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Trends in pivotal clinical trial design and biomarker use: a retrospective analysis of oncology drug approval in Switzerland from 2001 to 2020

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ABSTRACT

Introduction Cancer treatment has advanced rapidly in recent decades. Regulatory approval of cancer therapies relies on pivotal clinical trials, with phase III, randomised controlled trials (RCTs) regarded as the gold standard. However, there is growing concern about the increasing use of single-arm trials in cancer approvals. This study provides an overview of cancer drug approvals in Switzerland over the past 20 years. We assessed changes in approval patterns, characteristics of pivotal trials and the use of biomarkers in approvals.

Research design and methods We collected data on Swiss cancer drug approvals from 2001 to 2020, and their respective pivotal trials from Swissmedic's internal database and performed descriptive analyses.

Results Over 20 years, Swissmedic approved 362 cancer-related indications, 40.6% as new active substances. Solid tumours accounted for 63.3% of approvals, with lung cancer achieving top ranking with 22.3%. Approvals rose from 6 in 2001 to 34 in 2020, with biomarker-associated indications increasing from 16.7% in 2001 to 55.9% in 2020. Indications were mainly approved based on RCTs (71.3%). However, the proportion of single-arm trials supporting approvals for solid tumours increased from 14.3% in 2005 to 34.6% in 2020, with most approvals covering rare cancer entities and biomarker-associated indications.

Conclusions The notable rise in cancer drug approvals and biomarker-associated indications has expanded treatment options. While RCTs remained the primary basis for approvals, the growing reliance on single-arm trials, specifically for biomarker-associated approvals, introduces uncertainty for regulatory agencies in assessing benefit-risk profiles. This highlights the importance of postapproval evidence generation to confirm long-term safety and efficacy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cancer treatment has advanced significantly. Oncology approvals make up more than half of the global regulatory drug approvals. While phase III, randomised controlled trials remain the gold standard for oncology drug approvals, there is growing concern about the increasing use of single-arm trials.

WHAT THIS STUDY ADDS

⇒ This study provides a comprehensive overview of cancer drug approvals in Switzerland over two decades. It highlights the increasing number of approvals and indications associated with biomarkers by the Swiss Agency for Therapeutic Products (Swissmedic), and the increasing trend towards the use of single-arm pivotal trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings highlight the need to carefully consider single-arm trials and their limitations in regulatory decisions. They also emphasise that robust postapproval evidence generation is necessary to address remaining uncertainties after approval. Expanded international collaboration would contribute to increasing the quality of data available for regulatory drug approval and support structured postmarketing data capture for approved drugs.

INTRODUCTION

Cancer treatment has seen significant progress in recent decades. Since 2000, the development of therapeutic products in oncology has accelerated, with targeted therapies and biologics expanding rapidly while the number of new cytotoxic drugs has declined.[1] Small molecule targeted agents, antibody drug conjugates, cell-based and gene therapies have emerged as leading innovations, enabling precise tumour targeting, improved patient comfort and the potential to slow or reverse disease progression.[2]

Among therapeutic areas, oncology consistently accounts for the highest number of approvals by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Swiss Agency for Therapeutic Products (Swissmedic, SMC).[3–6] Pivotal clinical trials play a crucial role in the regulatory approval process for medicines and vaccines.[7] New drug indications are approved when a favourable benefit–risk balance is demonstrated based on quality, safety and efficacy endpoints.[8] Phase III, randomised controlled trials (RCTs) in oncology are the gold standard for assessing new cancer drugs.[9–12] However, in recent years, there has been a growing reliance on evidence from single-arm trials to support the approval of new drugs.[13] For example, according to Ribeiro *et al*, there has been a marked increase in the number of oncology drug approvals based on single-arm trials under the FDA's accelerated approval pathway, rising from 28 in 1992–2010 to 44 in 2010–2020.[14] In oncology, single-arm trials are often used for refractory, recurrent or metastatic cancers, where patients have a poor prognosis and limited survival, creating a need for more effective treatments.[13]

While several studies have examined different aspects of drug approvals by the FDA and EMA,[15–20] the growing use of single-arm trials and biomarker-associated indications has not been comprehensively explored yet. Furthermore, data from regulatory authorities such as Swissmedic remains limited.

