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Ambulatory Routine Care in Oncology in Germany: Real-World Survival Data

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Keywords
Cohort study · Oncology · Outpatient care · Cancer registries · Real-world data · Overall survival

Abstract

Introduction: Survival data reported by randomised controlled trials are collected in a highly selected patient population and can thus only be transferred to a limited extent to real-world patients: the patients in routine care are mostly older, present with more comorbidities and a worse general state of health. This so-called efficacy-effectiveness gap typically results in inferior survival data in routine healthcare. ***Methods:*** Six prospective clinical tumour registries recruited a total of 11,679 patients receiving systemic therapy in haemato-oncological practices in Germany between 2006 and 2020. For these patients with advanced colorectal cancer, breast cancer, lung cancer, pancreatic cancer, renal cell cancer, and lymphatic neoplasms, overall survival was analysed. A comprehensive literature search was performed to identify suitable pivotal randomised controlled trials. ***Results:*** Median overall survival of patients treated in German routine care, with advanced colorectal, breast, lung, and pancreatic cancer, as well as with diffuse large B-cell lymphoma and multiple myeloma, is not shorter than the respective survival data reported in trials. Patients with advanced renal cell carcinoma, chronic lymphocytic leukaemia, or indolent non-Hodgkin lymphoma showed slightly lower survival rates compared to clinical trials. ***Conclusions:*** Despite less favourable patient characteristics, survival data from patients with cancer treated in ambulatory routine care in Germany are in range with results from randomised controlled studies.

Introduction

Prospective tumour registries are becoming increasingly important as sources of information from routine oncological care, the so-called real-world treatment [1]. In addition to randomised controlled trials (RCTs), which are essential for the evaluation of new therapies and whose results are based on data from highly selected patient groups, data from prospective tumour registries provide valuable information on treatment results in everyday clinical practice, taking into account a broader patient population [2]. The strengths and limitations of RCTs versus population-based observational research have been described and discussed in detail [3]. In order to evaluate the efficacy of therapies in RCTs, it is essential that patients are selected according to defined criteria. However, these criteria entail that <10% of all patients with cancer are enrolled in a RCT, with <5% of adult patients with cancer in the USA [4]. They are therefore different from patients in routine healthcare, who are on average older and have poorer function and performance status and more comorbidities [5–7]. Indeed we have shown before that at least 60% of the patients with advanced renal cell carcinoma (RCC) in German routine practice would be ineligible for participation in clinical trials [8].

Published data on overall survival (OS) originate mainly from RCTs, and although these data are in general generated on a younger patient population with a better performance status, these survival estimates are also presented to prospectively documented patients in

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routine care. It has been shown that outcomes observed for patients in RCTs and real-world settings differ, with inferior outcome and greater toxicity in routine care [7, 9].

Our expertly set up tumour registries collect high-quality data from outpatient cancer centres in Germany for many years now. Reading about the efficacy-effectiveness gap raised some questions: what about survival in ambulatory routine care in Germany? Does it really differ from survival reported in RCTs? In order to answer these questions, we took a close look into our long-term survival data from six longitudinal, prospective, multicentre tumour registries.

Methods

Data Source

The six clinical tumour registries considered in this study are longitudinal, multicentre, observational, prospective cohort studies collecting data on the treatment of patients with advanced/metastatic cancer. All registries were approved by the responsible Ethics Committee and registered at ClinicalTrials.gov (Table 1). All patients were followed until up to 5 years after start of therapy. The documentation of data was performed by hospitals and office-based oncologists between 2006 and 2021, including patients with colorectal cancer, breast cancer, renal cell cancer, lung cancer, pancreatic cancer, and lymphatic neoplasms. Details on the number of recruiting practices, patients and the respective registration numbers are listed in Table 1. The methodology of the respective tumour registries has been described before [8, 10–16]. In breast cancer, the receptor status of the human epidermal growth factor receptor 2 (HER2) is indicated as HER2-positive throughout the whole manuscript, meaning HER2+++, HER2 +/++ and ISH-positive test results. A literature search has been performed to identify the pivotal studies for the respective recruitment time frames of the tumour registries.

