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Plain Language Summary of Publication

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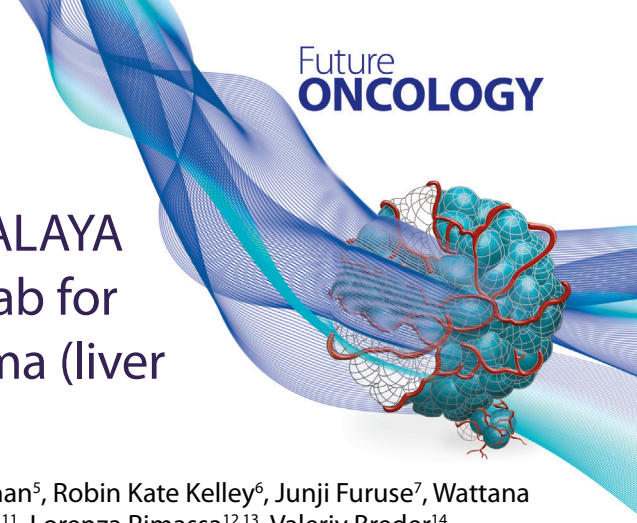

Plain language summary of the HIMALAYA study: tremelimumab and durvalumab for unresectable hepatocellular carcinoma (liver cancer)

Ghassan K. Abou-Alfa[1,2], George Lau[3], Masatoshi Kudo[4], Stephen L. Chan[5], Robin Kate Kelley[6], Junji Furuse[7], Wattana Sukeepaisarnjaroen[8], Yoon Koo Kang[9], Tu Van Dao[10], Enrico N. De Toni[11], Lorenza Rimassa[12,13], Valeriy Breder[14], Alexander Vasilyev[15], Alexandra Heurgué[16], Vincent C. Tam[17], Kabir Mody[18], Satheesh Chiradoni Thungappa[19], Yurii Ostapenko[20], Thomas Yau[21], Sergio Azevedo[22], María Varela[23], Ann-Lii Cheng[24], Shukui Qin[25], Peter R. Galle[26], Sajid Ali[27], Charu Gupta[28], Mallory Makowsky[27], John F. Kurland[27], Alejandra Negro[27], Bruno Sangro[29] for the HIMALAYA Investigators

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Summary

What is this summary about?
This is a summary of results from a **phase 3 clinical study** called HIMALAYA. HIMALAYA looked at treatment with one dose of a medication called tremelimumab combined with multiple doses of a medication called durvalumab (the STRIDE regimen) or multiple doses of durvalumab alone. These treatments were compared with a medication called sorafenib in participants with unresectable hepatocellular carcinoma (HCC).

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

- **Durvalumab:** dur-VAL-yoo-mab
- **Tremelimumab:** treh-meh-LIM-oo-mab
- **Sorafenib:** sor-A-feh-nib

HCC is a type of liver cancer that is difficult to treat because it is often diagnosed when it is unresectable, meaning it can no longer be removed with surgery. Sorafenib has been the main treatment for unresectable HCC since 2007. However, people who take sorafenib may experience side effects that can reduce their **quality of life**, so alternative medicines are being trialed. Tremelimumab and durvalumab are types of drugs called **immunotherapies**, and they both work in different ways to help the body's immune system fight cancer.

Phase 3 study: A study that tests the safety, and how well a new treatment works, compared with a standard treatment.
Quality of life: Quality of life is a person's sense of well-being and ability to carry out their normal daily activities.
Immunotherapies: Immunotherapies are treatments that target the immune system to help the body fight cancer.
Side effect: A side effect is an unintended problem that happens during treatment with a drug or other therapy.

What were the results of the study?
Participants who took STRIDE lived longer than participants who took sorafenib, whilst participants who took durvalumab alone lived a similar length of time as participants who took sorafenib. Participants who took STRIDE or durvalumab had a lower relative risk of experiencing worsening in their quality of life than participants who took sorafenib. The **side effects** that participants who received STRIDE or durvalumab experienced were expected for these types of treatments and could mostly be managed.