This study provides a comprehensive overview of cancer drug approvals in Switzerland over two decades (2001–2020), focusing on approved indications, pivotal clinical trials and the role of biomarkers. We aim to understand how approval patterns and the design of pivotal clinical trials have changed, alongside the integration of biomarkers.

MATERIAL AND METHODS

We conducted a retrospective analysis of cancer drug approvals in Switzerland between January 2001 and December 2020.

Search strategy and selection criteria

Authorised access to the relevant data was granted to the authors as employees of SMC, in accordance with institutional policies on data use and privacy. All approved applications for new active substance (NAS) and indication extension (IE) of antineoplastic agents with Anatomical Therapeutic Chemical Classification codes (L01–04) in Switzerland from January 2001 to December 2020 were retrieved from SMC's internal database. Data access was granted as part of the authors' role at SMC and conducted in accordance with institutional policies on data use and privacy. Duplicated applications were removed before screening. Based on the study eligibility criteria, applications containing non-systemic drugs (cream, gel and plaster), biosimilar active substances, non-cancer indications and supportive therapies were excluded. To avoid duplicates, only the most recent version of the dossier at the time of approval was included. In cases where multiple applications were submitted for the same indication, such as combination therapies involving two distinct agents submitted separately by two different companies, we included only one application to avoid double-counting. This approach was applied when the applications were based on the same pivotal clinical trial and targeted the same therapeutic indication.

Data collection

The data were collected from Swissmedic's clinical assessment reports, clinical trial protocols, statistical analysis plans and clinical study reports extracted from the internal SMC database. Moreover, we collected the final approved indication labels from the SMC disposition approval letter.

Data points

We collected data in four categories: application, drug, indication and pivotal clinical trial. For additional details on the collected data points, please refer to online supplemental table 1.

Data preparation

In five applications, each containing a single indication supported by multiple pivotal trials, we selected the trial with the highest level of clinical evidence, typically a phase III, randomised controlled double-blinded study. If trials were equivalent in design, the study conducted and reported first was chosen.

For cases where multiple indications were approved based on distinct cohorts or arms of a single study, we recorded each indication separately to ensure clarity and accuracy.

Indications were classified as 'biomarker associated' if the approved Swissmedic label explicitly referenced a specific biomarker as a condition for use (eg, genetic mutations, immunological markers or proteins expressed on the tumour). Biomarker profiles could be positive, negative (wild type) or defined by a specific threshold.

Data quality and completeness

Initial data extraction was performed by one researcher (PR). The SMC team conducted five rounds of thorough validation to ensure the data entry's correctness. An independent team member selected 30% of IE and 20% of NAS applications, which were then reviewed by the SMC oncology and haematology clinical assessment team.

Discrepancies were resolved by team consensus or through consultation with our team of oncologists. After five rounds of review, data discrepancies were reduced to under 2%, ensuring high-quality data for analysis.

Handling of missing data

We obtained missing data points from external sources, including the AIPS website, clinicaltrial.gov website and the original publication of the pivotal clinical trials.[21 22]

