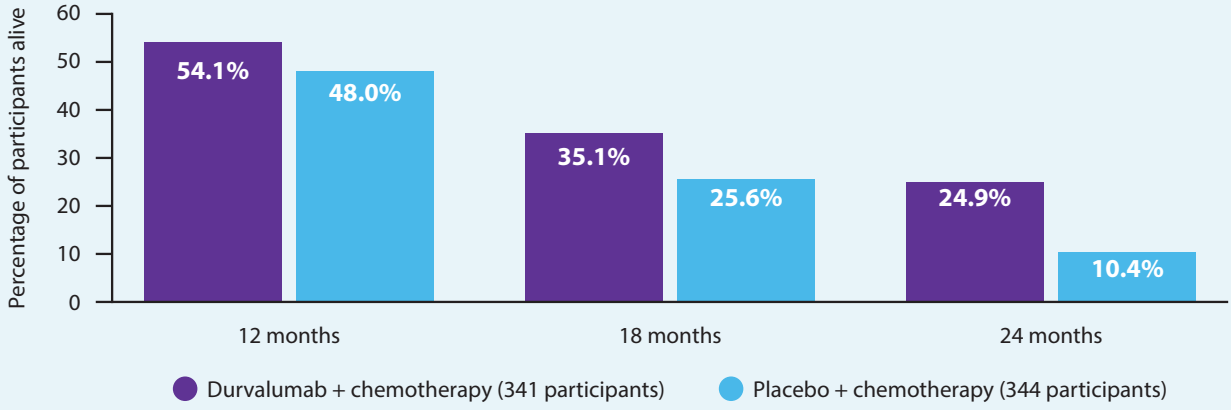
What did the results of the study show?

How well did the addition of durvalumab to chemotherapy help participants with BTC live longer?

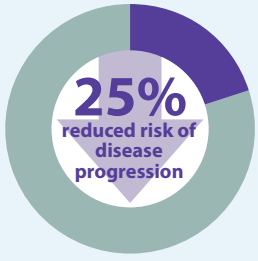


- Participants who received durvalumab and chemotherapy were 20% less likely to die (called reduced risk of death) compared with those who received placebo and chemotherapy
- Half of the participants still participating in the trial were alive 12.8 months after starting durvalumab and chemotherapy treatment, and half of the participants still participating in the trial were alive 11.5 months after starting placebo and chemotherapy treatment
- Among those still participating in the trial, more participants who received durvalumab and chemotherapy were alive at 12, 18, and 24 months after starting treatment than participants who received placebo and chemotherapy

Percentage of participants still participating in the trial who were alive at specific time points after starting treatment



Participants who received durvalumab and chemotherapy tended to live longer than those who received placebo and chemotherapy, regardless of where they lived in the world, the location of their cancer, and whether there was PD-L1 in their tumor

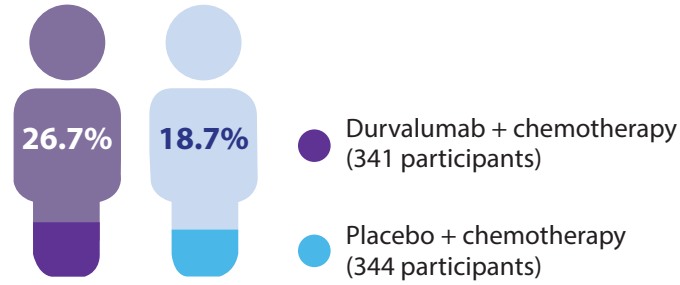


- Participants who received durvalumab and chemotherapy were 25% less likely to experience their cancer growing, spreading, or getting worse (called disease progression) than those who received placebo and chemotherapy
- Of those still participating in the trial, the length of time that half the participants were alive without their cancer growing, spreading, or getting worse (called disease progression-free survival) was 7.2 months with durvalumab and chemotherapy and 5.7 months with placebo and chemotherapy

Statistical tests (mathematical tests used to confirm a significant difference) showed that both survival and survival without cancer growth, spread or worsening were longer in the durvalumab and chemotherapy group compared with the placebo and chemotherapy group.

