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ADIS DRUG EVALUATION

Tremelimumab: A Review in Advanced or Unresectable Hepatocellular Carcinoma

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Abstract

Tremelimumab (tremelimumab-actl; Imjudo®) is a monoclonal antibody and immune checkpoint inhibitor (ICI) that blocks cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). A single, priming dose of intravenous tremelimumab is used in combination with durvalumab, an ICI that blocks programmed cell-death ligand 1, in a regimen known as STRIDE (Single Tremelimumab Regular Interval Durvalumab). STRIDE is approved for the treatment of adults with unresectable hepatocellular carcinoma (HCC) in the USA and Japan and for the first-line treatment of adults with advanced or unresectable HCC in Europe. In the phase III HIMALAYA trial, STRIDE significantly improved overall survival (OS) compared with sorafenib in adults with unresectable HCC and no prior systemic therapy. A higher proportion of STRIDE versus sorafenib recipients had an objective response to treatment. The OS benefit associated with STRIDE was sustained with 4 years' follow-up. STRIDE had a manageable safety profile that differed from that of sorafenib. Grade 3 or 4 treatment-related adverse events occurred in a lower proportion of STRIDE versus sorafenib recipients. Based on the available evidence, tremelimumab used as part of the STRIDE regimen is a valuable first-line agent that expands the treatment options available to patients with advanced or unresectable HCC.

Plain Language Summary

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer death worldwide. HCC is commonly associated with cirrhosis linked to chronic viral hepatitis and non-alcoholic fatty liver disease. Tremelimumab (tremelimumab-actl; Imjudo®) is a type of immunotherapy that helps the body's immune system attack HCC cells by binding to and blocking the action of an immune-checkpoint protein called cytotoxic T lymphocyte-associated antigen-4. A single dose of intravenous tremelimumab is used in combination with treatment with durvalumab, in a regimen known as STRIDE (Single Tremelimumab Regular Interval Durvalumab), for adults with unresectable HCC in the USA and Japan and as a first-line treatment for adults with advanced or unresectable HCC in the EU. In patients with unresectable HCC, STRIDE improved overall survival more than sorafenib, including at 4 years' follow-up. A higher proportion of patients responded to treatment with STRIDE compared with sorafenib. STRIDE had manageable adverse events. Tremelimumab used as part of the STRIDE regimen is a valuable first-line agent that expands the treatment options available to patients with HCC that is advanced or unable to be removed with surgery.

Digital Features for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.24736167

Tremelimumab: clinical considerations in advanced or unresectable HCC

Fully human monoclonal antibody that blocks the interaction of CTLA-4 with its ligands CD80 and CD86
Significantly improves OS when used in combination with durvalumab as part of the STRIDE regimen; benefits are sustained at 4-years' follow-up
Manageable safety profile

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1 Introduction

Hepatocellular carcinoma (HCC) accounts for ≈ 80% of liver cancers worldwide [1]. According to 2020 estimates, liver cancer is the third most common cause of cancer death [1]. HCC is more common in people with cirrhosis and is often associated with chronic hepatitis B infection in Asia and Africa and non-alcoholic fatty liver disease in western countries [1, 2]. Liver cancer is a growing problem, with new cases predicted to increase by 55% between 2020 and 2040 [1].

Sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI), was the first systemic treatment for unresectable HCC that improved overall survival (OS) [3]. Once approved, it became the new standard of care [3] and for many years it was the only option available until the arrival of lenvatinib, another multi-targeted TKI that was found to be noninferior to sorafenib in terms of OS [4]. Ongoing research, however, has led to the introduction of immune checkpoint inhibitor (ICI)-based therapies [5]. ICIs work by restoring T cell activation, enabling the body to mount an antitumour response [5, 6]. They bind to immune checkpoint proteins and block inhibitory signals that prevent T cell activation [5, 6]. ICIs that block programmed cell death 1, its ligand (PD-L1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) are well established for the treatment of a range of solid tumours [5], including atezolizumab, a PD-L1 blocker used in combination with the vascular endothelial growth factor inhibitor bevacizumab as a first-line systemic therapy for HCC [4, 7–10]. Combination immunotherapy has become an area of focus following the failure of ICI monotherapy to improve OS in patients with HCC [11–13].