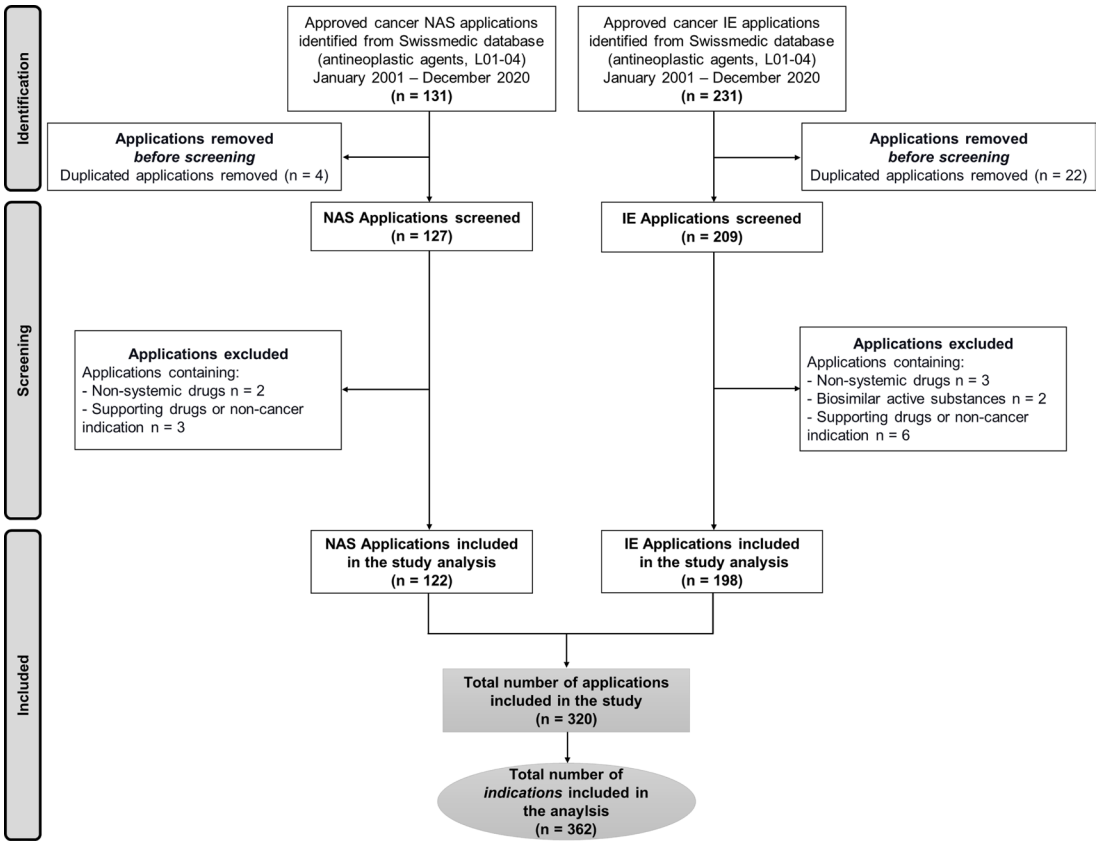

Figure 1 Identification and selection of cancer drug approvals by Swissmedic, 2001–2020. IE, indication extension; L01–04, Anatomical Therapeutic Chemical Classification codes; NAS, new active substance.

Statistical analysis

We conducted descriptive statistics stratified by cancer category (solid tumour vs haematologic neoplasm), submission category (NAS vs IE) and biomarker status (biomarker-associated indications vs non-biomarker-associated indications). We describe the changes in cancer categories and biomarker-associated indications over 20 years using four 5-year time intervals. The analysis was done using R software, V.4.2.0 (R Foundation for Statistical Computing) and R Studio software, V.4.0.3 (RStudio, PBC).[23 24]

RESULTS

Characteristics of oncology drug approvals

Between 2001 and 2020, Switzerland's SMC approved 320 cancer-related applications, encompassing a total of 362 indications and 136 distinct oncology drugs (figure 1). Among approvals, 10 (2.8%) indications received temporary authorisation. The annual number of approved indications increased from 6 in 2001 to 34 in 2020 (figure 2). Table 1 summarises the characteristics of all approved indications. Overall, 63.3% (229) of the indications targeted solid tumours with lung cancer accounting for the highest number of approvals (22.3%, 51), followed by gastrointestinal cancer (19.2%, 44) and breast cancer (17.9%, 41). The proportion of solid tumour indications remained relatively stable over time, ranging from 58.0% to 66.7% (figure 2). Almost 40% of approvals represented NAS, with haematologic neoplasms more frequently approved as NAS than IE.

Based on the regulatory labels, the highest number of drugs were approved for use in first-line (35.9%, 130) and second-line treatment (41.2%, 149). Molecular targeted agents with 41.7% (151) were the most common approved drug class. The approval of immune checkpoint inhibitors increased over time from 0% in 2001–2005 to 26.1% in 2016–2020. In contrast, the approval of cytotoxic agents declined over time from 38.9% in 2001–2005 to 6.2% in 2016–2020 (online supplemental figure 1).

