Life Years Gained From the FDA Accelerated Approval Program in Oncology: A Portfolio Model

Ágnes Benedict, MSc, MA¹; Gábor Szabó, MSc²; Kinga Marczell, PhD²; Bridget Doherty, MPH³; and Silas Martin, MSc³

Abstract

Background: Although the FDA Accelerated Approval Program (AAP) has come under scrutiny, the population-level health benefit of the program has not been quantified. Therefore, the objective of this study was to estimate the number of life years gained among patients with cancer that can be attributable to the therapies receiving FDA accelerated approvals in oncology between 2006 and 2022 in the United States. Methods: The data sources used were FDA listings, FDA approval letters and labels, published clinical trial data and other publications including relative effectiveness estimates, and the Ipsos Oncology Uptake Tool for product uptake. Data for 130 oncology treatments approved by the FDA under the AAP were extracted and validated. We developed a decision analytic model to estimate the survival gain for each indication and to accumulate life years gained for consecutive cohorts of patients receiving the therapies. Life year gains were estimated with and without the AAP, and the incremental life years gained were attributed to the program. Results: The analysis estimated that through December 2022 in the United States, the program gained approximately 263,000 life years across 69 products for which overall survival data were available, for approximately 911,000 patients with cancer. Conclusions: Policy discussions about the AAP cannot be complete without assessing its impact on its most important target outcome: patient survival. To date, there has been no estimation of the life year gain delivered by the AAP. Our research shows that substantial number of life years were gained for patients with high unmet need by the cancer therapies approved through the program.

Background

The FDA established the Accelerated Approval Program (AAP) in 1992.¹² The AAP was codified in 2012 under Section 901 of the FDA Safety and Innovation Act, amending the Federal Food, Drug, and Cosmetic Act (FD&C Act), which contains the rules of drug approval processes and FDA procedures.¹

The AAP was instituted to address unmet medical need by allowing earlier approval of drugs that treat serious conditions that typically do not have highly effective treatment options currently available based on surrogate endpoints.⁷ A surrogate endpoint is used in clinical trials on the assumption that it is a predictor of clinical benefit. It can be a laboratory measurement, a radiographic image, a physical sign, or another measure considered to predict clinical benefit adequately.⁴ The FDA decides whether to accept a proposed surrogate or intermediate clinical endpoint based on scientific evidence supporting the endpoint. Using a surrogate endpoint is especially advantageous when clinical outcomes take a long time to study.⁵ For example, under the AAP, the FDA can approve a treatment for cancer based on evidence that the drug shrinks the tumor, because such shrinkage is a predictor of real clinical benefit.

Manufacturers of AAP drugs are required to produce data establishing that a surrogate endpoint is “reasonably likely” to predict a drug’s intended clinical benefit. Postmarketing confirmatory studies must be conducted to verify the clinical benefit of the product. The FDA may withdraw or change the labeled indication of an AAP drug if the postmarketing confirmatory trials fail to verify the clinical benefit or do not demonstrate a sufficient clinical benefit to justify the risks associated with the drug (eg, a significantly smaller magnitude or duration of benefit than anticipated based on the observed effect on a surrogate).⁵

Approving therapies via surrogate clinical endpoints enables patients suffering from life-threatening diseases to receive potential life-changing therapies much sooner than with traditional approval based on patient survival. As the FDA AAP regulations specifically recognize, it is exactly the fatal diseases where patients and physicians are generally willing to accept greater level of risks and uncertainty.

Several recent papers have reported on the success and limitations of the AAP.⁶–⁸ However, a population-level assessment of the clinical benefit obtained via the AAP is urgently needed before addressing policy action to alter the program.

