esperoct®▼
turoctocog alfa pegol

novo nordisk®

MOVE BEYOND THE THRESHOLD

As an extended half-life recombinant FVIII, Esperoct®offers a simple way to reach higher trough FVIII activity levels compared to standard half-life treatments.**[1,4-9]

Mode of Action Video
Click here

In adults and adolescents (12 years and over)[†] with severe haemophilia A, Esperoct® demonstrated:

A simple, fixed dose:[††1,4]
50 IU/kg every 4 days

Higher trough FVIII activity levels vs. SHL treatments:[1,4-9]
Mean trough FVIII activity levels of 3%

Low ABR:[1,4]
Median total ABR[‡§] of 1.18

*40°C storage for up to 3 months before reconstitution[1] **Esperoct® is licenced for the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency). The safety and efficacy of Esperoct in previously untreated patients have not yet been established.[1]

This Novo Nordisk advertisement is intended for UK Healthcare Professionals

Prescribing Information

Esperoct®▼ powder and solvent for solution for injection Turoctocog alfa pegol Esperoct 500 IU Esperoct 1000 IU Esperoct 1500 IU Esperoct 2000 IU Esperoct 3000 IU **Indication:** Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency) **Posology and administration:** The dose, dosing interval and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding, on the targeted factor VIII activity level and the patient's clinical condition. On demand treatment and treatment of bleeding episodes: Required dose IU = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL). *Mild haemorrhage:* early haemarthrosis, mild muscle bleeding or mild oral bleeding. Factor VIII level required (IU/dL or % of normal): 20-40. Frequency of doses: 12-24, until the bleeding is resolved. *Moderate haemorrhage:* More extensive haemarthrosis, muscle bleeding, haematoma. Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses: 12-24, until the bleeding is resolved. *Severe or life-threatening haemorrhages:* Factor VIII level required (IU/dL or % of normal) – 60-100. Frequency of doses: 8-24, until the threat is resolved Perioperative management: *Minor surgery Including tooth extraction.* Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses (hours): within one hour before surgery; repeat after 24 hours if necessary. Duration of therapy: single dose or repeat injection every 24 hours for at least 1 day until healing is achieved. *Major surgery.* Factor VIII level required (IU/dL or % of normal): 80-100 (pre- and post-operative). Frequency of doses (hours): Within one hour before surgery to achieve factor VIII activity within the target range. Repeat every 8 to 24 hours to maintain factor VIII activity within the target range. Repeat injection every 8 to 24 hours as necessary until adequate wound healing is achieved. Consider continuing therapy for another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL). Prophylaxis: The recommended dose is 50 IU of Esperoct per kg body weight every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency. Paediatric population: The dose in adolescents (12 years and above) is the same as for adults. In children below 12 years long-term safety has not been established. Method of administration: Intravenous injection (over approximately 2 minutes) after reconstitution of the powder with 4 mL supplied solvent (sodium chloride 9 mg/mL (0.9%) solution for injection). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, or to hamster protein. **Special warnings and precautions for use:** Name and the batch number of the administered product should be clearly recorded to improve traceability. Hypersensitivity: Allergic-type hypersensitivity reactions are possible due to traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to immediately discontinue the use of the medicinal product and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented. Inhibitors: The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII pro-coagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon. The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors. Patients treated with coagulation factor VIII products should be monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Cardiovascular events: In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk. Catheter-related complications: If a central venous access device (CVAD) is required, the risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered. Paediatric population: Listed warnings and precautions apply both to adults and adolescents (12-18 years). Excipient-related considerations: Product contains 30.5 mg sodium per reconstituted vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2.0 g sodium for an adult. **Fertility, pregnancy and lactation:** Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated. **Undesirable effects:** Adverse events in clinical trials which could be considered **serious** include: (≥1/10): Rash, erythema, pruritis, injection site reactions (<1/10,000): Factor VIII inhibition, hypersensitivity The Summary of Product Characteristics should be consulted in relation to other adverse reactions. **MA numbers and Basic NHS Price:** Esperoct 500 IU EU/1/19/1374/001 £425 Esperoct 1000 IU EU/1/19/1374/002 £850 Esperoct 1500 IU EU/1/19/1374/003 £1,275 Esperoct 2000 IU EU/1/19/1374/004 £1,700 Esperoct 3000 IU EU/1/19/1374/005 £2,550 **Legal category:** POM. For full prescribing information please refer to the SmPC which can be obtained from the Marketing Authorisation Holder: Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA. **Marketing Authorisation Holder:** Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark. **Date last revised:** September 2020

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 6005055). Calls may be monitored for training purposes.

Esperoct® is a trademark owned by Novo Nordisk Health Care AG, Switzerland.