Biomarker-associated approvals

Over 20 years, 38.4% (139) of indications were approved with the inclusion of a specified biomarker in the final regulatory label (table 2). The number of biomarker-associated indications constantly increased over time, reaching more than half of the approved indications (55.9%, 19) in 2020 (figure 1). This increase was pronounced in solid tumours, where it rose from 8.3% in 2001–2005 to 57.7% in 2016–2020 (figure 2). Breast cancer with 32 and lung cancer with 31 were the most frequent solid tumour approvals associated with a biomarker (online supplemental table 2). The most frequently used biomarkers in solid tumours were the Human Epidermal Growth Factor Receptor 2, 21.1%,

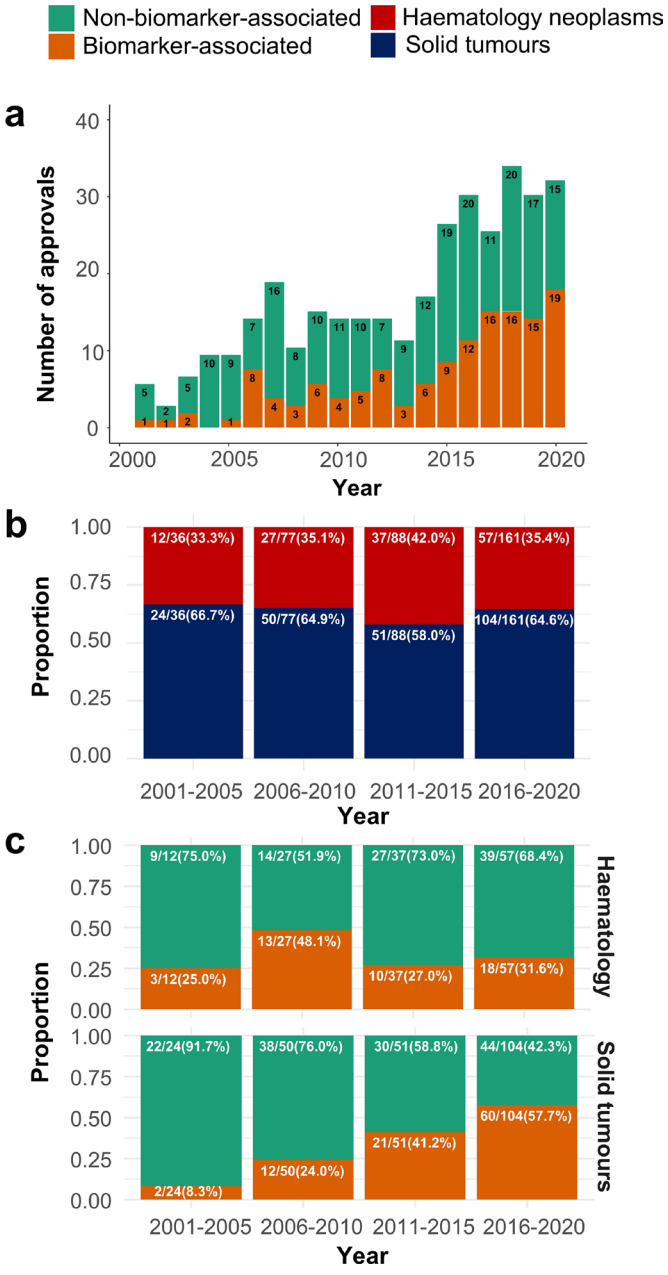

Figure 2 Changes of cancer approvals from 2001 to 2020. (a) Annual number of approved indications, categorised by biomarker-associated (orange) and non-biomarker-associated (green) approvals. (b) Proportion of approvals for solid tumours (blue) and haematological neoplasms (red). (c) Proportion of biomarker-associated approvals within haematological neoplasms (top panel) and solid tumours (bottom panel).

the Epidermal Growth Factor Receptor, 13.7%, and B-Raf Proto-Oncogene, 11.6%.

