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Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021

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IMPORTANCE Single-arm trials have allowed for transformative therapies to be made available to patients expeditiously. However, using single-arm trials to support drug approval presents several challenges that must be carefully considered.

OBSERVATIONS Between January 1, 2002, and December 31, 2021, the US Food and Drug Administration granted 176 new malignant hematology and oncology indications based on single-arm trials, including 116 accelerated approvals (AAs) and 60 traditional approvals. Overall, 87 approvals (49%) were for new molecular entities or original biologics and 89 (51%) were supplemental indications. Response rate (RR) was the most common end point used to support approval in these single-arm trials (173 of 176 [98%]). Of the 116 AAs based on single-arm trials, 45 (38%) fulfilled their postmarketing requirement to verify clinical benefit, 61 (52%) are pending verification of benefit, and 10 (9%) were withdrawn from the market as of December 31, 2021. Most (56 of 61 [92%]) AAs based on single-arm trials pending verification of benefit occurred during the previous 5 years and have ongoing confirmatory trials as of December 2021.

CONCLUSIONS AND RELEVANCE Single-arm trials have been a common development strategy to support regulatory approval as early-stage expansion cohorts with promising durable RRs have become more prevalent. In the appropriate context, single-arm trials using durable RRs can allow patients expedited access to novel therapies and will continue to serve a role in advancing drug development in oncology. However, single-arm trials have a smaller noncomparative safety data set, inability to use time-to-event end points, and other limitations that require careful consideration within the context of the disease and available therapies. The randomized clinical trial remains the preferred approach in clinical investigation.

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Single-arm trials (SATs) have been used to assess the safety and efficacy of anticancer drugs for several decades. US Food and Drug Administration (FDA) approval of oncology drugs during the 1970s was commonly based on response rates (RRs)[1,2] that were primarily evaluated in SATs. In the 1980s, an Oncologic Drugs Advisory Committee convened by the FDA determined that cancer drug approval should be based on more direct evidence of clinical benefit, such as improvements in survival, patients' quality of life, improved physical functioning, or improved tumor-related symptoms.[1,2] During subsequent decades, SATs continued to support drug approvals in certain circumstances but were primarily used to evaluate the preliminary safety, activity, and dosing of drugs early in development. More recently, higher levels of early efficacy in smaller biomarker-defined populations have been associated with increased use of RR evaluated in SATs to support drug approval once again.

Clinical investigation of previously untested drugs in oncology has historically proceeded in a stepwise fashion. In the traditional model, phase 1 trials characterize safety across a range of escalating doses and evaluate the pharmacologic properties of a drug in humans. Early evidence of efficacy may be seen in phase 1, but is typically further investigated in phase 2 trials before initiating a large randomized phase 3 trial to confirm benefit. The RRs observed in phase 1 trials have continued to rise during the last several decades. In the 1970s and 1980s, RRs were often low, typically less than 5%, with a slight increase to approximately 11% in the 1990s.[3-8] With the advent of precision medicine and biomarker-enriched populations, RRs have risen over time,[8-10] and contemporary early phase trials often have much stronger early clinical evidence of efficacy based on durable RR, which has been followed by a more seamless drug development paradigm.[11] Increasingly, promising and sometimes unprecedented durable RRs are followed by expansion of early-stage trials to include more patients and additional cohorts.[11] One analysis demonstrated that among more than 500 therapeutic phase 1 trials conducted over a 25-year span, the average sample size more than doubled.[12] Given the increase in the magnitude of efficacy and

Table 1. Malignant Hematology and Oncology Approvals Based on Single-Arm Trials, 2002-2021

Characteristic of approval	No. of approvals (%)
All new indications	176 (100)[a]
Approvals	
Accelerated	116 (66)
Traditional	60 (34)
New molecular entities	87 (49)
Supplemental indications	89 (51)
End points for approval	
RR	174 (99)
Event-free survival	1 (<1)
Castration rate	1 (<1)
Reduction of tumor burden by at least 50% or discontinuation of all antihypertensive medications for at least 6 mos	1 (<1)
Mechanism of action	
Inhibitors	
Kinase	67 (38)
Checkpoint	39 (22)
Other	70 (40)
Disease-defining biomarker present	
Yes	71 (40)
No	105 (60)
Patient population enrolled	
Locally advanced or metastatic diseases	174 (99)
Localized disease	2 (1)

Abbreviation: RR, response rate.