Tremelimumab (tremelimumab-actl; Imjudo®) is a monoclonal antibody and ICI that blocks CTLA-4 [14]. It is indicated for use in combination with durvalumab, an ICI which blocks PD-L1, as part of a regimen known as STRIDE (Single Tremelimumab Regular Interval Durvalumab) for the treatment of adults with unresectable HCC in the USA [15] and Japan [16], and for the first-line treatment of adults with advanced or unresectable HCC in the EU [17]. This article provides an overview of the pharmacological properties of tremelimumab when used as part of the STRIDE regimen and reviews clinical data relevant to its use in HCC. Tremelimumab in combination with durvalumab and platinum-based chemotherapy is also approved to treat certain non-small cell lung cancers [15–17]. However, discussion of this indication is outside of the scope of this review.

2 Pharmacodynamic Properties of Tremelimumab

Tremelimumab is a fully human immunoglobulin (Ig) G2 monoclonal antibody that blocks the interaction of CTLA-4 with its ligands CD80 and CD86 [15, 17]. CTLA-4 is primarily found on the surface of activated T cells [17]. By binding to and blocking CTLA-4, tremelimumab prevents CTLA-4-mediated inhibition of T-cell activation [15, 17]. In vitro, tremelimumab binds with > 500-fold higher selectivity for CTLA-4 than CD28, CD86 or Ig G1 [18]. Once bound to CTLA-4, tremelimumab blocked CTLA-4 from binding to immobilized CD80 and CD86 (mean half-maximal inhibitory concentration values of 0.65 and 0.50 nmol/L, respectively). In human T cell blasts stimulated with Raji cells expressing CD80 and CD86, tremelimumab enhanced the production of interleukin-2 (IL-2) and interferon-γ. Tremelimumab also dose-dependently enhanced the production of IL-2 in human and cynomolgus monkey whole blood and peripheral blood mononuclear cells stimulated with staphylococcal enterotoxin A superantigen [18].

In syngeneic mouse tumour models, blocking CTLA-4 activity led to a decrease in tumour cell growth and an increase in the proliferation of T cells in tumours [15, 19]. In a phase I/II trial (Study 22; Sect. 4), biomarker analysis showed expansion of proliferative CD8+ T cells during early treatment (day 15) with tremelimumab [20]. The highest median counts were observed in patients treated with the STRIDE regimen, the treatment arm associated with the highest objective response rate (ORR) [20]. The exposure-response relationship and time course of pharmacodynamic response for the safety and efficacy of tremelimumab are not fully characterized [15]. However, further analysis of data from Study 22 revealed a saturable relationship between tremelimumab exposure and percentage change from baseline in CD8+ T cells in patients with unresectable HCC, with higher levels of tremelimumab exposure not being associated with greater levels of CD8+ T-cell expansion or increased survival benefit [21]. A greater percentage change from baseline in CD8+ T-cell counts was observed in patients with lower rather than higher CD8+ T-cell levels at baseline. Taken together, the results suggest a critical threshold of CD8+ T-cell expansion may need to be met for patients with unresectable HCC to have a positive clinical response to tremelimumab [21].

3 Pharmacokinetic Properties of Tremelimumab

The pharmacokinetics of a single dose of intravenous tremelimumab 300 mg have been studied in patients with HCC. The pharmacokinetics of tremelimumab 1, 3 and 10 mg/kg given every 4 weeks for four doses have also been studied in patients with other solid tumours [15].

Tremelimumab pharmacokinetics are dose-proportional at doses ≥ 75 mg [17]. The geometric mean central and peripheral volume of distribution is 3.45 and 2.66 L, respectively [15]. After a single intravenous dose of tremelimumab,

the geometric mean terminal half-life is 16.9 days, and the geometric mean clearance is 0.286 L/day [15]. The pharmacokinetics of tremelimumab are not affected in a clinically meaningful way by age (18–87 years), body weight (34–149 kg), sex, race, positive anti-drug antibody (ADA) status, albumin levels, lactate dehydrogenase levels, soluble PD-L1, tumour type, Eastern Cooperative Oncology Group (ECOG)/WHO performance status, or mild to moderate kidney or hepatic impairment [15, 17]. The effect of severe kidney or hepatic impairment on the pharmacokinetics of tremelimumab is unknown [15, 17], but changes in hepatic function are not expected to impact tremelimumab exposure because Ig G monoclonal antibodies are not primarily cleared by hepatic pathways [17].

Results from population pharmacokinetic and exposure-response analyses, which included data from Study 22 and the phase III HIMALAYA trial (Sect. 4), support the use of the STRIDE regimen for the treatment of adults with unresectable HCC [21, 22]. No significant association between tremelimumab exposure and adverse events, OS or progression-free survival (PFS) was found [22].

No formal pharmacokinetic drug-drug interaction studies have been conducted with tremelimumab; however, no metabolic drug-drug interactions are expected because of the pathways involved in the elimination of the drug [17].