Statistical Analysis

Registry OS was calculated using the Kaplan-Meier method [17]. The beginning of the first systemic therapy for metastatic/inoperable tumours or haematologic neoplasia was defined as starting point. Patients alive at the time of analysis were censored at the last contact. All analyses were performed using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002–2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Results

In this study, comprehensive OS data from a total of 11,679 patients enrolled in six tumour registries were analysed. Of these, 8,742 patients presented with advanced/metastatic solid tumours, and 2,937 patients with haematological neoplasia. For a better overview, details on the respective tumour registries as well as patient numbers and number of recruiting sites are listed in Table 1.

Patients with advanced colorectal cancer recruited in German outpatient care from 2006 to 2018 had a median OS of 24.5 months with *KRAS* wildtype (n = 1,762) and 21.9 months with *KRAS* mutation (n = 1,265). The survival curves are shown in Figure 1a. These survival times are in range with the times reported by the suitable pivotal studies: 21.0–30.0 months for tumours with *KRAS* wildtype and 15.5–20.6 months for *KRAS* mutation (Table 2) [18–22]. A comprehensive overview over the key randomised trials and the respective OS data has been published by Mahipal and Grothey [23].

Median OS of the patients with advanced breast cancer recruited in routine care from 2007 to 2017 was analysed according to the respective hormone receptor (HR) and HER2 status: HR-positive, HER2-negative (n = 750): median OS 33.6 months; HR-positive, HER2-positive (n = 300): median OS 44.7 months; HR-negative, HER2-positive (n = 141): median OS 36.8 months and triple negative (n = 209): median OS 14.9 months (Fig. 1b). Putting these numbers into perspective with the pivotal trials, median OS of 27.6–30.5 months has been reported for HR-positive, HER2-negative tumours, 35.7–57.1 months for HER2-positive tumours and 11.1–24.4 months for triple negative tumours (Table 2) [24–29].

For advanced lung cancer, data of 1,244 patients with first-line treatment for non-small cell lung cancer (NSCLC) and 327 patients with advanced small cell lung cancer (SCLC) recruited in 2010–2013 were analysed, showing median OS of 10.8 months for NSCLC and 10.7 months for SCLC (Fig. 1c). These survival data are in range with the pivotal studies in the comparable time frame, reporting median OS of 10.3–12.3 months for advanced NSCLC and 8.9–9.8 months for extensive-disease SCLC (Table 2) [30–33].

Median OS of 1,689 patients with locally advanced/metastatic pancreatic cancer, recruitment in 2013–2020, was 9.3 months (Fig. 1d). Again, these numbers are comparable with the published results of RCTs reporting a median OS of 6.7–11.1 months (Table 2) [34, 35].

A total of 1,055 patients with advanced RCC have been recruited in 2007–2017, their median OS was 19.0 months (Fig. 1e); while pivotal RCTs on mRCC report median OS times of 17.4–29.3 months (Table 2) [36–41]. As these numbers differ markedly, we categorised the patients into two subgroups: "potentially trial-eligible" (n = 482) and "trial-ineligible" (n = 573) based on established exclusion criteria for phase III clinical trials; "trial-ineligible" was defined for patients with at least one of the following characteristics: Karnofsky performance status <80%, haemoglobin level

Table 1. Characteristics of tumour registries and subgroups of recruited patients evaluated in this study

Solid tumours				
Tumour registry (NCT identifier[a])	Subtype	Recruitment	Practices, *n*	Patients, *n*
TKK [10, 60] tumour registry colorectal cancer (NCT00910819)	*KRAS* wildtype	2006–2018	134	1,762
	KRAS mutation	2006–2018	126	1,265
TMK [11] tumour registry breast cancer (NCT01351584)	HR pos, HER2 neg	2007–2016	102	750
	HR pos, HER2 neg	2007–2016	82	300
	HR neg, HER2 pos	2007–2016	62	141
	Triple negative	2007–2016	75	209
TLK [13, 14] tumour registry lung cancer (NCT01192919)	NSCLC	2010–2013	100	1,244
	SCLC	2010–2013	75	327
TPK [15] tumour registry pancreatic cancer (NCT02089269)	NA	2013–2020	108	1,689
RCC registry [8, 12] tumour registry of advanced RCC (NCT00610012)	Potentially trial-eligible[b]	2007–2017	94	482
	Trial-ineligible[b]	2007–2017	98	573
Haematologic neoplasia				
Tumour registry	Entity	Therapy start period	Practices, *n*	Patients, *n*
TLN [16] tumour registry lymphatic neoplasms (NCT00889798)	CLL	2009–2014	104	746
	DLBCL	2009–2014	101	837
	iNHL	2009–2014	109	1,069
	MM[c]	2009–2011	74	285

CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; HER2, human epithelial growth factor receptor 2; HR, hormone receptor; iNHL, indolent non-Hodgkin's lymphoma; KRAS, Kirsten rat sarcoma; MM, multiple myeloma; NA, not applicable; neg, negative; NSCLC, non-small cell lung cancer; pos, positive; SCLC, small cell lung cancer. [a]ClinicalTrials.gov ID/National Clinical Trial (NCT) number. [b]Definition according to Results section. [c]Ineligible for stem cell transplant.

below lower limit of normal and/or a histology other than clear cell RCC [8, 12]. This subgroup analysis showed that patients "potentially trial-eligible" had a significantly higher median OS of 26.2 months than "trial-ineligible" patients with 12.9 months (Fig. 1f).

Looking at lymphatic neoplasms, data of patients with chronic lymphocytic leukaemia (CLL; $n = 746$), diffuse large B-cell lymphoma (DLBCL; $n = 837$) and indolent non-Hodgkin's lymphoma (iNHL; $n = 1{,}069$), recruited 2009–2014 were analysed. The median OS was not reached (Fig. 2a–c). For CLL, the 3-year OS-rate for patients in routine care was 84.1%, the 5-year OS-rate was 74.1%. In a comparable time frame, the CLL10 trial was conducted comparing the fludarabine/cyclophosphamide/rituximab and bendamustine/rituximab regimen; a 3-year OS-rate of 91–92% and a 5-year OS-rate of 80.1–80.9% was reported (Table 2) [42, 43]. For patients with DLBCL, the 3-year OS-rate for patients in routine care was 80.6%, the 5-year OS-rate 75.0%. These survival rates are comparable with the rates determined in RCTs ranging from 80.8 to 86.5% for 2-year OS and 77.5–78.5% for 5-year OS (Table 2) [44, 45]. The 3-year OS-rate for patients in routine care with iNHL was 86.4%, the 5-year OS-rate was 80.1%. Survival rates reported by RCTs range between 92.1 and 94.0% (3-year OS), 81.7–90.2% (5-year OS), and 87.4–88.7% (6-year OS) (Table 2) [46–51]; according to the quality of response, 5-year OS-rates of 77.5% (partial response) and 90.3% (complete response) have been published [52, 53]. For patients with multiple myeloma (MM) ineligible for stem cell transplantation in routine care ($n = 285$) recruited in 2009–2011, median OS was 52.0 months (Fig. 2d), which is within the range of data that have been reported by RCTs ranging from 43.1 to 62.3 months (Table 2) [54–57].

Discussion

Here, we show that the median OS of patients treated in routine care, receiving the standard therapy selected by the attending physician according to the guidelines, is not shorter than the median OS reported in RCTs. This was especially true for patients with advanced