ABR, annualised bleed rate; EHL, extended half-life; FVIII, factor VIII; rFVIII, recombinant factor VIII; SHL, standard half-life

[†]Previously treated patients, 12 years and above.[1] [††] Prophylaxis: The recommended dose is 50 IU of Esperoct per kg body weight every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency.[1] [§]Total ABR includes all bleeds: spontaneous, traumatic and joint bleeds[4]

References: 1. Esperoct® Summary of Product Characteristics. **2.** Adynovi® Summary of Product Characteristics. **3.** Elocta® Summary of Product Characteristics. **4.** Giangrande P et al. Thromb Haemost 2017; 117:252–261. **5.** Tiede A et al. J Thromb Haemost 2013; 11:670–678. **6.** Advate® Summary of Product Characteristics. **7.** NovoEight® Summary of Product Characteristics. **8.** Nuwiq® Summary of Product Characteristics. **9.** Refacto AF® Summary of Product Characteristics.

Novo Nordisk Ltd. 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA. Novo Nordisk Customer Care Line Tel: 0845 600 5055.
Calls may be monitored for training purposes. Novo Nordisk® is a trademark owned by Novo Nordisk A/S. Esperoct® is a trademark owned by Novo Nordisk Health Care AG.
Date of preparation: September 2020 UK20ESP00080

bjh short report

Adjuvant tyrosine kinase inhibitor therapy improves outcome for children and adolescents with acute lymphoblastic leukaemia who have an ABL-class fusion

Anthony V. Moorman,[1] Claire Schwab,[1] Emily Winterman,[1] Jerry Hancock,[2] Anna Castleton,[3] Michelle Cummins,[4] Brenda Gibson,[5] Nick Goulden,[6] Pam Kearns,[7] Beki James,[8] Amy A. Kirkwood,[9] Donna Lancaster,[10] Mabrouk Madi,[11] Andrew McMillan,[12] Jayashree Motwani,[13] Alice Norton,[13] Aengus O'Marcaigh,[14] **Katharine Patrick,[15] Neha Bhatnagar,[16] Amrana Qureshi,[16] Deborah Richardson,[17] Simone Stokley,[18] Gordon Taylor,[19] Frederik W. van Delft,[1] John Moppett,[4] Christine J. Harrison,[1] Sujith Samarasinghe[6] and Ajay Vora[6]**

[1]Wolfson Childhood Cancer Centre, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, [2]Bristol Genetics Laboratory, North Bristol NHS Trust, Bristol, [3]Department of Haematology, The Christie Hospital NHS Trust, Manchester, [4]Department of Paediatric Oncology, Bristol Royal Hospital for Children, Bristol, [5]Department of Haematology, Royal Hospital for Children, Glasgow, [6]Department of Haematology, Great Ormond Street Hospital, London, [7]Institute of Cancer and Genomic Sciences and NIHR Birmingham Biomedical Research Centre, University of Birmingham, Birmingham, [8]Regional Centre for Paediatric Haematology and Oncology, Leeds Children's Hospital, Leeds, [9]CR UK and UCL Cancer Trials Centre, UCL Cancer Institute, UCL, London, [10]Paediatric Oncology, The Royal Marsden Hospital, Sutton, [11]Department of Paediatric Oncology and Haematology, Leicester Royal Infirmary, Leicester, [12]Centre for Clinical Haematology,

Abstract

Patients with an ABL-class fusion have a high risk of relapse on standard chemotherapy but are sensitive to tyrosine kinase inhibitors (TKI). In UKALL2011, we screened patients with post-induction MRD ≥1% and positive patients (12%) received adjuvant TKI. As the intervention started during UKALL2011, not all eligible patients were screened prospectively. Retrospective screening of eligible patients allowed the outcome of equivalent ABL-class patients who did and did not receive a TKI in first remission to be compared. ABL-class patients who received a TKI in first remission had a reduced risk of relapse/refractory disease: 0% vs. 63% at four years (P = 0·009).

Keywords: paediatric acute lymphoblastic leukaemia, ABL-class fusion, tyrosine kinase inhibitor, targeted therapy, prognostic factors.

 doi: 10.1111/bjh.17093

Nottingham University Hospitals, Nottingham, [13]Department of Haematology, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK, [14]Department of Haematology, Children's Health Ireland, Dublin, Ireland, [15]Department of Haematology, Sheffield Children's NHS Foundation Trust, Sheffield, [16]Paediatric Haematology Department, Oxford Children's Hospital, Oxford, [17]Department of Haematology, Southampton University Hospitals Trust, Southampton, [18]Department of Paediatric Haematology, Nottingham Children's Hospital, Nottingham, and [19]Department of Haematology, Aberdeen Royal Infirmary, Aberdeen, UK