4 Therapeutic Efficacy of Tremelimumab

This section focuses on the efficacy of the STRIDE regimen for the treatment of adults with unresectable HCC as evaluated in the randomized, open-label (sponsor-blind), multicentre, phase III HIMALAYA trial [11]. A phase I/II trial ($n = 332$; Study 22) designed to inform HIMALAYA was ongoing when HIMALAYA was initiated [20]. This trial evaluated the safety, efficacy and pharmacodynamics of STRIDE (tremelimumab 300 mg for one dose plus durvalumab 1500 mg every 4 weeks), durvalumab 1500 mg every 4 weeks, tremelimumab 750 mg every 4 weeks for seven doses then every 12 weeks, and tremelimumab 75 mg every 4 weeks for four doses plus durvalumab 1500 mg every 4 weeks [20]. The results from Study 22 supported further investigation of STRIDE and were consistent with the findings of HIMALAYA [11, 20].

HIMALAYA enrolled patients aged ≥ 18 years with histologically confirmed HCC who had not previously received systemic therapy and who were ineligible for locoregional therapy. Patients had Barcelona Clinic Liver Cancer (BCLC) stage B or C, Child-Pugh class A, ECOG performance status score of 0 or 1, and ≥ 1 measurable lesion per response evaluation criteria in solid tumours version 1.1. Patients who had either ascites requiring nonpharmacological intervention, main portal vein thrombosis (Vp4), or co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), were excluded [11, 19].

After stratification by macrovascular invasion (yes or no), aetiology of liver disease [HBV or HCV (but not both) or nonviral], and ECOG performance status (0 or 1), patients were initially randomized 1:1:1:1 to treatment with STRIDE ($n = 393$), durvalumab 1500 mg every 4 weeks ($n = 389$), sorafenib 400 mg twice daily (control arm; $n = 389$) or tremelimumab 75 mg every 4 weeks for four doses plus durvalumab 1500 mg every 4 weeks ($n = 153$) until disease progression or unacceptable toxicity [11]. However, the results of a preplanned interim analysis of Study 22 showed that the efficacy of tremelimumab 75 mg plus durvalumab did not meaningfully differentiate from that of durvalumab monotherapy, which lead to enrolment in that arm of HIMALAYA being closed [11, 20]. Baseline characteristics were similar across the three remaining treatment groups which randomized a total of 1171 patients [11]. Across these groups, the median age was 64–65 years (range 18-88 years) and most patients were male (84.3%), had an ECOG performance status of 0 (61.7%), a Child-Pugh class/score of A/5 (73.1%) and a BCLC stage of C (81.0%), and 25.4% had macrovascular invasion. Comorbidities included HBV (30.7%) and HCV (27.4%) [11].

The primary endpoint was OS for STRIDE versus sorafenib [11]. Key secondary endpoints included non-inferiority and superiority for OS for durvalumab versus sorafenib. Additional secondary endpoints were OS rates at 18, 24 and 36 months, PFS, time to progression, ORR, duration of response (DOR) and patient-reported outcomes. Efficacy was assessed using data from the intent-to-treat population in the STRIDE, durvalumab and sorafenib arms only. At primary data cut-off, the median duration of follow-up was 33.18, 32.56 and 32.23 months in the STRIDE, durvalumab and sorafenib arms, respectively [11]. An updated OS analysis was also conducted at 48 months, at which time the respective median durations of follow-up were 49.12, 48.46 and 47.31 months [23].

4.1 Overall Survival

The STRIDE regimen significantly improved OS compared with sorafenib in adults with unresectable HCC and no prior systemic therapy in HIMALAYA [11]. At primary data cut-off, 66.7% of STRIDE recipients had died versus 75.3% of sorafenib recipients (primary endpoint), corresponding to a 22% reduction in the risk of death [OS hazard ratio (HR) 0.78; 96.02% confidence interval (CI) 0.65–0.93; $p = 0.0035$]. Median OS was prolonged by 2.66 months in STRIDE recipients (Table 1). A greater proportion of STRIDE recipients were alive at 18, 24 and 36 months compared with sorafenib recipients, with OS rates of 48.7%, 40.5% and 30.7% in the STRIDE arm and 41.5%, 32.6% and 20.2% in the sorafenib arm, respectively [11].

