SHORT REPORT

Second malignant neoplasms after treatment of 1487 children and adolescents with acute lymphoblastic leukemia—A population-based analysis of the Austrian ALL-BFM Study Group

Fiona Poyer1 | Karin Dieckmann2 | Michael Dworzak1,3 | Melanie Tamesberger4 | Oskar Haas3,5 | Neil Jones6 | Karin Nebral5 | Stefan Köhrer1,5 | Reinhard Moser7 | Gabriele Kropshofer8 | Christina Peters1 | Christian Urban9 | Georg Mann1,3 | Ulrike Pötschger3 | Andishe Attarbaschi1,3 | on behalf of the Austrian Berlin-Frankfurt-Münster (BFM) Study Group*

1Department of Pediatric Hematology and Oncology, St. Anna Children’s Hospital, Medical University of Vienna, Vienna, Austria
2Department of Radiotherapy, Medical University of Vienna, Vienna, Austria
3St. Anna Children’s Cancer Research Institute (CCRI), Vienna, Austria
4Department of Pediatrics and Adolescent Medicine, Kepler University Hospital Linz, Linz, Austria
5Labdia Diagnostics, Vienna, Austria
6Department of Pediatrics and Adolescent Medicine, University Clinics Salzburg, Salzburg, Austria
7Department of Pediatrics and Adolescent Medicine, State Hospital Leoben, Leoben, Austria
8Division of Pediatric Hematology and Oncology and Stem Cell Transplantation, Department of Pediatrics and Adolescent Medicine, Medical University of Innsbruck, Innsbruck, Austria
9Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

Correspondence
Andishe Attarbaschi, Department of Pediatric Hematology and Oncology, St. Anna Children’s Hospital, Kinderspitalgasse 6, 1090 Vienna, Austria.
Email: andishe.attarbaschi@stanna.at

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Abstract
Second malignant neoplasms (SMN) after primary childhood acute lymphoblastic leukemia (ALL) are rare. Among 1487 ALL patients diagnosed between 1981 and 2010 in Austria, the 10-year cumulative incidence of an SMN was 1.1% ± 0.3%. There was no difference in the 10-year incidence of SMNs with regard to diagnostic-, response- and therapy-related ALL characteristics except for a significantly higher incidence in patients with leukocytes ≥50.0 G/L at ALL diagnosis (2.1% ± 1.0% vs. 0% for 20.0–50.0 G/L, and 1.0% ± 0.3% for < 20.0 G/L; p = 0.033). Notably, there was no significant difference in the incidence of SMNs between patients with or without cranial radiotherapy (1.2% ± 0.5% vs. 0.8% ± 0.3%; p = 0.295). Future strategies must decrease the incidence of SMNs, as this event still leads to death in one-third (7/19) of the patients.

Ulrike Pötschger and Andishe Attarbaschi contributed equally to the manuscript.

*This paper is dedicated to our friend and mentor Helmut Gadner, the former Head of the St. Anna Children Hospital and founder of the Children’s Cancer Research Institute, Vienna, Austria, who chaired the Austrian ALL-BFM Study Group for 30 years and was not only instrumental in conceiving and conducting the Austrian ALL therapy studies, but also to get our clinical and diagnostic achievements internationally recognized.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood and adolescence [1]. With 5-year overall survival (OS) rates reaching 90%, the number of long-term survivors has risen, and it becomes increasingly important to not only focus on leukemia-free survival, but also on the quality of survival by evaluating the long-term toxicity of pediatric ALL treatment [1–3]. Long-term ALL survivors may suffer from chronic health conditions, ranging from organ dysfunctions to the development of secondary malignant neoplasms (SMN) [3–5]. SMNs cause considerable morbidity and, after relapse, are the main causes of death for ALL patients, making it imperative to reduce risk factors for their development without compromising ALL treatment efficacy [6]. Causes of SMNs are not fully clear, but seem to be due to an interplay of germline genetic variants in cancer predisposition genes and type of treatment, including cumulative cytotoxic drug and radiotherapy (RT) dosages [7, 8]. Herein, we present data on incidence, type, risk factors and outcome of SMNs in a population-based cohort of pediatric ALL patients treated according to Berlin–Frankfurt–Münster (BFM)-based protocols in Austria [9–11].