The objective of the current work is to estimate the clinical benefit of the FDA AAP by modeling the number of life years gained (LYG) by patients with cancer using drugs with accelerated approvals (AAs) relative to the standard of care (SoC). The focus on oncology was driven by its frequency in the AAP, accounting for 66% of all approvals since 1992 and 80% of approvals since 2006,¹⁰ and interest for policymakers as indicated by multiple papers recently published.⁶–⁸ From a modeling perspective, narrowing down the analysis to the oncology therapeutic area alleviates some of the computational burden; established methods used to model cancer therapies are relatively simple. Furthermore, the high frequency of AAP utilization for oncology treatments provides several data points to enable a robust analysis for informing policymakers on this important topic.

¹Evidera/PPD, Vienna, Austria; ²Evidera/PPD, Budapest, Hungary; and ³Janssen Scientific Affairs, Titusville, New Jersey.

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Methods
Modeling Approach
A model (Figure 1A) was developed to calculate the incremental LYG accumulated by cohorts of patients receiving AA products rather than the SoC they would have received in an unobserved counterfactual scenario with no AAP in place. The model uses a partitioned survival model with 2 health states: alive and dead. A simplified illustration of the flow of patient cohorts and accumulation of overall survival (OS) benefit is presented in Figure 1B and is described in the following sections.

Patient Cohorts and Time Horizon
The analysis considers cohorts newly starting an AA treatment who would not have received that therapy without the AAP. Ideally, these cohorts are those initiating the AA treatment between the AA date and when regular approval (RA) would have occurred in the counterfactual scenario with no AA. As the latter date is unknown, it is approximated with the observed time of RA in the base case analysis, and alternative dates are explored in scenario analyses by assuming that the RA would have happened earlier or later than in reality. Patients starting therapy after RA date are excluded, reflecting an implicit assumption that they could have received the treatment based on the RA in the counterfactual scenario too. For products that have not yet been converted, the RA date in the counterfactual scenario is set to AA date plus 36.8 months (ie, the calculated average time between AA and RA for all other oncology products).

Each cohort is tracked from model entry until December 31, 2022, in the base case, irrespective of the time of RA. This corresponds to the implicit assumption that the treatment course of patients receiving SoC is not disrupted due to the availability of a new drug on the market. Cohort sizes are based on observed product uptake.

Estimation of Survival Gain for Patients
For the counterfactual scenario, zero uptake is assumed before RA, and patients receive SoC instead. For cohorts entering each calendar month, the model tracks OS with the treatment and with SoC. The proportion alive is multiplied by the cohort size each month, thereby accumulating the months lived. Finally, the model calculates the difference between the life years accumulated with the new FDA AAP therapy versus those accumulated with the SoC (Figure 1B).

Clinical trials usually report the median OS obtained from Kaplan-Meier survival estimators. However, because the objective was to accumulate LYG for each cohort, an area under the curve (AUC) approach (blue-colored areas in Figure 1B) is more appropriate than assigning the median OS gain to all patients. Because the model estimates OS for 69 active and control treatment pairs, digitizing OS curves and fitting a distribution was simplified: the AUC was estimated by fitting an exponential curve through the median OS. When OS data were available but medians were not reached, other milestones (eg, OS estimates at 24 months follow-up) were used

Figure 1. Time horizon, uptake in observed and counterfactual scenario, and illustration of accumulating life year gain of an indication. (A) Uptake of a new therapy is assumed to be the same in both the observed and unobserved counterfactual scenarios (see light purple shaded area after RA). Therefore, the model takes into account patients who start therapy between the AA and RA date. There is no new cohort after RA, but cohorts starting before the RA date will have some follow-up time (see panel B). In the counterfactual scenario, patients who received the new therapy between the AA and RA date would receive the SoC. The model sets a hypothetical RA date for products that have not yet converted to the AA date plus the average time to approval for the rest of the products (36.8 months). Abbreviations: AA, accelerated approval; RA, regular approval; SoC, standard of care.

(continued on next page)
for fitting the exponential distribution. When a milestone was only available for SoC or the novel therapy, a published OS hazard ratio (HR) comparing the AA therapy versus SoC was used to estimate OS. For products where crossover-adjusted HR was available, it was used, but the reported gain may underestimate real OS gain due to lack of crossover adjustment in the reported results.

