
COST CONTAINMENT OF GLOBAL MONOCLONAL ANTIBODY DRUGS AND CANCER CLINICAL TRIALS VIA LLM FOCUSED REASONING

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ABSTRACT

Expenses related to monoclonal antibody drugs worldwide and cancer clinical studies must be reduced in order to increase pharmaceutical industry efficiency. These financial opportunities can be assisted using state-of-the-art Large Language Models (LLMs) for focused report generation and advanced reasoning of solutions and forecasts that are based on authors' original findings. Here, Claude 3.5 Sonnet utilized 45 articles totaling approximately 357,000 words to effectively generate 45 reports. OpenAI ChatGPT o3-mini processed 15 of the reports to obtain comprehensive monoclonal antibody (mAb) cost solutions and financial forecasts. This included a financial recommendation of mAb biosimilars for a 55.2 percent price per dose decrease vs. a bevacizumab biologic due to Japan financial incentives, as reported by Itoshima H. et al. The 30 additional reports were based on cancer clinical trial cost-effectiveness studies, with ChatGPT o3-mini reasoning to produce tables regarding economic strategies and projections. This included a "Total drug cost avoidance of "\$92,662,609" over 10 years" when sponsored clinical trial participation was employed for solid tumors using various mAb therapies, as detailed by Carreras M. et al. 2024. The primary advantages of this comprehensive approach were 1) Efficient report generations by 3.5 Sonnet of nearly 25,000 words in 20 minutes, 2) ChatGPT o3-mini's linear dependency prompt structure reduced narrative drift with structured outputs in less than 5 minutes, and 3) Ethical AI principles were strengthened: financial data was limited by rigorous prompts, yielding outputs that were highly traceable to source data using either LLM, as opposed to relying on the models' training data.

Keywords Cost-effectiveness · Monoclonal antibodies · Cancer clinical trials · LLM reasoning · Prompt engineering

1 Introduction

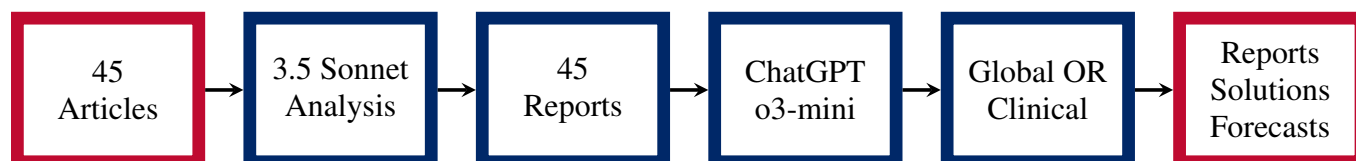


Figure 1: Simplified Report and Table Generations Process Diagram

The above process diagram represents the overall work flow in starting with complex and voluminous financial cancer drug articles, generating focused reports, and reasoning through reports to yield practical and standardized information. Guardrails such as de-identification of patient information relevant to GDPR, AI Act and HIPAA compliance were implemented; as well as structured report guidelines, and limiting LLMs only to information derived from pdfs and subsequent text generations strengthened ethical AI principles. In addition, two different LLM manufacturers were used to reduce compound bias throughout the process. LLMs continue to be utilized by researchers in efforts to decrease costs associated with drug searches, drug pair interactions, clinical trial protocol generations, and clinical trial patient matching.

Li T. et al. in February 2024 proposed a new model using a few-shot learning approach to predict the synergy of drug pairs in tissues that lack structured data and features. Their experiments involved rare tissues from different cancer types to demonstrate that their CancerGPT model achieved significant accuracy using approximately 124M parameters. This accomplishment was comparable to a larger fine-tuned GPT-3 model with approximately 175B parameters. The authors claimed their breakthrough had significant implications for drug development which may be used in a cost-effective manner [1].

Chaves J. et al. of Google Research in June 2024 introduced Tx-LLM as a generalist LLM fine-tuned from PaLM-2 that "encodes knowledge about diverse therapeutic modalities", and was based on 709 datasets targeting "66 tasks spanning various

stages of the drug discovery pipeline". The model "processes a wide variety of chemical or biological entities (small molecules, proteins, nucleic acids, cell lines, diseases)" to achieve competitive SOTA performance on 43 of 66 tasks [2].

Solovev G. et al. in December 2024 utilized a multi-agent pipeline for drug discovery of neurodegenerative diseases to address "end-to-end drug search complex tasks" with an accuracy of 92% on complex tasks compared to single LLMs achieving 71% on simple queries, which included GPT-4o, o1-mini, Claude 3.5 Sonnet, and Gemini 1.5 Pro. "We found that Llama-3.1-70b with an optimized system prompt was the best-performing model for routing agents (Figure 3). Notably, this model outperformed the strong baseline of o1-mini model and the newer generation Llama-3.2-90b, both of which also incurred higher costs." [3].

NVIDIA's Evo 2 LLM release in February 2025 improved on the previous generation model with "expanded data, enhanced architecture, and superior performance" to include all domains of life, and is based on a dataset of "8.85T nucleotides from 15,032 eukaryotic genomes and 113,379 prokaryotic genomes". The cutting edge 47B parameter model with a 1M token context length supports smarter generative drug design for more rational enzyme design and disease mechanism elucidation [4].

Google's AI co-scientist multi-agent system built on the Gemini 2.0 LLM released in February 2025 "is intended to help uncover new, original knowledge and to formulate demonstrably novel research hypotheses and proposals, building upon prior evidence and aligned to scientist-provided research objectives and guidance." The new innovation features "a tournament evolution process for self-improving hypotheses generation" for "drug repurposing, novel target discovery, and explaining mechanisms of bacterial evolution and anti-microbial resistance" that aims to work more efficiently, as "Phase III clinical trials can cost hundreds of millions of dollars" [5].

Regarding automating clinical trial protocol generations, Maleki M. et al. in April 2024 used GPT-4 and "Results demonstrated a significant improvement in protocol authoring, highlighted by increases in efficiency, accuracy, and the customization of protocols to specific trial requirements." "The gpt-4-turbo and gpt-4o models presented a more balanced approach, offering improved performance at a reduced cost compared to gpt-4 and gpt-4-1106-preview. With an annual cost of \$75,000, these models deliver better cost efficiency while still benefiting from the advancements in the GPT-4 series" [6]. Beattie J. et. al. in August 2024 used GPT-4 for screening a cohort of 54 patients using EHR data from a phase 2 clinical trial with head and neck cancer. Fourteen trial criteria were evaluated, with GPT-4 demonstrating a median accuracy of 0.838 (range: 0.758–0.886). GPT-4 took 12.4 minutes to screen a single patient, with costs of \$0.15–\$0.27 [7].

Shekhar A. et. al. in October 2024 utilized Fast Healthcare Interoperability Resources (FHIR's) and "advanced LLMs and Computer Engineering to streamline cancer clinical trials and discovery. By utilizing FHIR's resource-based approach and LLM-generated mCODE profiles, we ensure timely, accurate, and efficient sharing of patient information across disparate healthcare systems." "Our methodology involves transforming unstructured patient treatment data, PDFs, free-text information, and progress notes into enriched mCODE profiles, facilitating seamless integration with our novel AI and ML-based clinical trial matching engine." "The results of this study show a significant improvement in data standardization, with accuracy rates of our trained LLM peaking at over 92% with datasets consisting of thousands of patient data. Additionally, our LLM demonstrated an accuracy rate of 87% for SNOMED-CT, 90% for LOINC, and 84% for RxNorm codes. This improvement with LLMs such as GPT-4 and Claude's 3.5 peaking at an average of 77%" [8].