2 | PATIENTS AND METHODS

Between January 1981 and December 2009, 1487 children and adolescents < 23-years-old with newly diagnosed ALL were enrolled in one of six multicenter trials in Austria (A): ALL-BFM-A 81 (n = 141), ALL-A 84 (n = 127), ALL-BFM-A 86 (n = 142), ALL-BFM-A 90 (n = 256), ALL-BFM-A 95 (n = 230), and ALL-BFM-A 2000 (n = 591). Median follow-up was 9.5 years (Q1-Q3: 5.2–13.1 years; Supporting information: Table S18). All patients were registered at the national study center in Vienna (St. Anna Children’s Hospital and St. Anna Children’s Cancer Research Institute), and events such as relapse, death or SMNs as well as dates of last-follow-up were either reported ad hoc by the respective treatment centers or during regular follow-up queries/late effects screening performed by the national study center, and systematically recorded for the respective trials. Data collected on primary ALL disease included parameters with regard to demographics, response, treatment, and outcome. SMNs were defined as a non-lymphoid malignancy or, in selected central nervous system (CNS) tumors, also as non-malignant neoplasms (i.e., meningiomas). Notably, non-melanoma skin cancers were not included in this analysis. In case of multiple SMNs, only the first SMN was used for primary analysis.

The aim of this study was to determine the incidence and characteristics of SMNs as a first event for all children treated with BFM-based treatments for primary ALL in either of the 6 trials. Hence, as relapse was considered a competing risk, SMNs after ALL relapse were not considered as an event of interest. Data collected about the SMNs included clinical, histological, therapy, and outcome parameters. Details of the ALL-treatment protocols, RT, and cumulative cytotoxic drugs of the respective ALL trials are included in the Supporting information (Tables S1–S17) [9–11]. All patients were treated with informed consent.

TABLE 1A Initial characteristics of ALL patients with and without an SMN as a first event

| Number of patients | Number of patients with SMN | Number of patients without SMN |
|--------------------|-----------------------------|-------------------------------|
| Trial              |                             |                               |
| ALL-BFM-A 81       | 1 (5%)                      | 140 (10%)                     |
| ALL-A 84           | 5 (26%)                     | 122 (8%)                      |
| ALL-BFM-A 86       | 3 (16%)                     | 139 (9%)                      |
| ALL-BFM-A 90       | 3 (16%)                     | 253 (17%)                     |
| ALL-BFM-A 95       | 1 (5%)                      | 229 (16%)                     |
| ALL-BFM-A 2000     | 6 (32%)                     | 585 (40%)                     |
| Earlier era (81, 84, 86) | 9 (47%)                   | 401 (27%)                     |
| Later era (90, 95, 2000) | 10 (53%)                   | 1067 (73%)                    |
| Very early era (81, 84) | 6 (32%)                    | 262 (18%)                     |
| Later era (86, 90, 95, 2000) | 13 (68%)                  | 1206 (82%)                    |
| Gender             |                             |                               |
| female             | 10 (53%)                    | 651 (44%)                     |
| male               | 9 (47%)                     | 817 (56%)                     |
| Age (years)        |                             |                               |
| median             | 5.2                         | 5.0                           |
| range              | 1.5–15.4                    | 0.1–23.1                      |
| ≥10 years          | 5 (26%)                     | 331 (23%)                     |
| 0–10 years         | 15 (74%)                    | 1137 (77%)                    |
| WBC count (G/L)    |                             |                               |
| Median             | 14.0                        | 10.4                          |
| Range              | 1.5–720.0                   | 0.4–955.0                     |
| ≥20.0              | 7 (37%)                     | 521 (35%)                     |
| < 20.0             | 12 (63%)                    | 947 (65%)                     |
| ≥50.0              | 9 (47%)                     | 295 (20%)                     |
| < 50.0             | 12 (63%)                    | 1173 (80%)                    |
| CNS disease        |                             |                               |
| Negative           | 17 (89%)                    | 1408 (96%)                    |
| Positive           | 1 (5%)                      | 48 (3%)                       |
| Not available      | 1 (5%)                      | 12 (1%)                       |
### Table 1A (Continued)

| Immunophenotype | Number of patients with SMN | Number of patients without SMN |
|------------------|-----------------------------|-------------------------------|
| BCP-ALL          | 16 (84%)                    | 1223 (83%)                    |
| T-ALL            | 3 (16%)                     | 195 (13%)                     |
| Not available    | 0                           | 50 (3%)                       |