[a] Approvals granted by the US Food and Drug Administration's Center for Biologics and Research are included and may require additional considerations for cell and gene therapies.

amount of safety information accumulating in early-stage trials, single-arm cohorts have been used to support FDA approvals, particularly accelerated approvals (AAs).[13]

Tumor RR is a key end point unique to oncology that has allowed for the evaluation of efficacy in single-arm trials. Since cancer is a relentlessly progressive disease and tumors do not typically regress on their own, a decrease in tumor burden measured by RR can be associated with drug activity rather than spontaneous regression of the disease, placebo effect, or other confounding factors. While RR does not capture effects on survival and typically does not capture associations with symptoms or function, durable RR is a direct measure of antitumor activity and is a strong, objective, and clinically relevant end point. Patients and physicians accept substantial and prolonged reductions in tumor burden to be meaningful in clinical practice, as tumor growth is thought to indicate resistance and prompts changes in treatment, and reducing tumor burden may be associated with improvements in disease-related symptoms in patients with large tumors or areas of disease involving sensitive anatomic structures and organ systems.[14] Response rate can also be assessed earlier and in smaller sample sizes than other measures of efficacy commonly used in oncology trials, such as progression-free survival (PFS) and overall survival (OS), and is based on objective, quantitative, and verifiable assessments.[2] Time-to-event end points, such as PFS and OS, necessitate a randomized trial due to the sensitivity of these end points to baseline differences in patient, disease, and other clinical characteristics. This article reviews the FDA experience in using data from SATs to support FDA approval of new drugs and biologics for malignant hematology and oncology indications during the last 20 years and includes a discussion of the advantages and the challenges associated with this approach.

Methods

We identified all drug and biologic approvals for malignant hematology and oncology indications in FDA databases from 2002 to 2021. We selected all indication approvals that were primarily based on SATs. Data sources included approval letters, US prescribing information, and clinical review documents from the FDA's electronic record system.[15] The following information was abstracted from source documents for each approval: date of approval, indication, new molecular entity (NME) or original biologic or supplemental approval, approval pathway (AA or traditional approval [TA]), status of AA (clinical benefit verified, not verified, or withdrawn from market), end points assessed, drug class and mechanism of action, line of approval/disease setting, and association of a biomarker for the disease setting (if relevant). Definitions of RR included Response Evaluation Criteria in Solid Tumors criteria for solid tumors, complete response rates, hematologic responses (eg, major cytogenetic response and major molecular response), and other criteria (eg, International Myeloma Working Group criteria and Lugano Criteria).

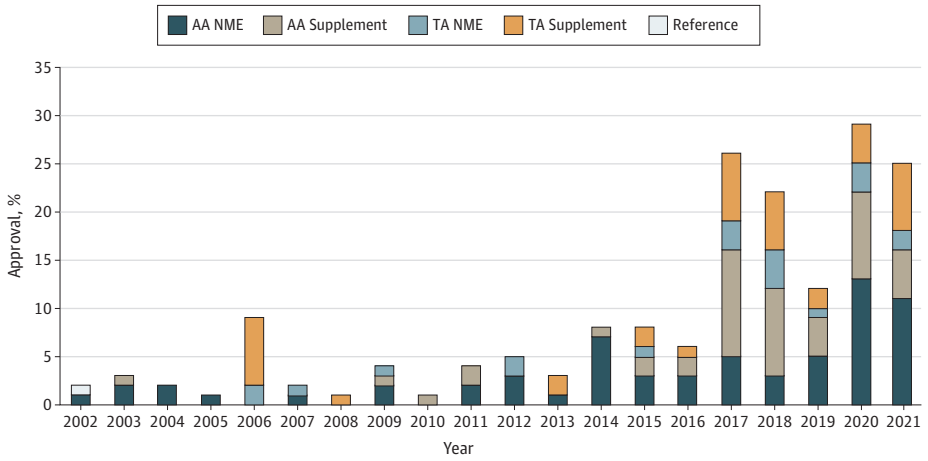
When multiple studies or cohorts were used to support an approval, we selected the trial or cohort reported in section 14 of the US prescribing information. The status of AA was assessed using a cutoff of December 31, 2021. When indications granted AA were subsequently converted to TA, often with a broadened indication, both approvals were included. Those products that received their initial FDA approval were classified as NMEs or original biologics and all subsequent approvals were considered supplemental indications. Approvals for nonmalignant or supportive indications or those providing dosing or formulation changes that were not clinically relevant were not included.

