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Tislelizumab plus zanubrutinib for Richter transformation: the phase 2 RT1 trial

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In patients with chronic lymphocytic leukemia, Richter transformation (RT) reflects the development of an aggressive lymphoma that is associated with poor response to chemotherapy and short survival. We initiated an international, investigator-initiated, prospective, open-label phase 2 study in which patients with RT received a combination of the PD-1 inhibitor tislelizumab plus the BTK inhibitor zanubrutinib for 12 cycles. Patients responding to treatment underwent maintenance treatment with both agents. The primary end point was overall response rate after six cycles. Of 59 enrolled patients, 48 patients received at least two cycles of treatment and comprised the analysis population according to the study protocol. The median observation time was 13.9 months, the median age was 67 (range 45–82) years. Ten patients (20.8%) had received previous RT-directed therapy. In total, 28 out of 48 patients responded to induction therapy with an overall response rate of 58.3% (95% confidence interval (CI) 43.2–72.4), including 9 (18.8%) complete reponse and 19 (39.6%) partial response, meeting the study's primary end point by rejecting the predefined null hypothesis of 40% ($P = 0.008$). Secondary end points included duration of response, progression-free survival and overall survival. The median duration of response was not reached, the median progression-free survival was 10.0 months (95% CI 3.8–16.3). Median overall survival was not reached with a 12-month overall survival rate of 74.7% (95% CI 58.4–91.0). The most common adverse events were infections (18.0%), gastrointestinal disorders (13.0%) and hematological toxicities (11.4%). These data suggest that combined checkpoint and BTK inhibition by tislelizumab plus zanubrutinib is an effective and well-tolerated treatment strategy for patients with RT. ClinicalTrials.gov Identifier: NCT04271956.

Chronic lymphocytic leukemia (CLL) is classified as an indolent B cell non-Hodgkin lymphoma according to the World Health Organization classification and is the most common type of leukemia in adults[1]. RT (also known as Richter's syndrome) describes the development of an aggressive lymphoma developing in patients with CLL, most commonly a diffuse large B cell lymphoma (DLBCL) or Hodgkin's lymphoma (HL)[2,3]. The incidence rates of RT among patients with CLL range from 2 to 10%[4]. RT can occur at any time during the course of CLL, though occurrence

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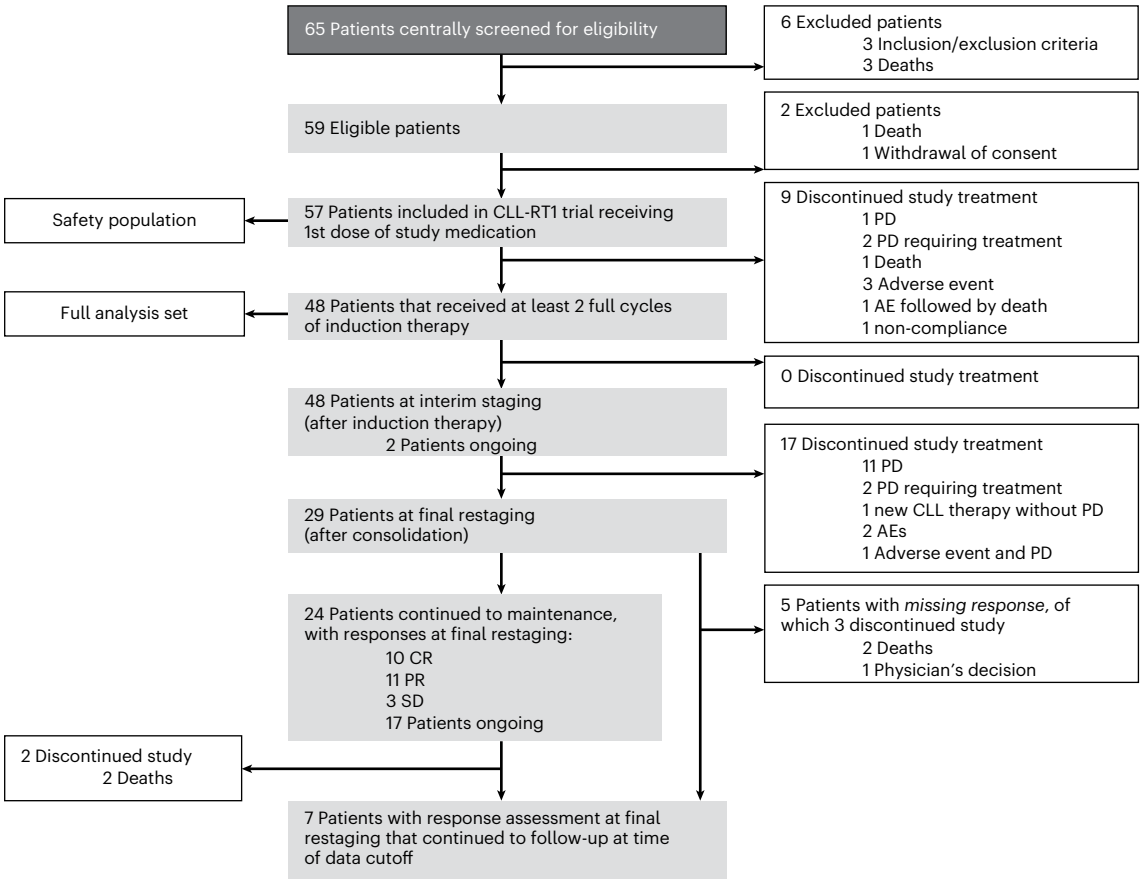

Fig. 1 | CONSORT diagram of RT1. PD, progressive disease; AE, adverse event.

in treatment-naive CLL is less frequent than in pretreated CLL. Patients with RT have a dismal prognosis with chemoimmunotherapy such as R-CHOP, with overall response rates (ORR) of <40% and median overall survival of 6–8 months[4,5]. Targeted therapies have the potential to improve outcomes, but few prospective studies have been run in this entity so far. Previous reports suggested efficacy of monotherapy with checkpoint inhibitors, BTK inhibitors, BCL-2 inhibitors and PI3K inhibitors[6–10], but sample sizes were limited and potentially underpowered for conclusive results.

Programmed cell death protein 1 (PD-1) is an important immune-checkpoint receptor that is predominantly expressed on activated T cells and transmits inhibitory signals into T cells after ligation with PD-L1 or PD-L2 on malignant cells and the tumor microenvironment[11,12]. Immunotherapy via blockade of PD-1 or PD-L1 has demonstrated high efficacy and has become an established component for the therapy of multiple cancers[13,14]. In the context of RT, PD-1 expression has been reported as a common feature[15] and several preclinical models have suggested a susceptibility of RT to checkpoint inhibition[16,17].

Though checkpoint inhibitors are promising candidates for treatment of RT, single-agent treatment with PD-1 inhibitors did not prevent progression of CLL[18], suggesting that a combinational approach might be needed to target both the aggressive and indolent components of RT.

BTK inhibitors have become a cornerstone of CLL therapy, as B cell receptor (BCR) signaling is a key dependency of CLL cells that is required to sustain prosurvival signals from the microenvironment[19]. Several BTK inhibitors are available for the treatment of CLL and have demonstrated good long-term efficacy[20]. In the context of RT, preclinical models have demonstrated BCR signaling dependency that suggests sensitivity to BCR inhibitors[21]. This was further substantiated in translational studies that outlined the role of BCR signaling in RT samples[22,23]; however, monotherapy of RT with BTK inhibitors such as acalabrutinib or pirtobrutinib monotherapy offered only short-term disease control, supporting the need for combination strategies[9,24].

Based on preclinical and translational data that suggested immune-checkpoint inhibition and BTK inhibition as possible vulnerabilities of RT, we hypothesized that a combination of tislelizumab and zanubrutinib could be an effective strategy to induce remissions in patients with RT, who are treatment-naive or have received up to one previous line of RT-directed therapy. Tislelizumab is a humanized, immunoglobulin G4-variant monoclonal antibody against PD-1 that has been explored in solid malignancies and has demonstrated low rates of immune-related adverse events and good efficacy. Tislelizumab has previously demonstrated efficacy in a variety of solid malignancies, including in the first-line treatment of advanced non-small cell lung cancer and esophageal cancer[25–28]. Zanubrutinib is a next-generation, covalent BTK inhibitor that has demonstrated limited off-targeted effects and thereby less toxicity and higher efficacy than the first-in class BTK inhibitor ibrutinib in patients with relapsed or refractory CLL[29,30].

Here, we present data of the international, investigator-initiated phase 2 RT1 trial, in which the PD-1 inhibitor tislelizumab was combined with the next-generation BTK inhibitor zanubrutinib to treat patients with RT, with the objective to compare the ORR after six cycles with the prespecified benchmark of 40%.

Results

Trial design and patients

Between 11 February 2020 and 2 January 2023, 65 patients were screened, of which 59 were enrolled. Of those, two did not receive study medication owing to death (one patient) and withdrawal of consent

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Table 1 | Baseline patient characteristics

Patient characteristics	
All patients	**48**
Age (years)	**48**
Median	67
IQR	60–74
Range	45–82
Sex, *n* (%)	**48**
Female	19 (39.6)
Male	29 (60.4)
Time between CLL diagnosis and study registration (months)	**48**
Median	79
IQR	49–136
Time between RT diagnosis and study registration (months)	**48**
Median	0.7
IQR	0.43–1.04
Number of previous CLL-directed therapies	**36**
Median	3
Range	1–6
Patients with previous CLL-directed therapies, *n* (%)	**36**
Chemo(immuno)therapy	25 (69.4)
SCT	3 (8.3)
BTK/BCL-2 inhibitors	32 (88.9)
BTK inhibitor	24 (66.7)
BCL-2 inhibitor	22 (61.1)
BTK + BCL-2 inhibitor	2 (5.6)
Other	9 (25.0)
Binet stage, *n* (%)	**48**
A	22 (45.8)
B	8 (16.7)
C	18 (37.5)
Severe constitutional symptoms, *n* (%)	**48**
No	28 (58.3)
Yes	20 (41.7)
ECOG performance status, *n* (%)	**48**
0	26 (54.2)
1	15 (31.3)
2	6 (12.5)
3	1 (2.1)
CIRS total score	**48**
Median	4
IQR	2–7
CIRS total score, *n* (%)	**48**
≤6	34 (70.8)
>6	14 (29.2)
LDH (U l^{-1})	**48**
Median	335
IQR	209–584
Patients with LDH > 250 U l^{-1}, *n* (%)	31 (64.6)

Table 1 (continued) | Baseline patient characteristics

Patient characteristics	
Cytogenetic subgroups hierarchical order (according to Döhner et al.[46]), *n* (%)	**46**
Deletion 17p	10 (21.7)
Deletion 11q	4 (8.7)
Trisomy 12	5 (10.9)
No abnormalities	19 (41.3)
Deletion 13q	8 (17.4)
Missing	2 (4.2)
***TP53* mutation status, *n* (%)**	**45**
Unmutated	32 (71.1)
Mutated	13 (28.9)
Missing	*3 (6.3)*
***TP53* status, *n* (%)**	**46**
None	30 (65.2)
Deleted and/or mutated	16 (34.8)
Missing	2 (4.2)
IGHV mutation status, *n* (%)	**41**
Unmutated	29 (70.7)
Mutated	12 (29.3)
Missing	7 (14.6)
Serum thymidine kinase (U l^{-1})	**47**
Median	40.1
IQR	18.5–108.3
Serum β_2-microglobulin (mg l^{-1})	**47**
Median	3.8
IQR	2.5–5.5
Complex karyotype, *n* (%)	**38**
<3 aberrations	22 (57.9)
≥3 aberrations	16 (42.1)
Missing	10 (20.8)
CLL-IPI risk group, *n* (%)	**39**
Low	3 (7.7)
Intermediate	11 (28.2)
High	10 (25.6)
Very high	15 (38.5)
Missing	9 (18.8)
RT features, *n* (%)	**48**
Previously untreated RT	38 (79.2)
Previously treated with RT-directed therapy	10 (20.8)
HL	2 (4.2)
DLBCL	46 (95.8)
Non-GCB	14 (29.2)
GCB	1 (2.1)
Unknown	33 (68.8)
Clonally unrelated	0 (0.0)
Clonally related	26 (54.2)
Unknown	22 (45.8)
Ki-67 (%)	**31**
Median	70
IQR	50–80

Cytogenetics, *TP53* and IGHV status and complex karyotype status were derived from peripheral blood and thus represent the CLL fraction.