What do the results of the study mean?
Overall, STRIDE is more effective than sorafenib for people with unresectable HCC.

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

The original article discussed in this summary, titled "Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma", 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/EVIDoa2100070

Who sponsored this clinical study?

The pharmaceutical company AstraZeneca (the manufacturers of durvalumab and tremelimumab) funded and was responsible for conducting this clinical study.

Who should read this article?

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

What is HCC and what are its treatment options?

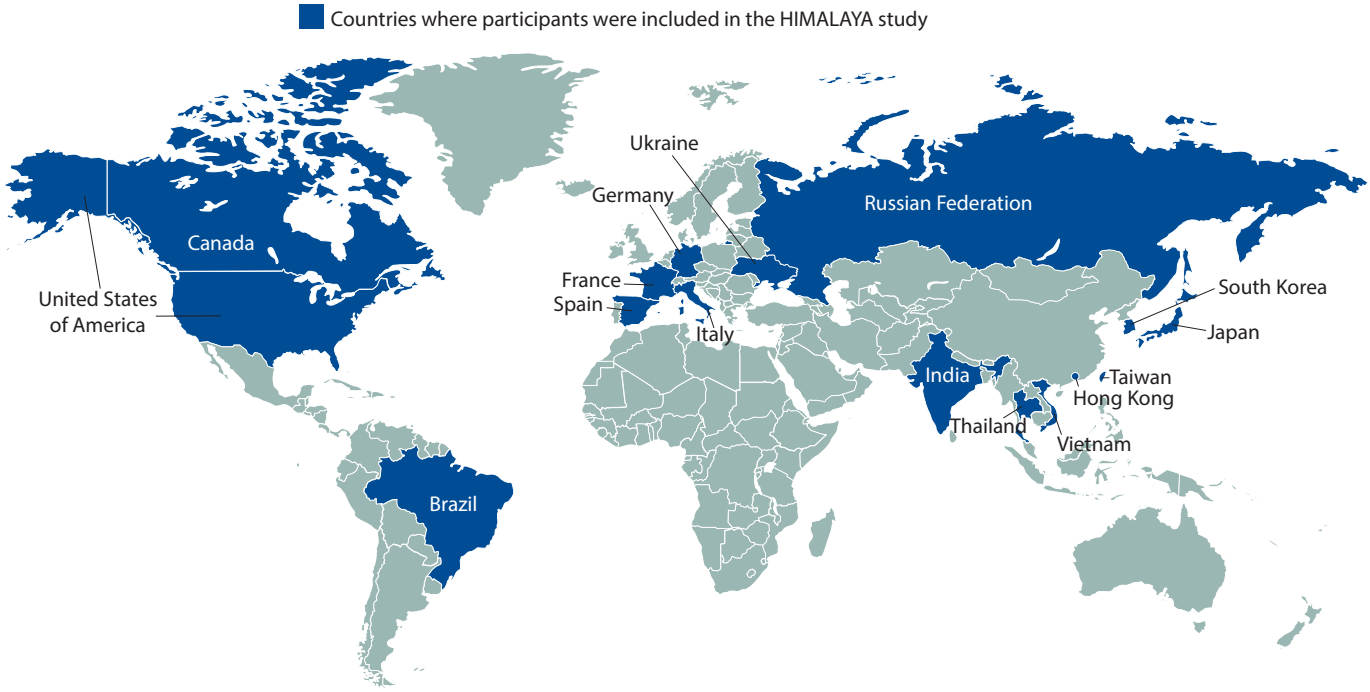
- HCC is the most common type of liver cancer and one of the most common causes of cancer-related deaths in the world
- HCC is often associated with liver damage, and for some people it can be caused by infection with the hepatitis B virus or hepatitis C virus
- Many people with HCC are not diagnosed until their tumor can no longer be removed with surgery. This disease stage is called unresectable HCC
- A medication called sorafenib has been used to treat people with unresectable HCC since 2007. However, people who take sorafenib may experience side effects that can reduce their quality of life
- New treatment options that could benefit people with unresectable HCC are being trialed
- While the HIMALAYA study was ongoing, another clinical study showed that participants with HCC who took a combination of two drugs, called atezolizumab and bevacizumab, lived longer than those who took sorafenib. This combination was approved for unresectable HCC by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2020

What are tremelimumab, durvalumab and sorafenib?