Results

Between January 1, 2002, and December 31, 2021, the FDA's Office of Oncologic Diseases granted 563 new indications; of these, 176 (31%) were based on SATs. Of those based on SATs, 87 approvals (49%) were for NMEs or original biologics and 89 (51%) were supplemental indications (**Table 1**; **Figure**).

Response rate was the most common end point used to support SAT approvals (173 of 176 [98%]). Durability of response was frequently cited to support RR. Three non-RR end points were used to support approval; for 3-year event-free survival, patient-level data were available for the historical controls and the drug had established clinical benefit in diseases with related biology; for castration rate, plasma testosterone was considered a validated surrogate end point to assess the efficacy of gonadotropin-releasing

Figure. Approval of Malignant Hematology and Oncology Drugs and Biologics Based on Single-Arm Trials (SATs) by Year, 2002-2021



AA indicates accelerated approval; NME, new molecular entity; TA, traditional approval.

hormone analogues[16]; for tumor reduction of at least 50% or discontinuation of all antihypertensive medications for at least 6 months, reduction in hypertension appeared to be associated with decreased tumor activity and was supported by evaluation of RR by established response criteria.

Of the 176 indications granted, 116 (66%) were AAs and 60 (34%) were TAs. Of the 116 AAs, 45 (38%) fulfilled their postmarketing requirement to verify clinical benefit and were converted to TA, 61 (52%) are pending verification of benefit, and 10 (9%) were withdrawn from the market. Of the 45 AAs that have verified benefit, 29 (64%) were evaluated in a trial that enrolled a patient population that differed from the original SAT population with respect to line of therapy, biomarker enrichment status, and other trial characteristics. Of the 61 AAs pending verification of benefit, 56 (92%) were approved during the previous 5 years (16 in 2021, 21 in 2020, 4 in 2019, 6 in 2018, and 9 in 2017) and had ongoing confirmatory trials as of December 31, 2021.

Sixty-seven new indications (38%) based on SATs were granted for kinase inhibitors, 39 (22%) for immune checkpoint inhibitors, and 70 (40%) for drugs with other mechanisms of action, including (but not limited to) antibody-drug conjugates, cytotoxic drugs, and non–checkpoint inhibitor monoclonal antibodies. Seventy-one SAT approvals (40%) were based on trials in patients enrolled who had disease that was at least partially defined by a biomarker.

Almost all SAT approvals (174 of 176 [99%]) were for treating locally advanced or metastatic disease, and most were indicated for treatment following at least 1 prior line of therapy; 26% of approvals were for treatment in the first line or later, 49% second line or later, 20% third line or later, 4% fourth line or later, and 1% fifth line or later. Two approvals (1%) were in localized disease settings: mitomycin (low-grade upper tract urothelial cancer) and pembrolizumab (BCG-unresponsive high-risk non–muscle-invasive bladder cancer).

Discussion

Randomized clinical trials (RCTs) are considered the preferred approach in clinical research to generate substantial evidence of effectiveness and robust safety evaluation to support drug approval. The FDA recommends RCTs when feasible, but there are several occasions when RCTs are difficult to conduct and/or equipoise is lost. For instance, demonstration of a high and durable RR with an acceptable safety profile in an early-phase SAT could make conducting a subsequent RCT challenging, as randomizing patients to a control that appears to have higher toxic effects and a substantially lower RR may violate principles of clinical equipoise.[17-19] Randomized clinical trials may be particularly challenging in these situations when there is suboptimal or no available therapy. In addition, as tumors are reclassified based on molecular and genetic factors into rare biomarker-defined subsets, enrollment and conduct of a randomized trial in these smaller populations may encounter feasibility issues. For instance, some biomarker-positive populations are uncommon, making the number needed to screen high, and the size of the eligible population challenging to power a randomized trial for an end point such as OS.[17-19] Demonstrating an improvement in OS can also be a challenge in cancers with long natural histories for which the length of a trial necessary to demonstrate an OS improvement may not be practical, or subsequent therapies (including crossover to the experimental therapy) may complicate OS interpretation.[14] In instances in which an RCT is infeasible, an SAT design may be appropriate.