| Genetics         | Number of patients with SMN | Number of patients without SMN |
|------------------|-----------------------------|-------------------------------|
| ETV6::RUNX1      |                            |                               |
| Positive         | 4 (21%)                     | 260 (18%)                     |
| Negative         | 9 (47%)                     | 946 (64%)                     |
| Not available    | 6 (32%)                     | 262 (18%)                     |
| TCF3::PBX1       |                            |                               |
| Positive         | 0                           | 37 (2%)                       |
| Negative         | 13 (68%)                    | 1169 (80%)                    |
| Not available    | 6 (32%)                     | 262 (18%)                     |
| BCR::ABL1        |                            |                               |
| Positive         | 0                           | 25 (2%)                       |
| Negative         | 13 (68%)                    | 1181 (80%)                    |
| Not available    | 6 (32%)                     | 262 (18%)                     |
| KMT2A-rearrangement |                          |                               |
| Positive         | 1 (5%)                      | 30 (2%)                       |
| Negative         | 12 (63%)                    | 1176 (80%)                    |
| Not available    | 6 (32%)                     | 262 (18%)                     |
| High-hyperdiploidy |                          |                               |
| Positive         | 2 (11%)                     | 291 (20%)                     |
| Negative         | 10 (53%)                    | 811 (55%)                     |
| Not available    | 7 (37%)                     | 362 (25%)                     |

**Abbreviations:** BCP, B-cell precursor; CNS, central nervous system; SMN, secondary malignant neoplasm; WBC count, white blood cell count.

### Table 1B (Continued)

| Remission status on day 33 | Number of patients with SMN | Number of patients without SMN |
|----------------------------|-----------------------------|-------------------------------|
| CR                         | 13 (68%)                    | 1161 (79%)                    |
| No CR                      | 0                           | 30 (2%)                       |
| Not available              | 6 (32%)                     | 277 (19%)                     |

| MRD group                  | Number of patients with SMN | Number of patients without SMN |
|----------------------------|-----------------------------|-------------------------------|
| Low-risk                   | 2 (11%)                     | 154 (11%)                     |
| Intermediate-risk          | 4 (21%)                     | 358 (24%)                     |
| High-risk                  | 0                           | 32 (2%)                       |
| Not available              | 13 (68%)                    | 924 (63%)                     |

| Final risk group           | Number of patients with SMN | Number of patients without SMN |
|----------------------------|-----------------------------|-------------------------------|
| Standard-risk              | 5 (26%)                     | 516 (35%)                     |
| Intermediate-risk          | 11 (58%)                    | 748 (51%)                     |
| High-risk                  | 3 (16%)                     | 185 (13%)                     |
| Not available              | 0                           | 19 (1%)                       |
| Low-risk                   | 16 (84%)                    | 1263 (86%)                    |
| High-risk                  | 3 (16%)                     | 186 (13%)                     |
| Not available              | 0                           | 19 (1%)                       |

| Allogeneic HSCT            | Number of patients with SMN | Number of patients without SMN |
|----------------------------|-----------------------------|-------------------------------|
| Yes                        | 4 (21%)*                    | 160 (11%)*                    |
| No                         | 15 (79%)                    | 1308 (89%)                    |

*All four HSCTs among the pts. with an SMN were performed in CR1, while the 160 HSCTs among the pts. without an SMN included HSCTs in CR1 as well as in ≥ CR2.

### Table 1C

| Radio- and chemotherapy of ALL patients with and without an SMN as a first event | Number of patients with SMN | Number of patients without SMN |
|---------------------------------------------------------------------------------|-----------------------------|-------------------------------|
| Number of patients                                                              | 19                          | 1468                          |
| Cyclophosphamide                                                               |                             |                               |
| ≥3.000 mg/m²                                                                    | 18 (95%)                    | 1366 (93%)                    |
| < 3.000 mg/m²                                                                  | 1 (5%)                      | 81 (6%)                       |
| Not available                                                                  | 0                           | 21 (1%)                       |
| Cranial radiotherapy                                                           |                             |                               |
| Yes                                                                             | 14 (74%)                    | 657 (45%)                     |
| No                                                                              | 5 (26%)                     | 778 (53%)                     |
| Not available                                                                  | 0                           | 33 (2%)                       |
| VP-16/VM-26                                                                    |                             |                               |
| Yes                                                                             | 2 (11%)                     | 159 (11%)                     |
| No                                                                              | 17 (89%)                    | 1288 (88%)                    |
| Not available                                                                  | 0                           | 21 (1%)                       |

**Abbreviations:** BM, bone marrow; CR, complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; SMN, secondary malignant neoplasm.