- Tremelimumab and durvalumab are types of drugs called immunotherapies, treatments that target the immune system to help the body fight cancer, that are given to participants directly into their veins
- Durvalumab is an immunotherapy that has been effective in treating certain types of cancers. Durvalumab binds to a protein called PD-L1 to help immune cells kill cancer cells
- Tremelimumab is a different type of immunotherapy to durvalumab. Tremelimumab may work with durvalumab to help patients with HCC live longer. Tremelimumab binds to a protein called CTLA-4 to make immune cells better at killing cancer cells
- Sorafenib is a type of medication called a tyrosine kinase inhibitor (TKI) which is given orally (by mouth). TKIs work differently from immunotherapies. TKIs target cancer cells directly to block pathways that promote cancer cell growth
- A previous clinical trial, called Study 22, found that the STRIDE regimen, as well as durvalumab alone, were both effective at treating HCC and had manageable side effects
- In HIMALAYA, treatment with STRIDE or durvalumab alone was compared to treatment with sorafenib

Where was the HIMALAYA study carried out?

HIMALAYA is a phase 3 clinical study that included participants with unresectable HCC from across the world.



Who was eligible to participate in the study?

Participants had to meet the following eligibility criteria in order to participate in the study:

- Aged 18 years or older with unresectable HCC that could not be treated with locoregional therapy (treatment that is directed into the tumor in the liver)
- People who had not previously been treated with systemic therapy (treatments that affect the whole body), such as chemotherapy, TKIs or immunotherapy for HCC
- Participants with HCC that was categorized as stage B or C according to the Barcelona Clinic Liver Cancer (BCLC) staging system
- Participants with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1

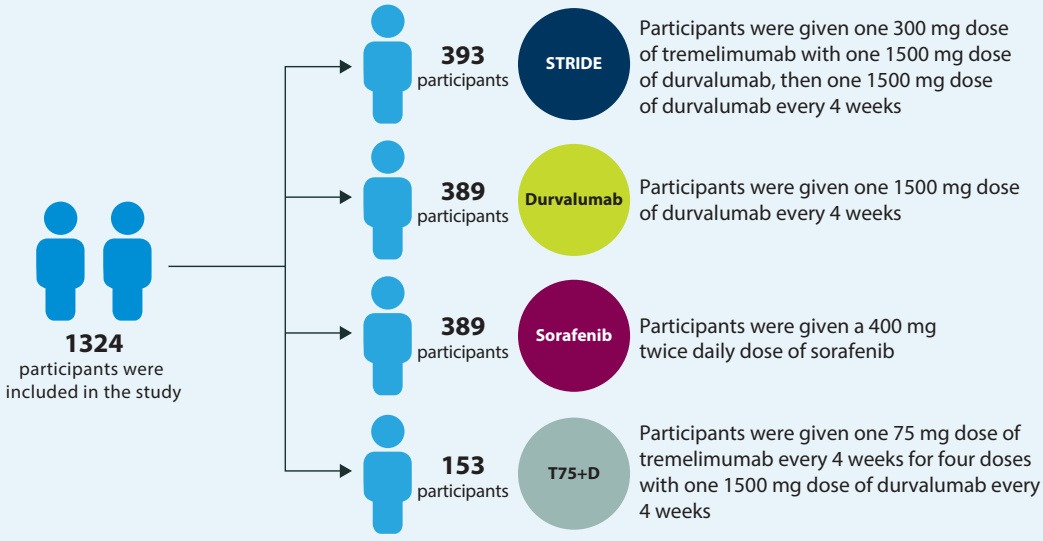
The version of the BCLC staging system that was used during the study is shown below:

BCLC staging system

Stage	**0 (Very early)**	**A (Early)**	**B (Intermediate)**	**C (Advanced)**	**D (End)**
Tumor characteristics	Single tumor not more than 2 cm	Single tumor of any size, or up to three tumors that are each not more than 3 cm	Multiple tumors	Cancer has spread into blood vessels, lymph nodes, or other organs	Any tumor characteristics
ECOG performance score	**0**: Able to carry out the same activities as before the disease without restriction			**1 or 2:** Restricted in physically challenging activity but able to walk around and carry out light work or capable of self-care and able to walk around but unable to carry out any work activities	**3 or 4:** Capable of only limited or no self-care and confined to a bed or chair for more than 50% of hours awake or totally confined to a bed or chair
Child-Pugh Score	**A:** Normal liver function	**A or B:** Normal (A) or mild-to-moderate (B) impairment in liver function			**C:** Severe impairment in liver function

The BCLC staging system assigns HCC a stage based on three criteria: the number, size, and location of tumors present; general health or daily living ability, according to the ECOG performance status scoring system; and how well the liver is working, according to the Child-Pugh Scoring system, which take into account several laboratory tests

What treatment did participants receive?



Tremelimumab and durvalumab were given directly into the participant's veins, and sorafenib was given by mouth.

During the HIMALAYA study, Study 22 found that T75+D was not more effective than durvalumab alone at treating HCC. Therefore, participants stopped being included in this treatment group during recruitment into the HIMALAYA study. Only the STRIDE arm and the durvalumab arm were compared with the sorafenib arm, and are reported here.

Participants continued treatment until they experienced tumor growth, experienced side effects that caused them to stop treatment, wanted to leave the study, or died.

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

What was measured in the study?

The main purpose of the study was to compare the survival of participants taking STRIDE with those taking sorafenib. The survival of participants taking durvalumab compared with those taking sorafenib was also assessed.

Other outcomes measured in the study included the following:

- 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 impact of the treatment or disease on a participant's quality of life, which was reported directly by the participant
- The side effects of the treatments

Who were the participants in the study?

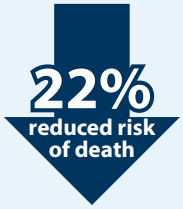
- From October 2017 to June 2019, 1950 people were screened at 181 study sites in 16 countries. 1171 participants were included in the study
- Participant characteristics were similar in the three treatment groups
- Unresectable HCC is difficult to treat. Participants with unresectable HCC often stop treatment in clinical trials due to their cancer growing, spreading, or getting worse
- By the end of the study, 88.7% of participants in the STRIDE group, 88.6% of participants in the durvalumab group, and 94.4% of participants in the sorafenib group had stopped treatment for any reason
  - The most common reason for participants stopping treatment was that their cancer grew, spread, or got worse; cancer growth, spread, or worsening was confirmed in 53.0% of participants who stopped treatment in the STRIDE group, 64.9% of participants who stopped treatment in the durvalumab group, and 48.2% of participants who stopped treatment in the sorafenib group
  - Other reasons for participants stopping treatment included the side effects they experienced, which caused them to stop treatment or leave the study

Median: The median is the middle value in a set.