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Table 2 | Adverse events

	Max CTC grade				57
Adverse event	**1–2**	**3**	**4**	**5**	**Total**
Blood and lymphatic system disorders	7 (12.3)	11 (19.3)	9 (15.8)	0 (0.0)	27 (47.4)
Anemia	3 (5.3)	8 (14.0)	0 (0.0)	0 (0.0)	11 (19.3)
Neutropenia	1 (1.8)	4 (7.0)	7 (12.3)	0 (0.0)	12 (21.1)
Thrombocytopenia	5 (8.8)	1 (1.8)	5 (8.8)	0 (0.0)	11 (19.3)
Cardiac disorders	4 (7.0)	1 (1.8)	0 (0.0)	0 (0.0)	5 (8.8)
Ear and labyrinth disorders	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)
Vertigo	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)
Eye disorders	7 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (12.3)
Gastrointestinal disorders	26 (45.6)	6 (10.5)	0 (0.0)	0 (0.0)	32 (56.1)
Abdominal pain	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)
Abdominal pain upper	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)
Diarrhea	13 (22.8)	3 (5.3)	0 (0.0)	0 (0.0)	16 (28.1)
Nausea	10 (17.5)	0 (0.0)	0 (0.0)	0 (0.0)	10 (17.5)
General disorders and administration site conditions	28 (49.1)	2 (3.5)	0 (0.0)	0 (0.0)	30 (52.6)
Fatigue	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)
Edema	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)
Edema peripheral	10 (17.5)	0 (0.0)	0 (0.0)	0 (0.0)	10 (17.5)
Pyrexia	10 (17.5)	1 (1.8)	0 (0.0)	0 (0.0)	11 (19.3)
Immune system disorders	2 (3.5)	3 (5.3)	0 (0.0)	0 (0.0)	5 (8.8)
Infections and infestations	21 (36.8)	20 (35.1)	1 (1.8)	3 (5.3)	45 (78.9)
COVID-19	12 (21.1)	1 (1.8)	0 (0.0)	0 (0.0)	13 (22.8)
Infection	0 (0.0)	4 (7.0)	0 (0.0)	0 (0.0)	4 (7.0)
Nasopharyngitis	8 (14.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (14.0)
Oral herpes	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.0)
Urinary tract infection	3 (5.3)	9 (15.8)	0 (0.0)	0 (0.0)	12 (21.1)
Injury, poisoning and procedural complications	9 (15.8)	1 (1.8)	0 (0.0)	0 (0.0)	10 (17.5)
Infusion related reaction	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)
Investigations	13 (22.8)	3 (5.3)	3 (5.3)	0 (0.0)	19 (33.3)
Blood creatinine increased	6 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.5)
Metabolism and nutrition disorders	7 (12.3)	10 (17.5)	0 (0.0)	0 (0.0)	17 (29.8)
Hypokalemia	7 (12.3)	2 (3.5)	0 (0.0)	0 (0.0)	9 (15.8)
Musculoskeletal and connective tissue disorders	17 (29.8)	4 (7.0)	0 (0.0)	0 (0.0)	21 (36.8)
Arthralgia	6 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.5)
Back pain	5 (8.8)	1 (1.8)	0 (0.0)	0 (0.0)	6 (10.5)
Nervous system disorders	13 (22.8)	7 (12.3)	0 (0.0)	0 (0.0)	20 (35.1)
Dizziness	7 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (12.3)
Headache	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)
Psychiatric disorders	7 (12.3)	1 (1.8)	0 (0.0)	0 (0.0)	8 (14.0)
Renal and urinary disorders	6 (10.5)	7 (12.3)	0 (0.0)	0 (0.0)	13 (22.8)
Reproductive system and breast disorders	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)
Respiratory, thoracic and mediastinal disorders	10 (17.5)	4 (7.0)	0 (0.0)	0 (0.0)	14 (24.6)
Cough	6 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.5)
Epistaxis	4 (7.0)	1 (1.8)	0 (0.0)	0 (0.0)	5 (8.8)
Skin and subcutaneous tissue disorders	23 (40.4)	1 (1.8)	0 (0.0)	0 (0.0)	24 (42.1)
Eczema	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.0)
Petechiae	6 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.5)
Pruritus	6 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.5)

Table 2 (continued) | Adverse events

	Max CTC grade				57
Adverse event	**1–2**	**3**	**4**	**5**	**Total**
Rash	10 (17.5)	1 (1.8)	0 (0.0)	0 (0.0)	11 (19.3)
Surgical and medical procedures	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.3)
Vascular disorders	8 (14.0)	4 (7.0)	0 (0.0)	0 (0.0)	12 (21.1)
Hematoma	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.0)
Hypotension	3 (5.3)	1 (1.8)	0 (0.0)	0 (0.0)	4 (7.0)

(one patient) and nine discontinued study treatment within the first two cycles owing to primary progressive disease (three patients), death (one patient), adverse events (four patients) and non-compliance (one patient). According to the study protocol, 48 patients who received at least two cycles of study treatment, including at least one administered dose in cycle three, comprised the analysis population (Fig. 1). The primary end point was ORR at interim staging and the secondary end points included ORR after consolidation therapy, duration of response (DOR), progression-free survival (PFS), overall survival, time to next treatment (TTNT) and safety. Post hoc analyses included ORR and time-to-event parameters in the intention-to-treat (ITT) population, ORR and PFS according to previous RT-directed therapy and according to previous BTK inhibitor exposure.

The median age was 67 (range 45–82) years, 29 (60.4%) patients were male and 19 (39.6%) were female (Table 1). Twenty-two (45.8%) patients had Eastern Cooperative Oncology Group (ECOG) performance status of 1 or higher and the median cumulative illness rating scale (CIRS) score was 4 (range 0–17). The median LDH at enrollment was 335 U l^{-1}. Sixteen (34.8%) patients had del(17p)/*TP53*mut, whereas 29 (70.7%) patients had unmutated IGHV. Overall, 25 (64.1%) patients had high or very high-risk CLL according to the chronic lymphocytic leukemia international prognostic index (CLL-IPI), 11 (28.2%) had intermediate risk and 3 (7.7%) had low risk. Complex karyotype (≥3 aberrations) was detected in 16 (42.1%) patients. A total of 46 (95.8%) patients had DLBCL-RT and 2 (4.2%) patients had HL-RT. In those 26 patients (54.2%) in whom clonal relatedness was evaluated by immunoglobulin heavy chain rearrangement analysis, all cases were reported as clonally related to the CLL (22 (45.8%) were unknown). The DLBCL subtype was evaluated in 15 patients with RT; 14 had a non-germinal center B cell (GCB) type and 1 had a GCB type. The median Ki-67 index was 70% (interquartile range (IQR) 50–80%). Overall, 36 (75.0%) patients had received previous CLL-directed therapy, including chemoimmunotherapy (CIT; 25 patients) and targeted agents (32 patients) as well as previous allogeneic stem cell transplant (SCT) in 3 patients. Of those patients with previous targeted treatment, 24 had received previous BTK inhibitor treatment, 22 patients had previous treatment with BCL-2 inhibitors and 2 patients had received previous combined BTK + BCL-2 inhibitor therapy (Table 1). Twelve (25.0%) patients had treatment-naive CLL. Ten patients (20.8%) had received previous RT-directed therapy, including R-CHOP-like regimens and one case of previous ibrutinib treatment. A total of 38 (79.2%) patients had not received previous RT-directed therapy (Table 1).

With a data cutoff of 2 May 2023, 19 patients were still under ongoing treatment (Fig. 2). Overall median observation time was 13.9 months (IQR 8.7–22.2) and median observation time for patients still alive was 12.0 months (IQR 8.4–22.1). The median number of treatment cycles of tislelizumab was 9 (IQR 4–23) and of zanubrutinib 11 (IQR 5–25).

Efficacy end points

Twenty-eight of 48 patients responded to induction therapy resulting in an ORR of 58.3% (95% CI 43.2–72.4), including 9 (18.8%) complete response and 19 (39.6%) partial response, meeting the study's primary end point ($P = 0.008$) by rejecting the predefined null hypothesis of 40% (Fig. 1). Stable disease was reported in 6 (12.5%) patients and 14 (29.2%) patients had progressive disease. The ORR as assessed according to the refined Lugano criteria agreed with the ORR according to iwCLL criteria. The median DOR was not reached; the 6-month DOR rate was 70.6% (95% CI 51.0–90.2; Fig. 3a). The median PFS was 10 months (95% CI 3.8–16.3) with a 12-month rate of 46.9% (95% CI 29.4–64.5; Fig. 3b). The median overall survival was not reached (12-month overall survival rate 74.7%, 95% CI 58.4–91.0) (Fig. 3c). All deaths were associated with disease progression. The median TTNT, defined as time to initiation of a next line of treatment with censoring of deaths, was 17.9 months (12-month TTNT rate 58.5%, 95% CI 40.7–76.4)) and 12.5 months (12-month TTNT rate 50.2%, 95% CI 32.2–68.1) when defined as time to initiation of a next line of treatment or death, whatever occurred first (Fig. 3d and Extended Data Fig. 1). Three of 48 patients have not reached the end of consolidation after 12 cycles so far. The ORR in the remaining 45 patients was 46.7% (95% CI 31.7–62.1) with a complete response in 10 patients (22.2%), partial response in 11 patients (24.4%), stable disease in 3 patients (6.7%), progressive disease in 3 patients (6.7%) and missing data in 18 patients (40.0%, including 16 patients with discontinuation of therapy before reaching the end of consolidation).

Post-protocol treatment included chemoimmunotherapy in 21 cases (50.0%), BTK/BCL-2 inhibition in 7 (16.7%) cases and 8 (19.0%) allogeneic SCT (Extended Data Table 1). SCT was conducted as consolidation in two patients with partial response and as salvage treatment for five patients with stable disease or progressive disease (one missing response) (Fig. 2).

None of the assessed baseline clinical, serological or genomic features was significantly associated with response or non-response (Extended Data Table 2). In a univariate analysis, factors significantly associated with shorter PFS were the presence of severe constitutional symptoms, ECOG > 0, LDH, thymidine kinase and serum β_2-microglobulin (>3.5 mg l^{-1}). Shorter overall survival was associated with Binet C, age, severe constitutional symptoms, LDH, thymidine kinase and serum β_2-microglobulin (>3.5 mg l^{-1}). Shorter DOR was associated with presence of Binet C, LDH, *TP53* deletion and/or mutation, thymidine kinase and serum β_2-microglobulin (Extended Data Tables 3–5).