Received 24 July 2020; accepted for publication 17 August 2020

Correspondence: Professor Anthony V. Moorman, Leukaemia Research Cytogenetics Group, Wolfson Childhood Cancer Research Centre, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK.
Email: anthony.moorman@newcastle.ac.uk

Patients with acute lymphoblastic leukaemia (ALL) who have a *BCR-ABL1*-like or Philadelphia chromosome(Ph)-like gene expression profile have a poor outcome.[1,2] ABL-class gene fusions are a network of chimaeric gene fusions whose functional consequence results in constitutive activation of the ABL pathway; mimicking *BCR-ABL1* fusion.[2] A subset of patients with *BCR-ABL1*-like ALL harbour an ABL-class fusion defined as a fusion between *ABL1*, *ABL2*, *PDGFRB/A* or *CSF1R* and a variable partner gene. Patients harbouring ABL-class fusions have high levels of minimal residual disease (MRD) at the end of induction (EOI) and a high risk of relapse.[3,4] There is experimental and pre-clinical evidence that ABL-class fusions are sensitive to treatment with tyrosine kinase inhibitors (TKI).[5] In addition, case reports and case series demonstrate good clinical responses to treatment with a TKI.[5,6] However, these fusions are rare and only one study has compared the outcome of ABL-class fusion patients treated with and without adjuvant TKI therapy.[7]

Patients with refractory disease on the UKALL2003 trial harboured a high frequency of ABL-class fusions (10%), and specifically *EBF1-PDFGRB* patients had high levels of EOI MRD and a high rate of relapse.[3,8] Hence, in the UKALL2011 trial, we screened patients who responded slowly to induction therapy for the presence of ABL-class fusions and, where positive, supplemented their therapy with imatinib. Here, we describe the total cohort and compare the outcome of those patients who received adjuvant TKI therapy in first remission with those patients who did not receive TKI in first remission, because they were diagnosed before the intervention was established.

Methods

Patients were enrolled and consented onto the UKALL2011 trial (ISRCTN number 64515327) and were diagnosed with ALL using standard morphological and immunophenotypic criteria. MRD was evaluated by PCR analysis of Ig/TCR rearrangements.[9] B-cell precursor and T-cell patients were eligible for ABL-class fusion screening if they had a MRD level ≥1%, induction failure or M2/M3 marrow at the EOI and did not harbour another class-defining chromosomal abnormality. ABL-class screening was performed using commercially available FISH probes for *BCR-ABL1*, *ABL1*, *ABL2* or *PDGFRB/CSF1R*, either centrally by the Leukaemia Research Cytogenetics Group (LRCG) or at regional NHS genetic laboratories. *FIP1L1-PDGFRA* fusion was identified by SNP array analysis (Illumina 850k SNP array) and *AGGF1-PDGFRB* by RNA fusion panel (Illumina TruSight) standard survival endpoints and statistical analysis were performed.[9]

Results and discussion

Among 191 patients who had a slow response to induction therapy, 43 patients were not tested due to their background cytogenetics: high hyperdiploidy ($n = 28$), *ETV6-RUNX1* ($n = 8$), *KMT2A* rearrangement ($n = 5$), t(1;19)(q23;p13) ($n = 1$) and iAMP21 ($n = 1$). A further 22 cases could not be screened due to lack of material. Among 126 patients tested, 21 (17%) harboured an ABL-class fusion. The frequency of ABL-class fusions among all B-cell precursor and T-cell ALL patients with a slow response to induction therapy was 16/122 (13%) and 5/47 (11%), respectively; in line with previous reports linking ABL-class fusions with high MRD.[7,8]

The 21 ABL-class fusion patients had a median age of nine years, comprised 15 males and six females and had a median white cell count at diagnosis, of 35×10^9/l (Table I). By definition, all patients had a high EOI MRD, but the mean level of 32% was considerably higher than the entry threshold (Table 1). Ten patients harboured *EBF1-PDGFRB* and their mean EOI MRD levels were significantly greater than the remaining cases (53% vs. 15%, $P = 0{\cdot}001$); in keeping with previous observations.[3,6] The partner gene was determined in six patients (Table I). All *EBF1-PDGFRB* patients had BCP-ALL, whereas the other fusions were split between BCP-ALL and T-ALL. *NUP214-ABL1* fusion in T-ALL is well documented, and rare cases of *FIP1L1-PDGFRA, ETV6-ABL2* and other *PDGFRB* fusions have been reported.[10-12]

Thirteen cases identified prospectively were treated with imatinib in first remission (TKI group). The remaining eight cases, identified retrospectively and diagnosed before the intervention started, received standard post-induction therapy without a TKI (control group). There were no differences between the TKI and control groups with regard to age, sex, white cell count or EOI MRD (Table I). In particular, the mean EOI MRD was 39% and 24% in the TKI and control groups, respectively, ($P = 0{\cdot}3$). Notably, 8/13 (62%) cases in the TKI group had *EBF1-PDGFRB* compared to 2/8 (25%) in the control group ($P = 0{\cdot}2$). As the intervention was initiated after the start of the trial, 9/13 patients in the TKI group were diagnosed after 2016, compared to 0/8 in the control group.