In an alternative calculation scenario (“lump sum”), median OS difference between AA product and SoC either directly reported or estimated using the exponential distribution (as described earlier) was assigned to each cohort. This method was only applied in a scenario analysis and only to cancers with <36 months’ median OS for SoC or AA therapy.

Given multiple sources for OS data, median OS values from the same source for both treatment and SoC were selected, with a preference for the more mature data from the RA trial, and in some cases for the mature AA trial to be aligned closely with the original AA indication, resulting in the use of a mix of AA and RA trial results (see Table S1 in the supplementary materials, available online with this article).

A list of assumptions appears in Table 1, along with an assessment of their impact on the results. Some assumptions were tested in scenario analyses. The model is implemented in Microsoft Excel with Visual Basic for Applications.

**Data**

**Oncology Therapy Approvals**

All oncology therapy AAs between January 1, 2006, and June 30, 2021, were reviewed regardless of their final approval status. A 15-year timeframe was selected to include most cancer therapies without returning to the chemotherapy era.

Data concerning the AA indications were extracted from the FDA Center for Drug Evaluation and Research (CDER) AA Database as of December 31, 2021, and from the FDA Oncology AA Database compiled from tables of ongoing, verified, and withdrawn AA indications.

Data related to AA and RA dates and exact indications for each indication/therapy pairs were extracted up until June 10, 2022.

The final dataset (see Supplementary Figure S1 for inclusion/exclusion criteria) contained 130 oncology indications with 57 verified (converted), 55 ongoing, and 18 withdrawn AAs as of June 10, 2022.

**Procedural Data**

For AAs, the postmarketing requirements are set by the FDA (presumably following discussion between the sponsor and the FDA) along with an expected submission date of confirmatory trial results. To determine whether a submission was late, the expected...
Table 1. List of Main Assumptions

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Impact on Estimated LY Gain of AAP</th>
<th>Justification/Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS gain is adequately captured by the difference between exponential survival curves</td>
<td>Indication-dependent</td>
<td>Exponential curves can be fitted using one parameter; does not imply long tail, and will be a reasonable fit for fast-progressing cancers</td>
</tr>
<tr>
<td>OS gain is accumulated continuously instead of assigned up-front for each patient</td>
<td>Downward</td>
<td>Tested in the “lump sum” approach, if each patient receives the full OS gain expected at the time of start of therapy, our estimated LY gains increase</td>
</tr>
<tr>
<td>SoC remains the same during the time interval between the AA and the RA</td>
<td>Upwards</td>
<td>To the extent other innovative therapies became available through RA that would replace the SoC, the OS gain would be overestimated</td>
</tr>
<tr>
<td>The RA would have occurred approximately at the same time regardless of the AA</td>
<td>Possibly upwards</td>
<td>In all cases, the approval letters specified the trial to be used for the RA, and these have already been ongoing, minimizing the room for influencing the time of publishing RA results (alternative assumptions about different counterfactual RA times are tested in scenarios)</td>
</tr>
<tr>
<td>Survival gain for patients in ongoing and late indications was only assumed to be 36.8 months</td>
<td>Downward compared with no cutoff</td>
<td>The model does not reward therapies that have not converted on time; cutoff applied is the average time to conversion, which is likely conservative</td>
</tr>
<tr>
<td>Patients who received the AA therapy before RA would not have been eligible for or would not have received the benefit of the therapy had they started it after RA</td>
<td>Upwards</td>
<td>Many cancers are in advanced stage and have short survival; it is likely that if a patient received some other therapy before the product’s RA, the patient would not have switched therapy just because RA happened, but rather could only get it in a later line</td>
</tr>
<tr>
<td>The AA has no impact on the choice of newly initiated treatments beyond the time of RA</td>
<td>Downward</td>
<td>After RA, uptake may take a while, even if it may be faster than after an AA; therefore, this is likely a conservative assumption</td>
</tr>
<tr>
<td>Uptake data adequately represent the number of patients treated in the United States</td>
<td>Neutral/Downward</td>
<td>Delays are observed in tracking new therapies in Ipsos; for smaller indications, samples indicate gaps (periods with zero patients in between)</td>
</tr>
</tbody>
</table>