The AA pathway has made many innovative therapies available years before confirmatory trials are typically completed, many of which are supported by SATs that demonstrated durable RR.[20] The indicated patient populations for these approvals are often those with incurable, metastatic cancers who have limited or no effective treatment options. Where therapies are available, they are often marginally effective and have substantial toxic effects, highlighting the unmet medical need in these patients. In this context, providing patients with an incurable cancer and high unmet medical need access to novel anticancer therapies based on SATs with an appropriate magnitude of response and duration while awaiting verification of benefit is felt to be justified. Postmarketing confirmatory trials are used to verify and describe the anticipated effect of the clinical benefit noted at the time of AA.[13] Sponsors are required to provide FDA with a timeline of completion of various confirmatory trial mile-

Table 2. FDA Hematology and Oncology Traditional Approvals Based on Single-Arm Trials

Drug name and MoA	Indicated population	Efficacy population and results from SAT	Regulatory considerations
Crizotinib[24]	Granted TA on March 11, 2016, for treating patients with ROS1-positive NSCLC	• 50 Patients with ROS1-positive metastatic NSCLC • RR, 66% (95% CI, 51%-79%) with a median DoR of 18.3 months (95% CI, 12.7 to NR)	• Rare population (1%-2% of NSCLC) • Limited efficacy of alternative therapies (RR approximately 10%-35% with relatively short DoR) • Safety profile already well characterized in other disease areas that used RCTs • Conducting subsequent RCT could violate principles of clinical equipoise
Vismodegib[25]	Granted TA on January 30, 2012 for treatment of adults with mBCC or with laBCC that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiation	• 96 Patients with pathologically confirmed laBCC or mBCC enrolled in an SAT • mBCC (n = 33): RR, 30.3% (95% CI, 15.6%-48.2%); median DoR, 7.6 months (95% CI, 5.6 to NE) • laBCC (n = 63): RR, 42.9% (95% CI, 30.5%-56%); median DoR, 7.6 (95% CI, 5.7-9.7) mo	• Lack of alternative therapies • Durable reduction of disfiguring and morbidity of lesions deemed direct evidence of benefit
Selumetinib[26]	Granted TA on April 10, 2020, for treating pediatric patients 2 years and older with NF1 who have symptomatic, inoperable PNs	• 33 Pediatric patients with NF1 and inoperable PN enrolled in the SAT SPRINT • RR, 66% (95% CI, 51%-79%), with 82% of responding patients having a DoR of ≥12 mo	• Disfiguring and morbid disease • Clinically meaningful RR with lasting DoR and improvements in disease-related morbidities deemed direct evidence of benefit
Pembrolizumab[27]	Granted TA on January 8, 2020, for treating patients with BCG-unresponsive, high-risk NMIBC with CIS with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy	• 96 Patients with BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors who were ineligible for or have elected not to undergo cystectomy • Complete response rate, 41% (95% CI, 31%-51%) with DoR of 16.2 (95% CI, 0-30.4) months with 46% with duration ≥12 mo	• Alternative treatment with radical cystectomy associated with substantial morbidity and potential mortality • Safety profile already well characterized in other disease areas that used RCTs • Obtaining a durable CR, delayed or avoided radical cystectomy, deemed direct evidence of clinical benefit
Tagraxofusperzs[28]	Granted TA on December 21, 2018, for treating BPDCN in adults and in pediatric patients 2 years and older	• 13 Patients with treatment-naive BPDCN • CR/CRc rate, 53.8% (95% CI, 25.1%-80.8%); median DoR not reached (range, 3.9, 12.2 mo) • 15 Patients with relapsed or refractory BPDCN • 1 Patient achieved a CR (duration, 111 d) and 1 patient achieved a CRc (duration, 424 d)	• Rare, aggressive hematologic cancer (estimated to be <1% of leukemias or lymphomas) • Lack of alternative therapies • Conducting RCT challenging due to rarity of tumor
Moxetumomab pasudotox-tdfk[29]	Granted TA on September 13, 2018, for treating patients with relapsed or refractory HCL who received at least 2 prior systemic therapies, including treatment with a PNA	• 80 Patients with HCL or HCL variant with a need for therapy based on presence of cytopenias or splenomegaly and who had received prior treatment with at least 2 systemic therapies, including 1 PNA • RR, 75% (95% CI, 64%-84%); median DoR not reached (95% CI, 0-43 mo)	• Rare and incurable cancer approximately 1000 new cases per year in the US) • Lack of alternative therapies • High RR with long duration • Conducting RCT challenging due to rarity of tumor