The ORR in patients without previous RT-directed therapy was 57.9% (95% CI 40.8–73.7) and 60.0% (95% CI 26.2–87.8) in patients with previous RT-directed therapy. Patients without previous RT-directed therapy had a 12-month PFS rate of 43.5% (95% CI 23.2–63.9) and patients with previous RT-directed therapy had a 12-month PFS rate of 60.0% (95% CI 19.9–100.0) (Extended Data Fig. 2a).

Patients without previous exposure to BTK inhibitors had an ORR of 69.6% (95% CI 47.1–86.8) and patients with previous BTK inhibitor therapy had an ORR of 48.0% (95% CI 27.8–68.7). The 12-month PFS rate in patients without previous BTK inhibitor therapy was 58.3% (95% CI 33.2–83.4) and 37.2% (95% CI 12.8–61.6) in patients with previous BTK inhibitor therapy (Extended Data Fig. 2b).

A post hoc analysis of all 59 eligible patients, including those not receiving study treatment for at least two cycles (ITT population), demonstrated an ORR of 47.5% (95% CI 34.3–60.9); both patients with HL responded with a partial response. The median PFS of all eligible

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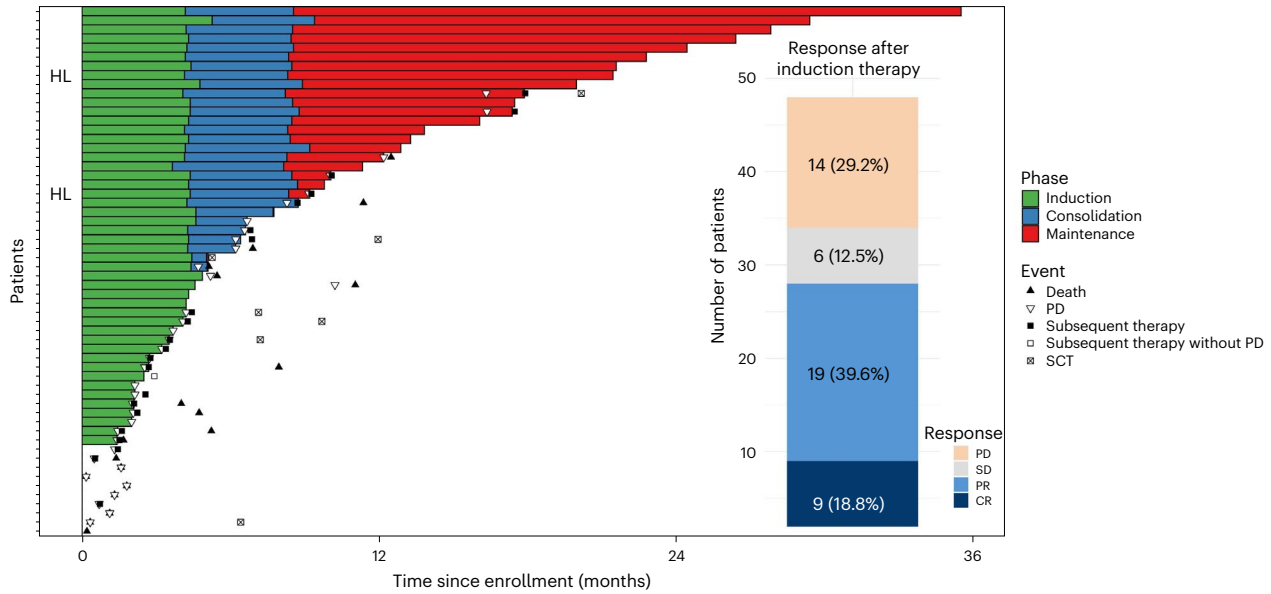

Fig. 2 | Response rates and duration of treatment. Swimmer plot depicts disease assessments and treatment phase and duration. Bar chart indicates response rates. CR, complete response; PR, partial response; SD, stable disease.

patients was 6.7 months (95% CI 2.3–11.0) with a 12-month rate of 39.5% (95% CI 23.8–55.3), median overall survival was not reached (12-month overall survival rate 65.7%, 95% CI 49.3–82.0) and median TTNT was 17.9 months (12-month TTNT rate 55.4%, 95% CI 38.0–72.7) (Extended Data Fig. 3 and Extended Data Table 6).

Safety end points

For the safety analysis, all 57 included patients who had received at least one dose of any study medication were considered. A total of 56 (98.2%) patients experienced at least one grade ≥1 adverse event during the observation period. The most common adverse events of any grade occurring during the observation period were gastrointestinal disorders (56.1%), including diarrhea (28.1%) and nausea (17.5%), general disorders (52.6%), including pyrexia (19.3%), peripheral edema (17.5%), edema (8.8%) and fatigue (8.8%), blood and lymphatic system disorders (47.4%), including anemia (19.3%), neutropenia (21.1%) and thrombocytopenia (19.3%) and infections and infestations (78.9%), including COVID-19 (22.8%) and urinary tract infections (21.1%).

Cardiac toxicities, of interest in the context of BTK inhibitors, were uncommon, with one case each of angina pectoris (grade 3), cardiac failure (grade 2), cardiovascular disorder (grade 1), mitral valve insufficiency (grade 2) and sinus bradycardia (grade 1); no atrial fibrillation episodes were reported. Grade 1 to 3 hypertension was reported in three cases, of which two patients had a previous history of arterial hypertension. Hematoma was reported in five cases (grade 1 and 2) and one case of grade 3 cerebral hemorrhage occurred in a patient on prophylactic concomitating aspirin.

Potentially immune-related disorders, of interest in the context of checkpoint inhibitors, included two cases of thyroid disorders (hypothyroidism, grade 2), pyrexia (12 cases, grade 1–3) and increased liver values (five cases, one hyperbilirubinemia and four transaminitis, grade 1–4).

Overall, three grade 5 adverse events were reported in the safety population and all of them were related to fatal sepsis.

Discussion

The improved understanding of the pathophysiology of CLL has led to the development of targeted agents that leverage distinct vulnerabilities and dependencies of malignant CLL cells. Targeted agents have thus demonstrated higher efficacy than chemotherapy in all risk groups of CLL[31,32]; however, the prevention and therapy RT remains one of the major clinical challenges in the management of CLL[2]. While recent studies have suggested multiple mechanisms contributing to transformation of CLL[33], the standard of care for RT has largely remained unchanged for a few decades, as chemoimmunotherapies such as R-CHOP or DA-EPOCH have remained the most commonly used therapies outside of clinical studies, despite short responses, high toxicity and short overall survival of less than a year[4,34,35].

Previously, several studies have explored the use of targeted agents in the context of RT. Covalent and non-covalent BTK inhibitors such as acalabrutinib and pirtobrutinib are very well tolerated in patients with RT; however, efficacy is limited owing to low ORRs with short durations[9,24]. Likewise, monotherapy with PD-1 inhibitors can induce responses that last very briefly when used as single agents[18,36]. Combination of targeted agents with R-CHOP and DA-EPOCH-R have also been clinically tested, with R-CHOP/DA-EPOCH-R plus venetoclax demonstrating high and durable responses, albeit with toxicity rates largely in line with previous reports on chemoimmunotherapy plus BCL-2 inhibitors in DLBCL[6,37]. Targeted combination therapies of RT have been explored with nivolumab plus ibrutinib in a monocentric study[38] as well as a triple combination of atezolizumab, venetoclax and obinutuzumab in the MOLTO study[39]. These approaches have demonstrated encouraging efficacy with good tolerability.

To the best of our knowledge, the RT1 study is so far, one of the largest prospective phase 2 studies of a targeted treatment approach in RT. Patients with previously treated as well as untreated RT experienced response to combined checkpoint and BTK inhibition with tislelizumab and zanubrutinib, while experiencing little and manageable toxicity rates. The ORR of 58%, including a complete response rate of 19%, lasted for 6 months or more in over 70% of patients, with the median DOR not reached. While the 12-month PFS rate of 47% indicates that most patients eventually experience disease relapses, the 12-month overall survival rate of 75% is higher than historical reports on the expected overall survival of patients with RT[4,34,35]. Of note, most patients with disease progressions received subsequent chemoimmunotherapy with CHOP-like regimens and overall, eight patients underwent allogeneic SCT, indicating the general feasibility of these salvage strategies after PD-1 and BTK inhibition.

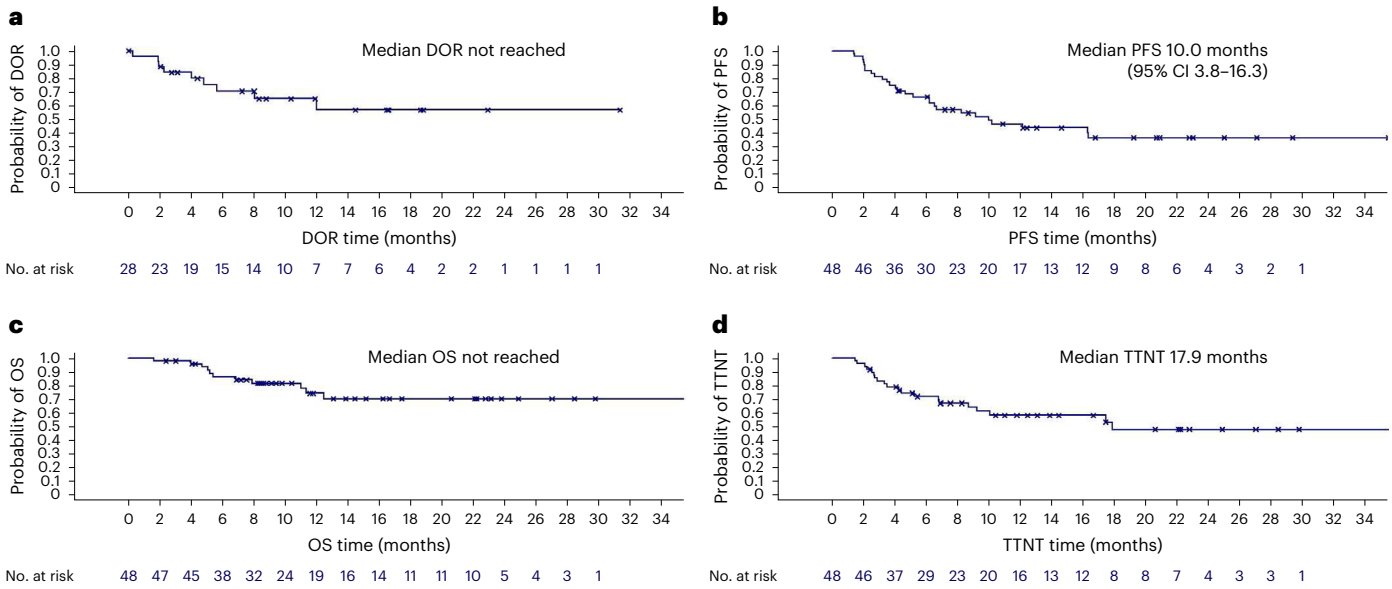

Fig. 3 | Kaplan–Meier analyses for secondary efficacy end points. a, DOR. **b**, PFS. **c**, Overall survival (OS). **d**, TTNT.

The regimen was generally very well tolerated, with a low number of immune-related adverse events, which have been previously observed with various checkpoint inhibitors[40], as well as a low incidence of cardiovascular toxicities, as seen by the lack of atrial fibrillation events, previously associated with first-generation BTK inhibitors[41].