	STRIDE (393 participants)	Durvalumab (389 participants)	Sorafenib (389 participants)	
Male (%)	83.2%	83.0%	86.6%	Most participants were male.
Median age (range), years	65.0 (22–86)	64.0 (20–86)	64.0 (18–88)	The median age was 64 to 65 years.
Geographical region (%)				
Asia (except Japan)	39.7%	42.9%	40.1%	Approximately 40% of participants were from Asia (except Japan).
Rest of the world (including Japan)	60.3%	57.1%	59.9%	
ECOG performance score (%)				
0	62.1%	60.9%	62.0%	Most participants had an ECOG performance score of 0, meaning they were able to carry out all of the same activities as before their disease without restriction.
1	37.7%	38.6%	37.8%	
2	0.3%	0.5%	0.3%	
BCLC stage (%)				
B	19.6%	20.6%	17.0%	Most participants had HCC classified as BCLC stage C, meaning they had advanced disease that had spread into blood vessels, lymph nodes, or other organs.
C	80.4%	79.4%	83.0%	
Viral status (%)				
Hepatitis B virus	31.0%	30.6%	30.6%	Approximately 60% of participants had hepatitis B or C virus infection that may have contributed to their HCC.
Hepatitis C virus	28.0%	27.5%	26.7%	
No virus	41.0%	41.9%	42.7%	
Spread of cancer into blood vessels	26.2%	24.2%	25.7%	Approximately 25% of participants had cancer that spread into their blood vessels.
Spread of cancer into tissues outside the liver	53.2%	54.5%	52.2%	Approximately 53% of participants had cancer that spread into tissues outside of their liver.

What did the results of the study show?

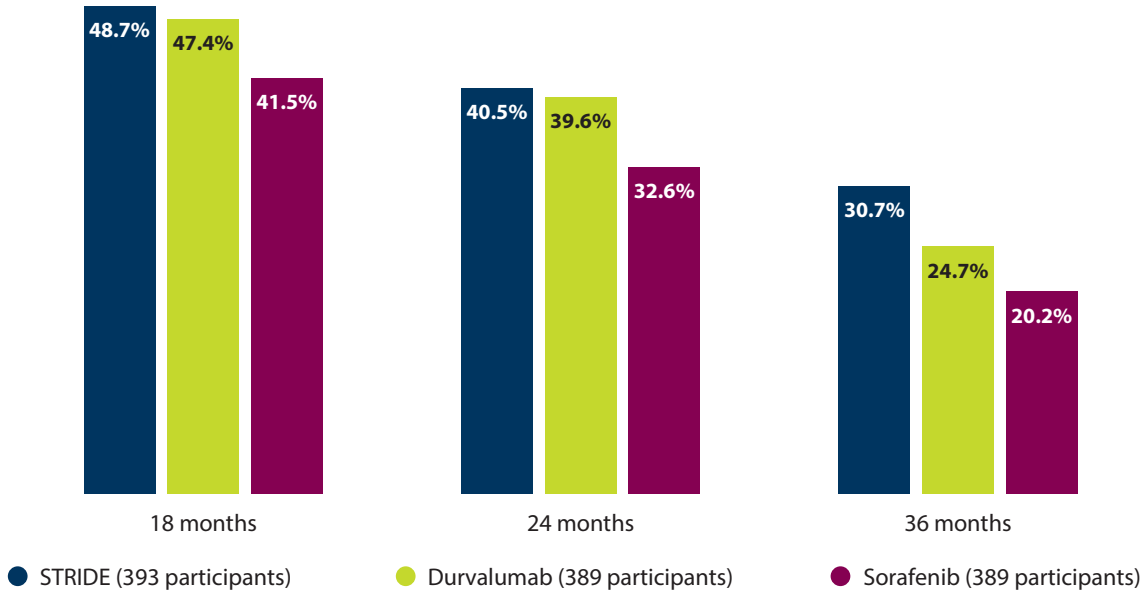
How well did STRIDE and durvalumab work in treating participants with HCC compared with sorafenib?



- Participants who took STRIDE were 22% less likely to die of any cause compared with those who took sorafenib. A statistical test showed that this improvement in survival with STRIDE, compared with sorafenib, was significant
- Participants who took STRIDE tended to live longer than those who took sorafenib, regardless of where they lived in the world or their ECOG performance status
- A statistical test showed that participants who took durvalumab alone had similar survival to those who took sorafenib

More participants still participating in the trial who took STRIDE or durvalumab were alive 18 months, 24 months, and 36 months after starting treatment than those who took sorafenib.