Pivotal clinical trials and changes in trial design over time

Most indications were approved based on phase III clinical trials (65.7%, 238). Table 2 provides a detailed summary of the characteristics of pivotal clinical trials. Of 353 pivotal clinical trials reviewed, the majority were randomised controlled (73.1%, 258), and most had an open-label design (72.2%, 255). Among the RCTs, 62% (160) included an active control arm. Out of 10 temporary approvals, 9 were approved based on single-arm trials. Progression-related endpoints were used as the primary endpoints in nearly half of the clinical trials (49.6%, 175). In RCTs, progression-free survival (52.3%, 135) and overall survival (30.6%, 79) were the most common primary endpoints, whereas single-arm trials predominantly used response-related binary endpoints (92.6%, 88). The differences in characteristics between RCTs and single-arm trials are listed in online supplemental table 3.

While most of the indications were supported by RCTs, the proportion of single-arm trials increased over time from 10% in 2005 to 35.2% in 2020 (figure 3). This trend was particularly notable in solid tumours, where the proportion of single-arm trials grew from 14.3% in 2005 to 34.6% in 2020. Despite fluctuations due to the small number of annual approvals, moving average analysis illustrated a clear upward trend in the use of single-arm trials for solid tumours in comparison to haematological neoplasms.

Single-arm trials supported a higher proportion of approvals for haematological neoplasms (40%, 52) compared with solid tumours (19.3%, 43). Among solid tumour indications approved based on single-arm trials, most involved rare and advanced cancer entities (online supplemental table 4).

Similarly, single-arm trials were more often used for biomarker-associated (34.1%, 47) than for the non-biomarker-associated approvals (22.3%, 48). Out of 16 lung cancer indications approved based on single-arm trials, 14 were biomarker associated (online supplemental table 4).

DISCUSSION

This study provides a comprehensive, two-decade overview of cancer drug approvals in Switzerland. Previously published studies focusing on regulatory decision patterns across the FDA, EMA and SMC have reported a high concordance in decision-making and low divergence rates for both oncology and non-oncology products.[25 26] Therefore, the findings derived from the Swiss drug approval are likely to be similar to those of the EMA and FDA. SMC has approved 362 cancer-related drug indications within two decades, primarily as IE, with a preponderance of solid tumours. One notable trend is the substantial increase in oncology drug approvals, particularly since 2015. This increase expands treatment options for patients and reflects advancements in understanding cancer biology and quickening drug development. Similar trends have been reported by Gloy *et al* who reported a continuous increase in the number of NAS cancer drug approvals by the FDA from 22 in 2000–2005 to 60 in 2016–2020 and an increase in the proportion of biomarker-associated indications from 27% to 47%.[27]

The genomic era enabled targeting products of cancer-associated genes and gene fusions, such as BCR-ABL

Table 1 Summary of characteristic of approved cancer indications in Switzerland, 2001–2020