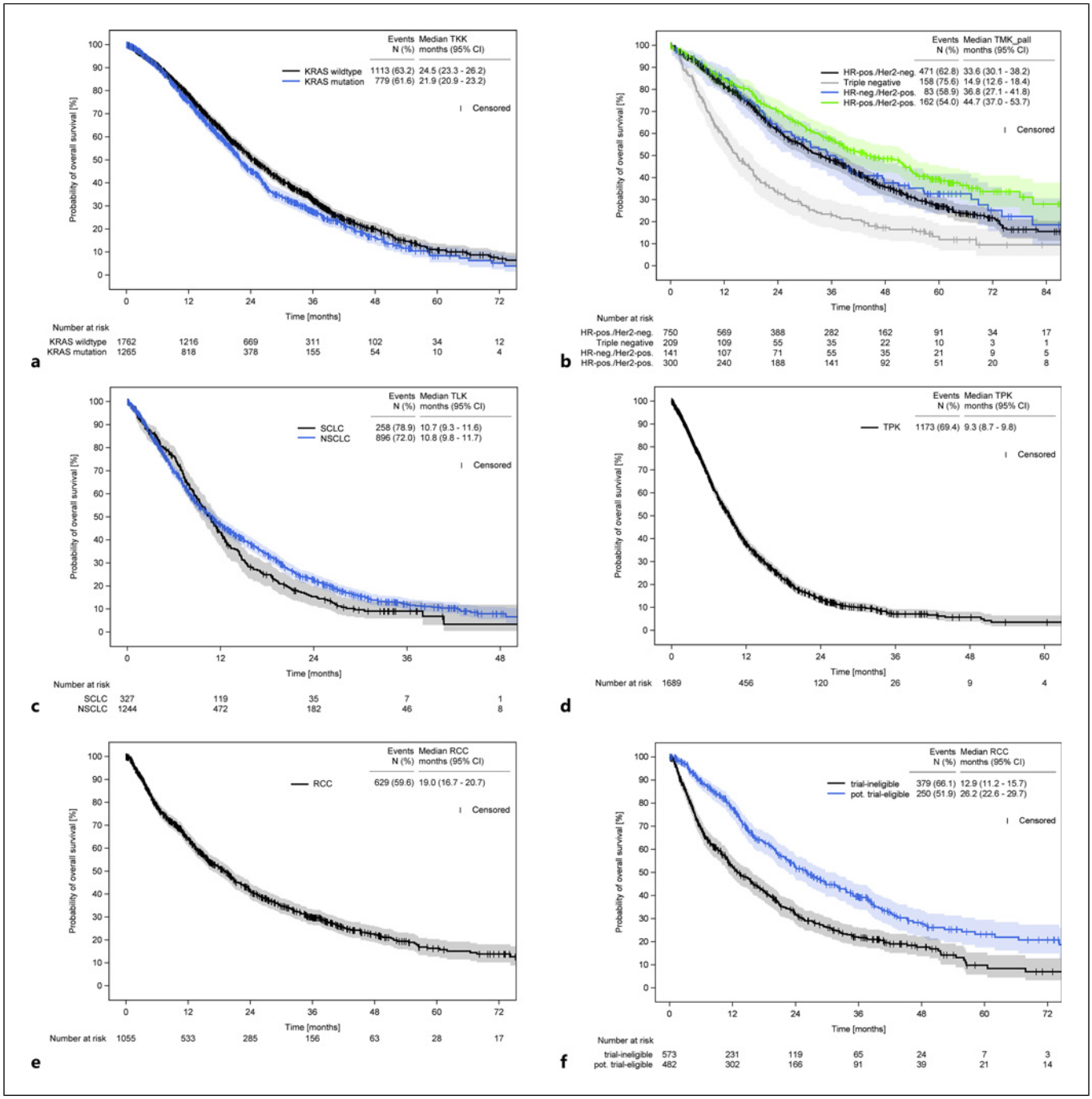

Fig. 1. OS – solid tumours first-line registry OS in patients with advanced colorectal cancer (**a**), advanced breast cancer (**b**), advanced lung cancer (**c**), advanced pancreatic cancer (**d**), and advanced renal cell carcinoma (**e, f**). TKK, tumour registry colorectal cancer; TMK_pal, tumour registry breast cancer; TLK, tumour registry lung cancer; TPK, tumour registry pancreatic cancer; RCC, tumour registry of advanced renal cell carcinoma; CI, confidence interval; KRAS, Kirsten rat sarcoma; HR, hormone receptor; HER2, human epithelial growth factor receptor 2; pos., positive; neg., negative; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; pot., potentially.

colorectal, breast, lung, and pancreatic cancer, as well as for patients with DLBCL and MM. Patients with advanced RCC, CLL, or iNHL showed slightly higher survival rates in RCTs, maybe at least in part due to the generally younger age and better performance status of patients included in these RCTs. Showing these results to the average patient in routine care will have a good influence on the trust in the recommended medication and the continuously improving, up-to-date standard of care in German routine healthcare.

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Table 2. Characteristics and median OS of patients in randomised clinical trials compared to data from routine healthcare (clinical tumour registries)