Although the TKI patients followed the UKALL2011 protocol, they were treated off-trial, as supplementing therapy with imatinib was not part of the protocol therapy. Patients started on imatinib in first remission with a median start time of 46 days from initial diagnosis (range 22–116). Patient 10 started TKI before EOI (day 22) because *FIP1L1-PDGFRA* fusion was detected serendipitously by SNP array during routine genetic analysis. Patient 13 was not tested until week 14, but started TKI within six days of detection of the fusion. Initially, all patients in the TKI group received imatinib at a daily dose of 300–400 mg/m^2, with two patients switching to dasatinib (Table I). None of the patients received TKI as a single agent and post-induction chemotherapy was administered at the discretion of the treating clinician (Table I). Among eight patients in the control group, six remained on-trial receiving regimen C, while two patients were taken off-trial and received regimen C plus additional chemotherapy (Table I). Nine of 13 (69%) patients in the TKI group had a bone marrow transplant in first remission, compared with 3/8 (38%) in the control group ($P = 0{\cdot}2$).

During the follow-up period (median 3·9 years), 0/13 patients in the TKI group suffered a leukaemia-related event, whereas among 6/8 patients in the control group relapsed or died of primary refractory disease (Fig 1). The four-year relapse/refractory rate for the TKI and control groups was 0% and 62·5% (95% CI 33–91%), respectively, (log rank $P = 0{\cdot}009$). The equivalent EFS and OS rates were 83·9% (49–96%) vs. 37·5% (9–67%), $P = 0{\cdot}07$ and 83·9% (49–96%) vs. 75% (31–93%), $P = 0{\cdot}4$, respectively. Three of the five patients in the control group who relapsed were treated with TKI post-relapse but two patients subsequently died of respiratory/multi-organ failure. Two patients in the TKI group died due to transplant complications. Overall, 2/13 (15%) patients in the TKI group died compared with 4/8 (50%) in the control group. Eight of 20 (40%) patients suffered one or more grade 3/4 toxicities which, although higher, is comparable to patients receiving similar high-dose chemotherapy on UKALL2003·[13] Only two toxicities, one in the TKI group and one post-relapse in the control group, were likely to be associated with the TKI treatment (Table I).

Ad hoc case reports of patients with refractory disease and an ABL-class fusion responding to TKI treatment initially highlighted the potential benefit of precision medicine for these patients.[2,14,15] Two studies have recently examined the efficacy of frontline TKI therapy in small cohorts.[6,7] The French study showed that ABL-class patients receiving adjuvant TKI therapy had a better than expected outcome compared with historical cohorts.[6] However, their study comprised children and adults, delivered a mix of TKI drugs and did not have a contemporary cohort for comparison. In contrast, the AIEOP-BFM study compared ABL-class fusion patients registered on a trial according to whether they receive a TKI in conjunction with chemotherapy.[7] They did not observe a survival advantage for patients receiving TKI therapy but their groups were not comparable. The screening and intervention policy they employed was based on institutional preference resulting in the TKI-treated cohort being more likely to be assigned to the high-risk treatment group, compared with the non-TKI cohort. In addition, the start time of TKI therapy ranged from post-induction to post-consolidation and, in one instance, to post-transplant. Evidence from *BCR-ABL1* positive ALL shows that early administration of TKI therapy is beneficial.[16]

The scarcity of these patients and the strong biological rationale for treating them with targeted therapy makes a randomised clinical trial very unlikely. Hence, evidence for the efficacy of TKI therapy in this subtype of ALL is likely to

Table I. Demographic, clinical, treatment and outcome details of 21 patients with ALL and an ABL-class fusion treated with or without a tyrosine kinase inhibitor in first remission