Abbreviations: BCG, Bacillus-Calmette-Guerin; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CIS, carcinoma in situ; CRc, clinical complete response; CR, complete response; DoR, duration of response; HCL, hairy cell leukemia; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; MoA, mechanism of action; NF1, neurofibromatosis type 1; NMIBC, non-muscle invasive bladder cancer; NSCLC, non-small cell lung cancer; PN, plexiform neurofibromas; PNA, purine nucleoside analog; RCT, randomized clinical trial; RR, response rate; SAT, single-arm trial; TA, traditional approval.

stone dates, and FDA must agree on this timeline before approval.[21] Confirmatory trials should be under way and substantially accrued at the time of AA to assure benefit can be verified within a reasonable period.[22] Because trials evaluating time to event outcomes (eg, OS and PFS) are often used to confirm benefit, and power depends on the number of events observed, the period for completion may vary with respect to the established milestone dates. Due to the aforementioned challenges in conducting an RCT with OS as the primary end point in certain disease settings, along with the understanding that PFS and RR with substantial duration of response (DOR) may represent clinical benefit in certain disease contexts, confirmatory RCTs have also used PFS to confirm benefit. In situations in which an RCT is believed to be infeasible, collection of longer follow-up data for DOR and RR with additional patients has been assessed in the

Table 3. Benefits and Limitations of Single-Arm and Randomized Trial Designs

Characteristic	Trials	
	Single arm	Randomized
Benefits	• Shorter completion time • Smaller sample size • Efficacy signals can be detected early • Objective, verifiable end point (RR) with supportive duration of response	• Mitigates bias • Can evaluate time-to-event end points (eg, PFS, OS) • Robust comparative safety evaluation
Limitations	• RR and DOR infeasible in tumor types with diffuse or poorly circumscribed tumors (eg, bone-only metastases, peritoneal carcinomatosis) • Comparison with historical control can be problematic • Attribution of adverse events is limited • Cannot distinguish contribution of effect if multiple drugs given • May not allow for optimal dose selection	• Longer time to trial completion • Larger sample size • Difficult to accrue necessary sample size for rare tumors • Potential loss of equipoise when early activity noted in drug development • End points, such as OS and PFS, may be confounded by subsequent therapies and censoring methods, respectively

Abbreviations: DOR, duration of response; OS, overall survival; PFS, progression-free survival; RR, response rate.

same SAT used to support the AA. An additional challenge with an AA is that there can be loss of equipoise and difficulty in accruing a randomized postmarketing trial in the same indicated population. Because it is generally believed that a drug approved in a refractory setting would be at least as effective in an earlier-line setting within the same cancer type, FDA has allowed sponsors to conduct their confirmatory trials in an earlier disease setting than the indication-granted AA.

The FDA has also granted TA to therapies treating rare diseases based on results from SATs. Considerations for whether a SAT strategy is appropriate to support TA include the rarity of the population, a mechanism of action supported by strong scientific rationale and/or preclinical data that identifies a well-defined population, the degree of unmet need, a high and durable RR, location of the tumor and likelihood of symptom or functional improvement, and other context-dependent considerations that are associated with an overall positive benefit-risk profile.[17,19,22,23] **Table 2**[24-29] provides several examples of drugs that received TA based on SATs. The safety profile must be well characterized, and several of the indications granted TA based on SAT were for already-approved drugs with well-understood safety profiles. While there is no requirement for a confirmatory trial to verify efficacy for drugs receiving TA, FDA maintains routine pharmacovigilance to ensure efficacy and safety in the postmarketing setting.