Abbreviations: AA, accelerated approval; LY, life years; OS, overall survival; RA, regular approval; SoC, standard of care.

submissions dates for confirmatory trial results were collected from the Project Confirm website for ongoing trials; for verified (converted) and withdrawn indications, they were collected from FDA letters written to the sponsor at the time of the AA. Information concerning breakthrough and orphan designations of the therapies were extracted.

Clinical Data

The primary sources of the efficacy data were the “clinical studies” sections of FDA labels published in their current format since 2007. These sources include relevant clinical trial results at the time of the drug’s initial AA and/or RA.

For OS data, trial results published on ClinicalTrials.gov and peer-reviewed publications were collected. If unavailable, the OS results were extracted from other sources, such as various oncology conference abstracts (eg, ASCO, ESMO), published health technology assessments, or, in rare cases, real-world evidence.

OS results were collected from the trials supporting AA and RA, covering multiple data timepoints; the most mature reported trial OS data were used. OS data were available for 69 of 130 indications. OS data were available for 50 of 57 converted AAs (Figure 2). Among withdrawn indications, OS was available for 12 of 18, and 7 of 55 ongoing indications contributed data to the model.

Importantly, for ethical and other practical reasons, RA trials are often conducted in an indication that differs from the original AA indication. Even within this group, the RA trial may report results for the population in the AA indication. This is not only
possible when the AA and RA indications are identical. In some cases, the RA was provided for a narrower population than the AA, yet data were available to represent the entire AA population because the RA trial covered a broader population than the RA label. In other instances, the AA indication was broader than the RA indication, but the RA trial publications reported results for the AA label’s subgroup. When OS data were only available in an indication that differed from the original AA, these were used to calculate OS. The relationship between the 69 AA and RA indications/trial populations was categorized as (1) having very good overlap between AA indication and trial results used for the calculation (51%), either because (i) mature AA trial results were used for confirmation, (ii) only the original AA trial results were available, or (iii) the RA trial reported on a population very similar to that in the AA trial; (2) a “line change down” (ie, the confirmatory trial was conducted in an earlier line of therapy [26%]); or (3) other changes (23%), such as from monotherapy indication to combination therapy, combined with a line change down; a broadening or narrowing of the patient population; a “biomarker change”; or a “line change up” (see Supplementary Table S2).

Based on the information collected regarding the expected submission dates and an assumed 90-day time frame needed for an FDA revision, 40 of 55 ongoing indications (84%) were categorized as “not yet due” as of June 10, 2022. Therefore, these indications were not expected to have any OS data at the time of writing. Of 50 converted AA indications, in 3 cases 2 drugs in combination received AA for a given indication. To avoid double-counting, only one of the drugs was used in the model to calculate the benefits.

**Market Data**

Market data concerning uptake were obtained to estimate the number of patients benefiting after the drug received AA. Number of patients newly starting a therapy each month after AA date was extracted from the Ipsos Oncology Uptake Tool (see Supplementary Figure S2), which includes data on oncology indications and their treatments spanning back to 2004. Uptake was extracted for AA indications (and not the possibly different RA indications), specific to tumor type, line of therapy, biomarkers, and combination versus monotherapy.

Of 69 indications with OS data, 3 had no uptake information due to very small populations in the approved indications; for 2 indications, data collection started after the RA date. For AAs based on trials including multiple tumor types, Ipsos data only cover the major cancer sites (lung and colon). For therapies without confirmation, uptake was only taken into account for 36.8 months (ie, the average time from AA to RA for the 57 converted products).

Overall, between January 2006 and December 2021, approximately 3.3 million people started therapies that received AA. Between the AA and RA date of each intervention, that number narrows to 1.1 million people, and ultimately, 910,757 patients were estimated to receive the 69 modeled interventions that had corresponding OS data (see Figure 2 and Supplementary Figure S2).