Patient	Group	Sex	Age at diagnosis	WCC	Immunophenotype	ABL-class fusion	Induction therapy	MRD @ EOI (%)	Time started TKI	TKI dose and schedule	MRD @ Week 9 (day)	MRD @ Week 14 (day)	Off -trial (If yes, when)	Post-induction therapy	Transplant Yes/No	Grade 3/4 Toxicity	If yes, related to TKI? With details	Relapse (yes/no)	Dead (yes/no)	Survival (months)
1	Early TKI	Female	5	167·40	B-cell precursor	*EBF1-PDGFRB*	B	50%	day 32	Imatinib (300 mg/day) until SCT (4.9 m).	6%	0·02%	Induction	Regimen B plus NOPHO High-risk blocks	Yes	Yes	No	No	Yes, post-transplant encephalopathy	12·9
2	Early TKI	Female	8	359·00	B-cell precursor	*EBF1-PDGFRB*	B	30%	day 38	Imatinib (300 mg/day) for 27 m.	0·4%	0% (day 118)	Induction	Regimen C	No	Yes	No	No	No	57·3
3	Early TKI	Male	12	34·00	T cell	*NUP214-ABL1*	B	30%	day 75	Imatinib (350 mg/day) for 2.7 m and then dasatinib (70 mg/day) for 3.9 m.	20% (day 75)	2% (day 125)	Induction	Regimen C, Nelarabine, FLAD, FLA, Bortezomib	Yes	Yes	No	No	No	47·3
4	Early TKI	Male	17	4·30	B-cell precursor	*EBF1-PDGFRB*	B	50%	day 52	Imatinib (600 mg/day) for 3 weeks.	50%	0·005% (day 108)	Induction	Regimen C, FLA-Ida, FLA	Yes	No	-	No	No	49·9
5	Early TKI	Male	18	36·90	B-cell precursor	*ZC3HAV1-ABL2*	B	20%	day 49	Imatinib (400 mg/day) for 4 weeks, dasatinib (140 mg/day) for 4 weeks, then post-SCT imatinib (100->600 mg/day) 3.5 years and ongoing.	n/day	0·9%	Consolidation	Regimen B, FLA-Ida, Blinatumomab	Yes	Yes	Yes, Stevens-Johnson Syndrome while on dasatinib (grade 4)	No	No	46·8
6	Early TKI	Male	9	26·00	B-cell precursor	*EBF1-PDGFRB*	A	90%	day 37	Imatinib (300 mg/day) for 3 years and ongoing.	0·0100%	0·002	Induction	Regimen C	No	No	-	No	No	43·7
7	Early TKI	Male	9	2·00	B-cell precursor	*EBF1-PDGFRB*	A	50%	day 42	Imatinib (400 mg/day) until week 16 and then switched to dasatinib (80 mg/day).	n/day	≥0·5%	Consolidation	Regimen C plus NOPHO High-risk blocks	Yes	Unknown	-	No	Yes, infection post -SCT	18·8
8	Early TKI	Female	9	381·00	T cell	*ETV6-ABL2*	B	1%	day 78	Imatinib (400 mg/day) for 33 m and ongoing.	5%	0·06%	Consolidation	Regimen C, NECTAR	No	No	-	No	No	33·6
9	Early TKI	Male	17	28·00	B-cell precursor	*EBF1-PDGFRB*	B	9%	day 40	Imatinib (400 mg/day) for 3.4 m until SCT. Restarted (200 mg/day) 9 m post-SCT for 1 year and ongoing.	0·05%	0%	Consolidation	Regimen C	Yes	No	-	No	No	3Im5·3
10	Early TKI	Male	15	325·00	T cell	*FIP1L1-PDGFRA*	B	4%	day 22	Imatinib (500 mg/day) for 7.1 m until SCT, restarted at same dose 7 m post-SCT for 1 year.	2% (day 71)	0·6% (day 128)	Induction	Regimen C plus NOPHO High-risk blocks	Yes	No	-	No	No	35·9

Table I. (*Continued*)