A conceptually similar approach to the RT1 study was previously tested in a monocentric study using nivolumab plus ibrutinib; however, while the data were encouraging with response rates of 42%, the sample size was limited[38]. Moreover, owing to the relevant cardiovascular toxicity of ibrutinib, it is increasingly replaced by next-generation inhibitors such as acalabrutinib and zanubrutinib, which demonstrated less toxicity and also, in the case of zanubrutinib, higher efficacy[29].

The data generated from this first analysis of the RT1 study have limitations. As this study is non-randomized, a direct comparison of the efficacy of tislelizumab plus zanubrutinib with the current standard of care of R-CHOP/EPOCH-R is not possible; however, the clinical outcomes observed in this study are consistently more favorable than what has been reported in retrospective analyses of RT[4,34,35]. The patient population enrolled in the RT1 study was relatively fit with half of the patients having an ECOG performance status of 0, albeit with a median CIRS score of 4; outside of clinical studies, the RT patient population is likely to be less fit owing to the aggressive nature of RT. The RT1 patient population did not include patients with non-response to a previous RT-directed therapy or more than one previous line of therapy. Therefore, the data cannot be directly extrapolated to patients with multiple previous treatments or with primary progressive RT.

While the study regimen is efficacious, the outcomes are still substantially poorer than what is commonly observed in non-transformed CLL[42–44], demonstrating the need to further optimize the regimen. To interrogate determinants of response versus non-response to the study regimen, correlative studies are ongoing to delineate the genomic, transcriptomic and immune profiles, including measurement of PD-L1 expression, in patients treated in the RT1 study. Finally, to further increase the rate and DOR, the RT1 protocol is currently being amended to add the next-generation BCL-2 inhibitor sonrotoclax to tislelizumab plus zanubrutinib to increase efficacy by a triple-therapy approach.

In conclusion, combined checkpoint and BTK inhibition by tislelizumab plus zanubrutinib is an effective and well-tolerated treatment strategy for patients with RT. The response to therapy and overall survival rates at 1 year in the RT1 study are encouraging given the otherwise poor prognosis of RT.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02722-9.

References

1. Alaggio, R. et al. The 5th edition of the World Health Organization Classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia* **36**, 1720–1748 (2022).
2. Rossi, D., Spina, V. & Gaidano, G. Biology and treatment of Richter syndrome. *Blood* **131**, 2761–2772 (2018).
3. Hallek, M. et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* **131**, 2745–2760 (2018).
4. Al-Sawaf, O. et al. Richter transformation in chronic lymphocytic leukemia (CLL)-a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials. *Leukemia* **35**, 169–176 (2021).
5. Condoluci, A. & Rossi, D. Biology and treatment of Richter transformation. *Front. Oncol.* https://doi.org/10.3389/fonc.2022.829983 (2022).
6. Davids, M. S. et al. Venetoclax plus dose-adjusted R-EPOCH (VR-EPOCH) for Richter's syndrome. *Blood* https://doi.org/10.1182/blood.2021011386 (2021).
7. Ding, W. et al. PD-1 blockade with pembrolizumab in relapsed CLL including Richter's transformation: an updated report from a phase 2 trial (MC1485). *Blood* **128**, 4392–4392 (2016).
8. Jain, N. et al. Nivolumab combined with ibrutinib for CLL and Richter transformation: a phase II trial. *Blood* **128**, 59–59 (2016).
9. Eyre, T. A. et al. Acalabrutinib monotherapy for treatment of chronic lymphocytic leukaemia (ACE-CL-001): analysis of the Richter transformation cohort of an open-label, single-arm, phase 1-2 study. *Lancet Haematol.* **8**, e912–e921 (2021).
10. Ding, W. Richter transformation in the era of novel agents. *Hematology Am. Soc. Hematol. Educ. Program* **2018**, 256–263 (2018).
11. Ishida, Y., Agata, Y., Shibahara, K. & Honjo, T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J.* **11**, 3887–3895 (1992).

12. Xu-Monette, Z. Y., Zhou, J. & Young, K. H. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. *Blood* **131**, 68–83 (2018).
13. Chang, E. et al. Systematic review of PD-1/PD-L1 inhibitors in oncology: from personalized medicine to public health. *Oncologist* **26**, e1786–e1799 (2021).
14. Goodman, A., Patel, S. P. & Kurzrock, R. PD-1–PD-L1 immune-checkpoint blockade in B-cell lymphomas. *Nat. Rev. Clin. Oncol.* **14**, 203–220 (2017).
15. He, R. et al. PD-1 expression in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and large B-cell Richter transformation (DLBCL-RT): a characteristic feature of DLBCL-RT and potential surrogate marker for clonal relatedness. *Am. J. Surg. Pathol.* **42**, 843–854 (2018).
16. Ten Hacken, E. et al. Immuno-genetic changes underlie response to immune checkpoint blockade therapy in Richter's syndrome mouse models. *Blood* **140**, 1538–1539 (2022).
17. Kohlhaas, V. et al. Active Akt signaling triggers CLL toward Richter transformation via overactivation of Notch1. *Blood* **137**, 646–660 (2021).
18. Ding, W. et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood* **129**, 3419–3427 (2017).
19. Wiestner, A. Emerging role of kinase-targeted strategies in chronic lymphocytic leukemia. *Blood* **120**, 4684–4691 (2012).
20. Easaw, S., Ezzati, S. & Coombs, C. C. SOHO state of the art updates and next questions: updates on BTK inhibitors for the treatment of chronic lymphocytic leukemia. *Clin. Lymphoma Myeloma Leuk.* **23**, 697–704 (2023).
21. Chakraborty, S. et al. B-cell receptor signaling and genetic lesions in TP53 and CDKN2A/CDKN2B cooperate in Richter transformation. *Blood* **138**, 1053–1066 (2021).
22. Nadeu, F. et al. Detection of early seeding of Richter transformation in chronic lymphocytic leukemia. *Nat. Med.* **28**, 1662–1671 (2022).
23. Broséus, J. et al. Molecular characterization of Richter syndrome identifies de novo diffuse large B-cell lymphomas with poor prognosis. *Nat. Commun.* **14**, 309 (2023).
24. Wierda, W. G. et al. Efficacy of pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in richter transformation: results from the phase 1/2 BRUIN study. *Blood* **140**, 846–849 (2022).
25. Lu, S. et al. Tislelizumab plus chemotherapy as first-line treatment for locally advanced or metastatic nonsquamous NSCLC (RATIONALE 304): a randomized phase 3 trial. *J. Thorac. Oncol.* **16**, 1512–1522 (2021).
26. Xu, J. et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* **24**, 483–495 (2023).
27. Desai, J. et al. Phase IA/IB study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. *J. Immunother. Cancer* **8**, e000453 (2020).
28. Gavin Cull, S. O. et al. Safety and activity of the highly specific BTK inhibitor BGB-3111 in combination with the PD-1 inhibitor BGB-A317 in patients with B-cell lymphoid malignancies. in *ASH Meeting* (Atlanta, 2017).
29. Brown, J. R. et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N. Engl. J. Med.* **388**, 319–332 (2023).
30. Tam, C. S. et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol.* **23**, 1031–1043 (2022).
31. Burger, J. A. Treatment of chronic lymphocytic leukemia. *N. Engl. J. Med.* **383**, 460–473 (2020).
32. Hallek, M., Shanafelt, T. D. & Eichhorst, B. Chronic lymphocytic leukaemia. *Lancet* **391**, 1524–1537 (2018).
33. Parry, E. M. et al. Evolutionary history of transformation from chronic lymphocytic leukemia to Richter syndrome. *Nat. Med.* **29**, 158–169 (2023).
34. Wang, Y. et al. Clinical characteristics and outcomes of Richter transformation: experience of 204 patients from a single center. *Haematologica* **105**, 765–773 (2020).
35. Tsimberidou, A. M. et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *J. Clin. Oncol.* **24**, 2343–2351 (2006).
36. Rogers, K. A. et al. Use of PD-1 (PDCD1) inhibitors for the treatment of Richter syndrome: experience at a single academic centre. *Br. J. Haematol.* **185**, 363–366 (2019).
37. Davids, M. S. et al. Initial results of a multicenter phase 2 study of venetoclax in combination with R-CHOP (VR-CHOP) for patients with Richter syndrome. *Hematol.Oncol.* **41**, 466–468 (2023).
38. Jain, N. et al. A phase 2 study of nivolumab combined with ibrutinib in patients with diffuse large B-cell Richter transformation of CLL. *Blood Adv.* **7**, 1958–1966 (2023).
39. Frustaci, A. M. et al. Results of MOLTO, a multicenter, open label, phase II clinical trial evaluating venetoclax, atezolizumab and obinutuzumab combination in Richter syndrome. *J. Clin. Oncol.* **41**, 7502–7502 (2023).
40. Sullivan, R. J. & Weber, J. S. Immune-related toxicities of checkpoint inhibitors: mechanisms and mitigation strategies. *Nat. Rev. Drug Discov.* **21**, 495–508 (2022).
41. Lipsky, A. & Lamanna, N. Managing toxicities of Bruton tyrosine kinase inhibitors. *Hematology Am. Soc. Hematol. Educ. Program* **2020**, 336–345 (2020).
42. Kajüter, H. et al. Survival of patients with chronic lymphocytic leukemia before and after the introduction of chemoimmunotherapy in Germany. *Blood Cancer J.* **11**, 174 (2021).
43. da Cunha-Bang, C. et al. Improved survival for patients diagnosed with chronic lymphocytic leukemia in the era of chemo-immunotherapy: a Danish population-based study of 10455 patients. *Blood Cancer J.* **6**, e499 (2016).
44. Pulte, D. et al. Trends in survival of chronic lymphocytic leukemia patients in Germany and the USA in the first decade of the twenty-first century. *J. Hematol. Oncol.* **9**, 28 (2016).
46. Döhner, H. et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N. Engl. J. Med.* **343**, 1910–1916 (2000).

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Methods

Study design and participants

RT1 is an investigator-initiated, prospective, open-label, multicenter phase 2 study (NCT04271956) that enrolled patients from February 2020 to January 2023 at 12 investigative centers. Patients were recruited from ten sites in Germany (University Hospital of Cologne, University Hospital Kiel, University Hospital Essen, Otto-von-Guericke University Magdeburg, University Hospital Rostock, University Hospital Dresden, University Hospital Ulm, Munich Clinic Schwabing, Brüderkrankenhaus Paderborn and MVZ Dr Vehling-Kaiser Landshut), one site in Austria (Medical University of Vienna) and one site in Denmark (Rigshospitalet Copenhagen). Eligible patients aged ≥18 years had a diagnosis of CLL as defined by iwCLL criteria[3] and a confirmed diagnosis of RT based on histopathological examination by an expert hematopathologist. Patients were allowed to have up to one previous line of RT-directed therapy. As further inclusion criteria adequate kidney (creatinine clearance ≥30 ml min^{-1}) and liver function (total bilirubin ≤2×, AST/ALT ≤ 2.5× the institutional upper limit of normal value, unless directly attributable to the patient's CLL/RT or to Gilbert's syndrome) were required as well as negative serological testing for hepatitis B virus (patients positive for anti-HBc were included if PCR for hepatitis B virus DNA was negative and hepatitis B virus DNA PCR was performed every two months until 2 months after last dose of zanubrutinib), hepatitis C and HIV. Patients with an ECOG performance status of 0–2 or 3 (if due to underlying CLL/RT) were eligible. Eligible patients had a life expectancy equal to or greater than 3 months and were able to provide informed written consent. Exclusion criteria were primary progressive disease (non-response to previous RT-directed therapy, as it was initially not clear how fast the study regimen could induce remissions in patients with RT), patients with more than one previous line of RT therapy and allogeneic SCT within the last 100 days or signs of active graft-versus-host disease. Further exclusion criteria were confirmed progressive multifocal leukoencephalopathy, an uncontrolled autoimmune condition, malignancies other than CLL requiring system therapy, active infections requiring systemic treatment, organ system impairments with a CIRS score of 4 or higher, excluding eyes, ears, nose, throat or larynx organ system, requirement of treatment with strong CYP3A4 inhibitors or inducers, requirement of treatment with phenprocoumon or other vitamin K antagonists, use of other investigational agents, known hypersensitivity to tislelizumab or zanubrutinib, pregnant women and nursing mothers, live vaccination within 28 days previous to enrollment, legal incapacity, prisoners or institutionalized persons and persons in dependence to the sponsor or investigator.