A delayed separation of the OS Kaplan-Meier curves for STRIDE and sorafenib was observed at ≈ 4 months, suggesting non-proportional hazards [11, 19]. Post hoc analysis calculating the piecewise constant treatment effects favoured STRIDE over sorafenib at all time intervals selected (from 0 up to 9 months and beyond) and showed the delayed separation did not negatively impact OS in STRIDE recipients. At 0–9 months the piecewise HR for STRIDE versus sorafenib was 0.87 (95% CI 0.68–1.11) and at > 9 months it was 0.70 (95% CI 0.56–0.89). [11, 19].

The effects of STRIDE versus sorafenib on OS were generally consistent across patient subgroups including the stratification criteria used for randomization, age (< or ≥ 65 years), region [Asia (except Japan) or rest of world (including Japan)] and other criteria describing tumour characteristics [11]. Of note, the OS benefit associated with STRIDE versus sorafenib was sustained at 48 months' follow-up, with a 22% reduction in the risk of death still observed (OS HR 0.78; 95.0% CI 0.67–0.92; $p = 0.0037$) and an OS rate of 25.2% in STRIDE recipients compared with 15.1% in sorafenib recipients [23]. The long-term OS benefit associated with STRIDE was not linked to any particular subgroup. The OS rates at 36 and 48 months in the 60.1% of STRIDE recipients who achieved disease control, were nearly 45% and 36%, respectively [11, 23].

Durvalumab monotherapy was noninferior, but not superior, to sorafenib for OS (secondary endpoint) in HIMALAYA (Table 1) [11]. At primary data cut-off, 72.0% of durvalumab recipients had died versus 75.3% of sorafenib recipients (OS HR 0.86; 95.67% CI 0.73–1.03; noninferiority margin CI upper bound of 1.08). OS rates at 18, 24 and 36 months in durvalumab recipients were 47.4%, 39.6% and 24.7%, respectively [11].

4.2 Other Secondary Endpoints

The STRIDE regimen was associated with similar or better outcomes than sorafenib in terms of other secondary endpoints in HIMALAYA (Table 1) [11]. The higher ORR observed in STRIDE recipients (Table 1) included higher rates of both complete (3.1 vs 0%) and partial (17.0 vs 5.1%) response in STRIDE versus sorafenib recipients. The median DOR in STRIDE recipients was ≈ 4 months longer than that seen in sorafenib recipients (Table 1). The upper limit of the interquartile range DOR was not reached in STRIDE recipients but was 25.99 months with sorafenib (Table 1). At 12 months, 65.8%, 57.8% and 63.2% of STRIDE, durvalumab and sorafenib recipients, respectively, remained in response [11].

Patients receiving STRIDE had a prolonged median time to deterioration of patient-reported global health status or quality of life (QOL) compared with patients receiving sorafenib (Table 1), as assessed using the European Organization for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire (EORTC QLQ-C30) [11]. STRIDE was also associated with better health state utilities (HSU)

Table 1 Efficacy of tremelimumab in combination with durvalumab in adult patients with unresectable hepatocellular carcinoma in the HIMALAYA trial

Endpoint [11]	STRIDE ($n = 393$)	Durvalumab ($n = 389$)	Sorafenib ($n = 389$)
Median OS (months)	16.43[a*]	16.56	13.77
	HR[b] 0.78 (96.02% CI 0.65–0.93)	HR[b] 0.86 (95.67% CI 0.73–1.03)	
OS at 36 months (% of pts)	30.7	24.7	20.2
Median PFS (months)	3.78	3.65	4.07
	HR[b] 0.90 (95% CI 0.77–1.05)	HR[b] 1.02 (95% CI 0.88–1.19)	
Median TTP (months)	5.4	3.8	5.6
ORR (% of pts)	20.1	17.0	5.1
DCR (% of pts)	60.1	54.8	60.7
Median DOR (months)	22.34	16.82	18.43
Interquartile range DOR (months)	8.54–NR	7.43–NR	6.51–25.99
Median time to response (months)	2.17	2.09	3.78
Median time to deterioration on EORTC QLQ-C30[c] (months)	7.5	7.4	5.7
	HR[b] 0.76 (95% CI 0.61–0.96)	HR[b] 0.77 (95% CI 0.62–0.96)	

DCR disease control rate, *DOR* duration of response, *EORTC QLQ*-C30 European Organization for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire, *HR* hazard ratio, *NR* not reached, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *pts* patients, *STRIDE* Single Tremelimumab Regular Interval Durvalumab, *TTP* time to progression

*$p = 0.0035$ vs sorafenib

[a]Primary endpoint vs sorafenib

[b]HR for STRIDE or durvalumab versus sorafenib

[c]Deterioration defined as a decrease in score from baseline of ≥ 10; scores range from 1 to 100, with higher scores indicating better health status

compared with sorafenib or being off treatment, as assessed using EuroQol, 5-Dimension, 5-Level health state utility index (EQ-5D-5L) and visual analogue scale [24].