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



The length of time before half of participants experienced cancer growth, spreading, or worsening was similar for participants who took STRIDE, durvalumab or sorafenib.

The length of time before half of participants experienced cancer growth, spreading, or worsening

More participants had their cancer shrink by at least 30% or disappear after treatment in the STRIDE and durvalumab groups compared with the sorafenib group.

Percentage of participants who had their cancer shrink or disappear after treatment

20.1% of the 393 participants who took **STRIDE**

17.0% of the 389 participants who took **durvalumab**

5.1% of the 389 participants who took **sorafenib**

Participants who took STRIDE or durvalumab maintained their quality of life, or did not feel worse because of their disease or the treatment, for longer than participants who took sorafenib.

The length of time until half of participants experienced worsening in quality of life

Compared to participants who took sorafenib, participants who took STRIDE had a 24% lower relative risk of experiencing worsening in their quality of life, and participants who took durvalumab had a 23% lower relative risk.

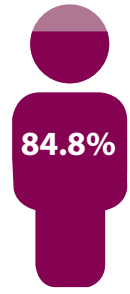
How safe were STRIDE, durvalumab alone and sorafenib?

Participants who took STRIDE or durvalumab were less likely to experience side effects considered to be related to the treatment being studied, **Grade 3 or 4 side effects** considered to be related to the treatment being studied, and side effects considered to be related to the treatment being studied that led them to stop treatment than participants who took sorafenib.

Percentage of patients who had side effects considered to be related to the treatment being studied

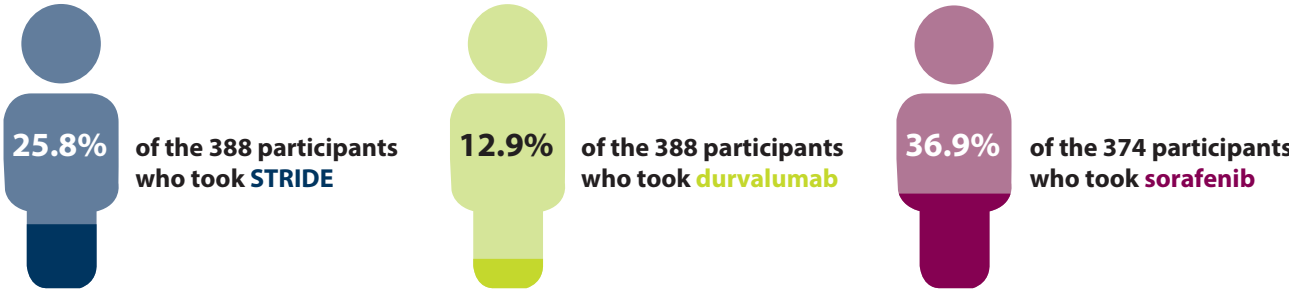
75.8% of the 388 participants who took **STRIDE**

52.1% of the 388 participants who took **durvalumab**

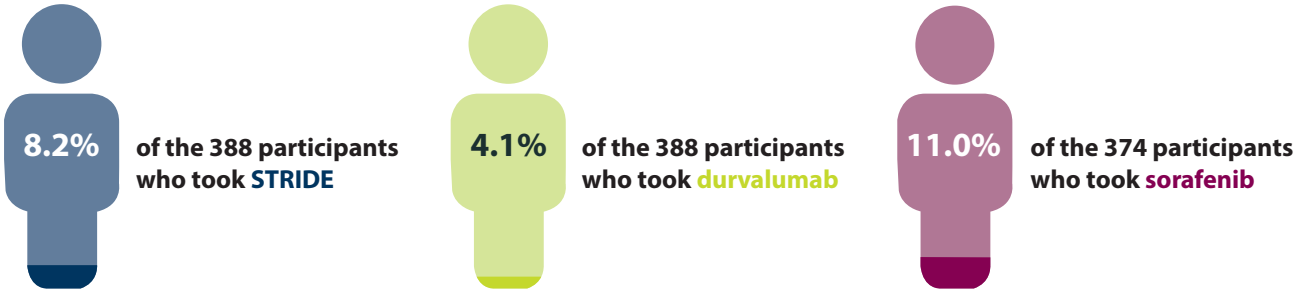


84.8% of the 374 participants who took **sorafenib**

Percentage of patients who had Grade 3 or 4 side effects considered to be related to the treatment being studied



Percentage of patients who had side effects considered to be related to the treatment being studied that led them to stop treatment



These findings suggest that most side effects with STRIDE and durvalumab could be managed according to treatment guidelines.