(Continues)
### Table 1D
Characteristics of the 19 primary ALL patients with a secondary malignant neoplasm as a first event

| Pt. Number | Study         | Age at ALL (years) | Gender | Phenotype of ALL | Age at SMN (years) | Time to SMN (years) | Cranial radiotherapy | Type of SMN | Therapy of SMN* | Outcome of SMN | Survival time from SMN (months) |
|------------|---------------|---------------------|--------|------------------|---------------------|---------------------|----------------------|-------------|----------------|----------------|---------------------------------|
| 1          | ALL-BFM-A 81  | 10.2                | m      | C-ALL            | 13.7                | 3.6                 | 24 Gy                | AML M1      | 1              | dead (progression of SMN)       | 4                                |
| 2          | ALL-A 84      | 3.1                 | m      | C-ALL            | 13.6                | 10.6                | 18 Gy                | Thyroid carcinoma  | 2              | alive            | 143                             |
| 3          | ALL-A 84      | 10.4                | f      | C-ALL            | 33.2                | 22.8                | 18 Gy                | Meningioma       | 2              | alive            | 2 (lost to FU)                  |
| 4          | ALL-A 84      | 5.2                 | m      | T-ALL            | 19.4                | 14.2                | 18 Gy                | Astrocytoma       | 1,2,3           | dead (progression of SMN)       | 23                               |
| 5          | ALL-A 84      | 2.8                 | f      | C-ALL            | 14.9                | 12.2                | 18 Gy                | Meningioma        | 2              | alive            | 108                             |
| 6          | ALL-A 84      | 3.4                 | m      | C-ALL            | 13.6                | 10.2                | 18 Gy                | Astrocytoma       | 2,3             | dead (progression of SMN)       | 11                               |
| 7          | ALL-BFM-A 86  | 7.7                 | m      | C-ALL            | 12.0                | 4.5                 | 12 Gy                | AML M1           | 1,4             | alive            | 105                             |
| 8          | ALL-BFM-A 86  | 3.5                 | f      | C-ALL            | 7.1                 | 3.8                 | 12 Gy                | PNET, pelvis      | 1,2,3           | dead (AML as 2. SMN)            | 21                               |
| 9          | ALL-BFM-A 86  | 8.5                 | f      | T-ALL            | 28.7                | 20.2                | 18 Gy                | CCCA (Hep. C)     | unknown         | dead (progression of SMN)       | 9                                |
| 10         | ALL-BFM-A 90  | 2.6                 | f      | C-ALL            | 11.2                | 8.6                 | 12 Gy                | Glioblastoma multiiforme | 1,2,3   | dead (progression of SMN)       | 14                               |
| 11         | ALL-BFM-A 90  | 1.5                 | f      | C-ALL            | 6.7                 | 5.3                 | 12 Gy                | Ewing’s sarcoma, occipital | 1,2      | alive            | 120                             |
| 12         | ALL-BFM-A 90  | 2.8                 | m      | C-ALL            | 9.6                 | 6.9                 | 12 Gy                | PNET, brain       | 1,2,3           | alive            | 87                              |
| 13         | ALL-BFM-A 95  | 3.3                 | m      | C-ALL            | 6.5                 | 3.3                 | no                   | AML M4            | 1,4             | alive            | 33                              |
| 14         | ALL-BFM-A 2000| 11.7                | f      | C-ALL            | 14.2                | 2.5                 | no                   | MDS - RAEB - T    | 1,4             | alive            | 70                              |
| 15         | ALL-BFM-A 2000| 15.4                | m      | T-ALL            | 24.1                | 8.7                 | 12 Gy                | Osteosarcoma (right femur) | 1,2      | alive            | lost to FU                  |
| 16         | ALL-BFM-A 2000| 5.5                 | m      | C-ALL            | 9.2                 | 3.6                 | no                   | MDS - RAEB        | 1,4             | alive            | 68                              |
| 17         | ALL-BFM-A 2000| 11.2                | f      | C-ALL            | 14.8                | 3.6                 | no                   | Astrocytoma       | 1,2,3           | dead (progression of SMN)       | 9                                |
| 18         | ALL-BFM-A 2000| 8.7                 | f      | C-ALL            | 11.6                | 3.0                 | no                   | CMML              | 1,4             | alive            | 17                              |
| 19         | ALL-BFM-A 2000| 4.0                 | f      | pre-B-ALL        | 14.4                | 10.4                | no                   | PNET, brain       | 1,2             | alive            | 16                              |

*Therapy of SMN: 1 = chemotherapy, 2 = operation, 3 = radiation, 4 = SCT = stem cell transplantation.