Patient	Group	Sex	Age at diagnosis	WCC	Immunophenotype	ABL-class fusion	Induction therapy	MRD @ EOI (%)	Time started TKI	TKI dose and schedule	MRD @ Week 9 (day)	MRD @ Week 14 (day)	Off -trial (If yes, when)	Post-induction therapy	Transplant Yes/No	Grade 3/4 Toxicity	If yes, related to TKI? With details	Relapse (yes/no)	Dead (yes/no)	Survival (months)
11	Early TKI	Male	5	29·00	B-cell precursor	*EBF1-PDGFRB*	A->C	90%	Week 5	Imatinib for 5 m until SCT (6 m).	60% (day 69)	0·8% (day 108)	Induction	Regimen C plus NOPHO High-risk blocks	Yes	No	-	No	No	21·7
12	Early TKI	Male	5	127·00	B-cell precursor	*AGGF1-PDGFRB*	B	10%	day 43	Imatinib (300 mg/day) until SCT (7.3 m).	0·2%	0·07% (day 113)	Induction	Regimen C, Blinatumomab	Yes	Yes	No	No	No	20·3
13	Early TKI	Male	10	367·00	B-cell precursor	*EBF1-PDGFRB*	B	70·00%	day 116*	Imatinib (320 mg/day) for 4 weeks until CAR-T.	70%†	23% (day 108)†	Consolidation	CAR-T	No	No	-	No	No	13·4
14	Control	Male	8	31·80	B-cell precursor	*EBF1-PDGFRB*	A	50%	Post-relapse	Imatinib	n/d	0·07%	On-trial	Regimen C	Yes (CR2)	Yes	No	Isolated BM (56 m)	Respiratory failure post-transplant	70·3
15	Control	Female	1	35·00	B-cell precursor	*PDGFRB/CSF1R rearrangement*	A	20%	Not received	n/a	0·4%	0%	On-trial	Regimen C	No	No	-	No	No	72·5
16	Control	Female	18	92·00	B-cell precursor	*EBF1-PDGFRB*	B	50%	Post-relapse	Imatinib (400 mg) for 19 m until SCT and then same dose post-SCT for 2 m and ongoing.	n/d	0·60%	On-trial	Regimen C	Yes (CR1 and CR2)	Yes	No	Marrow & CNS (41 m)	No	74·9
17	Control	Male	2	469·00	T cell	*PDGFRB/CSF1R rearrangement*	B	10%	Not received	n/a	20%	10%	Induction	Regimen C, Nelarabine, AraC	Yes (CR1)	No	-	Marrow (6.2 m)	Yes, relapse	6·5
18	Control	Female	12	22·80	B-cell precursor	*RANBP2-ABL1*	B	20%	Post-relapse	Dasatinib (100 mg/day) for 2.2 m until death.	4%	0%	On-trial	Regimen C	Yes (CR1)	Yes	Yes, nausea and headaches	Marrow & CNS (47 m)	Multi-organ failure post-transplant	50·9
19	Control	Male	3	32·00	B-cell precursor	*PDGFRB/CSF1R rearrangement*	A	5%	Not received	n/a	0·1%	0·01%	On-trial	Regimen C	No	No	-	Isolated eye relapse (24m)	No	57·6
20	Control	Male	14	4·30	T cell	*PDGFRB/CSF1R rearrangement*	B	7%	Not received	n/a	n/d	0·009%	On-trial	Regimen C	No	No	-	No	No	67·6
21	Control	Male	23	62·40	B-cell precursor	*ABL2 rearrangement*	B	30%	Not received	n/a	50%	20%	Induction	Regimen C, FLAG-IDA	No	No	-	Never remitted	Yes, primary refractory disease and infection	3·5

*Late start was due to delay in detection but TKI started within six days of detecting fusion.
†MRD measured by flow cytometry.