Characteristic	Overall N (%)	Approval category	
		New active substance	Indication extension
Total number of indications	362 (100)	147 (40.6)	215 (59.4)
Treatment type			
Monotherapy	216 (59.7)	111 (75.5)	105 (48.8)
Combination therapy	146 (40.3)	36 (24.5)	110 (51.2)
Drug class			
Molecular targeted agent	151 (41.7)	73 (49.7)	78 (36.3)
Monoclonal antibody	64 (17.7)	19 (12.9)	45 (20.9)
Cytotoxic agent	58 (16.0)	24 (16.3)	34 (15.8)
Immune checkpoint inhibitor	47 (13.0)	7 (4.8)	40 (18.6)
Antibody–drug conjugate	16 (4.4)	5 (3.4)	11 (5.1)
Endocrine therapy	6 (1.7)	6 (4.1)	0 (0.0)
Other*	20 (5.5)	13 (8.8)	7 (3.3)
Cancer type			
Solid tumours	229 (63.3)	86 (58.5)	143 (66.5)
Lung	51 (22.3)	20 (23.3)	31 (21.7)
Gastrointestinal	44 (19.2)	8 (9.3)	36 (25.2)
Breast	41 (17.9)	17 (19.8)	24 (16.8)
Genitourinary	23 (10.0)	12 (14.0)	11 (7.7)
Skin	20 (8.7)	12 (14.0)	8 (5.6)
Gynaecological	14 (6.1)	3 (3.5)	11 (7.7)
Sarcoma/GIST	11 (4.8)	5 (5.8)	6 (4.2)
Thyroid/neuroendocrine	7 (3.1)	5 (5.8)	2 (1.4)
Head and neck	7 (3.1)	0 (0.0)	7 (4.9)
Nervous system/brain	6 (2.6)	2 (2.3)	4 (2.8)
Tumour-agnostic	3 (1.3)	2 (2.3)	1 (0.7)
Other†	2 (0.9)	0 (0.0)	2 (1.4)
Hematologic neoplasms	133 (36.7)	61 (41.5)	72 (33.5)
Leukaemia	62 (46.6)	30 (49.2)	32 (44.4)
Lymphoma	35 (26.3)	16 (26.2)	19 (26.4)
Multiple myeloma	22 (16.5)	8 (13.1)	14 (19.4)
Other‡	14 (10.5)	7 (11.5)	7 (9.7)
Paediatric indication	16 (4.4)	6 (4.1)	10 (4.7)
Treatment line			
Neoadjuvant	3 (0.8)	0 (0.0)	3 (1.4)
Adjuvant	18 (5.0)	3 (2.0)	15 (7.0)
First line	130 (35.9)	35 (23.8)	95 (44.2)
Second line	149 (41.2)	72 (49.0)	77 (35.8)
Second line and further line	28 (7.7)	22 (15.0)	6 (2.8)
Any line	34 (9.4)	15 (10.2)	19 (8.8)

*Hedgehog signalling inhibitors, hypomethylating agents, immunomodulatory agents, oncolytic virus therapies, Chimeric Antigen Receptor (CAR) T-cell therapy
†Angiomyolipoma, tuberous sclerosis complex.
‡Waldenstrom macroglobulinemia, polycythaemia vera, myelodysplastic syndromes, atypical myelodysplastic/myeloproliferative neoplasm with neutrophilia, aggressive systemic mastocytosis.
GIST, gastrointestinal stromal tumour.

(The Breakpoint Cluster Region-Abelson), leading to the birth of precision oncology with imatinib's success in chronic myeloid leukaemia in 2001.[28] Our data indicate that by 2020, more than half of the approvals included a biomarker in the regulatory label, predominantly in solid tumours, and driven by approvals of molecularly targeted agents. This shift suggests a move from traditional cytotoxic therapies towards more precise, targeted drug interventions. This finding is in line with an analysis of EMA cancer approvals, which showed that

Table 2 Summary of pivotal clinical trials across approval category, cancer type and biomarker association