Abbreviations: AML, acute myeloid leukaemia; C-ALL, common ALL; CCCA, cholangio-cellular carcinoma; CMML, chronic myelomonocytic leukaemia; f, female; FU, follow-up; Hep. C, hepatitis C; m, male; MDS, myelodysplastic syndrome; PNET, primitive neuroectodermal tumor; Pt, patient; RAEB, refractory anemia with excess blasts.
RESULTS AND DISCUSSION

Nineteen of the 1487 patients (1.3%) developed an SMN as a first event, with all of them occurring after completion of primary ALL therapy (Table S19). One patient developed a further neoplasm (first SMN: primitive neuroectodermal tumor of the pelvis, subsequent SMN: acute myeloid leukemia), in four of the 1487 patients, an SMN developed after ALL relapse therapy (Supporting information: Table S18). Leukemia-related initial characteristics, trial, chemo- and RT composition, early response during and after completion of ALL induction and consolidation therapy, and final risk group of the 19 patients with and 1468 patients without an SMN as a first event are shown in Tables 1A–1C. The 10-year CI of an SMN with death and relapse as competing events among the 1487 patients was 1.1% ± 0.3% (Table 2A, Figure S1). The 10-year CI of first relapses, death as a first event and SMNs with deaths as the only competing event, are shown in Figures S2–S4. There was no statistically significant difference in the 10-year CI of an SMN with regard to leukemia-associated parameters such as the underlying trial, trial periods, gender, age, CNS status, genetics, immunophenotype, chemotheraphy, cytomorphological response during and after induction therapy, minimal residual disease, and final risk group (Tables 2A–2C). Only patients with higher leukocyte counts (≥50.0 G/L) had a significantly higher 10-year CI of an SMN (Table 2A, p = 0.033). In addition, we run a model to assess the risk of SMNs, including relapse and death as competing events and the most relevant parameters such as the trial enrolled into, age at ALL diagnosis, leukocyte counts, and CRT to assess hazard ratios and confidence intervals, but did not find any of the parameters to be statistically relevant (Supporting information: Table S20).

Characteristics of the 19 patients with an SMN are summarized in Tables 1D and 1E. Six patients (32%) developed a hematologic SMN, nine (47%) a CNS tumor, and four (21%) suffered from "other" SMNs. All patients with hematologic SMNs originally suffered from B-cell precursor ALL, as did eight of nine patients in the CNS tumor group and two of the four patients with "other" SMNs. The median time from ALL diagnosis to the diagnosis of an SMN was 3.5 years for hematologic, 10.2 years for CNS, and 9.6 years for "other" SMNs, respectively (see Table 1E).

14/671 and 5/783 patients with and without CRT developed an SMN with a 10-year CI of 1.2% ± 0.5% and 0.8% ± 0.3%, respectively (p = 0.295, Figure S5). Seven of nine patients who developed a CNS tumor had initially been treated with CRT (12 Gy: n = 3; 18 Gy: n = 4), whereas in the hematologic SMN group, only two of six patients had previously received CRT (12 Gy: n = 1, 24 Gy: n = 1). All patients with "other" SMNs had been initially treated with CRT (12 Gy: n = 2; 18 Gy: n = 2).

Regarding cytotoxic drugs, all patients who developed an SMN had previously received cyclophosphamide, which had been combined with CRT in two of six patients with hematologic, eight of nine patients with CNS and all patients with "other" SMNs, respectively. Only one patient each of the hematologic and the "other" SMN group had received VP-16/VM-26. The 10-year OS rate for the 19 patients with an SMN was 55.0% ± 12.7%.

The continuously improving treatment strategies in pediatric ALL have led to a growing cohort of long-term survivors, making it pivotal to seriously consider late effects. SMNs belong to the most devastating consequences of the childhood ALL treatment. Herein, we assessed the incidence, type, and outcome of SMNs after the primary pediatric ALL treatment with BFM-based regimens in Austria over a period of 30 years, putting the focus on identifying risk factors.

### Table 1E: Characteristics of the three secondary malignant neoplasm subgroups

| Characteristics                              | Hematologic SMN | Central nervous system tumors | "Other" SMN |
|----------------------------------------------|-----------------|-------------------------------|-------------|
| Number of patients                          | 6               | 8                             | 4           |
| Male:female ratio                           | 4:2             | 3:6                           | 2:2         |
| Median age at ALL (years)                   | 8.1             | 3.4                           | 6.1         |
| Range (years)                               | 3.3–11.7        | 1.5–11.2                      | 3.1–15.4    |
| BCP-ALL                                      | 6               | 8                             | 2           |
| Median time to SMN (years)                  | 3.5             | 10.2                          | 9.6         |
| Range (years)                               | 2.5–4.5         | 3.6–22.8                      | 3.8–20.2    |
| Median age at SMN (years)                   | 11.8            | 14.4                          | 18.9        |
| Range (years)                               | 6.5–14.2        | 6.7–33.2                      | 7.1–18.7    |

Abbreviations: BCP-ALL, B-cell precursor ALL; SMN, secondary malignant neoplasms.