**Results**

The base-case analysis includes all oncology AA indications with analyzable OS data regardless of their conversion status (69 as of June 10, 2022; see Supplementary Table S2). The model uses the latest available OS data (mostly from RA trials and, in some cases, AA trials; see Supplementary Table S1), and for the counterfactual scenario it assumes that RA would occur at the same time as it originally happened.

It was estimated that by end of 2022, 263,378 life years were accrued overall for 910,757 patients with cancer who initiated an AA therapy before the RA date. The total is composed of total net life years, including those lost for patients with triple-negative breast cancer on AA therapies that eventually proved inferior to SoC (−3,027) and the large gains for patients in other indications, with the highest number of LYG (73,667) in non-small cell lung cancer (Figure 3 and Supplementary Table S3).

Scenario analyses assuming that all products have worse or better OS results, varied according to the 50% confidence limits of the HR, showed that results would range between 147,917 to 367,834 LYG. Allowing accumulation of benefits until 2026 and 2030 increased the number of LYG by 45.2% and 82.0%, respectively (Table 2). If RA were 3 or 6 months later (or to similar effect, the start of uptake following RA would be delayed) in the counterfactual scenario, the number of patients benefitting from AA therapy increased by 12.5% or 24.9% and the number of LYG increased by 21.3% or 41.4%, respectively. If RA in the counterfactual situation occurred 3 months earlier, LYG and number of patients would drop by 18.4% and 11.9%, respectively. A scenario combining the more favorable AAs with ≥6 months of use and time horizon extended to 2026 and a scenario combining the upper limit of OS HRs with a limited time horizon for benefit accumulation are also presented.

Examining AA by approval status indicates that most LYG are brought about by fully approved products (Table 2). The 12 withdrawn indications have on average a small benefit. Overall, 5 products are included with negative LYG. Ongoing assessments that have survival data in the public domain contribute 5% of the results (38,429 LYG) impacting only approximately 4% (13,212 LYG) of patients, partly due to the limited time for uptake. Relative to SoC, the subgroups of 41 AAs with orphan designation and 26 with breakthrough therapy designation resulted in the highest life years gained. The 24 hematology indications comprise 20 orphan indications, and therefore these results are relatively similar.

A subgroup analysis was conducted including only advanced cancers with a median life expectancy of <4 years (“fast-progressing cancers”), because the exponential distribution assumption is more tenable in these indications. Running this analysis increases the proportional LYG to 16.2% (212,074 LYG). When median OS is immediately assigned to patients (“lump sum”), LYG increased to 454,916 (35.2%).

**Discussion**

**Interpreting Results**

In the most comprehensive analysis to date, we estimate that AA of cancer products between 2006 and 2021 contributed approximately 263,000 additional life years in approximately 911,000 patients who received these therapies before RA. Extending the time horizon to 2026 would increase LYG to approximately 382,000 years.

A wide range of cancer drugs were approved in the FDA AAP in the selected time frame, including a small group of chemotherapy, several targeted therapies, antibody–drug conjugates, and immunotherapies across 44 different cancer types.
This analysis incorporated cancer therapies with an AA regardless of the final outcome, including all withdrawn indications. It calculated the benefit for patients newly starting therapy in the AA indication between AA and RA, and for yet unapproved products, for a limited amount of time.

Extensive data collection covered each AA in detail, including letters of approval, FDA labels, populations and outcomes of trials cited for AA, and the confirmatory trials, including their long-term follow-up. A standardized methodology was applied throughout to be consistent across products. The impact of assumptions was considered in Table 1.