This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. All patients provided written informed consent. The study protocol and relevant documents were approved by an independent institutional review board or ethics committee at each investigative center. The study was reviewed and approved by all responsible ethics committees (Ethics Committee of the Medical Faculty of the Christian Albrechts University in Kiel; Ethics Committee of the Medical Faculty of the University of Duisburg-Essen; Ethics Committee of the University of Cologne (Central Ethics Committee in Germany); OVGU Ethics Committee at the Medical Faculty; Ethics Committee of the Medical Faculty of the University of Rostock; Ethics Committee of the Medical Faculty of the TU Dresden; Ethics Committee of the University of Ulm; Ethics Committee of the Medical Faculty of the LMU Munich; Ethics committee of the Westfalen-Lippe Medical Association and the Medical Faculty of the Westphalian Wilhelms University of Münster; Ethics Committee of the Bavarian State Medical Association; Ethics Committee of the Medical University of Vienna; and the National Videnskabsetisk Komité, Copenhagen). No data safety monitoring board was implemented in the RT1 protocol. The study protocol and statistical analysis plan are provided in the Supplementary Information.

Procedures

Each treatment cycle consisted of 21 days. Patients received tislelizumab intravenously at a fixed dose of 200 mg on day 1 of each cycle. Previous to the first infusion of tislelizumab, a pre-medication with an antihistamine and paracetamol was permitted, in addition to oral or intravenous glucocorticoids if considered indicated by the investigator. The first infusion was administered over 60 min and subsequent infusions over 30 min. Zanubrutinib was administered orally at a fixed dose of 160 mg twice daily from day 1 onwards. Dose modifications or interruptions were permitted for management of adverse events. Before the induction phase, a pre-phase therapy with steroids, vincristine (up to 2 mg intravenously) or cyclophosphamide (up to 200 mg^2 for a maximum of 3 d) was permitted in cases with urgent need for treatment. The induction phase consisted of six treatment cycles, followed by a consolidation phase of six further cycles. Patients with response or stable disease after 12 cycles were allowed to proceed with maintenance treatment with tislelizumab plus zanubrutinib at the investigator's discretion.

Outcomes

Per protocol, the primary end point was the ORR at the interim staging after end of induction therapy (after six cycles), for patients who received at least two cycles of study treatment, including at least one administered dose in cycle three, who comprised the full analysis set (FAS; see below). Response was assessed according to the refined Lugano criteria based on positron emission tomography–computed tomography or, if not available, based on computed tomography scans[45]. Secondary end points included ORR after the end of induction therapy (after six cycles) according to iwCLL criteria and ORR after consolidation therapy (12 cycles), DOR (for patients responding to induction therapy and defined as the time from enrollment to first assessment of response until disease progression or death from any cause), PFS (defined as the time from enrollment until disease progression or death from any cause), overall survival (defined as the time from enrollment until death from any cause), TTNT (defined as the time from enrollment until initiation of next treatment for CLL/RT) and safety parameters, including type, frequency and severity of adverse events.

Post hoc exploratory analyses included the assessment of ORR after six cycles and time-to-event analyses for all enrolled patients of the ITT population, the assessment of a modified TTNT (defined as the time from enrollment until initiation of next treatment for CLL/RT or death from any cause), univariate analyses of potential prognostic factors for ORR after six cycles, overall survival, PFS, DOR and the assessment of ORR and PFS, comparing of the RT and BTK-naive patients to previously treated patients.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0. An interim safety analysis was conducted by the principal investigator, coordinating physician, statistician and safety management team of the German CLL Study Group (GCLLSG), after the first six patients had been treated for three cycles. Recruitment was only continued if no safety concerns were raised by the interim safety review.

Statistical analysis

The protocol defined two patient populations for the statistical analyses. For the safety analysis, all patients who received at least one dose of study treatment were considered as the safety population. For the efficacy analysis, all patients who received at least two cycles of induction therapy, including at least one administered dose in cycle three, were considered as FAS; the FAS was used for the analysis of all

study end points, apart from safety. Given the experimental nature of the study regimen, this FAS definition was chosen to ensure reliable data acquisition on the actual efficacy of the regimen and to reduce interactions— for example, due to comorbidities or non-adherence to study treatment — which was anticipated to be a possible confounder given the heterogeneous clinical presentation of RT. To account for selection bias possibly introduced by this approach, a post hoc analysis was conducted in all patients enrolled in the study (ITT population).

The primary end point ORR at the end of induction therapy was used to determine the sample size of the study. The null hypothesis was ORR ≤ 0.40 with the alternative hypothesis of ORR > 0.40. The type I error was set to $\alpha = 2.5\%$ and the type II error should not exceed $\beta = 20\%$ to achieve a power of at least $(1 - \beta) = 80\%$. Based on these parameters, a one-sided one-sample binomial test with an overall significance level of 2.5% provided the sample size of $n = 48$, to achieve a statistical significance with a power of 80%. The 95% CIs for the primary end point and secondary or exploratory response end points were calculated according to the Clopper–Pearson method and the Kaplan–Meier method was used for the time-to-event analyses of the secondary or exploratory end points. Univariate analyses of potential prognostic factors were performed for ORR after six cycles using logistic regression modeling and for overall survival, PFS and DOR using Cox proportional hazards regression modeling, each without adjustment for multiple testing. Statistical analyses were performed with EAST v.5, SPSS v.28 and R v.4.2.1. This study is registered with ClinicalTrials.gov (NCT04271956).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Access to individual patient-level data can be requested after publication via the corresponding authors (othman.al-sawaf@uk-koeln.de and barbara.eichhorst@uk-koeln.de), who will facilitate a central review by the GCLLSG within 6 months. The data will be released to such requesters with necessary agreements to enforce terms such as security, patient privacy and consent of specified data use, consistent with evolving, applicable data protection laws.

References

45. Cheson, B. D. et al. Refinement of the Lugano classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood* **128**, 2489–2496 (2016).

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Author contributions

O.A.S., R.L., S.R. and B.E. conducted the analyses, interpreted the data and wrote the manuscript. J.S. and A.M.F. managed and reviewed the data. A.M.F. supervised the clinical safety analyses. E.T., C.S. and S.S. provided the FISH, *TP53* and IGHV data. K.A.K. conducted flow cytometry analyses. S.B., M.M., M.R., E.T., C.S., S.S., J.S., J.v.T., U.V.K., T.G., C.M.W., P.S. and C.N. enrolled and managed study patients, reviewed the data and the manuscript. B.C., K.F. and M.H. reviewed the data and the manuscript.

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Competing interests

O.A.S. reports personal fees and honoraria from AbbVie, Adaptive, Ascentage, AstraZeneca, BeiGene, Genmab, Gilead, Janssen, Eli Lilly and Roche; and research funding from AbbVie, BeiGene, Janssen and Roche. A.M.F. received research funding from Celgene; is on the advisory board of Janssen; and received travel grants from AbbVie. E.T. reports advisory board (AbbVie, Janssen-Cilag and BeiGene), speaker honoraria (AstraZeneca, AbbVie, BeiGene, Gilead, Janssen and Roche) and research funding (Roche, AbbVie and Gilead). C.S. reports speaker honoraria (AstraZeneca and AbbVie). S.B. received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from Roche, AbbVie, Novartis, Becton Dickinson, Janssen, AstraZeneca and Sanofi; and received grants or contracts from Janssen-Cilag. M.R. reports grants from F. Hoffman-La Roche; and personal fees from F. Hoffmann-La Roche and AbbVie. J.S. reports consultancy honoraria from AstraZeneca, Janssen, Roche, Gilead, AbbVie and Sanofi. J.v.T. received research support from Janssen/Roche; received travel grants from AbbVie, Janssen, Roche and Celgene; received honoraria from Roche, Janssen, AbbVie and AstraZeneca; and is on the advisory boards of Janssen, Roche and AbbVie. C.M.W. reports grants and personal fees from Janssen-Cilag during the conduct of the study; and grants and personal fees from Janssen-Cilag, Hoffmann-La Roche, AbbVie and Gilead outside the submitted work. K.F. reports honoraria by AbbVie and Roche and is an advisor for AstraZeneca. B.C. reports grants from Gilead Sciences and personal fees and honoraria from Janssen, F. Hoffmann-La Roche, AstraZeneca, AbbVie, BMS, Gilead, Sobi and Incyte. K.A.K. reports grants from F. Hoffmann-La Roche and AbbVie, during the conduct of the study; and personal fees from F. Hoffmann-La Roche and AbbVie. S.S. received advisory board honoraria, research support, travel support and speaker fees from AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann-La Roche, Janssen, Novartis and Sunesis. P.S. has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Takeda, Bristol Myers Squibb, Novartis, BeiGene, Incyte, GlaxoSmithKline, Janssen, Roche, MedMedia, AstraZeneca, AbbVie, Amgen, Medahead, Sanofi and Merck Sharp & Dome. C.N. received research funding from Novo Nordisk Foundation grant NF16OC0019302 and research support, consultancy fees and/or travel grants from AbbVie, Gilead, Janssen, Roche, CSL Behring, Genmab, Sunesis and Acerta/AstraZeneca. M.H. is an advisor or consultant for Roche, Gilead, Janssen, Bristol Myers Squibb, AbbVie and AstraZeneca and reports honoraria from Roche, Gilead, Janssen, Bristol Myers Squibb, AbbVie and AstraZeneca. A.-M.F. reports research funding by AstraZeneca and Celgene and travel support by AbbVie. B.E. is an advisor or consultant for Janssen, AbbVie, Kite, AstraZeneca, MSD and Miltenyi and received honoraria from Janssen, Roche, AbbVie, Lilly, Kite, AstraZeneca, BeiGene and MSD; and reports research funding by Janssen, Gilead, Roche, AbbVie, BeiGene and AstraZeneca. The remaining authors declare no competing interests.