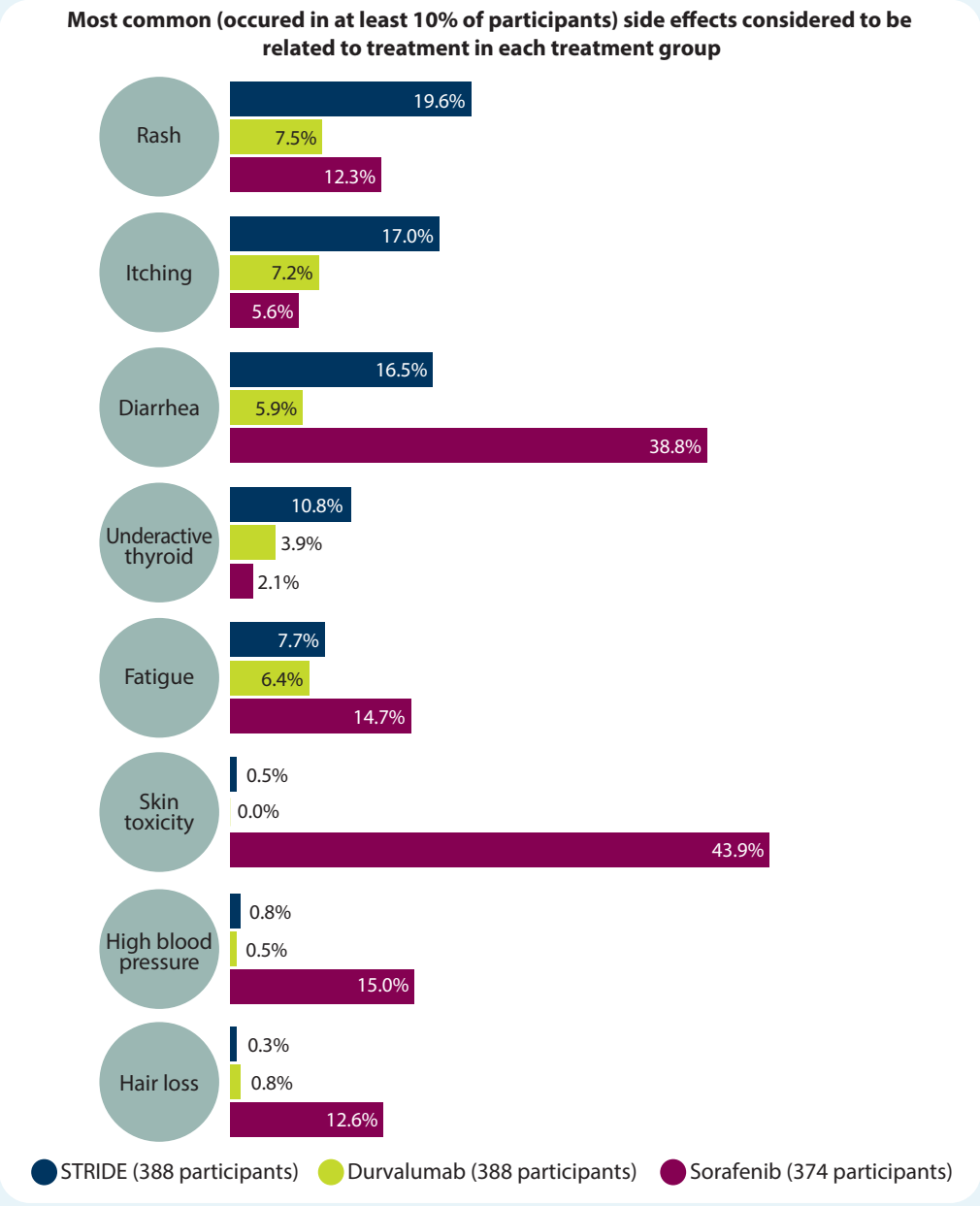
Serious side effects considered to be related to the treatment being studied occurred in 17.5% of participants in the STRIDE group, 8.2% of participants in the durvalumab group, and 9.4% of participants in the sorafenib group.