Rybinksi M. et al. in October 2024 included LLMs in an information retrieval pipeline for matching patients to clinical trials. The semantic processing capabilities of re-ranking with a fine-tuned LLM outperformed traditional methods in terms of nDCG and Precision measures [9]. Wornow M. et al. in December 2024 utilized LLMs for clinical trial patient matching that "evaluates a patient's medical history (as unstructured clinical text) against trial inclusion criteria (also specified as free text)". In this case, "a novel two-stage retrieval pipeline to reduce the number of tokens processed by up to a third while sustaining high performance." achieving "state-of-the-art performance on the 2018 n2c2 cohort selection challenge, the largest public benchmark for clinical trial patient matching" and was "coherent in 97% of correct decisions and 75% of incorrect ones." (Funded by the Clinical Excellence Research Center at Stanford Medicine and others) [10].

Datta S. et al. in January 2025 used GPT-4 to assist patients "with specific conditions to directly find eligible trials by completing disorder-specific questionnaires." "We obtained clinical trial eligibility criteria (from ClinicalTrials.gov) and simulated patient questionnaires (or topics) from the Text REtrieval Conference (TREC) 2023 Clinical Trials Track conducted by the National Institute of Standards and Technology (NIST), in which we also participated." "The system achieved an overall Precision@10 (proportion of relevant trials) of 0.7351 and NDCG@10 (considers ranking order of relevant trials) of 0.8109, indicating its effectiveness in retrieving ranked lists of suitable trials for patients. Notably, for eight out of 37 patient topics, all the top 10 retrieved trials were relevant. The system scored the highest on breast cancer (NDCG@10 = 0.9347, Precision@10 = 0.84) and the lowest on type 2 diabetes (NDCG@10 = 0.61, Precision@10 = 0.475)" [11].

Komandur R. et al. in February 2025 utilized Gemini Advanced and GPT-4 to evaluate "their ability to recapitulate the analysis of a clinical trial that evaluated LY2510924 in combination with carboplatin and etoposide for the treatment of extensive-stage small cell lung cancer (ES-SCLC)." "While LLMs could process the trial data and generate relevant insights, discrepancies were observed across the investigators' analyses, particularly in primary and secondary endpoints. One investigator found a significant improvement in PFS with LY2510924, contradicting other results. Variations in reporting objective response rate (ORR) and adverse event analyses also highlighted challenges in reporting between different LLMs" [12]. The reviews above typically did not thoroughly address mAb cancer drug costs and cancer clinical trial cost-effectiveness. Therefore, this study uses two appropriate LLMs for effective financial report and table production.

2 Methods

A literature study based on 8 monoclonal antibody related Google Scholar [13] searches screening 614 entries was conducted to obtain the 45 articles, as shown in Figure 3. Records excluded were based on document availability, license type, relevancy, and originality. 15 retrospective global cost studies and 30 retrospective clinical cost studies were identified. The resulting 45 articles are represented in Table 2, totaling 357,381 words. AI software used in this study were unmodified LLMs with generation times being obtained from a digital stop watch. 3.5 Sonnet was utilized with document retrieval of full article pdfs found only in Table 2 using the paper clip option and text prompts. Supplementary TRA is a traceability study of 279 human-in-the-loop verifications comparing output fidelity to inputs primarily regarding financial data. Each of the 15 reports for Part B were combined as plain text into the 9,022 word Dataset B15.

ChatGPT o3-mini processed text queries plus datasets. The LLM has a 200K token limit through "Pro" service (ChatGPT o3-mini-high model was not used). Prompts were first optimized with several text experiments for Parts B and C. Once the output quality was sufficient, a chain of prompts were then further optimized into a single conversation. Each of the 30 reports for Part C were combined as plain text into the 16,845 word Dataset C30. Supplementary B14G and C14G contain Part B and Part C generations. Supplementary TRB is a traceability study of 61 human-in-the-loop verifications comparing output fidelity to inputs primarily regarding financial data. Supplementary TRC is a similar traceability study of 61 Part C human-in-the-loop verifications. Generations shown here attempted to reproduce visual outputs presented by the LLMs. The author conducted experiments, analysis, and wrote the manuscript, with ChatGPT 4o and ChatGPT o3-mini primarily being utilized as a research tool. Author abbreviations: Jakovl. = Jakovljevic, Sripho. = Sriphoosanaphan, Khoirunn. = Khoirunnisa, Gunasek. = Gunasekara.

2.1 Large Language Models

1. 3.5 Sonnet: Claude website chat interface was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.205 (Official Build) (arm64) [14].
2. ChatGPT o3-mini: ChatGPT website pro subscription was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.205 (Official Build) (arm64) [15, 16].
3. ChatGPT 4o: ChatGPT website pro subscription was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.205 (Official Build) (arm64) [17].
4. Preliminary - ChatGPT o3-mini-high: ChatGPT website pro subscription was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.205 (Official Build) (arm64) [15, 16].
5. Preliminary - Gemini 2.0 Flash Thinking Experimental 01-21: Google AI Studio website chat interface was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.205 (Official Build) (arm64). Safety = block none for all. Temperature = 0.7, Top P = 0.95, Output length [max] = 65536 tokens. [18].

3 Part A Results: 45 Reports

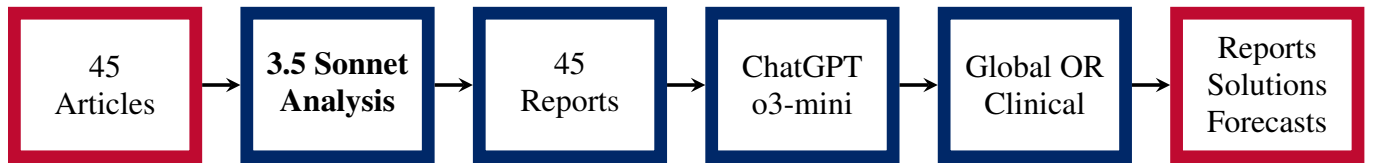


Figure 2: Standard A 3.5 Sonnet Process Diagram

Standard A: Monoclonal Antibody Cancer Cost Analysis Reports

Prompt A: Write a four page report based on the attached article regarding the authors' Monoclonal antibody cancer cost analysis using the following format: "Executive Summary", "Technical Details", "Key Insights". Only include results affecting mAb cancer economics, de-identifying any patient information if present. Cite values in \$ signs enclosed in quotation marks corresponding to the authors' names in this format Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the attachment throughout the report without adding additional quotations. [Single Article Attached] [Single Generation]

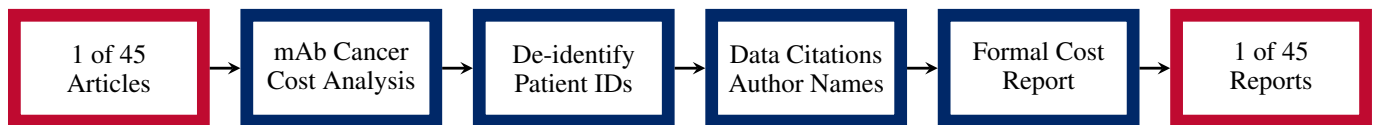


Table 1: Standard A Process Diagram

The literature search conducted across 614 entries using monoclonal antibody cancer drugs and general mAb searches provided the 45 retrospective global cancer drug and clinical articles, as shown in Figure 3. Authors, dates, word counts, subjects, and journals are shown in Table 2. Of interest for the first 15 articles were the variety of topics being covered such as biologic vs. biosimilar cost, evergreening, and a number of different mAb types. The clinical studies in articles 16-45 focused heavily on the type of mAb being used for respective cancer types. The sum of all articles was 357,381, with an average word count of 7,942 and a standard deviation of 2,411.