Additional information

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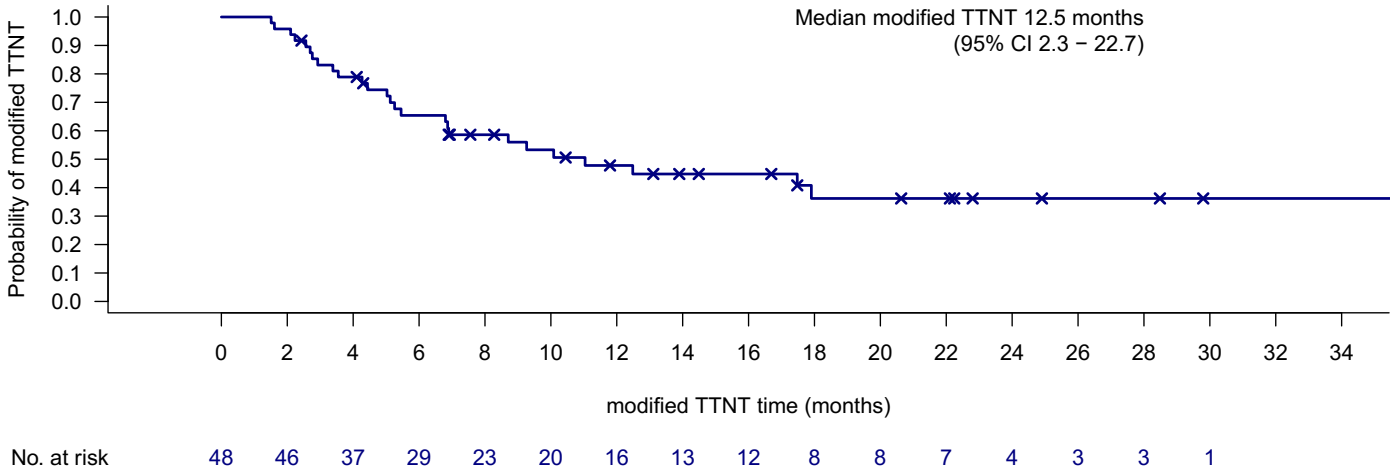
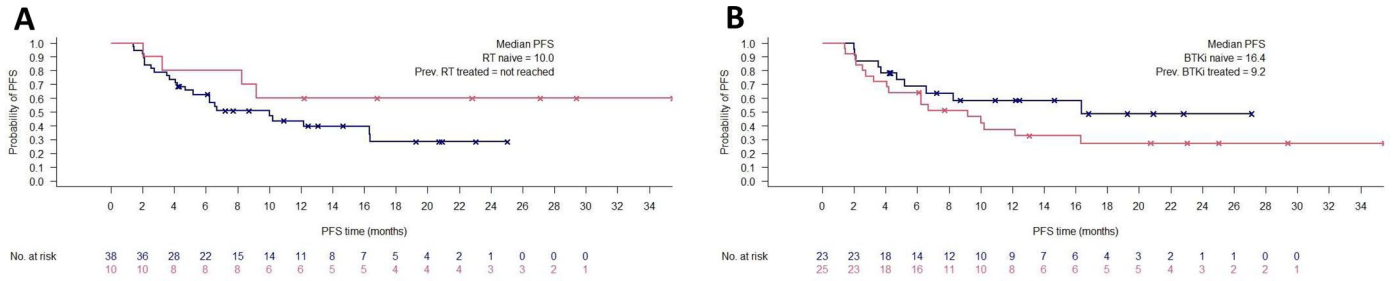


Extended Data Fig. 1 | Modified time-to-next-treatment. Time-to-next-treatment defined as initiation of a next line of treatment or death, whichever occurred first.

https://doi.org/10.1038/s41591-023-02722-9



Extended Data Fig. 2 | Survival analysis according to prior RT-directed treatment status and BTK inhibitor exposure. Progression-free survival (PFS) in patients with (red) and without (blue) prior RT-directed therapy (**A**) and patients with (red) and without (blue) prior BTK inhibitor exposure (**B**).

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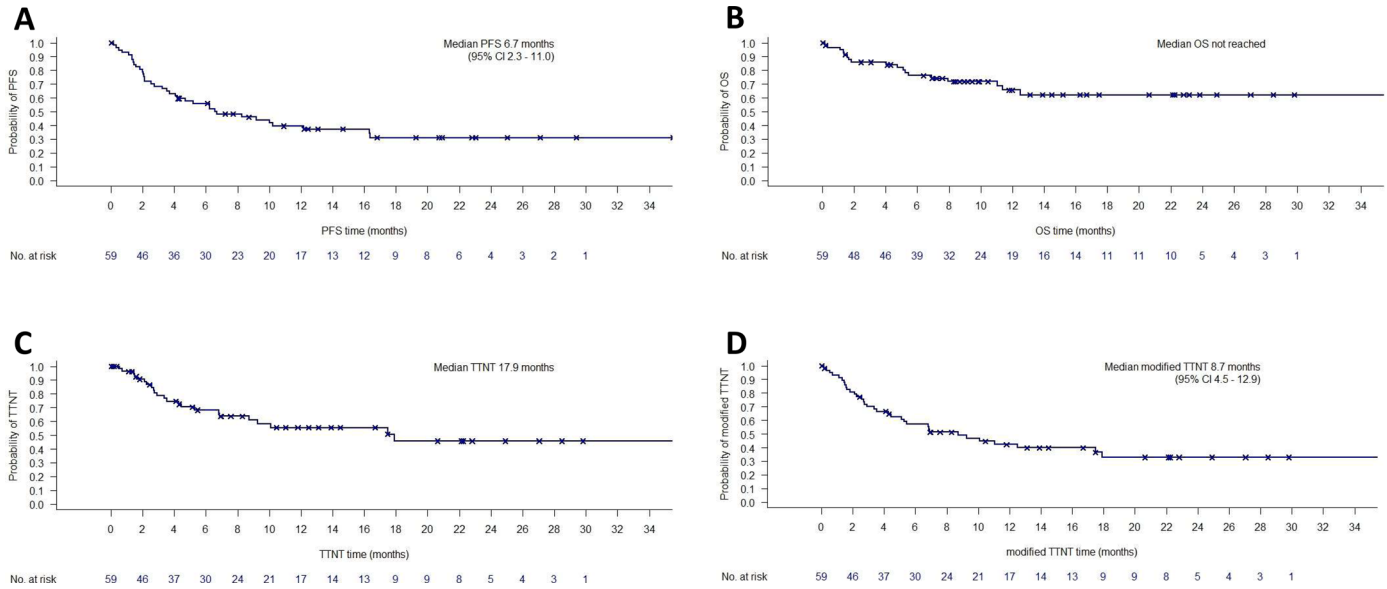

Extended Data Fig. 3 | Post-hoc survival analyses of all study eligible patients. Analysis of all study eligible patients, including those 9 patients who did not complete two cycles of therapy due to primary progressive disease, adverse events, death or non-compliance. **a** Progression-free survival (PFS). **b** Overall survival (OS). **c** Time-to-next-treatment (TTNT). **d** Modified time-to-next-treatment (defined as next line of treatment or death, whichever occurred first).

https://doi.org/10.1038/s41591-023-02722-9

Extended Data Table 1 | Post-protocol therapies (full analysis set)

All subsequent therapies	FAS	
All subsequent therapies	**42**	
Chemo(immuno)therapy	**21**	(50.0)
Bendamustine/Polatuzumab/Rituximab	2	(4.8)
Bendamustine/Rituximab	1	(2.4)
Cisplatin/Cytarabine/Dexamethasone	1	(2.4)
Cisplatin/Cytarabine/Dexamethasone/Rituximab	1	(2.4)
Cyclophosphamide/Doxorubicin/Etoposide/Prednisolone/Vincristine	1	(2.4)
Cyclophosphamide/Doxorubicin/Etoposide/Prednisone/Rituximab/Vincristine	1	(2.4)
Cyclophosphamide/Doxorubicin/Polatuzumab/Prednisone/Rituximab/Vincristine	1	(2.4)
Cyclophosphamide/Doxorubicin/Prednisolone/Rituximab/Vincristine	1	(2.4)
Cyclophosphamide/Doxorubicin/Prednisone/Rituximab/Vincristine	8	(19.0)
Cyclophosphamide/Prednisolone	1	(2.4)
Cyclophosphamide/Prednisolone/Rituximab	1	(2.4)
Cytarabine/Dexamethasone/Oxaliplatin/Rituximab	1	(2.4)
Cytarabine/Dexamethasone/Rituximab	1	(2.4)
SCT	**8**	(19.0)
SCT	8	(19.0)
BTK/BCL2 inhibitors	**7**	(16.7)
Ibrutinib/Lenalidomide/Obinutuzumab/Prednisone/Venetoclax	1	(2.4)
Nemtabrutinib	1	(2.4)
Obinutuzumab/Pembrolizumab/Venetoclax	1	(2.4)
Obinutuzumab/Venetoclax	2	(4.8)
Rituximab/Venetoclax	1	(2.4)
Venetoclax	1	(2.4)
Other	**6**	(14.3)
Lenalidomide	1	(2.4)
Lenalidomide/Rituximab	1	(2.4)
Lenalidomide/Tafasitamab	1	(2.4)
Obinutuzumab	1	(2.4)
Polatuzumab/Rituximab	1	(2.4)
Rituximab	1	(2.4)

NE, not evaluable.

https://doi.org/10.1038/s41591-023-02722-9

Extended Data Table 2 | Univariate logistic regression analysis of baseline features for overall response rate after 6 cycles

Logistic regression (ORR) Potential prognostic factors	Odds Ratio	95% CI		Two-sided p-value
Age (years)	1.019	0.955	1.088	0.571
> 65 vs. ≤ 65	1.030	0.319	3.329	0.960
Sex				
Male vs. Female	2.111	0.647	6.885	0.215
Time between first diagnosis and registration (months)	0.998	0.990	1.006	0.624
Binet stage				
B vs. A	1.714	0.278	10.589	0.562
C vs. A	0.457	0.128	1.632	0.228
Severe constitutional symptoms				
Yes vs. No	0.556	0.173	1.788	0.324
ECOG performance status				
= 1 vs. = 0	0.296	0.079	1.117	0.072
= 2 vs. = 0	0.444	0.073	2.700	0.378
= 3 vs. = 0	NE	NE	NE	1.000
> 0 vs. = 0	0.370	0.114	1.208	0.100
CIRS total score	0.987	0.839	1.162	0.879
> 0 vs. = 0	1.444	0.186	11.221	0.725
> 6 vs. ≤ 6	0.619	0.176	2.172	0.454
LDH (U/L)	0.999	0.997	1.000	0.128
Cytogenetic subgroups hierarchical order				
Deletion 11q vs. Deletion 17p	NE	NE	NE	0.999
Trisomy 12 vs. Deletion 17p	6.000	0.478	75.344	0.165
No abnormalities vs. Deletion 17p	1.667	0.353	7.875	0.519
Deletion 13q vs. Deletion 17p	2.500	0.370	16.888	0.347
***TP53* mutation status, N (%)**				
Mutated vs. Unmutated	0.798	0.218	2.925	0.734
***TP53* status, N (%)**				
Deleted and/or mutated vs. None	0.579	0.169	1.980	0.384
IGHV mutation status, N (%)				
Mutated vs. Unmutated	1.625	0.398	6.628	0.498
Serum thymidine kinase (U/L)	0.993	0.986	1.000	0.053
> 10 U/L vs. ≤ 10 U/L	0.658	0.055	7.805	0.740
Serum β2-microglobulin (mg/L)	0.983	0.845	1.144	0.825
> 3.5 mg/L vs. ≤ 3.5 mg/L	0.431	0.131	1.419	0.166
Complex karyotype, N (%)				
≥ 3 aberrations vs. < 3 aberrations	0.280	0.072	1.083	0.065
CLL-IPI Risk Group, N (%)				
Intermediate vs. Low	9.000	0.522	155.242	0.130
High vs. Low	3.000	0.199	45.244	0.427
Very high vs. Low	1.750	0.129	23.703	0.674
Ki-67 (%)	0.982	0.947	1.019	0.330

Logistic regression analysis unadjusted for multiple testing.