- The length of time that half the participants had their cancer shrink or disappear was 6.4 months with durvalumab and chemotherapy and 6.2 months with placebo and chemotherapy. In total, 26.1% of participants in the durvalumab and chemotherapy group still had their cancer shrink or disappear 12 months or more after starting treatment, compared with 15.0% in the placebo and chemotherapy group
- Participants who received durvalumab and chemotherapy had a shorter time to their cancer shrinking or disappearing than participants who received placebo and chemotherapy. The time point at which half the participants had their cancer shrink or disappear was 1.6 months with durvalumab and chemotherapy compared to 2.7 months with placebo and chemotherapy

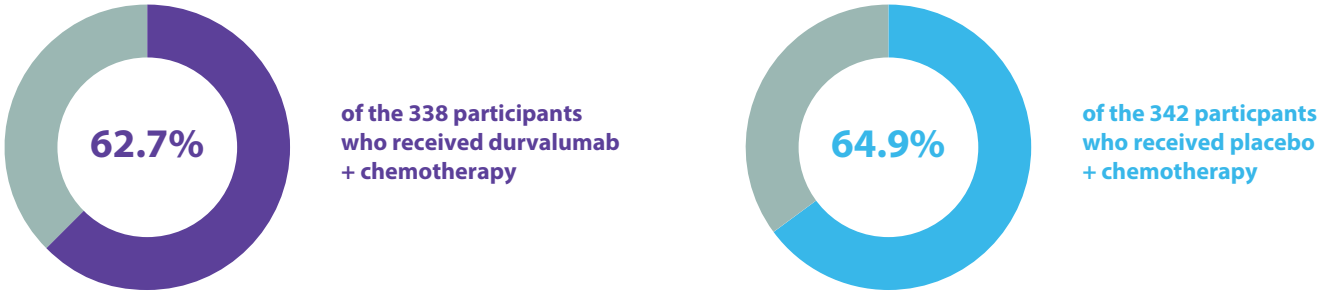
Percentage of participants who had their cancer shrink by at least 30% or disappear after treatment



How safe was durvalumab and chemotherapy treatment?

A similar proportion of participants in each treatment group experienced severe side effects considered to be related to the treatment.

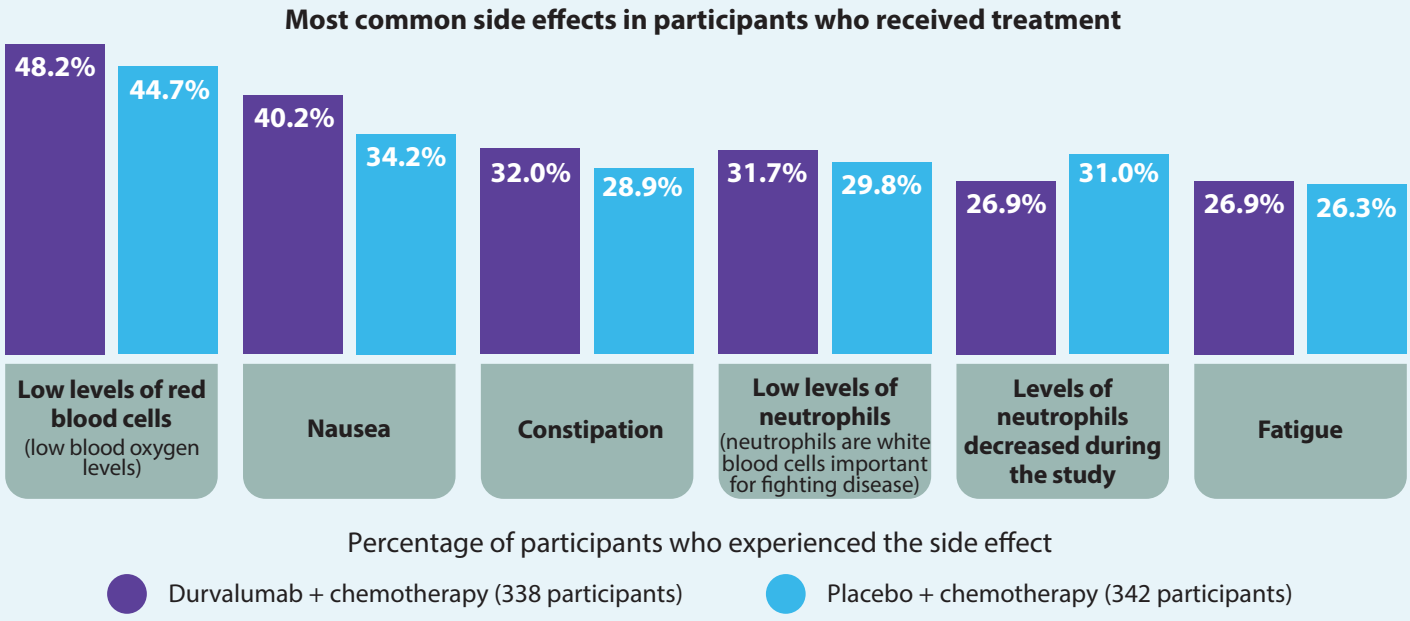
Percentage of patients who had severe side effects related to the treatment