Characteristic	Overall N (%)	Approval category		Cancer type		Biomarker-associated	
		New active substance	Indication extension	Solid tumour	Haematologic neoplasm	Yes	No
Total indications	362 (100)	147 (40.6)	215 (59.4)	229 (63.3)	133 (36.7)	139 (38.4)	223 (61.6)
Clinical trial phase							
I/II	12 (3.3)	10 (6.8)	2 (0.9)	9 (3.9)	3 (2.3)	9 (6.5)	3 (1.3)
II	101 (27.9)	61 (41.5)	40 (18.6)	47 (20.5)	54 (40.6)	46 (33.1)	55 (24.7)
II/III	2 (0.6)	0 (0.00)	2 (0.9)	1 (0.4)	1 (0.8)	2 (1.4)	0 (0.00)
III	238 (65.7)	70 (47.6)	168 (78.1)	166 (72.5)	72 (54.1)	81 (58.3)	157 (70.4)
Cumulative literature*	9 (2.5)	6 (4.1)	3 (1.4)	6 (2.6)	3 (2.3)	1 (0.7)	8 (3.6)
Total clinical trials *(excluding cumulative literature)*	353 (100)	141 (39.9)	212 (60.1)	223 (63.2)	130 (36.8)	138 (39.1)	215 (60.9)
Trial design							
RCT	258 (73.1)	84 (59.6)	174 (82.1)	180 (80.7)	78 (60.0)	91 (65.9)	167 (77.7)
Single arm†	95 (26.9)	57 (40.4)	38 (17.9)	43 (19.3)	52 (40.0)	47 (34.1)	48 (22.3)
Type of blinding							
Open label	255 (72.2)	100 (70.9)	155 (73.1)	141 (63.2)	114 (87.7)	106 (76.8)	149 (69.3)
Double blinded‡	98 (27.8)	41 (29.1)	57 (26.9)	82 (36.8)	16 (12.3)	32 (23.2)	66 (30.7)
Control arm in RCTs							
Active	160 (62.0)	45 (53.6)	115 (66.1)	101 (56.1)	59 (75.6)	55 (60.4)	105 (62.9)
Placebo/add-on placebo	91 (35.3)	37 (44.1)	54 (31.0)	75 (41.6)	16 (20.5)	32 (35.2)	59 (35.4)
No treatment (observation)	7 (2.7)	2 (2.4)	5 (2.9)	4 (2.2)	3 (3.8)	4 (4.4)	3 (1.8)
(Co)primary endpoints§							
Overall survival	80 (22.7)	24 (17.0)	56 (26.4)	71 (31.8)	9 (6.9)	17 (12.3)	63 (29.3)
Progression-related time to event¶	175 (49.6)	54 (38.3)	121 (57.1)	118 (52.9)	57 (43.8)	74 (53.6)	101 (47.0)
Response-related binary**	117 (33.1)	69 (48.9)	48 (22.6)	52 (23.3)	65 (50.0)	57 (41.3)	60 (27.9)
Other††	16 (4.5)	8 (5.7)	8 (3.8)	10 (4.5)	6 (4.6)	5 (3.6)	11 (5.1)

*The approval was based on a cumulative body of publicly available evidence or published clinical studies.
†Dose-comparative randomised clinical trials are counted as single-arm clinical trials, as they did not compare the study drug against an independent control or placebo group, but rather evaluated different dosing regimens within the same treatment.
‡Of double-blinded clinical trials, two are dose-comparative randomised clinical trials, which are labelled as single-arm trials.
§In some clinical trials, multiple primary endpoints (co-primary endpoint) were used, causing the total percentage to exceed 100%.
¶Progression-free survival, disease-free survival, relapse-free survival, event-free survival, time to progression and metastasis-free survival.
**Objective response rate, response rate (with various definitions in hematologic neoplasms approvals).
††Difference in locoregional disease control, duration of response, change in Subependymal Giant Cell Astrocytoma (SEGA) volume during the core 6-month treatment phase, Red Blood Cell (RBC) transfusion independence, cardiac toxicity, symptom improvement rate, suppression of testosterone, freedom from transplant, treatment-related mortality, 50% decrease in the incidence of high-titre antibodies.
RCT, randomised controlled trial.

between 2015 and 2020, almost half (47%) of the drug indications for solid tumours were approved based on a specific biomarker.[8]

While phase III and RCTs remain the primary source establishing drug efficacy and safety profile, we observed a growing reliance on single-arm trials over time. By 2020, single-arm trials accounted for over one-third of pivotal trials supporting solid tumour approvals. In line with our findings, the FDA's use of single-arm trials for the approval of solid tumour therapies increased from 2.6% to 40% between 2013 and 2021.[29] Single-arm trials are often considered acceptable when phase III, RCTs are not feasible. Our data show that single-arm trials were predominantly used in approvals of haematological neoplasms, rare cancers, and in biomarker-defined populations.