Targeted therapies for rare subpopulations based on molecular and genomic drivers of disease are often studied in SATs. Recent advancements in identifying and implementing molecular and genomic biomarkers have allowed enrichment of histology-defined cancer populations with selection biomarkers, which has been associated with a demonstration of improved efficacy in the biomarker-selected populations that were greater than with previous standards of care. For example, non–small-cell lung cancer (NSCLC) has undergone substantial reclassification based on molecular and genomic characteristics that has been followed by the development of numerous innovative targeted therapies. The high durable RRs that were seen in the early development of NSCLC-targeted therapies illustrate the challenges with requiring RCTs with OS end points in contemporary drug development. Population-level mortality from NSCLC in the US decreased from 2013 to 2016, which coincided with the approval of several immunotherapy and targeted therapies that were granted initial FDA approval based not on OS, but on durable RR as assessed in SATs.[30,31]

Single-arm trials can be an important source of evidence, but this approach has limitations that must be considered (**Table 3**). Because SATs have no comparator arm, differentiating drug-related adverse events from those associated with the underlying cancer or other causes can be complicated. A focus on attaining the highest RR possible without adequately characterizing toxic effects in an SAT can have important implications on the assessment of overall benefit-risk as drug development progresses. For example, a recent oncologic drugs advisory committee[32] discussed classwide safety findings observed with phosphoinositide 3-kinase inhibitors in hematologic cancers. While several phosphoinositide 3-kinase inhibitors demonstrated durable RR in SATs, subsequent RCTs that evaluated these drugs in patients with indolent non-Hodgkin lymphoma or chronic lymphocytic leukemia raised concerns for potential detriments in OS due to increased toxic effects. Overall survival is not only an efficacy end point but also a safety end point, and because SATs cannot evaluate time-to-event end points, such as OS, this trial design is limited in its ability to evaluate accurate benefit-risk due to the absence of a control arm.[33] The FDA discourages use of SATs to assess this class of drug.

Identifying the optimal dose of drug in an SAT remains challenging, and while a lack of equipoise is one reason to not randomize patients to receive an inferior therapy, there is an opportunity to use RCTs to compare 2 or more doses or determine contribution of effect in a multiagent regimen. An early RCT that evaluates RR can be performed with prespecified dose-response analyses for dose selection, and the trial can be continued as an SAT thereafter, including patients who were treated with the selected doses and additional, newly enrolled patients.[34] The lack of a comparator arm may also make identifying a comparative data set to use for the presumed RR in a historical control difficult, particularly in molecularly defined and/or small patient populations.[19] There is also no standard for what constitutes clinically relevant thresholds for durable RR end points. Clinical and regulatory decision-making include several other considerations, including the number of complete responses, magnitude of increase in response, and location of the responses.[35]

Response rate may not be a surrogate or even a correlate for OS. While many approvals based on RR in SATs of targeted therapies and cytotoxic drugs have predicted substantial improvement in PFS or survival observed in subsequent trials,[13] this has not always been the case, and is notable with the anti–programmed cell

death (PD) 1 and anti–PD ligand 1 antibodies. Our recent evaluation of AA found that 9 checkpoint inhibitor AAs based on SATs with RR as an end point did not achieve results that verified benefit in confirmatory trials.[36,37] While these are clearly active drugs, results from SATs that demonstrate low but durable RRs for this drug class may not be a good predictor of long-term outcomes, and FDA discourages the use of SATs to support approval for this drug class when RR is low to moderate in magnitude.[36]

Randomized clinical trials, when feasible, are preferred vs SATs for evidence generation due to their ability to account for known and unknown prognostic and clinical factors. While not a regulatory requirement, sponsors should approach the FDA early in development to discuss the rationale for use of a SAT design to support an approval decision. In cases in which RCTs are feasible, unjustified pursuit of an SAT design may potentially delay initiation of an RCT, when more robust data can be generated and more patients can potentially benefit. Importantly, AA need not be relegated to the SAT context. A randomized trial that incorporates predefined statistical testing procedures could be designed to detect early efficacy by assessing RR at an interim analysis to potentially support AA. Longer-term follow-up of the same trial could serve as the confirmatory trial, with PFS or OS and longer-term safety data used to characterize the benefit-risk profile and support subsequent conversion to TA.