Disease progression or death occurred in 85.2%, 88.7% and 84.1% of STRIDE, durvalumab and sorafenib recipients, respectively. Median PFS was similar between recipients of STRIDE and sorafenib (Table 1). However, 12.5% of STRIDE versus 4.9% of sorafenib recipients remained progression-free at primary data cut-off [11].

5 Tolerability of Tremelimumab

The STRIDE regimen had a manageable safety profile in adults with unresectable HCC participating in the HIMALAYA trial discussed in Sect. 4 [11]. The safety profile of STRIDE was consistent with the known safety profiles of tremelimumab and durvalumab, and no new safety concerns were identified. The safety population in HIMALAYA included patients who received ≥ one dose in the STRIDE, sorafenib, durvalumab and tremelimumab 75 mg plus durvalumab arms. The median duration of treatment with durvalumab in the STRIDE, durvalumab and tremelimumab 75 mg plus durvalumab arms was 5.5, 5.5 and 4.6 months, respectively, while the medium duration of treatment with sorafenib was 4.1 months [11].

The incidence of treatment-related adverse events (TRAEs) was 75.8%, 84.8%, 69.7% and 52.1% in the STRIDE, sorafenib, tremelimumab 75 mg plus durvalumab and durvalumab arms, respectively [11]. Serious TRAEs occurred in 17.5% and 18.4% of patients receiving STRIDE and tremelimumab 75 mg plus durvalumab, respectively, compared with 8.2% and 9.4% of those receiving monotherapy with durvalumab and sorafenib, respectively. Grade 3 or 4 TRAEs, TRAEs leading to delayed treatment and TRAEs leading to discontinuation occurred in 25.8%, 21.4% and 8.2% of STRIDE versus 36.9%, 38.5% and 11.0% of sorafenib recipients, respectively. The most common TRAEs (incidence ≥ 10%) and grade 3 or 4 TRAEs (incidence ≥ 2%) are shown in Figs. 1 and 2, respectively [11]. TRAEs resulting in death occurred in 2.3% and 1.3% of patients receiving STRIDE and tremelimumab 75 mg plus durvalumab, respectively, compared with 0% and 0.8% of those receiving monotherapy with durvalumab and sorafenib, respectively [11]. At 48 months' follow-up, there were no new serious TRAEs in STRIDE recipients since the primary analysis cut-off [23].

5.1 Adverse Events of Special Interest

Tremelimumab may cause immune-mediated adverse reactions (Sect. 6), which can occur in any organ and may be severe or fatal [15, 17]. In HIMALAYA, treatment-related immune-mediated adverse events (IMAEs) occurred in 34.5%, 14.9% and 32.2% of STRIDE, durvalumab, and tremelimumab 75 mg plus durvalumab recipients, respectively, compared with 5.6% of sorafenib recipients [11]. Serious treatment-related IMAEs, treatment-related grade 3 or 4 IMAEs, IMAEs requiring treatment with high-dose steroids, and IMAEs leading to discontinuation occurred in 10.6%, 12.6%, 20.1% and 5.7% of STRIDE recipients