RCT					Tumour registry		
Tumour entity/trial	Pat., *n*	Age, years	Performance status	Median OS, months[a]	Age, years	Comorbidity/PS	Median OS [95% CI], months[a]
Colorectal cancer *KRAS* wt							
CRYSTAL [19] 2004–05	348	61	96% ECOG 0/1	21.0–24.9	67	72% CM	24.5 [23.3–26.2]
PRIME [18] 2006–08	656	61–62	94% ECOG 0/1	19.7–23.9		87% ECOG 0/1[b]	
CALGB80405 [21] 2005–12	1,137	59	100% ECOG 0/1	29.0–30.0			
FIRE-3 [22] 2007–12	592	64–65	98–99% ECOG 0/1	25.0–28.7			
Colorectal cancer *KRAS* mut							
CRYSTAL [19] 2004–05	192	62–63	96–100% ECOG 0/1	17.5–17.7	69	72% CM	21.9 [20.9–23.2]
PRIME [18] 2006–08	440	61–63	96% ECOG 0/1	15.5–19.3		83% ECOG 0/1[b]	
FIRE-3 [22] 2007–12	65	NA	NA	16.4–20.6			
Breast cancer HR pos HER2 neg							
TURANDOT [24, 26] 2008–10	416	59[c]	94–98% ECOG 0/1[c]	27.6–30.5	65	66% CM	33.6 [30.1–38.2]
BOLERO-2 [63, 64] 2009–11	724	61–62	94–96% ECOG 0/1	26.6–31.0		81% ECOG 0/1[b]	
Breast cancer HER2 pos							
HERNATA [28] 2004–08	284	56	93% ECOG 0/1	35.7–38.8	62	53–61%	36.8–44.7
CLEOPATRA [27, 29] 2008–10	808	54	99% ECOG 0/1	40.8–57.1		CM 83% ECOG 0/1[b]	
EMILIA [65] 2009–11	991	53	99% ECOG 0/1	25.9–29.9			
Breast cancer TNBC							
O'Shaughnessy [25] 2009–10	519	53–54	98% ECOG 0/1	11.1–12.2	60	59% CM	14.9 [12.6–18.4]
TURANDOT [24, 26] 2008–10	130	59[c]	94–98% ECOG 0/1[c]	17.7–24.4		76% ECOG 0/1[b]	
Lung cancer NSCLC							
Sandler [32] 2001–04	878	NA	100% ECOG 0/1	10.3–12.3	67	78% CM	10.8 [9.8–11.7]
Scagliotti [33] 2004–05	1,725	61	100% ECOG 0/1	10.3		72.5% ECOG 0/1[b]	
Lung cancer SCLC							
COCIS meta-anal. [31] 2008–09	663	67	72% ECOG 0/1	9.4–9.6	66	76% CM	10.7 [9.3–11.6]
FARM6PMFJM [30] 2009–15	204	63–64	89–94% ECOG 0/1	8.9–9.8		74.6% ECOG 0/1[b]	
Pancreatic cancer							
Conroy [34] 2005–09	342	61	100% ECOG 0/1	6.8–11.1	70	85% CM	9.3 [8.7–9.8]
Von Hoff [35] 2009–12	861	63	92% KPS ≥80%	6.7–8.5		90% ECOG 0/1	
RCC							
COMPARZ [38] 2008–11	1,110	61–62	75–76% KPS >80%	28.4–29.3	70	*Total cohort*	*Total cohort* 19.0 [16.7–20.7]
CALGB90206 [39, 40] 2003–05	732	62	98% ECOG 0/1	17.4–18.3		74% KPS ≥80%[b]	*Pot. trial-eligible*[d] 26.2
AVOREN [36, 37] 2004–05	649	60–61	76–78% KPS >80%	21.3–23.3		*Pot. trial-eligible*[d] 78% CM	[22.6–29.7]
VEG105192 [41] 2006–07	435	59–60	100% ECOG 0/1	20.5–22.9		*Trial-ineligible*[d] 85% CM	*Trial-ineligible*[d] 12.9 [11.2–15.7]

Table 2 (continued)

RCT					Tumour registry		
Tumour entity/trial	Pat., *n*	Age, years	Performance status	Median OS, months[a]	Age, years	Comorbidity/PS	Median OS [95% CI], months[a]
Chronic lymphocytic leukaemia (CLL)							
CLL10 [42, 43] 2008–11	561	61–62	99% ECOG 0/1	3y: 91–92% 5y: 80.1–80.9%	71	71% CM 85% ECOG 0/1[b]	3y: 84.1% [81.1–86.6] 5y: 74.1% [70.6–77.3]
Diffuse large B-cell lymphoma (DLBCL)							
R-CHOP 14 v 21 [44] 2005–08	1,080	61	87% WHO PS 0/1	2y: 80.8–82.7%	69	69% CM	3y: 80.6% [77.6–83.2]
Alliance/CALGB50303 [45] 2005–13	491	58	88% ECOG 0/1	2y: 85.7–86.5% 5y: 77.5–78.5%		84% ECOG 0/1[b]	5y: 75.0% [71.7–78.0]
Indolent non-Hodgkin's lymphoma (iNHL)							
GALLIUM [46–48] 2011–14	1,202	58–60	97% ECOG 0/1	3y: 92.1–94.0% 5y: 894–90.2%	69	65% CM 85% ECOG 0/1[b]	3y: 86.4% [84.1–88.4] 5y: 80.1% [77.4–82.5]
PRIMA [51] 2004–07	1,018	55–57	35% ECOG ≥1 4% ECOG >1	6y: 87.4–88.7%[e]			
StiL NHL1 [52, 53] 2003–08	514	63–64	NA	5y: 77.5–90.3%[f]			
BRIGHT [49, 50] 2009–12	447	58–60	95% ECOG 0/1	5y: 81.7–85.0%			
Multiple myeloma (MM)							
VISTA[g] [54, 55] 2004–06	682	71	34% KPS ≤70%	43.1–56.4	74	78% CM[b]	52.0 [43.5–58.7]
FIRST[g] [56, 57] 2008–11	1,623	73	78% ECOG 0/1	49.1–62.3			