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Extended Data Table 3 | Univariate Cox regression analysis for progression-free survival

Cox regression (PFS) Potential prognostic factors	Hazard Ratio	95% CI		Two-sided p-value
Age (years)	1.015	0.970	1.063	0.521
> 65 vs. ≤ 65	1.104	0.504	2.418	0.804
Sex				
Male vs. Female	1.054	0.481	2.310	0.895
Time between first diagnosis and registration (months)	1.000	0.996	1.005	0.956
Binet stage				
B vs. A	0.912	0.289	2.881	0.875
C vs. A	1.654	0.728	3.759	0.229
Severe constitutional symptoms				
Yes vs. No	2.827	1.312	6.094	**0.008**
ECOG performance status				
= 1 vs. = 0	2.505	1.072	5.852	**0.034**
= 2 vs. = 0	1.968	0.624	6.203	0.248
= 3 vs. = 0	1.876	0.240	14.667	0.549
> 0 vs. = 0	2.295	1.056	4.992	**0.036**
CIRS total score	1.053	0.965	1.150	0.247
> 0 vs. = 0	2.087	0.282	15.473	0.472
> 6 vs. ≤ 6	1.632	0.745	3.572	0.221
LDH (U/L)	1.001	1.000	1.001	**< 0.001**
Cytogenetic subgroups hierarchical order				
Deletion 11q vs. Deletion 17p	0.464	0.096	2.251	0.341
Trisomy 12 vs. Deletion 17p	0.232	0.028	1.900	0.173
No abnormalities vs. Deletion 17p	0.875	0.342	2.240	0.781
Deletion 13q vs. Deletion 17p	0.508	0.147	1.753	0.284
***TP53* mutation status, N (%)**				
Mutated vs. Unmutated	1.729	0.782	3.823	0.176
***TP53* status, N (%)**				
Deleted and/or mutated vs. None	1.938	0.890	4.222	0.096
IGHV mutation status, N (%)				
Mutated vs. Unmutated	0.998	0.410	2.433	0.997
Serum thymidine kinase (U/L)	1.007	1.003	1.011	**< 0.001**
> 10 U/L vs. ≤ 10 U/L	2.238	0.303	16.514	0.429
Serum β2-microglobulin (mg/L)	1.054	0.972	1.143	0.202
> 3.5 mg/L vs. ≤ 3.5 mg/L	2.494	1.121	5.548	**0.025**
Complex karyotype, N (%)				
≥ 3 aberrations vs. < 3 aberrations	2.171	0.929	5.072	0.074
CLL-IPI Risk Group, N (%)				
Intermediate vs. Low	1.068	0.119	9.601	0.953
High vs. Low	2.497	0.298	20.941	0.399
Very high vs. Low	2.820	0.360	22.093	0.324
Ki-67 (%)	1.025	0.997	1.054	0.078

Univariate Cox regression analysis unadjusted for multiple comparisons. P-values < 0.05 are highlighted in bold.

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Extended Data Table 4 | Univariate Cox regression analysis for overall survival

Cox regression (OS) Potential prognostic factors	Hazard Ratio	95% CI		Two-sided p-value
Age (years)	1.107	1.013	1.209	**0.024**
> 65 vs. ≤ 65	6.618	0.846	51.749	0.072
Sex				
Male vs. Female	1.127	0.330	3.850	0.849
Time between first diagnosis and registration (months)	1.002	0.996	1.009	0.490
Binet stage				
B vs. A	NE	NE	NE	0.975
C vs. A	6.798	1.454	31.781	**0.015**
Severe constitutional symptoms				
Yes vs. No	5.755	1.500	22.074	**0.011**
ECOG performance status				
= 1 vs. = 0	3.609	0.858	15.177	0.080
= 2 vs. = 0	3.331	0.554	20.010	0.188
= 3 vs. = 0	6.222	0.643	60.183	0.114
> 0 vs. = 0	3.737	0.988	14.135	0.052
CIRS total score	1.121	0.992	1.265	0.067
> 0 vs. = 0	NE	NE	NE	0.557
> 6 vs. ≤ 6	2.079	0.634	6.820	0.227
LDH (U/L)	1.001	1.000	1.002	**0.002**
Cytogenetic subgroups hierarchical order				
Deletion 11q vs. Deletion 17p	NE	NE	NE	0.989
Trisomy 12 vs. Deletion 17p	0.645	0.066	6.356	0.707
No abnormalities vs. Deletion 17p	0.898	0.211	3.820	0.884
Deletion 13q vs. Deletion 17p	0.685	0.112	4.174	0.682
TP53 mutation status, N (%)				
Mutated vs. Unmutated	2.087	0.633	6.882	0.227
TP53 status, N (%)				
Deleted and/or mutated vs. None	2.458	0.739	8.178	0.143
IGHV mutation status, N (%)				
Mutated vs. Unmutated	0.952	0.252	3.602	0.942
Serum thymidine kinase (U/L)	1.007	1.001	1.012	**0.022**
> 10 U/L vs. ≤ 10 U/L	0.756	0.097	5.923	0.790
Serum β2-microglobulin (mg/L)	1.106	0.987	1.240	0.083
> 3.5 mg/L vs. ≤ 3.5 mg/L	14.634	1.831	116.974	**0.011**
Complex karyotype, N (%)				
≥ 3 aberrations vs. < 3 aberrations	2.438	0.677	8.780	0.173
CLL-IPI Risk Group, N (%)				
Intermediate vs. Low	NE	NE	NE	1.000
High vs. Low	NE	NE	NE	0.933
Very high vs. Low	NE	NE	NE	0.937
Ki-67 (%)	1.003	0.965	1.043	0.876

Univariate Cox regression analysis unadjusted for multiple comparisons. P-values < 0.05 are highlighted in bold.

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Extended Data Table 5 | Univariate Cox regression analysis for duration of response

Cox regression (DOR) Potential prognostic factors	Hazard Ratio	95% CI		Two-sided p-value
Age (years)	1.085	0.984	1.197	0.103
> 65 vs. ≤ 65	2.029	0.418	9.842	0.380
Sex				
Male vs. Female	0.489	0.130	1.831	0.288
Time between first diagnosis and registration (months)	1.004	0.996	1.011	0.313
Binet stage				
B vs. A	1.902	0.261	13.846	0.525
C vs. A	5.501	1.058	28.612	**0.043**
Severe constitutional symptoms				
Yes vs. No	1.804	0.479	6.786	0.383
ECOG performance status				
= 1 vs. = 0	1.778	0.321	9.863	0.510
= 2 vs. = 0	4.729	0.807	27.714	0.085
= 3 vs. = 0	3.899	0.416	36.552	0.233
> 0 vs. = 0	2.724	0.711	10.435	0.144
CIRS total score	1.079	0.946	1.232	0.257
> 0 vs. = 0	NE	NE	NE	NE
> 6 vs. ≤ 6	2.397	0.635	9.049	0.197
LDH (U/L)	1.002	1.000	1.004	**0.022**
Cytogenetic subgroups hierarchical order				
Deletion 11q vs. Deletion 17p	NE	NE	NE	0.178
Trisomy 12 vs. Deletion 17p	NE	NE	NE	0.986
No abnormalities vs. Deletion 17p	NE	NE	NE	0.095
Deletion 13q vs. Deletion 17p	NE	NE	NE	0.168
***TP53* mutation status, N (%)**				
Mutated vs. Unmutated	7.134	1.757	28.967	**0.006**
***TP53* status, N (%)**				
Deleted and/or mutated vs. None	6.722	1.644	27.481	**0.008**
IGHV mutation status, N (%)				
Mutated vs. Unmutated	2.086	0.515	8.455	0.303
Serum thymidine kinase (U/L)	1.009	1.001	1.017	**0.024**
> 10 U/L vs. ≤ 10 U/L	0.322	0.039	2.686	0.295
Serum β2-microglobulin (mg/L)	1.131	1.003	1.275	**0.045**
> 3.5 mg/L vs. ≤ 3.5 mg/L	3.971	0.950	16.594	0.059
Complex karyotype, N (%)				
≥ 3 aberrations vs. < 3 aberrations	3.552	0.878	14.366	0.075
CLL-IPI Risk Group, N (%)				
Intermediate vs. Low	NE	NE	NE	0.954
High vs. Low	NE	NE	NE	0.948
Very high vs. Low	NE	NE	NE	0.943
Ki-67 (%)	1.034	0.983	1.087	0.193

Univariate Cox regression analysis unadjusted for multiple comparisons. P-values < 0.05 are highlighted in bold.

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Extended Data Table 6 | Patient characteristics (all study eligible patients)

Patient characteristics	ITT	
Age (years)	**59**	
Median	69	
IQR	62 – 76	
Sex, N (%)	**59**	
Female	21	(35.6)
Male	38	(64.4)
Time between first diagnosis and registration (months)	**59**	
Median	80	
IQR	50 – 136	
Binet stage, N (%)	**59**	
A	27	(45.8)
B	10	(16.9)
C	22	(37.3)
Severe constitutional symptoms, N (%)	**59**	
No	32	(54.2)
Yes	27	(45.8)
ECOG performance status, N (%)	**59**	
= 0	28	(47.5)
= 1	19	(32.2)
= 2	9	(15.3)
= 3	3	(5.1)
CIRS total score	**59**	
Median	4	
IQR	2 – 7	
CIRS total score, N (%)	**59**	
≤ 6	40	(67.8)
> 6	19	(32.2)
LDH (U/L)	**59**	
Median	341	
IQR	211 – 678	
Cytogenetic subgroups hierarchical order (according to Döhner et al.), N (%)	**56**	
Deletion 17p	13	(23.2)
Deletion 11q	5	(8.9)
Trisomy 12	7	(12.5)
No abnormalities	22	(39.3)
Deletion 13q	9	(16.1)
Missing	*3*	*(5.1)*
***TP53* mutation status, N (%)**	**55**	
Unmutated	38	(69.1)
Mutated	17	(30.9)
Missing	*4*	*(6.8)*
***TP53* status, N (%)**	**56**	
None	36	(64.3)
Deleted and/or mutated	20	(35.7)
Missing	*3*	*(5.1)*
IGHV mutation status, N (%)	**50**	
Unmutated	33	(66.0)
Mutated	17	(34.0)
Missing	*9*	*(15.3)*
Serum thymidine kinase (U/L)	**58**	
Median	40.3	
IQR	19.4 – 109.4	
Serum β2-microglobulin (mg/L)	**58**	
Median	4.0	
IQR	2.6 – 6.3	
Complex karyotype, N (%)	**47**	
< 3 aberrations	27	(57.4)
≥ 3 aberrations	20	(42.6)
Missing	*12*	*(20.3)*
CLL-IPI Risk Group, N (%)	**48**	
Low	4	(8.3)
Intermediate	12	(25.0)
High	13	(27.1)
Very high	19	(39.6)
Missing	*11*	*(18.6)*

nature portfolio

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
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☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The TrialMaster version 5 system from OmniComm (OmniComm Europe GmbH, An Anju Software Company) is used as the study database. Technical support as well as software development and maintenance are provided by the provider OmniComm.
Data analysis	Sample size calculations were performed with EAST 6 software and validated with Binomial tables. Analyses were performed using IBM SPSS Statistics version 29.0 and R version 4.2.1.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Access to individual patient-level data can be requested after publication via the corresponding authors (othman.al-sawaf@uk-koeln.de, barbara.eichhorst@uk-