Severe side effects are medically significant (Grade 3) or potentially life-threatening (Grade 4) side effects, as described by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Percentage of patients who had a side effect related to the treatment that led them to stop treatment

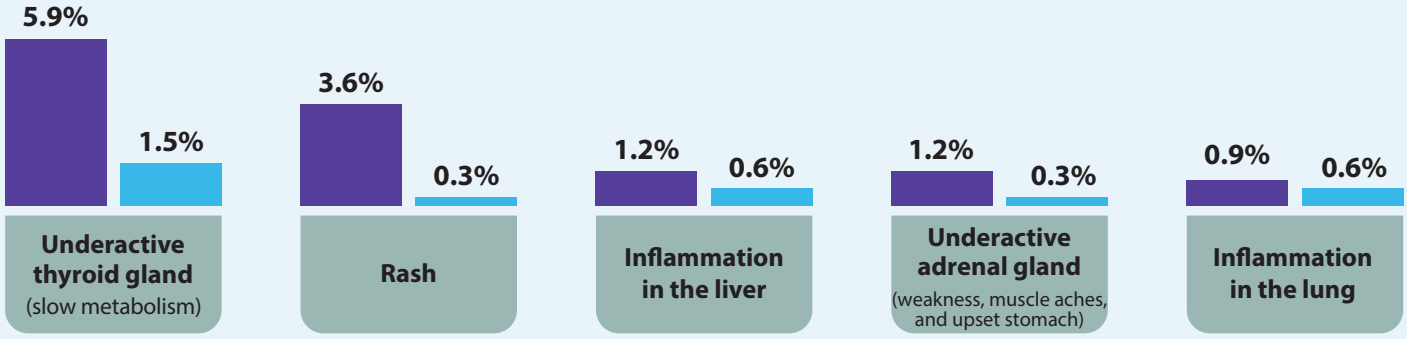
The number of deaths due to side effects caused by the treatment was low in each group: 2 (0.6%) deaths in the durvalumab and chemotherapy group and 1 (0.3%) death in the placebo and chemotherapy group.



As durvalumab is a type of immunotherapy, it can cause the immune system to become overactive, causing side effects.

- As expected with immunotherapies, the proportion of participants who experienced a side effect related to the immune system was higher in the durvalumab and chemotherapy group (12.7%) than in the placebo and chemotherapy group (4.7%)
- The proportion of participants who experienced a severe or medically significant (Grade 3) or potentially life-threatening (Grade 4) side effect related to the immune system was 2.4% with durvalumab and chemotherapy and 1.5% with placebo and chemotherapy

Most common side effects related to the immune system in participants who received treatment



Overall, the addition of durvalumab to chemotherapy did not cause any more side effects than chemotherapy alone, and the side effects that were observed were expected with immunotherapy or chemotherapy.

What do the results of the study mean?

- This study showed that participants with advanced BTC who received durvalumab and chemotherapy lived significantly longer than participants who received placebo and chemotherapy
- The addition of durvalumab did not make the side effects from chemotherapy worse, and participants experienced side effects that are common with immunotherapy and chemotherapy, most of which were manageable
- The results of this large, global, Phase III study support that durvalumab and chemotherapy are a new initial treatment option for people with advanced BTCs
- Based on the results of this study, durvalumab is now approved for the treatment of adults with advanced BTCs in combination with chemotherapy

Where can I find more information?

This is a summary of an article called "Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer" originally published in *NEJM Evidence*: Oh D-Y et al. *NEJM Evid.* 1(8), EVIDoa2200015 (2022).

You can read the full article at: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200015.

You can read more about the TOPAZ-1 study on the ClinicalTrials.gov website: https://clinicaltrials.gov/ct2/show/NCT03875235

People with BTCs should ask their healthcare providers for more information about the benefits and risks of any treatment.

Affiliations

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