CI, confidence interval; CM, comorbidities; ECOG, Eastern Cooperative Oncology Group; HER2, human epithelial growth factor receptor 2; HR, hormone receptor; KRAS, Kirsten rat sarcoma; KPS, Karnofsky performance status; mut, mutation; NA, not available; neg, negative; NSCLC, non-small cell lung cancer; OS, overall survival; Pat., patients; pos, positive; PS, performance status; SCLC, small cell lung cancer; TNBC, triple negative breast cancer; WHO PS, WHO performance score; wt, wildtype; y/yrs, year/years. [a]Unless indicated otherwise. [b]Missing/unknown ECOG/KPS data for TKK: *KRAS* wt 8%, *KRAS* mut 9%, TMK: HR pos HER2 neg 12%, HER2 pos 11%, TNBC 17%, TLK: NSCLC 12%, SCLC 9%; RCC: 6%; TLK: CLL 9%, DLBCL 10%, iNHL 8%, for MM no ECOG data was collected. [c]ECOG PS for the whole intention-to-treat population. [d]Definition according to Results section. [e]Estimated at the time of the data cut-off (according to: https://doi.org/10.1182/blood.V122.21.509.509). [f]5-year OS rate for all patients according to quality of response (77.5% 5-year OS rate for patients with partial response, 90.3% for patients with complete response). [g]Ineligible for stem cell transplant.