Conclusions

We are in the midst of a period of growth in oncology drug development in which therapies are being made available to patients with incurable diseases that have limited or no treatment options in much shorter time frames than in the past. An increasing understanding of cancer biology has been followed by the development of more targeted investigational agents that select patients who are most likely to benefit, which are often associated with deep and durable RRs in smaller biomarker-defined populations. While SATs continue to demonstrate their use as a valuable tool to evaluate and approve cancer therapies, RCTs remain the preferred approach in clinical investigation and are the preferred design to support the approval of new anticancer therapies.

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REFERENCES

1. Pazdur R. Endpoints for assessing drug activity in clinical trials. *Oncologist*. 2008;13(suppl 2):19-21. doi:10.1634/theoncologist.13-S2-19

2. US Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. Accessed May 4, 2021. https://www.fda.gov/media/71195/download

3. Estey E, Hoth D, Simon R, Marsoni S, Leyland-Jones B, Wittes R. Therapeutic response in phase I trials of antineoplastic agents. *Cancer Treat Rep*. 1986;70(9):1105-1115.

4. Decoster G, Stein G, Holdener EE. Responses and toxic deaths in phase I clinical trials. *Ann Oncol*. 1990;1(3):175-181. doi:10.1093/oxfordjournals.annonc.a057716

5. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. *N Engl J Med*. 2005;352(9):895-904. doi:10.1056/NEJMsa042220

6. Roberts TG Jr, Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. *JAMA*. 2004;292(17):2130-2140. doi:10.1001/jama.292.17.2130

7. Waligora M, Bala MM, Koperny M, et al. Risk and surrogate benefit for pediatric phase I trials in oncology: a systematic review with meta-analysis. *PLoS Med*. 2018;15(2):e1002505. doi:10.1371/journal.pmed.1002505

8. Adashek JJ, LoRusso PM, Hong DS, Kurzrock R. Phase I trials as valid therapeutic options for patients with cancer. *Nat Rev Clin Oncol*. 2019;16(12):773-778. doi:10.1038/s41571-019-0262-9

9. Schwaederle M, Zhao M, Lee JJ, et al. Association of biomarker-based treatment strategies with response rates and progression-free survival in refractory malignant neoplasms: a meta-analysis. *JAMA Oncol*. 2016;2(11):1452-1459. doi:10.1001/jamaoncol.2016.2129

10. Chakiba C, Grellety T, Bellera C, Italiano A. Encouraging trends in modern phase 1 oncology trials. *N Engl J Med*. 2018;378(23):2242-2243. doi:10.1056/NEJMc1803837

11. Prowell TM, Theoret MR, Pazdur R. Seamless oncology—drug development. *N Engl J Med*. 2016;374(21):2001-2003. doi:10.1056/NEJMp1603747

12. Dahlberg SE, Shapiro GI, Clark JW, Johnson BE. Evaluation of statistical designs in phase I expansion cohorts: the Dana-Farber/Harvard Cancer Center experience. *J Natl Cancer Inst*. 2014;106(7):dju163. doi:10.1093/jnci/dju163

13. US Food and Drug Administration. Guidance for industry: expedited programs for serious conditions—drug and biologics. Accessed August 12, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

14. Blumenthal GM, Kluetz PG, Schneider J, Goldberg KB, McKee AE, Pazdur R. Oncology drug approvals: evaluating endpoints and evidence in an era of breakthrough therapies. *Oncologist*. 2017;22(7):762-767. doi:10.1634/theoncologist.2017-0152

15. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Accessed June 1, 2022. https://www.accessdata.fda.gov/scripts/cder/daf/