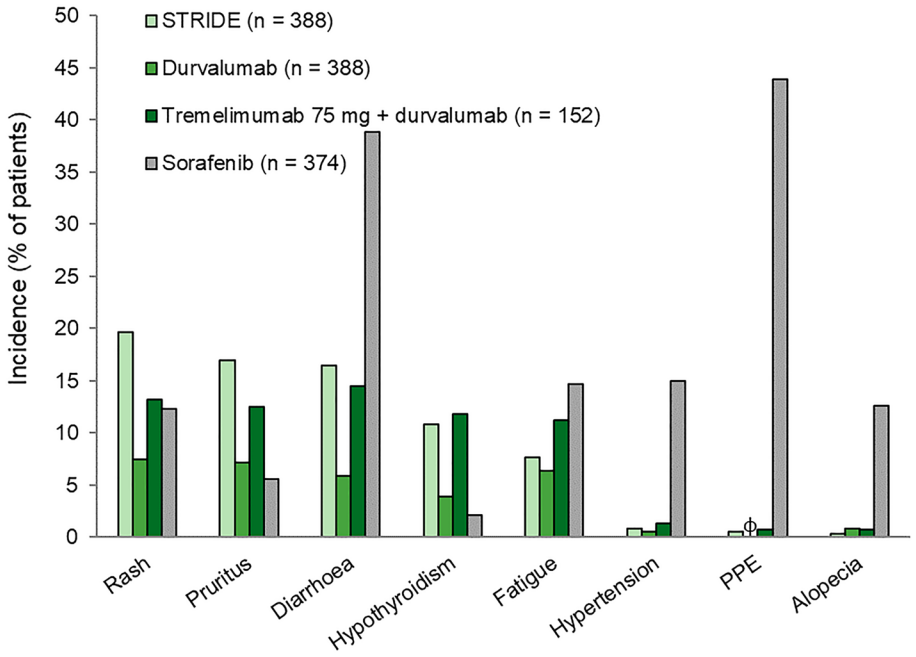

Fig. 1 Most common treatment-related adverse events occurring in ≥ 10% of patients in any treatment arm in the safety analysis population of the phase III HIMALAYA trial [11]. *PPE* palmar-plantar erythrodysesthesia syndrome, *STRIDE* Single Tremelimumab Regular Interval Durvalumab, ϕ zero value

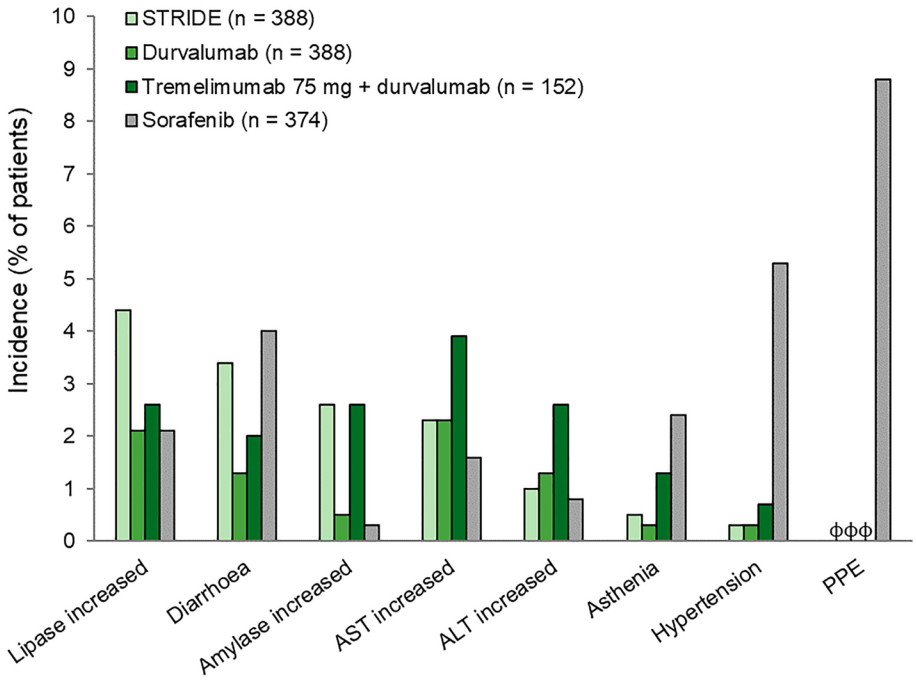

Fig. 2 Grade 3 or 4 treatment-related adverse events occurring in ≥ 2% of patients in any treatment arm in the safety analysis population in the phase III HIMALAYA trial [11]. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *PPE* palmar-plantar erythrodysesthesia syndrome, *STRIDE* Single Tremelimumab Regular Interval Durvalumab, ϕ zero value

versus 1.1%, 2.4%, 1.9% and 1.6% of sorafenib recipients, respectively [11]. Grade 3 or 4 IMAEs in STRIDE recipients most commonly occurred ≤ 3 months after treatment, according to an exploratory post hoc analysis [25]. The most frequent (incidence ≥ 2%) IMAEs in STRIDE recipients requiring treatment with high-dose steroids were hepatic events (7.5%), diarrhoea/colitis (5.2%) and dermatitis/rash (3.1%) [11]. The most frequent (incidence ≥ 2%) IMAEs leading to treatment discontinuation in STRIDE recipients were hepatic events (2.3%). No IMAEs requiring treatment with high-dose steroids or leading to treatment discontinuation occurred in ≥ 2% of sorafenib recipients. All six cases of death due to treatment-related IMAEs in HIMALAYA occurred in STRIDE recipients and included one case each of pneumonitis, hepatitis, myocarditis, myasthenia gravis, and two cases of immune-mediated hepatitis [11]. The role of STRIDE in these deaths could not be ruled out [19]. If immune-mediated adverse reactions occur, STRIDE may need to be withheld or permanently discontinued [15, 17]. An exploratory analysis found median OS was longer (OS HR 0.73; 95% CI 0.56–0.95) in STRIDE recipients who experienced IMAEs than in those who didn't (23.2 vs 14.1 months) [26].