More participants died due to side effects considered to be related to the treatment in the STRIDE group (2.3%) compared with the durvalumab (0%) and sorafenib (0.8%) groups. However, the number of deaths due to side effects considered to be related to treatment was generally low across treatment groups.

Grade 3 or 4 side effects: Grade 3 side effects are not immediately life-threatening but require hospital care, are disabling, or limit basic daily activities. Grade 4 side effects are life-threatening and require urgent medical intervention.

Serious side effects: Serious side effects are life-threatening, require hospitalization, cause lasting problems or death, or result in a birth defect.

The most common side effects considered to be related to the treatment being studied were consistent with what is expected for these types of treatments.



Underactive thyroid: Underactive thyroid is a condition in which the thyroid gland doesn't make enough thyroid hormones for the body's needs.

Skin toxicity: Skin toxicity is a side effect of some chemotherapy drugs and TKIs. In this study, skin toxicity included palmar–plantar erythrodysesthesia syndrome, which includes hand–foot syndrome or hand–foot skin reaction. Skin toxicity can cause redness, swelling and blistering on the hands, feet and genitals, and can limit activities and affect quality of life.

Side effects related to the immune system can occur in people who take immunotherapies. Most side effects related to the immune system that occurred in the HIMALAYA study were manageable by available treatment guidelines, and those that required treatment with high-dose corticosteroids (anti-inflammatory medicines) occurred in 20.1% of participants who took STRIDE, 9.5% of participants who took durvalumab, and 1.9% of participants who took sorafenib.

What do the results of the study mean?

- The results of the large, global, Phase 3 HIMALAYA study showed that STRIDE is a more effective treatment than sorafenib, and durvalumab alone is just as effective as sorafenib, for people with unresectable HCC
- Participants who took STRIDE or durvalumab alone had a lower relative risk of experiencing worsening in their quality of life than participants who took sorafenib
- The side effects that participants who received STRIDE or durvalumab alone experienced were expected for these types of treatments and could be managed according to treatment guidelines. Severe or life-threatening side effects occurred less frequently for participants who took STRIDE or durvalumab alone than for those who took sorafenib
- As STRIDE helped participants to live longer than those taking sorafenib, it may be a promising new treatment option for people with unresectable HCC
- Durvalumab was just as effective at treating unresectable HCC as sorafenib and caused fewer side effects, and therefore may also be a promising new treatment option for people with unresectable HCC
- Based on the results of this study, STRIDE is now approved for the treatment of adults with unresectable HCC in the United States, the European Union and Japan

Where can I find more information on the study?

- This is a summary of an article called "Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma" originally published in *NEJM Evidence*: Abou-Alfa GK, Lau G, Kudo M *et al. NEJM Evid.* 1(8), EVIDoa2100070 (2022).
- You can read the full article at: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100070
- You can read more about the HIMALAYA clinical study on the ClinicalTrials.gov website: https://clinicaltrials.gov/ct2/show/NCT03298451
- You can read more about Study 22 in the article at https://ascopubs.org/doi/full/10.1200/JCO.20.03555 or on the ClinicalTrials.gov website: https://clinicaltrials.gov/ct2/show/NCT02519348
- People with HCC should ask their healthcare providers for more information about the benefits and risks of any treatment.

Financial & competing interests disclosure

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