The process diagram in Figure 2 illustrates the 3.5 Sonnet LLM’s role in creating 45 focused reports for the later reasoning steps. The two pie charts in Table 3 illustrate words counts as slices for each author, while its table shows word counts and generation times for each focused report. The average report word count was 552 at a standard deviation of 62.7, while the average time was 26.06 seconds at a standard deviation of 3.11. Prompt A from Table 1 details the request for a four page report, structured format, and de-identification of patient information. Additional information regarding a strict format for financial information and author names was also included. The results from Traceability TRA Supplementary included 279 total input-output traces among the 45 reports.

There was one output that correctly included a summation of two article financial numbers, 4 in-context conversions of direct 1:1 EUR to USD conversions, 6 financial detail repetitions from earlier parts of reports, 1 abbreviation of financial information, and 1 incorrect conversion from Swedish Krona (SEK) to USD. An example generation of Report 06 at 537 words and 23.75 seconds with correct report format and financial information in quotations based on the Lu B. et al. article is shown in Table 4. Each of the 15 reports in Supplementary Dataset B15 had the correct report format with numerous financial information in \$USD. Each of the 30 reports in Supplementary Dataset C30 had the correct report format with numerous financial information in \$USD. Some reports in both datasets did not include the author’s name, but were included as headings in datasets by the manuscript author for the next two parts.

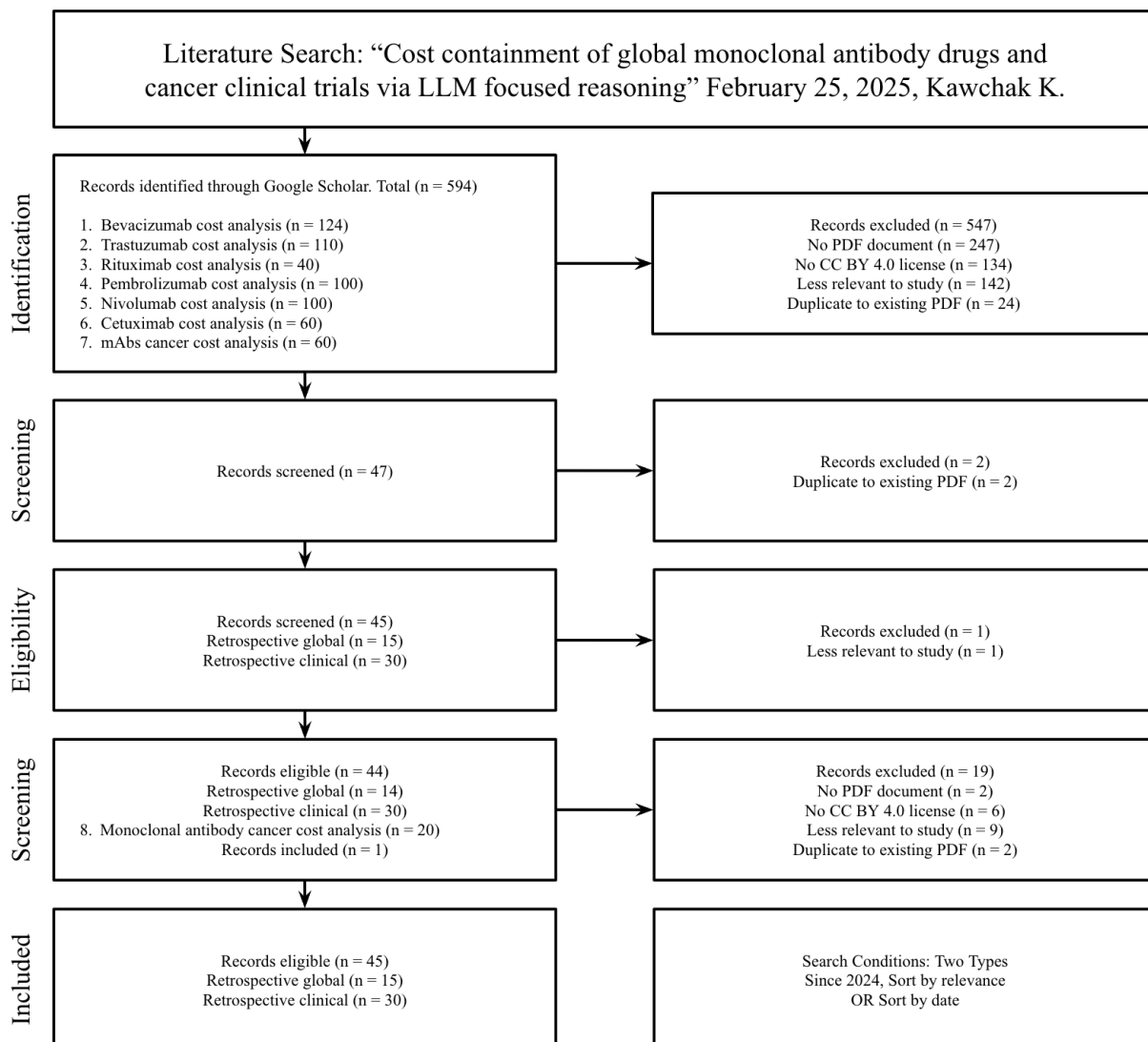


Figure 3: Literature Search Identifying 45 Articles

Articles 01-15: Global Monoclonal Antibody Cancer Cost-Effectiveness

Article	Authors	Date	Words	Subject	Journal
01	Feng K. et al. ^[19]	03/29/2024	6,500	Biologics vs. Biosimilars Cost	<i>JAMA Health Forum</i>
02	Chen H. et al. ^[20]	06/06/2024	8,153	Biologics vs. Biosimilars Cost	<i>PLoS One</i>
03	Itoshima H. et al. ^[21]	11/14/2024	7,117	Biosimilars Cancer Incentives	<i>PLoS One</i>
04	Kirshner G. et al. ^[22]	01/08/2024	10,912	Trastuzumab Evergreening	<i>Eur J Health Econ</i>
05	Wu Q. et al. ^[23]	10/05/2024	9,555	Trastuzumab Consumption	<i>Glob Health Res Policy</i>
06	Lu B. et al. ^[24]	08/09/2024	7,220	Bev Biosimilar vs. Biologic	<i>Value in Health</i>
07	Jakovl. M. et al. ^[25]	06/16/2024	16,377	20 Yr Breast/Prostate Cancer	<i>Cost Eff Resour Alloc</i>
08	Figallo M. et al. ^[26]	11/11/2024	7,889	PH FDC SC HER2 Min Cost	<i>PLoS One</i>
09	Hemati H. et al. ^[27]	12/17/2024	5,863	Trastuzumab-Emtansine Cost	<i>Iran J Pharm Res</i>
10	Otoya I. et al. ^[28]	05/31/2024	6,595	SC vs. IV Trastuzumab Cost	<i>Ecancermedicalscience</i>
11	Heine R. et al. ^[29]	02/01/2024	8,040	Pembro/Dara Ind. Expansion	<i>PLoS One</i>
12	Malmberg R. et al. ^[30]	11/01/2024	7,703	Pembro/Nivo Dose/Emission	<i>Lancet Planet Health</i>
13	Yeong S. et al. ^[31]	07/22/2024	9,520	Breast Cancer Cost Review	<i>Health Econ Rev</i>
14	Whitacre R. et al. ^[32]	01/24/2024	10,319	US Biopharma Shareholders	<i>Soc Sci Med</i>
15	Gentili N. et al. ^[33]	01/30/2024	8,941	Metastatic NSCLC Resources	<i>Cancers</i>