koeln.de), who will facilitate a central review by the GCLLSG within 6 months. The data will be released to such requesters with necessary agreements to enforce terms such as security, patient privacy, and consent of specified data use, consistent with evolving, applicable data protection laws.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex and gender were not considered in the study design. Self-reported sex was collected and used in the analyses. The ratio of male to female patients enrolled in the study was ~1.5:1, in line with the general incidence of CLL and RT, which is slightly more common in male persons than female persons. Given the sample size, a post hoc sex-based analysis would not yield reliable or representative findings. However, sex was included as a variable in univariate tests.
Reporting on race, ethnicity, or other socially relevant groupings	No information on race or ethnicity were collected on the CRFs.
Population characteristics	Based on the inclusion and exclusion criteria (see below), patients were recruited from 10 sites in Germany, 1 site in Austria plus 1 site in Denmark. Between 11 February 2020 and 2 January 2023. Inclusion criteria: • Confirmed diagnosis of CLL according to iwCLL criteria (Hallek et al, 2018). • Confirmed histopathological diagnosis of RT (diffuse large B-cell lymphoma or Hodgkin's lymphoma) • Previously untreated RT or patients with objective response or non-tolerance to first-line RT treatment • Creatinine clearance ≥30ml/min calculated according to the modified formula of Cockcroft and Gault or directly measured with 24hr urine collection or an equivalent method. • Adequate liver function as indicated by a total bilirubin ≤ 2, AST/ALT ≤ 2.5 the institutional ULN value, unless directly attributable to the patient's CLL or to Gilbert's Syndrome, in which case a max. total bilirubin ≤ 4 and AST/ALT ≤ 5 the institutional ULN value are required. • Negative serological testing for hepatitis B (HBsAg negative and anti-HBc negative; patients positive for anti-HBc may be included if PCR for HBV DNA is negative and HBV-DNA PCR is performed every two months until 2 months after last dose of zanubrutinib), negative testing for hepatitis-C RNA and negative HIV test within 6 weeks prior to registration • Age at least 18 years • ECOG performance status 0-2, ECOG 3 is only permitted if related to CLL (e.g. due to anaemia or severe constitutional symptoms) • Life expectancy ≥ 3 months • Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements Exclusion criteria: • Patients who did not respond to previous line of RT therapy (i.e. primary progressive patients) • Patients with more than one prior line of RT therapy • Allogenic stem cell transplantation within the last 100 days or signs of active GVHD after prior allogeneic stem cell transplantation within any time • Patients with confirmed PML • Uncontrolled autoimmune condition • Malignancies other than CLL currently requiring systemic therapies (unless the malignant disease is in a stable remission at the discretion of the treating physician) • Active infection currently requiring systemic treatment • Any comorbidity or organ system impairment rated with a CIRS (cumulative illness rating scale) score of 4, excluding the eyes/ears/nose/throat/larynx organ system 1 or any other life-threatening illness, medical condition or organ system dysfunction that – in the investigator´s opinion could comprise the patient's safety or interfere with the absorption or metabolism of the study drugs • Requirement of therapy with strong CYP3A4 inhibitors/inducers • Requirement of therapy with phenprocoumon or other vitamin K antagonists. • Use of investigational agents, e.g. monoclonal antibodies or other experimental drugs within clinical trials, which might interfere with the study drug within 28 days (or 5 times half-life of the compound, whichever is longer) prior to registration • Known hypersensitivity to tislelizumab, zanubrutinib or any of the excipients • Pregnant women and nursing mothers (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of treatment) • Fertile men or women of childbearing potential unless: - surgically sterile or ≥ 2 years after the onset of menopause, or - willing to use two methods of reliable contraception including one highly effective contraceptive method (Pearl Index < 1) and one additional effective (barrier) method during study treatment and for 12 months after the end of study treatment. • Vaccination with a live vaccine < 28 days prior to randomization • Legal incapacity • Prisoners or subjects who are institutionalized by regulatory or court order • Persons who are in dependence to the sponsor or an investigator Covariate-relevant patient characteristics: Age (range 45-82 years), self-reported sex, Binet stage (A/B/C), severe constitutional symptoms (absent/present), ECOG performance status (range 0-3), Cumulative illness rating scale (CIRS; IQR 0-7), LDH (U/L; IQR 209-584), Cytogenetic subgroups (deletion 17p, 11q, trisomy 12, none, deletion 13q), TP53 and IGHV mutation status (unmutated/mutated), Serum thymidine kinase (U/L; IQR 18.5-108.3), Serum β2-microglobulin (mg/L; IQR 2.5-5.5), Complex karyotype (≥ 3 aberrations), and CLL-IPI Risk Group (Low/Intermediate/High/Very high).
Recruitment	Based on the inclusion and exclusion criteria (see below), patients were recruited from 10 sites in Germany, 1 site in Austria

Recruitment	plus 1 site in Denmark. Between 11 February 2020 and 2 January 2023. Patients were considered from routine clinical care based on a diagnosis of Richter-Transformation. As selection bias towards patients without primary progressive disease cannot be excluded, as these patients were excluded from the study based on the protocol-based exclusion criteria. The study therefore focuses on patients with previously untreated RT or up to one prior line of effective RT-directed therapy.
Ethics oversight	The Sponsor (University of Cologne) and all investigators agree to conduct this study in accordance with the protocol and with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable ICH Good Clinical Practice (GCP) Guidelines and applicable laws and regulations. The participating investigators/institutions permit trial-related monitoring, audits, IRB/IEC review and regulatory inspections and provide direct access to source documents/data. The investigator assumes the responsibility of obtaining written informed consent for each patient before any study-specific procedures are performed and before any study drug is administered. If an amendment to the protocol changes the risk participation schedule in scope or activity, or increases the potential risk to the subject, the informed consent document must be used to obtain re-consent from any patients currently enrolled in the study if the patient is affected by the amendment and must be used to document consent from any new patients enrolled after the approval date of the amendment. The Sponsor and the investigators affirm and uphold the principle of the patients' right to privacy. The investigators shall comply with applicable privacy laws. The investigator must assure that the patients' anonymity will be maintained and that the identities are protected from unauthorized parties. The investigator should maintain documents not for submission to the GCLLSG study office e.g. subjects written informed consent forms, in strict confidence. All clinical and scientific data are collected under a unique code or "pseudonym" composed of an abbreviation of the study and a random string of 6 digits and is stored in the main clinical trial database. All data exchange with the study center is made solely via the unique code. All participating study centers are obliged to keep a secret trial subject identification list. The study was reviewed and approved by all responsible ethics committees (Ethics Committee of the Medical Faculty of the Christian Albrechts University in Kiel; Ethics Committee of the Medical Faculty of the University of Duisburg-Essen; Ethics Committee of the University of Cologne (Central Ethics Committee in Germany); OVGU Ethics Committee at the Medical Faculty; Ethics Committee of the Medical Faculty of the University of Rostock; Ethics Committee of the Medical Faculty of the TU Dresden; Ethics Committee of the University of Ulm; Ethics Committee of the Medical Faculty of the LMU Munich; Ethics committee of the Westfalen-Lippe Medical Association and the Medical Faculty of the Westphalian Wilhelms University of Münster; Ethics Committee of the Bavarian State Medical Association; Ethics Committee of the Medical University of Vienna; National Videnskabsetisk Komité, Copenhagen).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The primary endpoint ORR at end of induction therapy was used to determine the sample size of the study. The ORR for a conventional regimen is assumed to be 40%, with corresponding null hypothesis ORR <= 0.40 and alternative hypothesis ORR > 0.40. The investigated regimen was considered potentially useful and worthy of further research if we can reject the null hypothesis in favour of the alternative hypothesis. The type I error is set to 2.5% and defines the chance that the investigated regimen will be investigated further although the true ORR is lower or equal to 40 %. The type II error is the chance that an effective treatment will not be studied further. It is assumed to improve the ORR to at least 60 % with the investigated regimen. The type II error should not exceed 20%, so that it is aimed to achieve a statistical power of at least 80%. According to these study parameters a one-sided one-sample binomial-test with an overall significance level of 2.5% provides the sample size N = 48, such that statistical significance is achieved with a power of 80%.
Data exclusions	Missing data will not be replaced or imputed. For all analyses the number of patients available and the proportion of patients for whom data are missing will be described with respect to the reported analyses populations.
Replication	The study protocol is reported in the CLL-RT1 Protocol version 3.0 (GCLLSG), data handling and statistical analyses are fully documented in the RT1 Data Management Plan and the CLL-RT1 Statistical Analysis Plan. Measurements were taken from distinct samples.
Randomization	The study is a phase-II open label trial, which is designed as a prospective, multicentre, single-arm trial. Randomization is not relevant. Covariates were controlled for by the screening of patients by inclusion and exclusion criteria (above).
Blinding	The study is a phase-II open label trial, which is designed as a prospective, multicentre, single-arm trial. Blinding is not relevant.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	EudraCT Number: 2018-002492-17, ClinicalTrials.gov Identifier: NCT04271956
Study protocol	Study protocol will be made available in the supplements.
Data collection	Patients were recruited from 10 sites in Germany (University Hospital of Cologne, University Hospital Kiel, University Hospital Essen, Otto-von-Guericke University Magdeburg, University Hospital Rostock, University Hospital Dresden, University Hospital Ulm, Munich Clinic Schwabing, Brüderkrankenhaus Paderborn, MVZ Dr. Vehling-Kaiser GmbH Landshut), 1 site in Austria (Medical University of Vienna) plus 1 site in Denmark (Rigshospitalet Copenhagen). Between 11 February 2020 and 2 January 2023. Data cut-off on May 2nd 2023.
Outcomes	Primary endpoint: Overall response rate (ORR) after induction therapy (i.e. 6 cycles) according to the refined Lugano Classification. Secondary endpoints: • ORR after induction therapy (i.e. 6 cycles) according to IWCLL criteria • ORR after consolidation therapy (i.e. 12 cycles) • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) • Time to next treatment (TTNT) • Proportion of patients receiving SCT for consolidation • Safety parameters: type, frequency, severity of adverse events, and their relationship to study treatment. ORR is determined by the proportion of patients with a response after induction therapy. PFS will be measured from the date of registration to the date of first occurrence of disease progression (PD) or relapse or death from any cause, whichever occurs first. These will be counted as events for PFS. Start of a subsequent CLL/RT treatment after the study treatment will not be counted as an event nor as a reason for censoring. Patients for whom no documented event for PFS is available at the time of analysis will be censored at the time point of last observation they were assessed to be event-free. DOR will be calculated for patients with response after induction therapy according to Lugano Classification. DOR will be measured from the date of first documented response to the first occurrence of progression or relapse or death by any cause, whichever occurs first. Patients for whom no documented event for DOR is available at the time of analysis will be censored on the date of the last tumor assessment. If no tumor assessments were performed after the screening visit, DOR will be censored at the time of first documented response + 1 day. OS will be measured from the date of registration to the date of death due to any cause. Patients who have not yet died at the time of analysis will be censored at the time of last observation they were assessed to be alive after registration. TTNT will be measured from date of registration to the date of first subsequent CLL/RT treatment (including transplantation). These will be counted as event for TTNT. Alive patients for whom no subsequent CLL/RT treatment is documented will be censored at the time of last observation they were assessed to be alive. Deceased patients for whom no subsequent CLL/RT treatment is documented will be censored at the date of death. Adverse events (AE) will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the AEs will be graded according to the recent updated NCI CTCAE version 5.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*