Behind the standard methods, each approved indication has its unique story. The indications covered rare and fast-progressing late-line cancers, such as persistent, recurrent, or metastatic cervical cancer with a median OS of 16 months with 6 months of improvement in life-expectancy for approximately 3,600 patients, and therapies for slow-progressing cancers, such as the tyrosine kinase inhibitors for approximately 40,000 patients with chronic myeloid leukemia. All 5 indications with point estimates for the OS HR > 1 were included, reducing the total estimated number of LYG. For completeness, indications that were omitted due to missing OS data were tabulated (Supplementary Table S4). Although OS data were not identified in the published literature for 13 of the converted or withdrawn therapies, their extent of use was established. Approximately 46,800 patients used the 7 products that were converted, but had no OS data available, mostly because the studies were single-arm trials. Overall, 7,750 patients used the 6 therapies that were eventually withdrawn and had no OS data, representing only approximately 0.7% of the total population that used AAs.

Strengths and Limitations

Benefits of therapies were quantified in terms of LYG, the ultimate outcome of interest. The LYG were accumulated continuously for the cohorts, up to a cutoff date—a more accurate approach than assigning the median gain compared with SoC to all patients. Furthermore, if available, the OS data from the confirmatory trial were selected for the population closest to that in the AA.

Identifying OS data required extensive research and relied on the fact that in almost all cases, the FDA’s letters of approval identified the trial that would serve as the confirmation of the AA. Decisions were well documented (Supplementary Table S1), and the analysis is reproducible based on that documentation. Actual uptake based on chart reviews for very specific indications were used instead of relying on prescription data, which are not linked to an exact indication. Furthermore, some relatively prevalent indications lack market share data (Supplementary Figure S3), and for the not-yet-converted indications, the uptake was only included for approximately 3 years rather than their full duration, truncating the time frame for indications with very long trials/time to conversion. Therefore, the number of patients benefitting from the program was underestimated. Furthermore, we assumed no additional time to a peak uptake after the RA, even though it is likely that uptake after RA is not immediate. Lastly, the counterfactual assumes that RA occurs at the same time as following an AA, which may be conservative given that RA trials are ongoing at time of AA and their assessment may be faster due to familiarity with the therapies.

The model has several limitations. The exponential distribution may not be the optimal fit to cancer survival data, but use of other distributions would require additional data points or assumptions. For fast-progressing cancers, the exponential distribution is a reasonable approximation; for slow-progressing cancers with long median survival, the exponential may overestimate or underestimate LYG depending on the time course of the hazards. The model time horizon is limited, and therefore the LYG estimate is truncated. Modeling OS by digitizing survival curves and finding the best fitting distribution was beyond the scope of this study. LYG is a patient-relevant metric that can be easily operationalized. Its disadvantage is that it does not incorporate health-related quality of life impact of...
therapies. Modeling health-related quality of life associated with conditions and with adverse events of therapies was beyond the scope of this study. Because new therapies replacing chemotherapies have favorable safety profiles, the impact of the latter may be small. However, quality of life with advanced oncology is often severely impaired, and therefore the impact in terms of quality-adjusted life years is likely smaller.

The Ipsos data had gaps for some indications and small samples for some late-line cancers (see Supplementary Figure S3). For several products, some months had zero uptake, with positive values in the months before and after, likely biasing the estimation downward. Using OS data for the RA indication that is in an earlier line compared with the AA indication in some instances may bias the LYG results upwards. Finally, the model did not include costs associated with new therapies, and therefore did not consider the full opportunity cost of AAs, leaving the question of value for money for future research.

### Conclusions

Policy discussions about AAP are incomplete without assessing its impact on survival. To date, LYG due to AAP have not been estimated, presumably due to the lack of databases covering outcomes related to AAs. Any major change to the program should consider the impact on patient outcomes for groups with a high unmet need.

We have provided an assessment of the AAP as it played out between 2006 and 2022 in cancer-related indications. Our results are a snapshot in time, specific to the time frame examined, and...
may not be generalizable for the future; the oncology therapies approved now include cell and gene therapies with curative potential, and the program itself may be changing.

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Correspondence: Agnes Benedict, MSc, MA, QBC 4 - Am Belvedere 4, 1100 Wien, Austria. Email: Agnes.Benedict@evidera.com

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