The increased use of single-arm trials poses a challenge for regulatory agencies when evaluating the benefit–risk of new drugs. While the proportion of single-arm trials in 2020 may still appear acceptable and justified in certain cancer entities, the upward trend raises concerns about the strength of the evidence underpinning future approvals and the ability to ensure meaningful benefits for patients. The lack of a parallel control arm, reduced robustness in interpreting results, and risk of bias, particularly when using external comparators, represent limitations of single-arm trials.[13] Furthermore, single-arm trials often rely on primary response-based endpoints, which

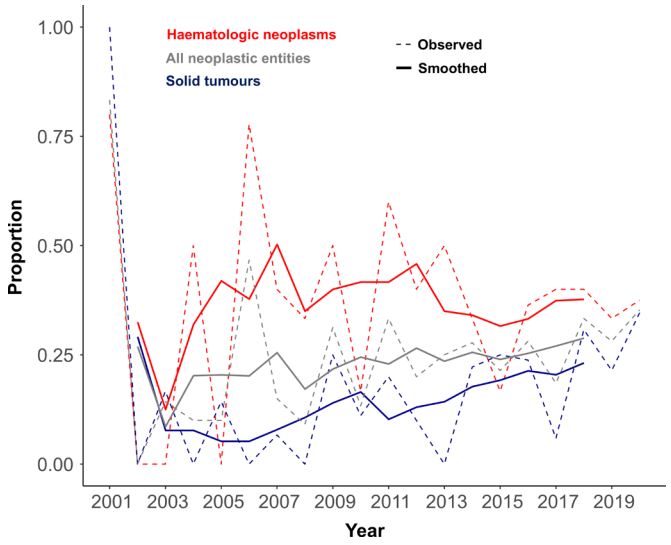

Figure 3 Temporal trends in the use of single-arm trials supporting oncology drug approvals. This shows temporal trends in the use of single-arm trials as pivotal clinical trials supporting oncology drug approvals, stratified by: all neoplastic entities; solid tumours and haematological neoplasms combined (gray), solid tumours (blue) and haematological neoplasms (red). Dashed lines represent observed annual proportions; solid lines show smoothed trends based on a 4-year moving average analysis.

may not fully capture long-term clinical benefits compared with the time-to-event endpoints, and this reliance leads to higher uncertainty when regulatory agencies conclude the benefit/risk of a new drug or indication.

These findings highlight the importance of conducting confirmatory trials following expedited approvals, along with the evaluation of postmarketing safety concerns. Such measures are necessary and should be requested by regulatory agencies. International collaboration among regulatory agencies can and should improve the efficiency, quality and speed of approvals. 'Project Orbis' is an excellent example of such a collaboration among FDA, SMC and other agencies,[30] leading to reduced submission gaps and review times and numerically higher consensus decisions.[31] Such international collaboration could also help to increase the quality of data available for regulatory drug approval and support structured postmarketing data capture for approved drugs.

Strengths and limitations

Our study examined two decades of cancer drug approvals in Switzerland, focusing on both IE and NAS cancer approvals. We extracted data directly from the agency's assessment reports, which provide more granularity than the published study reports. While our study offers valuable insights, limitations must be acknowledged. First, we focused only on approved applications due to challenges in retrieving precise data on withdrawn and not approved applications. Accessing the information on refused or retracted applications would have allowed us to report the approval rate and compare approved and rejected applications.

Moreover, the temporary approval pathway for NAS was introduced in Switzerland in 2019 and for IE in early 2023. Given our study's cut-off date, only a handful of those approvals could be included in the analysis, limiting the interpretability of the temporary authorisation.

CONCLUSION

The number of cancer drug approvals in Switzerland has risen over the past two decades, expanding treatment options. While most approvals are still based on RCTs, the increasing use of single-arm trials presents challenges for regulatory decision-making. This trend highlights the importance of robust postmarketing data and international regulatory collaboration to ensure long-term safety and efficacy of cancer drug approvals.

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Contributors AWi, PR and U-PR contributed to the study concept and design. PR collected and analysed the data. QL provided statistical expertise. SDTdS provided the list of approvals. AWi, PR, U-PR, AWo, QL and LR were involved in the interpretation of the data. AWi, PR, U-PR and EC-R were involved in writing and editing the manuscript. QL, LR, SDTdS, NM, JB, NB, AG, MI, EB, SJ, KS, BM, CR, EZ, MZ-P and AWo conducted data monitoring and quality assurance. All authors reviewed and approved the manuscript. AWi is the guarantor of this study.

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Provenance and peer review Not commissioned; internally peer reviewed.

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