Statistical analysis of the data was performed using the Kaplan–Meier method and compared by the log-rank test. In the calculation of the 10-year cumulative incidence (CI) of SMNs, other failures such as relapse and death were treated as competing events. The CI of these competing events was also calculated. The CI of an SMN with regard to leukemia-associated parameters such as the underlying trial, trial periods, gender, age, CNS status, genetics, immunophenotype, chemotheraphy, cytomorphological response during and after induction therapy, minimal residual disease, and final risk group (Tables 2A–2C). Only patients with higher leukocyte counts (≥50.0 G/L) had a significantly higher 10-year CI of an SMN (Table 2A, p = 0.033). In addition, we run a model to assess the risk of SMNs, including relapse and death as competing events and the most relevant parameters such as the trial enrolled into, age at ALL diagnosis, leukocyte counts, and CRT to assess hazard ratios and confidence intervals, but did not find any of the parameters to be statistically relevant (Supporting information: Table S20).

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The continuously improving treatment strategies in pediatric ALL have led to a growing cohort of long-term survivors, making it pivotal to seriously consider late effects. SMNs belong to the most devastating consequences of the childhood ALL treatment. Herein, we assessed the incidence, type, and outcome of SMNs after the primary pediatric ALL treatment with BFM-based regimens in Austria over a period of 30 years, putting the focus on identifying risk factors.
### TABLE 2A 10-year CI of an SMN and competing events and event-free survival according to the initial characteristics