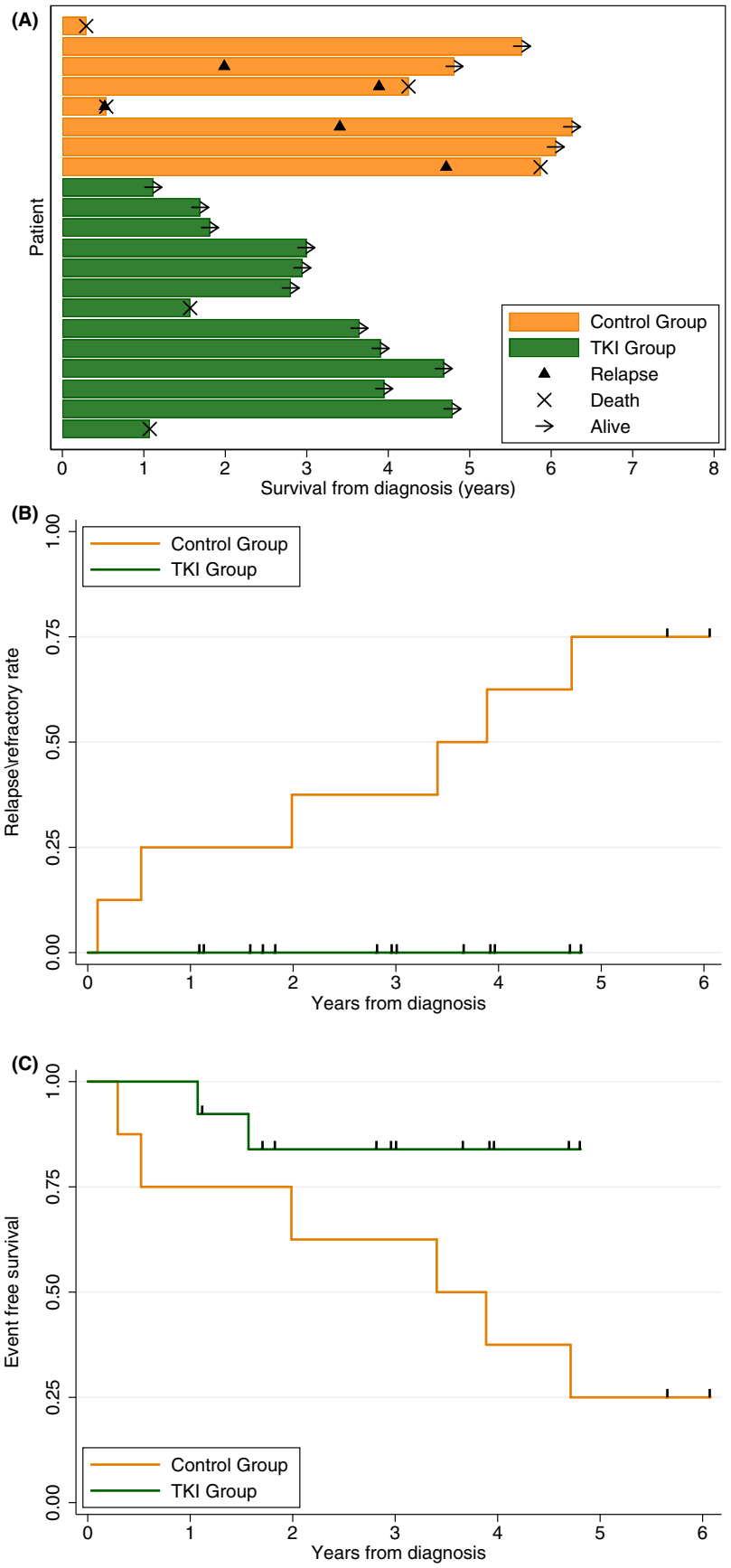

Fig 1. (A) Swimmer plot illustrating the outcome of patients with an ABL-class fusion treated with and without adjuvant imatinib therapy in first remission; (B) Kaplan–Meier graph showing the relapse/refractory rate among ABL-class fusion patients treated with and without adjuvant imatinib therapy in first remission. Time to relapse was measured from diagnosis to relapse, censoring at time of death in remission. In this graph, patient 21, who did not achieve a complete, was counted as having an event on day 35; (C) Kaplan–Meier graph showing the event-free survival of patients in the TKI and control groups. [Colour figure can be viewed at wileyonline library.com]

be limited to retrospective studies such as this one and the other two discussed above.[6,7] Even though our study was not a randomised clinical trial for TKI therapy, it has a number of advantages compared with previous studies. Most importantly, because our two treatment cohorts were due to a protocol change, they were comparable in terms of key risk factors and can be thought of as randomly chosen. However, it should be noted that all patients received additional and different high-dose chemotherapy and many patients were transplanted. Even though TKI therapy was administered according to the physicians' choice, the patients received similar doses of imatinib and, crucially, started TKI early during treatment, mostly within a few weeks after induction. Our cohort was restricted to those patients with EOI MRD ≥1% but it is well established that the majority of ABL-class patients have a slow response to initial therapy.[3,6,7]

In conclusion, ABL-class fusions are frequent among BCP and T-ALL patients who respond slowly to induction therapy. We have demonstrated a reduced risk of relapse for ABL-class fusion patients with EOI MRD ≥1% treated with adjuvant TKI without a significant increased risk of severe toxicity. The ALLTogether 01 trial (EUDRACT number: 2018-001795-38) will screen patients at diagnosis for ABL-class fusions and add imatinib from day 15 (day 28 if aged ≥16 years) to a standard chemotherapy backbone to investigate whether early TKI reduces EOI MRD and improves outcome for all patients with an ABL-class fusion.

Acknowledgements

We would like thank all the patients who took part in this study as well as their families. We acknowledge Blood Cancer UK (formerly Bloodwise) for financial support and the member laboratories of the UK Cancer Cytogenetic Group (UKCCG) for providing cytogenetic data and material; in particular Gavin Cuthbert at the Northern Genetics Service (Newcastle upon Tyne Hospitals NHS Trust) for additional genomic analyses. We acknowledge the input of all the scientists and technicians working in the MRD laboratories: Bristol Genetics Laboratory, Southmead Hospital, Bristol; Molecular Biology Laboratory, Royal Hospital for Sick Children, Glasgow; Molecular Haematology Laboratory, Royal London Hospital, London; and the Molecular Genetics Service, Sheffield Children's Hospital, Sheffield. Primary childhood leukaemia samples used in this study were provided by the Blood Cancer UK Childhood Leukaemia Cell Bank working with the aforementioned MRD laboratories.