16. US Food and Drug Administration. Advanced prostate cancer: developing gonadotropin-releasing hormone analogues. Accessed June 1, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/advanced-prostate-cancer-developing-gonadotropin-releasing-hormone-analogues-guidance-industry

17. Blumenthal GM, Pazdur R. Response rate as an approval end point in oncology: back to the future. *JAMA Oncol*. 2016;2(6):780-781. doi:10.1001/jamaoncol.2015.6352

18. Kurzrock R, Stewart DJ. Equipoise abandoned? randomization and clinical trials. *Ann Oncol*. 2013;24(10):2471-2474. doi:10.1093/annonc/mdt358

19. Simon R, Blumenthal GM, Rothenberg ML, et al. The role of nonrandomized trials in the evaluation of oncology drugs. *Clin Pharmacol Ther*. 2015;97(5):502-507. doi:10.1002/cpt.86

20. Beaver JA, Howie LJ, Pelosof L, et al. A 25-year experience of US Food and Drug Administration accelerated approval of malignant hematology and oncology drugs and biologics: a review. *JAMA Oncol*. 2018;4(6):849-856. doi:10.1001/jamaoncol.2017.5618

21. US Food and Drug Administration. Guidance for industry: postmarketing studies and clinical

trials—implementation of section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. Accessed August 12, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-studies-and-clinical-trials-implementation-section-505o3-federal-food-drug-and

22. Code of Federal Regulations. Applications for FDA Approval to market a new drug. Accessed March 31, 2022. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-H/section-314.510

23. Fleming T, Sekeres M, Lieberman G, et al. Development paths for new drugs with large treatment effects seen early. Accessed June 1, 2022. https://www.focr.org/sites/default/files/Panel4FINAL11411.pdf

24. US Food and Drug Administration. Xalkori (crizotinib). Accessed June 1, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202570s016lbl.pdf

25. US Food and Drug Administration. Erivedge (vismodegib). Accessed June 1, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203388lbl.pdf. Accessed June 1, 2022.

26. US Food and Drug Administration. Koselugo (selmetinib). Accessed June 1, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213756s000lbl.pdf

27. US Food and Drug Administration. Keytruda (pembrolizumab). Accessed June 1, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s066lbl.pdf

28. US Food and Drug Administration. Elzonris (tagraxofusp-erzs). Accessed June 1, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761116s000lbl.pdf

29. US Food and Drug Administration. Lumoxiti (moxetumomab). Accessed June 1, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761104s000lbl.pdf

30. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med*. 2020;383(7):640-649. doi:10.1056/NEJMoa1916623

31. Singh H, Pazdur R. Contribution of early clinical benefit end points to decreased lung cancer mortality rates. *JAMA Oncol*. 2021;7(6):829-830. doi:10.1001/jamaoncol.2020.8090

32. US Food and Drug Administration. Oncologic drugs advisory committee meeting April 21-22, 2022. Accessed June 1, 2022. https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-information-april-21-22-2022-meeting-oncologic-drugs-advisory-committee-meeting-announcement#event-materials

33. Richardson NC, Kasamon Y, Pazdur R, Gormley N. The saga of PI3K inhibitors in haematological malignancies: survival is the ultimate safety endpoint. *Lancet Oncol*. 2022;23(5):563-566. doi:10.1016/S1470-2045(22)00200-5

34. Shah M, Rahman A, Theoret MR, Pazdur R. The drug-dosing conundrum in oncology—when less is more. *N Engl J Med*. 2021;385(16):1445-1447. doi:10.1056/NEJMp2109826

35. Pazdur R. Response rates, survival, and chemotherapy trials. *J Natl Cancer Inst*. 2000;92(19):1552-1553. doi:10.1093/jnci/92.19.1552

36. Beaver JA, Pazdur R. "Dangling" accelerated approvals in oncology. *N Engl J Med*. 2021;384(18):e68. doi:10.1056/NEJMp2104846

37. US Food and Drug Administration; Oncologic Drugs Advisory Committee. Notice of meeting: establishment of a public docket: request for comments posted. Accessed June 1, 2022. https://www.federalregister.gov/documents/2021/03/12/2021-05202/oncologic-drugs-advisory-committee-notice-of-meeting-establishment-of-a-public-docket-request-for