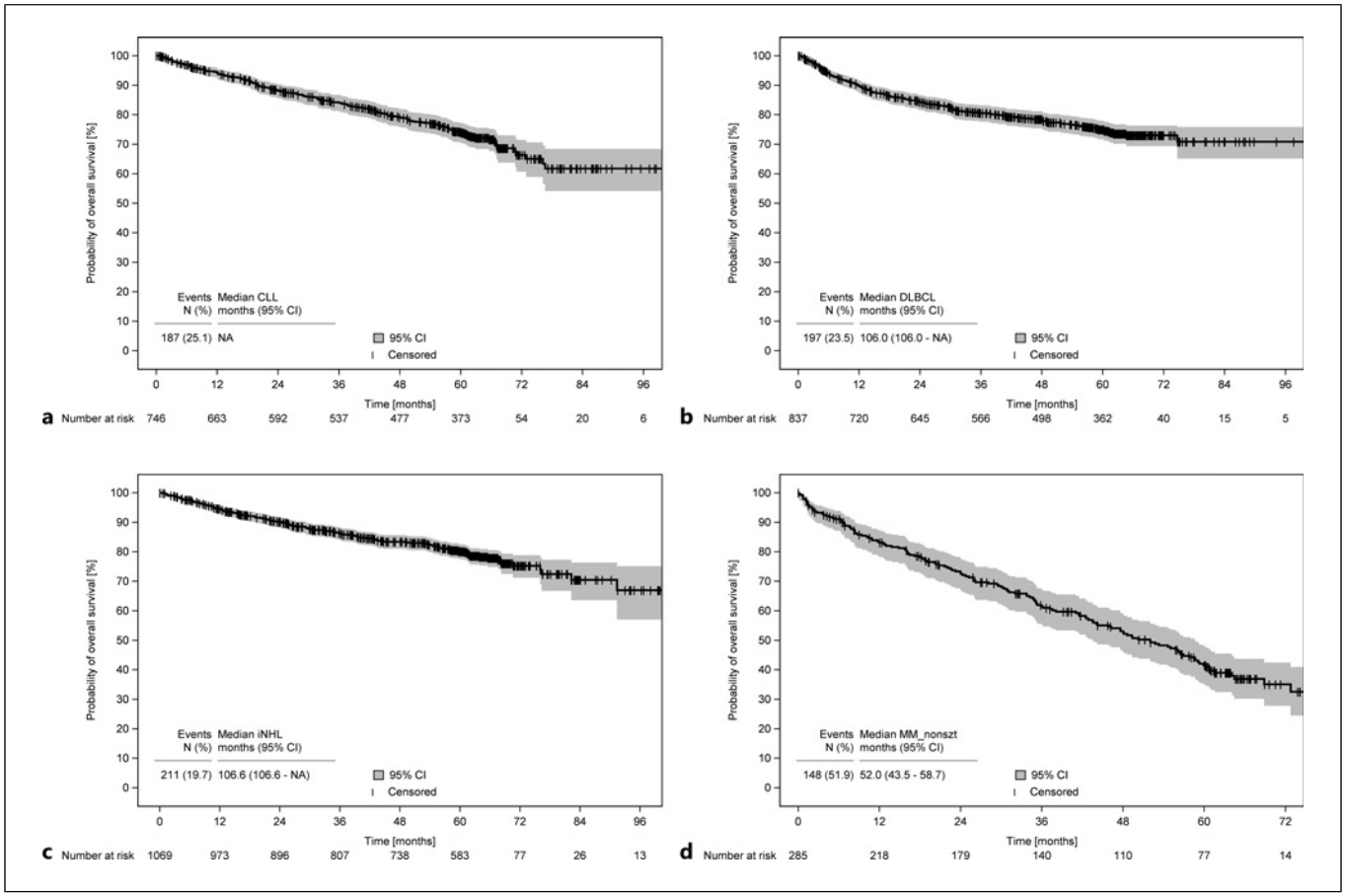

Fig. 2. OS – haematological tumours first-line registry OS in patients with chronic lymphocytic leukaemia (CLL; **a**), diffuse large B-cell lymphoma (DLBCL; **b**), indolent Non-Hodgkin's lymphoma (iNHL; **c**), and multiple myeloma (MM; **d**). CI, confidence interval; NA, not applicable; nonszt, ineligible for stem cell transplantation.

It is well known and has been discussed before that the patient populations included in clinical trials are mostly not representative of the majority of patients treated in routine care [1, 3]. The patients visiting their individual physician are older and more frail, have less social support and a poorer function and performance status, and experience inferior survival and inferior tolerance of comparable medications [7]. The resulting so-called efficacy-effectiveness gap explains this difference in numbers, especially regarding OS and toxicity [7]. Real-world data extend the knowledge gained from clinical trials, especially for rare diseases, rare patient populations and improve the generalisability of conclusions – real-world data and RCTs are complementary forms of medical evidence [reviewed in 1].

It may be surprising that the results from our registries are in the same range as RCT data, especially as inferior survival times are expected and have been shown in previous real-world studies – however, the large gap in results in these studies has been justified by the need for quality improvement, whereas we have diligently set up our prospective tumour registries with high-quality standards [1, 58, 59]. The results on the effectiveness of therapies in routine practice obtained from registry data are of particular interest for the physicians discussing treatment options and disease progression with their patients. As described above, median OS observed in RCTs can only be transferred to the total population to a limited extend. On the other hand, medical advances and recommendations in oncological treatment are quickly implemented in routine healthcare. This underlines the relevance of considering the individual patient when selecting the appropriate treatment. Our results indicate a very high-quality level of medical care of ambulatory patients in Germany. The rapid implementation of new treatment options and the treatment reality over time in the respective cancer types have been published before [11, 12, 15, 16, 60].