Articles 16-45: Clinical Monoclonal Antibody Cancer Cost-Effectiveness

Article	Authors	Date	Words	Subject	Journal
16	Lin Y. ^[34]	11/27/2024	7,808	Atezo/Bev Cervical Cancer	<i>Front Immunol</i>
17	Cai H. et al. ^[35]	10/21/2024	7,301	Atezo/Bev/Chemo Cervical	<i>Front Pharmacol</i>
18	Chen Z. et al. ^[36]	05/30/2024	3,825	Bev/Lomustine Glioblastoma	<i>Front Public Health</i>
19	Li Y. et al. ^[37]	01/08/2024	7,011	Bev/Chemo Colorectal Cancer	<i>Cancer Medicine</i>
20	Liang Y. et al. ^[38]	11/29/2024	5,161	ICI HPV/HIV Cervical Cancer	<i>Medicine</i>
21	Huang, L. et al. ^[39]	11/13/2024	6,319	FTD–TPI/Bev Colorectal Cancer	<i>Front. Public Health</i>
22	Gong H. et al. ^[40]	07/05/2024	10,116	ICI First Line Advanced HCC	<i>Health Econ Rev</i>
23	Sripho. S. et al. ^[41]	03/21/2024	6,887	Atezo/Bev Unresectable HCC	<i>PLoS One</i>
24	Broer L. et al. ^[42]	05/24/2024	15,514	Monoclonal Antibodies Review	<i>iScience</i>
25	Peng J. et al. ^[43]	10/18/2024	5,891	Sinti/Chemo Bev NSCLC Cost	<i>PLoS One</i>
26	Nguyen A. et al. ^[44]	03/15/2024	9,114	Adjuvant Trastuzumab HER2+	<i>PLoS One</i>
27	Gunasek. A. et al. ^[45]	07/20/2024	9,525	Neoadjuvant Dual HER2 Breast	<i>Scientific Reports</i>
28	Khoirunn. S. et al. ^[46]	05/24/2024	7,242	Trastuzumab HER2-Positive Cost	<i>PLoS One</i>
29	Landeiro L. et al. ^[47]	08/19/2024	10,743	HER2-Positive Systemic Therapy	<i>Front Pharmacol</i>
30	Lin Y. et al. ^[48]	01/11/2024	9,177	Pembro/Chemo Cervical Cancer	<i>Front Immunol</i>
31	Rieger C. et al. ^[49]	10/15/2024	5,509	Metastatic Urothelial Carcinoma	<i>EAU</i>
32	Lang W. et al. ^[50]	01/07/2025	7,458	Pembro/Chemo Mesothelioma	<i>Front Pharmacol</i>
33	Li A. et al. ^[51]	09/09/2024	5,636	EV/Pembro Metastatic UC	<i>Front Immunol</i>
34	Cheng M. et al. ^[52]	03/06/2024	9,423	Advanced Squamous NSCLC	<i>BMC Cancer</i>
35	Nie J. et al. ^[53]	01/24/2024	5,589	Pembrolizumab/Chemo NPC	<i>CERA</i>
36	You M. et al. ^[54]	09/26/2024	7,677	EV/Pembro Advanced UC Cost	<i>Front Pharmacol</i>
37	Yang X. et al. ^[55]	05/29/2024	7,251	ICI Advanced ESCC Cost	<i>BMC Cancer</i>
38	Yang L. et al. ^[56]	03/26/2024	6,160	ICI Metastatic Urothelial Cancer	<i>Front Pharmacol</i>
39	Xiang G. et al. ^[57]	09/13/2024	7,414	Nivo/Gem/Cis Advanced UC	<i>Front Immunol</i>
40	Meng K. et al. ^[58]	11/05/2024	5,125	Nivo/Gem/Cis Advanced UC	<i>Front Pharmacol</i>
41	Ye D. et al. ^[59]	03/21/2024	6,405	Nivo/Ipi EXTREME SCCHN	<i>Scientific Reports</i>
42	Li J. et al. ^[60]	01/27/2024	6,967	Serplu/Chemo Advanced ESCC	<i>CERA</i>
43	Xiang Z. et al. ^[61]	09/04/2024	6,055	Sinti/Chemo Advanced GC/GEJC	<i>Front Pharmacol</i>
44	Carreras M. et al. ^[62]	04/17/2024	10,543	Clinical Trial Drug Cost Avoidance	<i>Cancers</i>
45	Gan Y. et al. ^[63]	06/10/2024	7,831	Durva/Treme/Chemo mNSCLC	<i>Front Pharmacol</i>

Articles Total Words = 357,381, Average Words = 7,942, SD Words = 2,411

Table 2: 45 Articles Used for Generating 45 LLM Reports

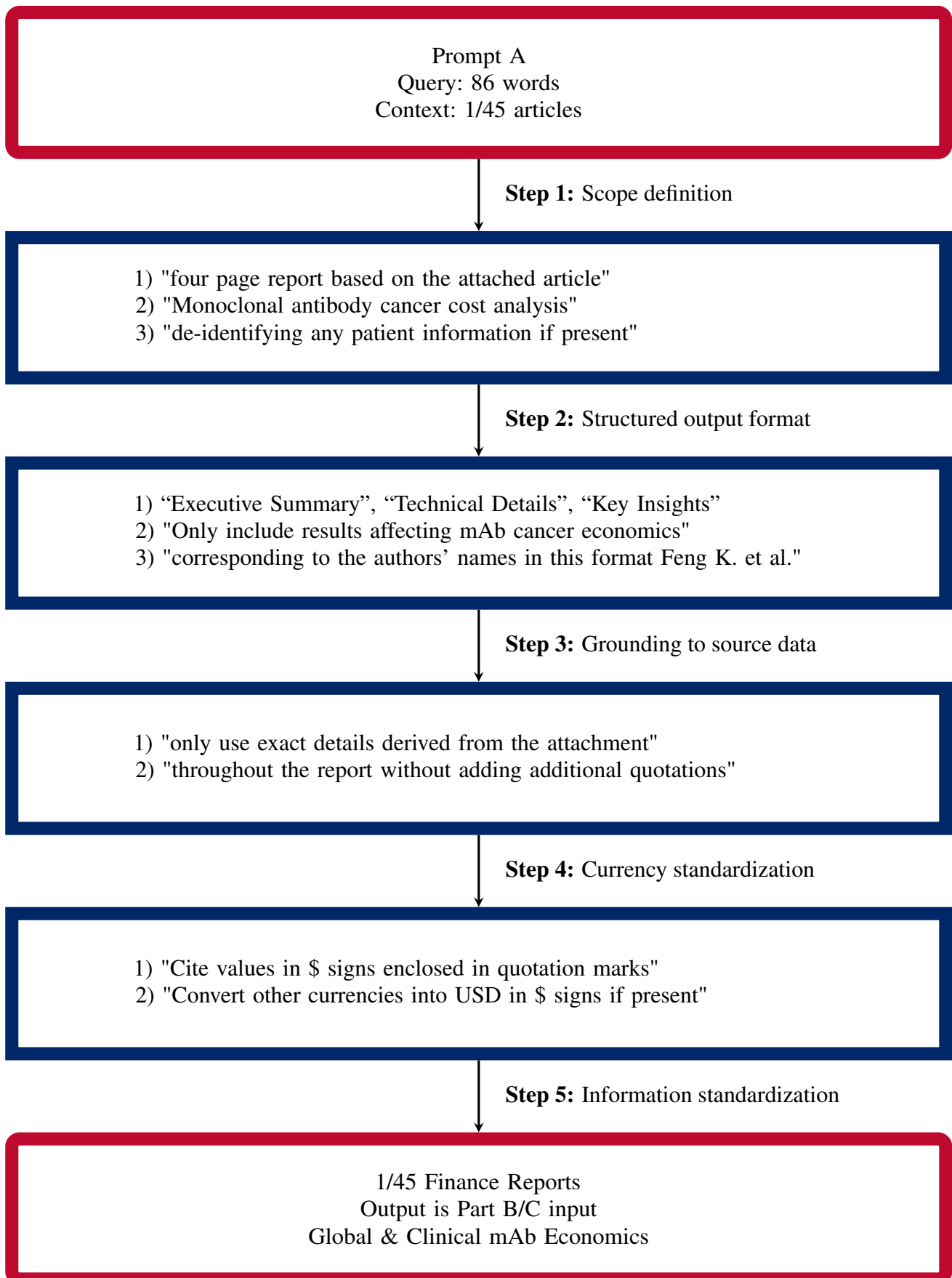


Figure 4: Standard A Objectives

Traceability: Detailed Report 06. Lu B. et al. 2024, Table 4. 8 Traces to Ground Outputs to Input