Tremelimumab may also cause infusion-related reactions (IRRs) [Sect. 6] [15, 17]. In a pooled analysis of safety data from HIMALAYA and Study 22, IRRs and urticaria occurred in 1.3% of patients treated with STRIDE [17]. Infusion of tremelimumab may need to be slowed, interrupted or discontinued if IRRs occur [15, 17].

A total of 11% (20/182) of STRIDE recipients in HIMALAYA tested positive for ADAs against tremelimumab, with neutralizing antibodies detected in 40% (8/20) of these patients [11, 15]. ADAs against durvalumab were found in 3.1% (9/294) of STRIDE recipients, with 56% (5/9) of these patients testing positive for neutralizing antibodies [11]. ADAs had no impact on the pharmacokinetics or safety of tremelimumab, but their effect on the efficacy of tremelimumab is unknown due to their low occurrence [15, 19]. No trend in IRRs based on ADA status was identified [19].

6 Dosage and Administration of Tremelimumab

Tremelimumab is indicated for use in combination with durvalumab for the treatment of adults with unresectable HCC in the USA [15] and Japan [16], and for the first-line treatment of adults with advanced or unresectable HCC in the EU [17] and several other countries. The recommended tremelimumab regimen, called STRIDE, is a single dose of tremelimumab 300 mg administered by intravenous infusion over 60 min, followed by a separate intravenous infusion of durvalumab 1500 mg at cycle 1/day 1, then durvalumab 1500 mg as a single agent every 4 weeks until disease progression or unacceptable toxicity, except in patients with extremely low body weight, where weight-based dosing is recommended [15, 17]. The recommended dosage of tremelimumab in patients weighing < 30 kg (USA) or ≤ 40 kg (EU) is 4 mg/kg in combination

with durvalumab 20 mg/kg (in patients weighing < 30 kg in the USA or ≤ 30 kg in the EU). Dose escalation or reduction is not recommended during administration of STRIDE, but safety and tolerability issues may require treatment be delayed or discontinued. The US and EU product labels for tremelimumab carry warnings regarding immune-mediated adverse reactions (Sect. 5.1) and IRRs (Sect. 5.1) [15, 17]. The US product label also carries a warning regarding embryo-foetal toxicity [15].

There are no data available on the use of tremelimumab in pregnant people but based on data from animal studies and its mechanism of action, tremelimumab may cause foetal harm [15, 17]. People of childbearing potential should be advised to use effective contraception during treatment and for ≥ 3 months after the last dose of tremelimumab. It is also advised to avoid breastfeeding during treatment and for ≥ 3 months after the last dose of tremelimumab because of the potential for adverse reactions in breastfed children [15, 17]. Local prescribing information should be consulted for further detailed information regarding preparation, storage and administration procedures, warnings and precautions and use in special populations.

7 Place of Tremelimumab in the Management of Advanced or Unresectable Hepatocellular Carcinoma

Clinical practice guidelines for HCC place patient preferences and characteristics, including tumour stage, hepatic function and performance status, at the centre of the decision-making process regarding treatment. Liver transplant, resection and locoregional treatments, such as ablation, arterially directed therapies and radiation therapy, are recommended for early- and intermediate-stage HCC, while systemic treatments are generally reserved for advanced disease and best supportive care for end-stage disease [4, 7–10].

For many years the multi-targeted TKI sorafenib was the standard of care for the first-line treatment of advanced HCC [3, 9, 10]. However, ICI-containing regimens have recently become the preferred option for patients requiring systemic therapy because they provide an OS benefit compared with sorafenib [4, 7, 8, 11, 27]. Combination immunotherapy, in particular, has superior antitumour activity and immune-stimulating effects that are different from those seen with ICI monotherapy, which fails to improve OS in patients with HCC compared with sorafenib [11–13].