| Parameters                  | Pts. | Secondary malignancies | Competing events | Event-free survival |
|-----------------------------|------|------------------------|------------------|--------------------|
|                             |      | Events | 10-year CI | p-Value | Events | 10-year CI | p-Value | 10-year EFS | p-value |
| All patients                | 1487 | 19     | 1.1% ± 0.3% |        | 328    | 24.0% ± 1.2% |        | 75.0 ± 1.2% |        |
| Trial                       |      |        |            |        |        |            |        |            |        |
| ALL-BFM-A 81                | 141  | 1      | 0.7% ± 0.7% | 0.202  | 59     | 42.6% ± 4.2% | <0.001 | 56.5 ± 4.2% | <0.001 |
| ALL-A 84                    | 127  | 5      | 0.0% ± 0.0% |        | 44     | 34.2% ± 4.2% |        | 65.8 ± 4.2% |        |
| ALL-BFM-A 86                | 142  | 3      | 1.4% ± 1.0% |        | 33     | 22.6% ± 3.5% |        | 76.0 ± 3.6% |        |
| ALL-BFM-A 90                | 256  | 3      | 1.3% ± 0.7% |        | 61     | 24.1% ± 2.7% |        | 74.7 ± 2.7% |        |
| ALL-BFM-A 95                | 230  | 1      | 0.4% ± 0.4% |        | 48     | 21.1% ± 2.7% |        | 78.5 ± 2.7% |        |
| ALL-BFM-A 2000              | 591  | 6      | 2.2% ± 1.3% |        | 83     | 18.3% ± 2.0% |        | 79.5 ± 2.4% |        |
| Earlier era (81, 84, 86)     | 410  | 9      | 0.7% ± 0.4% | 0.983  | 136    | 33.1% ± 2.3% | <0.001 | 66.2 ± 2.4% | <0.001 |
| Later era (90, 95, 2000)     | 1077 | 10     | 1.3% ± 0.4% |        | 192    | 20.5% ± 1.4% |        | 78.3 ± 1.4% |        |
| Gender                      |      |        |            |        |        |            |        |            |        |
| Male                        | 826  | 9      | 1.0% ± 0.4% | 0.544  | 185    | 24.6% ± 1.6% | 0.82   | 74.4 ± 1.6% | 0.939  |
| Female                      | 661  | 10     | 1.2% ± 0.5% |        | 143    | 23.1% ± 1.7% |        | 75.7 ± 1.8% |        |
| Age (years)                 |      |        |            |        |        |            |        |            |        |
| < 1                         | 25   | 0      | 0.0% ± 0.0% | 0.559  | 16     | 65.3% ± 9.7% | <0.001 | 34.7 ± 9.7% | <0.001 |
| 1–10                        | 1126 | 14     | 0.9% ± 0.3% |        | 213    | 20.6% ± 1.3% |        | 78.5 ± 1.3% |        |
| ≥10                         | 336  | 5      | 1.7% ± 0.9% |        | 98     | 32.2% ± 2.8% |        | 65.8 ± 2.8% |        |
| WBC count (G/L)             |      |        |            |        |        |            |        |            |        |
| < 20.0                      | 959  | 12     | 1.0% ± 0.3% | 0.033  | 181    | 20.9% ± 1.4% | <0.001 | 78.1 ± 1.4% | <0.001 |
| 20.0–50.0                   | 226  | 0      | 0.0% ± 0.0% |        | 52     | 24.4% ± 3.0% |        | 75.6 ± 3.0% |        |
| ≥50.0                       | 302  | 7      | 2.1% ± 1.1% |        | 94     | 33.2% ± 2.8% |        | 64.7 ± 2.9% |        |
| CNS disease                 |      |        |            |        |        |            |        |            |        |
| Negative                    | 1425 | 17     | 1.0% ± 0.3% | 0.595  | 308    | 23.5% ± 1.2% | 0.027  | 75.5 ± 1.2% | 0.015  |
| Positive                    | 49   | 1      | 0.0% ± 0.0% |        | 16     | 34.1% ± 7.0% |        | 65.9 ± 7.0% |        |
| Immunophenotype             |      |        |            |        |        |            |        |            |        |
| BCP-ALL                     | 1237 | 16     | 1.1% ± 0.3% | 0.929  | 256    | 22.8% ± 1.3% | 0.1    | 76.1 ± 1.3% | 0.097  |
| T-ALL                       | 198  | 3      | 1.0% ± 0.9% |        | 49     | 25.6% ± 3.2% |        | 73.5 ± 3.3% |        |
| Genetics                    |      |        |            |        |        |            |        |            |        |
| ETV6::RUNX1                 |      |        |            |        |        |            |        |            |        |
| Positive                    | 264  | 4      | 1.9% ± 0.9% | 0.416  | 27     | 12.5% ± 2.4% | <0.001 | 85.6 ± 2.5% | <0.001 |
| Negative                    | 953  | 9      | 1.1% ± 0.4% |        | 196    | 22.6% ± 1.4% |        | 76.3 ± 1.5% |        |
| TCF3::PBX1                  |      |        |            |        |        |            |        |            |        |
| Positive                    | 37   | 0      | 0.0% ± 0.0% | 0.531  | 4      | 11.6% ± 5.5% | 0.26   | 88.4 ± 5.5% | 0.215  |
| Negative                    | 1180 | 13     | 1.3% ± 0.4% |        | 219    | 20.7% ± 1.3% |        | 78.0 ± 1.3% |        |
| BCR::ABL I                  |      |        |            |        |        |            |        |            |        |
| Positive                    | 24   | 0      | 0.0% ± 0.0% | 0.637  | 14     | 67.4% ± 11.1%| <0.001 | 32.6 ± 11.3%| <0.001 |
| Negative                    | 1193 | 13     | 1.3% ± 0.4% |        | 209    | 19.5% ± 1.2% |        | 79.2 ± 1.3% |        |
| KMT2A-rearrangement         |      |        |            |        |        |            |        |            |        |
| Positive                    | 31   | 1      | 0.0% ± 0.0% | 0.38   | 10     | 33.8% ± 8.8% | 0.029  | 66.2 ± 8.8% | 0.012  |
| Negative                    | 1186 | 12     | 1.3% ± 0.4% |        | 213    | 20.0% ± 1.3% |        | 78.6 ± 1.3% |        |
| High-hyperdiploidy          |      |        |            |        |        |            |        |            |        |
| Positive                    | 292  | 2      | 1.2% ± 0.8% | 0.521  | 44     | 17.5% ± 2.5% | 0.062  | 81.3 ± 2.6% | 0.048  |
| Negative                    | 820  | 10     | 1.3% ± 0.5% |        | 161    | 21.9% ± 1.6% |        | 76.8 ± 1.6% |        |

Note: Analyses were only performed for those parameters with available results.
Abbreviations: BCP, B-cell precursor; CI, cumulative incidence; CNS, central nervous system; EFS, event-free survival; Pts, patients; SMN, secondary malignant neoplasm; WBC count, white blood cell count.
We found a 10-year CI of 1.1% ± 0.3% for the development of an SMN, which is comparable to previous reports \([12–17]\). Nevertheless, long-term follow-up studies suggest that the CI of SMNs usually does not reach a plateau, thus, continued follow-up of our patient cohort is still necessary \([18–20]\). Our analyses did not show statistically significant differences in the CI of an SMN with regard to initial characteristics of the primary ALL, response criteria, and therapy-related factors. In particular, we did not find a significant relation between CNS disease, female gender, or younger age at primary ALL diagnosis and a higher CI of SMNs, as has been previously described \([12, 14, 18, 20]\).