Article 06: "Bevacizumab biosimilars were associated with an incremental cost of -\$6379 (95%CI: -9417, -3537) (ie, cost saving)"

Trace 01: "Mean total one-year cost savings of "\$6,379" per patient with biosimilars"

Article 06: "Incremental net monetary benefit and INHB estimates were \$6331 (95% CI: 6245, 6417) and 0.127 LY (95% CI: 0.125, 0.128), respectively, at a willingness-to-pay threshold of \$50 000/life year gained"

Trace 02: "Positive incremental net monetary benefit of "\$6,331" at a \$50,000/life-year gained willingness-to-pay threshold"

Article 06: "Bevacizumab biosimilars were associated with a mean total cost of \$84 162 versus \$90 541 incurred by patients receiving originator bevacizumab, resulting in a 1-year incremental cost of -\$6379 (95% CI: -9417, -3537) (ie, cost saving)."

Trace 03: "* Biosimilar group: ""\$84,162"" per patient

* Originator group: ""\$90,541"" per patient

* Incremental cost savings: ""\$6,379"" (95% CI: ""\$9,417"" to ""\$3,537"")"

Article 06: "Incremental net monetary benefit and INHB estimates were \$6331 (95% CI: 6245, 6417)"

Trace 04: "Incremental net monetary benefit: "\$6,331" (95% CI: "\$6,245" to "\$6,417")"

Article 06: "MVASI 83 890 0.86 0.63 -6552"

Trace 05: "MVASI cohort:

- Mean total cost: ""\$83,890""

- Incremental cost savings: ""\$6,552""

Quote 5 Article: "MVASI 83 890 0.86 0.63 -6552"

Article 06: "Zirabev 85 772 0.92 0.66 -5372"

Trace 06: "Zirabev cohort:

- Mean total cost: ""\$85,772""

- Incremental cost savings: ""\$5,372""

Article 06: "2-year mean total costs were \$120 819 and \$134 112 for the biosimilar and originator groups, respectively (Table 2). Bevacizumab biosimilars were associated with an incremental cost of -\$13 293"

Trace 07: "- Mean total costs:

* Biosimilar group: ""\$120,819""

* Originator group: ""\$134,112""

- Incremental cost savings: ""\$13,293"

Article 06: "1-year population-level gain of \$4 729 257 and 95 LYs since the introduction of bevacizumab biosimilars in Ontario."

Trace 08: "- At the Ontario population level, the introduction of biosimilars translated to: * Annual monetary gain of "\$4,729,257""

4 Part A Discussion: 45 Reports

Each of the Standard A objectives to define scope, structure the output format, and ground the output to source data were typically followed by 3.5 Sonnet, as shown in Figure 4. The report generation performed here was modified to a "four page report" from a "two page report" approach in a recent clinical decision support study performed by the manuscript author [64]. This modification to maximize report detail yielded an average word increase to 552 from 463 words while increasing generation time to 26.06 seconds from 22.86 seconds. Prompt A requirements from Table 1 were typically met with generations including "Cite values in \$ signs enclosed in quotation marks corresponding to the authors' names in this format Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the attachment throughout the report without adding additional quotations".

Minor currency conversion issues in standardizing information were sometimes present for the 45 reports. Patient information should not be included in the original articles, and a request of "de-identifying any patient information if present" was included as an additional guardrail. Of the 279 total traces, currencies were either in USD, converted directly from EUR to USD with an exchange rate of 1 (Heine R. et al. 2024), or left in EUR (Kirshner G. et al. 2024, Jakovljevic M. et al. 2024, Gentili N. et al. 2024). Report 06 included by Lu B. et al. in Table 4 for example, included 8 pieces of financial information passages, which were found to be in-context with the original article, shown in Traceability TRA Supplementary numbers 28-35.

Only one case was found where the model made a major error in a complex financial passage containing four currency types (RMB ¥, \$, £, and SEK) where 3.5 Sonnet partially misinterpreted a statement "SEK 568,895 per QALY for Sweden" for "\$568,895/QALY" for Swedish patients" in Cheng M. et al. 2024. This is incorrect, as 1 Swedish Krona (SEK) = 0.094 USD at time of publishing. 6 repetitious statements found across Itoshima H. et al. 2024, Wu Q. et al. 2024, Jakovljevic M. et al. 2024, and Figallo M. et al. 2024 may be due to these articles containing less usable financial information than in Part C, so the longer four-page reports may have caused more duplications. The financial abbreviation with the Ye D. et al. 2024 report was seen in the article "EXTREME had a probability of 63.86%" compared to the generation "EXTREME had a 64% probability".