Both the STRIDE regimen and atezolizumab + bevacizumab are recommended as preferred first-line systemic therapies for HCC in the National Comprehensive Cancer Network (NCCN) guidelines, the American Association for the Study of Liver Diseases (AASLD) guidelines, the Society for Immunotherapy of Cancer (SITC) guideline on immunotherapy for HCC and the BCLC strategy, with the NCCN and BCLC recommending the latter combination for Child-Pugh class A patients only and the AASLD and SITC recommending both combinations for Child-Pugh class A patients only [4, 7, 10, 28]. The AASLD recommends STRIDE ahead of atezolizumab + bevacizumab in patients at high-risk of gastrointestinal or oesophageal bleeding [10], while the BCLC preferred atezolizumab + bevacizumab over STRIDE at a time when full results from HIMALAYA were not available [7]. Sorafenib and lenvatinib are other first-line regimens that may be used when immune-based regimens are contraindicated [4, 7, 10, 28]. NCCN, BCLC and the European Medicines Agency also recommend durvalumab alone as a possible first-line regimen following HIMALAYA [4, 7, 29]. Other treatment guidelines have not been updated yet to include tremelimumab or STRIDE [8, 9, 30]. Following HIMALAYA, tremelimumab has been assigned a European Society for Medical Oncology-Magnitude of Clinical Benefit Scale score of 5 [31].

The STRIDE regimen adds a single priming dose of intravenous tremelimumab 300 mg to durvalumab 1500 mg given every 4 weeks from cycle 1/day 1 until disease progression or unacceptable toxicity (Sect. 6). Approval of tremelimumab was based on data from the randomized phase III HIMALAYA trial (Sect. 4), which found that STRIDE significantly improved OS in patients with unresectable HCC compared with sorafenib (Sect. 4.1). Durvalumab alone was non-inferior to sorafenib (Sect. 4.1). A higher proportion of STRIDE versus sorafenib recipients had an objective response (Sect. 4.2). The OS benefit associated with STRIDE was found to be sustained at 48 months' follow-up (Sect. 4.1). STRIDE was also associated with better HSUs compared with sorafenib or being off treatment and a prolonged median time to deterioration of global health status or QOL compared with sorafenib (Sect. 4.2). Limitations of the HIMALAYA trial included the open-label design, a lack of randomization stratified by geographical location and the exclusion of patients with Vp4 thrombosis [11].

The STRIDE regimen had a manageable safety profile in patients with unresectable HCC in HIMALAYA, in keeping with the known safety profiles of tremelimumab and durvalumab (Sect. 5). Grade 3 or 4 TRAEs occurred in a lower proportion of STRIDE versus sorafenib recipients (Sect. 5). STRIDE did not significantly increase the incidence of hepatotoxicity or haemorrhage, an important finding given that HCC typically develops on a background of chronic liver disease [2, 11]. IMAEs requiring treatment with high-dose steroids or leading to treatment discontinuation were more common in STRIDE versus sorafenib recipients (Sect. 5.1), which was expected as IMAEs are more common with ICIs than other cancer therapies [19]. Monitoring for signs and symptoms of IMAEs and IRRs is recommended (Sect. 5.1) [15, 17].

Head-to-head data comparing STRIDE with atezolizumab + bevacizumab are lacking. While results of indirect comparisons should be interpreted with caution, a network metanalysis found that atezolizumab + bevacizumab was not superior to STRIDE in reducing the risk of death [32], while a matching adjusted indirect comparison (MAIC) reported the two treatments were associated with similar OS and ORRs [33]. The MAIC also found STRIDE was associated with fewer grade 3 or 4 TEAEs, and TEAEs leading to discontinuation were halved in STRIDE recipients. The long-term OS benefits of these two options have not been compared because data for atezolizumab + bevacizumab are lacking [33].

Specific disease and patient characteristics should be taken into account when selecting a treatment [34], with consideration given to the risk of bleeding, a known adverse reaction of bevacizumab, and the presence of Vp4 thrombosis, which was an exclusion criterion in HIMALAYA, but not in the IMbrave150 trial comparing atezolizumab + bevacizumab with sorafenib [27, 34]. Further research to identify biomarkers and characteristics that can be used to inform treatment decisions is warranted. Real-world data are also needed to help clarify the role of STRIDE in HCC. Cost-effectiveness analyses would also be of interest.

In conclusion, when used to prime the immune system, a single dose of tremelimumab used with durvalumab given every 4 weeks improves OS compared with sorafenib and has a manageable safety profile. Based on the available evidence, tremelimumab used as part of the STRIDE regimen is a valuable first-line agent that expands the treatment options available to patients with advanced or unresectable HCC.

Data Selection Tremelimumab: 129 records identified	
Duplicates removed	1
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	48
Excluded during writing (e.g. reviews; duplicate data; small patient number)	46
Cited efficacy/tolerability articles	9
Cited articles not efficacy/tolerability	25
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were tremelimumab, Imjudo, HIMALAYA, STRIDE, durvalumab, Imfinzi, hepatocellular, HCC, liver cancer. Records were limited to those in English language. Searches last updated 5 December 2023	

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