Authorship contributions

Conception and Design: Anthony V Moorman, Christine J Harrison, John Moppett, Sujith Samarasinghe, Ajay Vora. Collection and assembly of laboratory and trial data: Claire Schwab, Emily Winterman, Jerry Hancock, Pam Kearns, Amy A Kirkwood. Data analysis and interpretation: Anthony V Moorman, Claire Schwab, Ajay Vora. Financial and administrative support: Anthony V Moorman, Nick Goulden, Christine J Harrison, Pam Kearns, John Moppett, Sujith Samarasinghe, Ajay Vora. Provision of patients and outcome data: Neha Bhatnagar, Anna Castleton, Michelle Cummins, Brenda Gibson, Donna Lancaster, Madhi Mabrouk, Andrew McMillan, Jayashree Motwani, Alice Norton, Aengus O'Marcaigh, Katharine Patrick, Armana Qureshi, Deborah Richardson, Simone Stockley, Gordon Taylor, Frederik van Delft, Ajay Vora. Manuscript writing: Anthony V Moorman. Final approval of manuscript: All authors.

Disclosure of Conflict of Interest

None.

References

1. Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JGCAM, Peters STCJM, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol*. 2009;**10**(2):125–34.
2. Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang Y-L, Pei D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med*. 2014;**371**(11):1005–15.
3. Schwab C, Ryan SL, Chilton L, Elliott A, Murray J, Richardson S, et al. EBF1-PDGFRB fusion in pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL): genetic profile and clinical implications. *Blood*. 2016;**127**(18):2214–8.
4. Roberts KG, Pei D, Campana D, Payne-Turner D, Li L, Cheng C, et al. Outcomes of children with BCR-ABL1-like acute lymphoblastic leukemia treated with risk-directed therapy based on the levels of minimal residual disease. *J Clin Oncol*. 2014;**32**(27):3012–20.
5. Boer JM, den Boer ML. BCR-ABL1-like acute lymphoblastic leukaemia: From bench to bedside. *Eur J Cancer*. 2017;**82**:203–18.
6. Tanasi I, Ba I, Sirvent N, Braun T, Cuccuini W, Ballerini P, et al. Efficacy of tyrosine kinase inhibitors in Ph-like acute lymphoblastic leukemia harboring ABL-class rearrangements. *Blood*. 2019;**134**(16):1351–5.
7. Cario G, Leoni V, Conter V, Attarbaschi A, Zaliova M, Sramkova L, et al. Relapses and treatment-related events contributed equally to poor prognosis in children with ABL-class fusion positive B-cell acute lymphoblastic leukemia treated according to AIEOP-BFM protocols. *Haematologica*. 2020;**105**(7):1887–94.
8. O'Connor D, Moorman AV, Wade R, Hancock J, Tan RMR, Bartram J, et al. Use of Minimal Residual Disease Assessment to Redefine Induction Failure in Pediatric Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2017;**35**(6):660–7.
9. O'Connor D, Enshaei A, Bartram J, Hancock J, Harrison CJ, Hough R, et al. Genotype-Specific Minimal Residual Disease Interpretation Improves Stratification in Pediatric Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2018;**36**(1):34–43.
10. Heilmann AM, Schrock AB, He J, Nahas M, Curran K, Shukla N, et al. Novel PDGFRB fusions in childhood B- and T-acute lymphoblastic leukemia. *Leukemia*. 2017;**31**(9):1989–92.
11. Griesinger F, Janke A, Podleschny M, Bohlander SK. Identification of an ETV6-ABL2 fusion transcript in combination with an ETV6 point mutation in a T-cell acute lymphoblastic leukaemia cell line. *Br J Haematol*. 2002;**119**(2):454–8.
12. Metzgeroth G, Schwaab J, Gosenca D, Fabarius A, Haferlach C, Hochhaus A, et al. Long-term follow-up of treatment with imatinib in eosinophilia-associated myeloid/lymphoid neoplasms with PDGFR rearrangements in blast phase. *Leukemia*. 2013;**27**(11):2254–6.

13. Vora A, Goulden N, Mitchell C, Hancock J, Hough R, Rowntree C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. *Lancet Oncol*. 2014;**15**(8):809–18.
14. Lengline E, Beldjord K, Dombret H, Soulier J, Boissel N, Clappier E. Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor acute lymphoblastic leukemia with EBF1-PDGFRB fusion. *Haematologica*. 2013;**98**(11):e146–e148.
15. Weston BW, Hayden MA, Roberts KG, Bowyer S, Hsu J, Fedoriw G, et al. Tyrosine kinase inhibitor therapy induces remission in a patient with refractory EBF1-PDGFRB-positive acute lymphoblastic leukemia. *J Clin Oncol*. 2013;**31**(25):e413–e416.
16. Slayton WB, Schultz KR, Kairalla JA, Devidas M, Mi X, Pulsipher MA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with philadelphia chromosome-positive acute lymphoblastic leukemia: results of children's oncology group trial AALL0622. *J Clin Oncol*. 2018;**36**(22):2306–14.