45 LLM Generated Reports: Word Counts by Slice, and Response Times

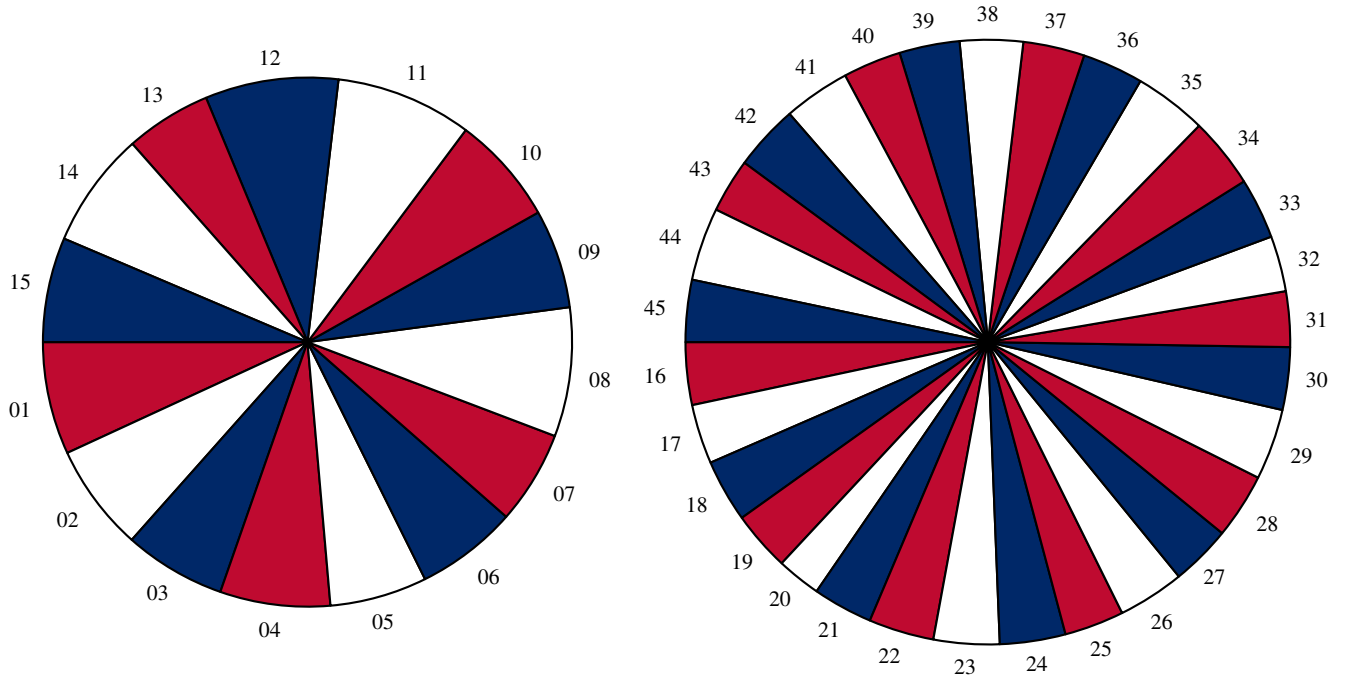


Figure 5: Left: 15 3.5 Sonnet Global Cost Reports. Right: 30 3.5 Sonnet Clinical Cost Reports

Reports 01-15: Global mAb Cancer Cost, and Reports 16-45: Clinical mAb Cancer Cost							
Report	Authors	Words	Time (s)	Report	Authors	Words	Time (s)
01	Feng K. et al. ^[19]	596	25.49	24	Broer L. et al. ^[42]	567	28.68
02	Chen H. et al. ^[20]	568	25.22	25	Peng J. et al. ^[43]	515	30.08
03	Itoshima H. et al. ^[21]	539	24.21	26	Nguyen A. et al. ^[44]	575	33.90
04	Kirshner G. et al. ^[22]	583	28.06	27	Gunasek. A. et al. ^[45]	522	32.01
05	Wu Q. et al. ^[23]	515	24.44	28	Khoirunn. S. et al. ^[46]	564	27.96
06	Lu B. et al. ^[24]	537	23.75	29	Landeiro L. et al. ^[47]	613	26.12
07	Jakovl. M. et al. ^[25]	494	25.46	30	Lin Y. et al. ^[48]	540	27.13
08	Figallo M. et al. ^[26]	683	28.16	31	Rieger C. et al. ^[49]	479	22.63
09	Hemati H. et al. ^[27]	523	25.24	32	Lang W. et al. ^[50]	480	26.17
10	Otoya I. et al. ^[28]	576	24.09	33	Li A. et al. ^[51]	525	26.16
11	Heine R. et al. ^[29]	722	29.30	34	Cheng M. et al. ^[52]	610	27.48
12	Malmberg R. et al. ^[30]	705	28.15	35	Nie J. et al. et al. ^[53]	629	27.89
13	Yeong S. et al. ^[31]	455	20.79	36	You M. et al. ^[54]	527	29.40
14	Whitacre R. et al. ^[32]	614	26.86	37	Yang X. et al. ^[55]	530	26.76
15	Gentili N. et al. ^[33]	554	25.02	38	Yang L. et al. ^[56]	545	21.96
16	Lin Y. et al. ^[34]	541	23.83	39	Xiang G. et al. ^[57]	521	24.96
17	Cai H. et al. ^[35]	514	23.37	40	Meng K. et al. ^[58]	502	21.54
18	Chen Z. et al. ^[36]	541	22.16	41	Ye D. et al. ^[59]	576	25.71
19	Li Y. et al. ^[37]	515	24.57	42	Li J. et al. ^[60]	567	31.64
20	Liang Y. et al. ^[38]	381	17.52	43	Xiang Z. et al. ^[61]	467	22.34
21	Huang, L. et al. ^[39]	518	26.97	44	Carreras M. et al. ^[62]	631	29.41
22	Gong H. et al. ^[40]	564	26.36	45	Gan Y. et al. ^[63]	535	25.92
23	Sripho. S. et al. ^[41]	569	27.81	–	All Reports Total	24,827	1,172.68

Reports Average Words = 552, SD Words = 62.7; Average Time = 26.06 Seconds, SD Time = 3.11

Table 3: 45 Reports Generated by 3.5 Sonnet

LLM Detailed Report 06 of 45: Lu B. et al. 2024. 537 words, 23.75 seconds

Here is a 4-page report analyzing the monoclonal antibody cancer cost analysis from the attached article:

Cost-Effectiveness Analysis of Bevacizumab Biosimilars for Metastatic Colorectal Cancer

Executive Summary

This report examines the real-world cost-effectiveness analysis comparing bevacizumab biosimilars (MVASI and Zirabev) versus originator bevacizumab (Avastin) for first-line treatment of metastatic colorectal cancer (mCRC) in Ontario, Canada. The study by Lu B. et al. demonstrated that bevacizumab biosimilars provided significant cost savings while maintaining similar clinical outcomes compared to the originator product.

Key findings include:

- Mean total one-year cost savings of "\$6,379" per patient with biosimilars
- No significant differences in survival outcomes between biosimilars and originator
- Positive incremental net monetary benefit of "\$6,331" at a \$50,000/life-year gained willingness-to-pay threshold
- Consistent cost-effectiveness results across both analyzed biosimilar products (MVASI and Zirabev)

The analysis confirms that implementing bevacizumab biosimilars can help reduce healthcare spending while maintaining therapeutic effectiveness in treating mCRC patients.

Technical Details

Study Design:

- Population-based retrospective cohort study in Ontario, Canada
- Included 747 biosimilar cases and 2,945 originator comparators matched 1:4 using propensity score matching
- Study period: January 2008 to March 2021
- Primary outcomes: incremental net monetary benefit and incremental net health benefit

Cost Analysis:

- One-year mean total costs:
 - Biosimilar group: "\$84,162" per patient
 - Originator group: "\$90,541" per patient
- Incremental cost savings: "\$6,379" (95% CI: "\$9,417" to "\$3,537")

Clinical Outcomes:

- No significant differences in life years gained or quality-adjusted life years
- Incremental effect of 0.0 life years gained (95% CI: -0.02 to 0.02)
- Incremental effect of -0.01 QALYs (95% CI: -0.03 to 0)

Cost-Effectiveness Results:

At \$50,000/LYG threshold:

- Incremental net monetary benefit: "\$6,331" (95% CI: "\$6,245" to "\$6,417")
- Incremental net health benefit: 0.127 life years (95% CI: 0.125 to 0.128)
- 99.9% probability of being cost-effective

Subgroup Analysis:

MVASI cohort:

- Mean total cost: "\$83,890"
- Incremental cost savings: "\$6,552"

Zirabev cohort:

- Mean total cost: "\$85,772"
- Incremental cost savings: "\$5,372"

Two-year Analysis:

- Mean total costs:
 - Biosimilar group: "\$120,819"
 - Originator group: "\$134,112"
- Incremental cost savings: "\$13,293"

Key Insights

1. Real-World Cost Savings
 - The implementation of bevacizumab biosimilars demonstrated meaningful cost reductions while maintaining similar clinical outcomes
 - Primary cost savings were driven by lower drug acquisition costs
 - Cost-effectiveness remained consistent across both analyzed biosimilar products and time horizons
2. Population Health Impact
 - At the Ontario population level, the introduction of biosimilars translated to:
 - Annual monetary gain of "\$4,729,257"
 - Annual health gain of 95 life years
 - Projected nationwide adoption could generate approximately 196 life years gained annually across Canada
3. Healthcare System Implications
 - Results support policies mandating biosimilar use for new mCRC patients
 - Findings demonstrate that biosimilar implementation can improve healthcare system sustainability
 - Cost savings could potentially be reinvested into other healthcare services
4. Future Considerations
 - Long-term safety and effectiveness monitoring remains important
 - Additional real-world cost-effectiveness analyses of other biosimilar products would be valuable
 - Results can inform policy decisions regarding implementation of future biosimilar products

The study provides strong evidence supporting the economic value of bevacizumab biosimilars in mCRC treatment, demonstrating both individual patient-level and population-level benefits. These findings can help guide healthcare policy decisions regarding biosimilar implementation across various jurisdictions.