Now we took a closer look at those registry survival data, which differed markedly from the respective pivotal trials. In CLL, the 5-year survival rate of 74.1% was lower

than the reported 80.1–80.9% survival rate in the CLL10 trial [42, 43]; similarly, in iNHL, the 5-year survival rate was 80.1% in the registry and 81.7–90.2% in the respective trials [46–53]. These differences could be caused by the higher average age of 9 years (CLL) up to 13 years (iNHL) and the higher comorbidity of patients included in the respective registry since age is known to be a prognostic factor for both diseases [61]. In the metastatic RCC registry, median OS was 19.0 months, while median OS in RCTs ranged from 17.4 to 29.3 months (clear-cell mRCC) [36–41]. Also here, median age was at least 7 years higher in the registry. This prompted us to analyse two distinct subgroups of patients within this tumour registry: patients defined as "potentially trial-eligible" or "trial-ineligible" (based on standard inclusion and exclusion criteria). Indeed these subgroups differed significantly regarding median OS, with "potentially trial-eligible" patients showing a significantly longer median OS of 26.2 months, which was then comparable to the OS reported in RCTs [8]. We also evaluated the impact of trial eligibility on treatment, survival, and patient-reported outcome of patients with advanced NSCLC treated with pembrolizumab monotherapy in first line in routine care, seeing that almost 50% of the patients would not have met eligibility criteria for RCTs [62]. These findings are of substantial relevance for physicians discussing outcomes with their patients.

It will be interesting to see the effect of the newly approved agents, especially in immuno-oncology in the past few years. We set up registry platforms, stepping into the shoes of the tumour registries and as soon as the survival follow-up is long enough, we will be able to see whether the survival data in routine care is still comparable to RCTs.

This is particularly interesting, as eligibility criteria for RCTs become increasingly restrictive. Especially for trials sponsored by pharmaceutical companies, the prospect of success and a timely approval of new agents is higher, while the adverse events are expected to be lower, with highly selected patient populations [reviewed in 7]. An extension of inclusion criteria is advocated by many [1, 7, 9] – with the prospect of improving the evidence necessary for the individual treatment decision – for all patients in the real-world setting.

This study has some limitations. There were no specifications as to the timing, frequency, or criteria of tumour assessment and thus registry survival data should be considered as best clinical approximation and might not be directly comparable to data from clinical trials. The registries were designed for patients receiving systemic therapy; therefore, results may not be generalisable to the small group not receiving any systemic treatment. Strengths of this project are the prospective data collection and the participation of both hospitals and (office-based) oncologists in private practice all over Germany, recruiting a large, representative study cohort.

Conclusion

Haemato-oncological specialist practices represent an important pillar in routine healthcare for patients with malignant diseases. Data on efficacy of newly developed therapies from RCTs including selected patient populations can only be transferred to a limited extent to the real-world patient population: patients in routine care are mostly older, present with more comorbidities and a worse general state of health compared to patients included in RCTs. Despite these less favourable prognostic characteristics for patients in routine healthcare, treatment results are comparable with results from RCTs; registry data can provide important insights on routine outpatient healthcare.

Statement of Ethics

All experiments comply with the current laws in Germany, where they were performed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the National Research Committee and with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all patients. All tumour registries were reviewed and approved by the responsible Ethics Committee (Ethik-Kommission 70027 bei der Landesärztekammer Baden-Württemberg, Stuttgart, Germany), approval numbers F-2010-050#A2 (TKK), 133-06-f (TMK), 2009-161-ff (TLK), F-2016-096 (TPK), 2007-071-f (RCC), 2009-006-f (TLN). All tumour registries are registered at ClinicalTrials.gov (Table 1).

Conflict of Interest Statement

N.M. and W.K. declare no conflict of interest concerning the topic of this publication. Outside of the published work, N.M. declares stock ownership and upper management responsibility (iOMEDICO), consultant/advisory role: Amgen, BeiGene, BMS, GSK, IPSEN, Lilly, medac, Merck, Mylan, MSD, OncoVis, Pierre Fabre, Pfizer, Roche, and Servier; contracted research: Amgen, Astellas, AstraZeneca, BeiGene, BMS, EISAI, Gilead, GSK, IPSEN, J&J, Lilly, medac, Merck, Mylan, MSD, Novartis, OncoVis, Pierre Fabre, Pfizer, Roche and Seagen, and Servier. W.K.: consultant/advisory role, travel expenses, honraria: AbbVie, Amgen, AstraZeneca, BeiGene, BMS, Celgene, GSK, Janssen, Mundipharma, Pfizer, Roche, Sanofi and Celgene.

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Author Contributions

N.M.: conceptualisation, funding acquisition, investigation, project administration, resources, supervision, and writing – review andediting. W.K.: conceptualisation, investigation, supervision, and writing – review andediting.

Data Availability Statement

The data supporting the findings of the study are not openly available due to data privacy protection regulations. Enquiries regarding the data used for this study can be directed to the corresponding author.

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