While our analyses could suggest an increasing incidence of SMNs in the more recent as compared to the earlier treatment era, the incidence rates were not statistically different and, possibly, capture of late events such as SMNs may have been missed in the earlier times.
However, our analysis showed that patients with leukocyte counts \( \geq 50.0 \, \text{G/L} \) at ALL diagnosis had a significantly higher CI of an SMN (2.1\% \pm 1.1\%) than children with lower counts which is hard to interpret. Hijiya et al. also analyzed the relationship between leukocytes and risk of SMNs, but could not find a statistically significant relevance of this parameter [18].

A clear relationship between SMNs and previous irradiation therapy has been repeatedly described in the literature [14, 21–23]. Our findings are consistent with that, considering that 75\% of patients who developed an SMN underwent CRT, in contrast to 45\% of patients without an SMN. However, probably due to the low number of patients, the 10-year CI of an SMN was not significantly different between patients with and without CRT (1.2\% \pm 0.5\% vs. 0.8\% \pm 0.3\%; \( p = 0.295 \)). Notably, the incidence of an SMN continued to increase for the irradiated patients, whereas there was a plateau after 10 years in patients without irradiation. This might be explained by the fact that especially brain tumors develop with a longer latency compared to other SMNs, in particular myeloid neoplasms, and CRT is the strongest risk factor for secondary brain tumors. Several chemotherapeutic agents, especially alkylating agents and topoisomerase-II inhibitors have been accused of increasing the risk for SMNs, particularly, of secondary myeloid neoplasms [24–26]. In our study, however, we could not observe any significant relations between VP-16/VM-26 or cyclophosphamide and a higher incidence of SMNs. This might be because BFM-based ALL protocols since their introduction have mainly relied on VP-16/VM-26-free chemotherapy regimens [9–11]. Importantly, in a recent report of the childhood cancer survivor study, it was shown that in survivors treated in recent eras without CRT and low doses of anthracyclines and alkylating agents, risk of SMNs was decreased and even not significantly different from the general population [27].

As our study included patients from as early as 1981 covering six trials, some SMNs may have been missed and detailed family histories indicating a cancer predisposition syndrome, leading to genetic germline investigations, are lacking, which has certainly resulted in the failure to elucidate an underlying cancer predisposition syndrome in either of the 19 patients. Nevertheless, the excellent cooperation between competent pediatric tertiary-care oncologic centers in Austria enabled the nearly 100\% complete registration of all children and adolescents up to 18 years of age in the ALL-BFM trials since 1981, thus, providing well-documented population-based data with long-term follow-ups.

In conclusion, our results show a low risk of developing an SMN after BFM-based treatment protocols for primary ALL. Although a moderate outcome, the 5-year OS of 55.0\% \pm 12.7\% of the SMNs, with 12 of 19 patients still alive, suggests treating these patients as aggressively as children with primary analogous malignancies. However, future strategies should aim at identifying ALL patients at risk rigorously, such as children with cancer predisposition syndromes and immunodeficiencies, in order to adapt chemotherapy (i.e., alkylating agents, anthracyclines), if justified by growing evidence to have an effect and without losing anti-leukemic efficacy. Furthermore, consortia should aim to establish standardized surveillance programs to detect SMNs as early as possible, especially in these at-risk populations [3]. This may help increasing OS rates, as SMNs still are a prominent non-relapse cause of death among pediatric ALL survivors.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

ETHICS STATEMENT
Studies were conducted according to the Declaration of Helsinki, approved by the respective ethics committees and, since trial ALL-BFM-A 2000, registered at clinicaltrials.gov (NCT00430118).

AUTHORS’ CONTRIBUTION
Fiona Poyer and Andishe Attarbaschi were involved in designing and planning the study. Fiona Poyer, Ulrike Pötschger, and Andishe Attarbaschi wrote the manuscript. Michael Dworzak, Melanie Tamesberger, Neil Jones, Reinhard Moser, Christian Urban, Georg Mann, and Andishe Attarbaschi were principal or co-investigators in their institutions, provided study materials and recruited patients. Karin Dieckmann was in charge of cranial radiotherapy planning when indicated, and Michael Dworzak and Stefan Köhrer were in charge of minimal residual disease analysis. Christina Peters was the reference physician for allogeneic hematopoietic stem cell transplantations in patients having an indication in first remission and Oskar Haas and Karin Nebral were in charge of genetic analysis. Ulrike Pötschger performed the statistical analyses. Fiona Poyer, Georg Mann, and Andishe Attarbaschi oversaw data checking, pooling, and reporting during the study period and analyzed the data. All authors have approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT
All data pertinent to this work are available by contacting Andishe Attarbaschi at Andishe.attarbaschi@stanna.at

ORCID
Andishe Attarbaschi https://orcid.org/0000-0002-9285-6898

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SUPPORTING INFORMATION
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