Table 4: 1 of 45 LLM 3.5 Sonnet Generations. All generations as Full Text: Datasets B15,C30

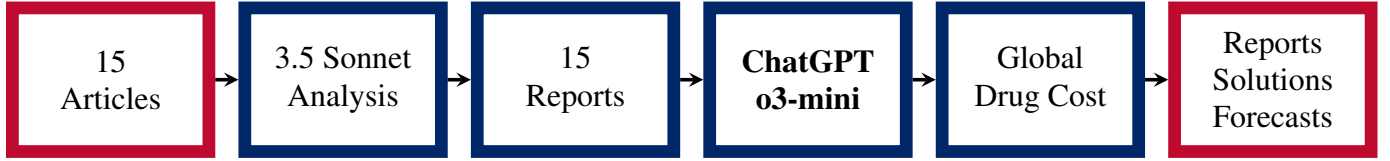


Figure 6: Standard B ChatGPT o3-mini Process Diagram

Standard B: Global mAb Cancer Cost Containment					
<p>Prompt B1: Write a four page report based only on the 15 attached summaries under “Global mAb Cancer Cost” regarding the authors’ Monoclonal antibody cancer cost analysis using the following format: “Executive Summary”, “Technical Details”, “Key Insights”. Only include results affecting mAb therapy and mAb combination therapy cancer economics, de-identifying any patient information if present. Cite financial information in \$ signs using no abbreviations enclosed in quotation marks corresponding to the authors’ names in this format, Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the 15 attached summaries under “Global mAb Cancer Cost” throughout the report without adding additional quotations. [15 Reports Attached] [First Prompt in Conversation]</p>					
<p>Prompt B2: Provide solutions based only on the previous generation in this conversation regarding the Global mAb Cancer Cost problem. Only include solutions affecting Global mAb Cancer economics, de-identifying any patient information if present. Cite financial information in \$ signs using no abbreviations enclosed in quotation marks corresponding to the authors’ names in this format, Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the previous generation in this conversation throughout the solutions without adding additional quotations. [Second Prompt]</p>					
<p>Prompt B3: Construct a very large and comprehensive table based only on the previous generation in this conversation regarding the Global mAb Cancer Cost problem solutions. Only include results affecting Global mAb Cancer Cost problem solution economics, de-identifying any patient information if present. Cite financial information in \$ signs using no abbreviations enclosed in quotation marks corresponding to the authors’ names in this format, Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the previous generation in this conversation throughout the table without adding additional quotations. [Third Prompt in Conversation]</p>					
<p>Prompt B4: Construct a very large and comprehensive table of financial forecasts based only on the two previous generations in this conversation regarding the Global mAb Cancer Cost problem solutions. Only include results affecting Global mAb Cancer Cost problem financial forecasts, de-identifying any patient information if present. Cite financial information in \$ signs using no abbreviations enclosed in quotation marks corresponding to the authors’ names in this format, Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the two previous generations in this conversation throughout the table without adding additional quotations. [Fourth Prompt in Conversation]</p>					
15 Global mAb Reports	De-identify Patient IDs	Global mAb Cancer Report	mAb Cost Solutions	Table Cost Solutions	Table Cost Forecasts

Table 5: Standard B Process Diagram

5 Part B Results: Global mAb Cancer Cost

The process diagram in Figure 6 illustrates the reasoning task of 15 reports by ChatGPT o3-mini for the global drug cost outputs. The prompts in Table 5 assisted the LLM to yield a longer "four page report", cost solutions based on the conversation, a large and comprehensive cost table, and a large and comprehensive financial forecasts table. In general, there was not an increase in words from a prior study that requested a two page report [64]. Reports typically followed the requested "Feng K. et al." format, returned currencies in quotations, and the Generation B1 was in the correct “Executive Summary”, “Technical Details”, “Key Insights” format. The Standard B objectives path in Figure 7 was primarily followed. Generations utilized data from either the 9,022 word Dataset B15 or within the conversation which was appropriate, but did not have more fine level control to include information "based only on the two previous generations".

The divide and conquer approach in producing a 1,539 word detailed report, 496 word focused solutions, a 463 word cost solutions table, and a 450 word financial forecast was likely the correct approach to avoid OpenAI inference-time compute, inference-time budget, and output-length constraints that were apparent in prior works [65, 66, 67]. There were 39 Generation B1 author citations regarding financial information among 12 different authors (Table 6). Generation B2 had 9 author citations regarding financial information among 7 different authors (Table 7). Generation B3 had 8 author citations regarding financial information among 8 different authors (Table 8). Generation B4 had 8 author citations regarding financial information among 8 different authors (Table 9). Traceability across all four generations consisted of 6 in-context traces using a 1.1 USD to EUR exchange rate, 1 in-context approximation, 7 in-context repetitive pieces of financial information, 4 in-context, approximation, with repetition, and 4 in-context traces within the 15 reports where information was appropriately utilized.

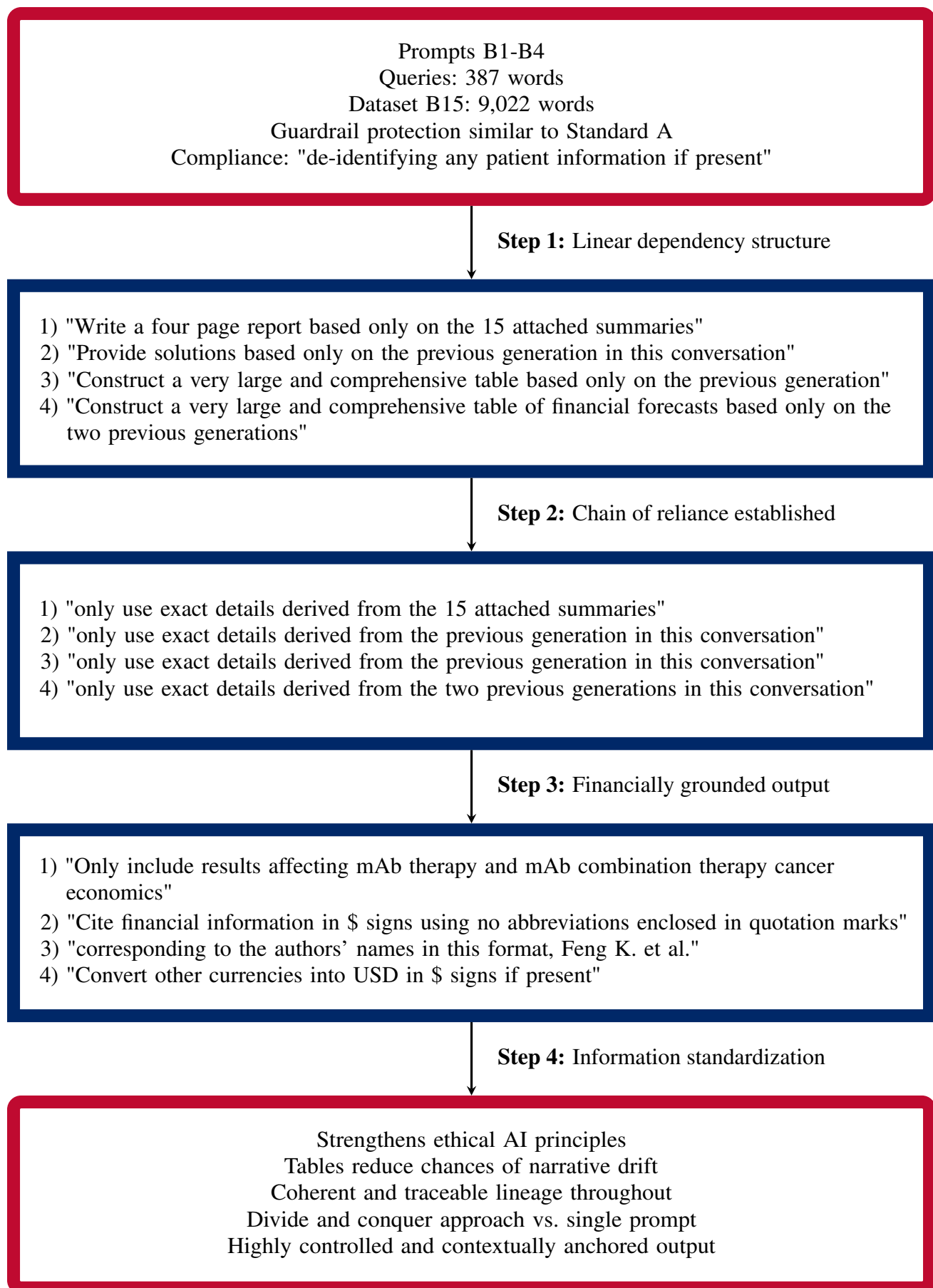


Figure 7: Standard B Objectives

Traceability: Generation B4. Global mAb Table Cost Forecasts, Table 9 Various authors. 2024

Dataset B15: "(e.g., bevacizumab 400mg biosimilar at "\$377.3" vs reference at "\$843.4")"

Trace 01: ""\$377.3" per dose (biosimilar price)"

Dataset B15: "- Calculated cost-based prices were significantly lower than current list prices for pembrolizumab, ranging from "\$52 to \$885" per vial "

Trace 02: ""\$52" to "\$885" per vial (cost-based forecast)"

Dataset B15: "- Total annual savings of "\$5,727" per patient when including all direct and indirect costs"

Trace 03: "Annual savings of "\$5,727" per patient"

Dataset B15: "reduces total treatment costs by approximately \$4,071.72 over a full 18-cycle treatment course"

Trace 04: "Reduction of "\$4,071.72" per treatment course"

Dataset B15: "Post-biosimilar mean OOP cost: "\$707" (Feng K. et al.)"

Trace 05: ""\$707" per claim"

Dataset B15: "Mean costs were "€1,718.27" for IV Herceptin®, "€1,620.66" for subcutaneous Herceptin®, and "€987.97" for biosimilars"

Trace 06: "Biosimilar trastuzumab at "\$1,087" per treatment" In-Context, Note: 1.1 USD to EUR

Dataset B15: "- Mean total one-year cost savings of "\$6,379" per patient with biosimilars"

Trace 07: "Savings of "\$6,379" per patient annually"

Dataset B15: "could reduce carbon emissions by 21-26% for pembrolizumab"

Trace 08: "21–26% reduction in emissions (indirect cost proxy)"

6 Part B Discussion: Global mAb Cancer Cost

ChatGPT o3-mini provided a substantial 1,539 word report that was based on Dataset B15 and a strict Prompt B1. The main techniques used to standardize information such as scope definition, a structured output format, and grounding the output to source data were applied by the AI model across global mAb cancer cost insights. A limited number of currencies that were in EUR were converted to USD from Part A by the model. Although there were 39 citations which helped to solidify key details, the report did have repetition in financial detail between each section. This may have been due to the smaller dataset with 12/15 authors cited, as some articles contained less relevant financial information based on Prompt B1's request for "mAb therapy and mAb combination therapy cancer economics". Generation B2 contained a convincing report on cost solutions, and the total citations were reduced to 9 as a greater degree of focus was required than the prior generation.

The Generation B3 table of cost solutions retained much of the financial metrics from the prior report with several financial metrics under the "Key Financial Metrics/Targets" heading such as "Incentive payment of "\$10.4" per patient monthly (up to "\$31.2" per patient)" by Itoshima H. et al. 2024, and "Mean out-of-pocket costs reduced from "\$911" to "\$707" after biosimilar entry." by Feng K. et al. 2024. The final Generation B4 in the conversation compliments the prior table, as additional headings were used such as "Baseline Value" and "Forecasted Value/Target" to provide more financially driven insights. However, both Table 8 and Table 9 should be used together, as context is greater in B3 while B4 provides rapid insights. The following two options represent use cases to utilize the manuscript findings most effectively. **Instruction 1:** Use cost solutions and economic forecasts as an initial screening by following Table 8 and Table 9 guidance, followed by additional context gained from Table 6, Table 7, and supporting Dataset B15 if necessary. **Instruction 2:** Read full reports from Table 6, Table 7 or Dataset B15 for a more extensive understanding of financial synergies.

Global Economic Analysis of mAb Cancer Therapies

This report synthesizes findings from recent analyses of monoclonal antibody (mAb) cancer treatments and biosimilar strategies. The included studies examine patient out-of-pocket costs, pricing dynamics, cost-effectiveness, administration methods, and pricing models. Overall, the analyses reveal that while biosimilar competition and innovative administration strategies can lower unit costs and improve resource utilization, the net economic impact on mAb therapy varies by product, region, and policy environment.

Executive Summary

Studies focused on mAb therapies have shown that biosimilar competition can lead to meaningful price reductions and cost-savings for both patients and health systems. For example, one analysis found that after biosimilar entry, mean out-of-pocket costs declined from "\$911" to "\$707" while product-specific trends were mixed—biosimilar bevacizumab claims had 21% higher patient spending, whereas biosimilar rituximab and trastuzumab claims reduced costs by 10% and 8%, respectively ("Feng K. et al. 2024"). In parallel, research across 57 countries demonstrated immediate per-dose price reductions for bevacizumab and trastuzumab of "\$110" and "\$438" and ongoing annual reductions, underscoring the rapid and sustained impact of biosimilar availability ("Chen H. et al. 2024").

Financial incentives in Japan further increased biosimilar uptake by 9.2% for rituximab, trastuzumab, and bevacizumab, with modest incentive costs of "\$10.4" per patient per month and biosimilar pricing between 40% and 60% of reference products ("Itoshima H. et al. 2024"). In the Netherlands, an evergreening strategy that introduced a subcutaneous trastuzumab formulation temporarily maintained higher pricing, with average treatment costs of approximately "\$1,889" for intravenous and "\$1,783" for subcutaneous formulations compared to "\$1,087" for biosimilars (converted from "€1,718.27", "€1,620.66", and "€987.97" respectively; see "Kirshner G. et al. 2024"). Similar trends were observed in China, where biosimilar trastuzumab uptake reached 27% and negotiations reduced originator pricing from "\$3,500/440mg" to "\$800/440mg", resulting in an average saving of "\$421.11" per treatment course ("Wu Q. et al. 2024").

Cost-effectiveness analyses further support the economic value of biosimilars. A Canadian study comparing bevacizumab biosimilars to the originator in metastatic colorectal cancer reported one-year per-patient savings of "\$6,379" and positive net monetary benefits ("Lu B. et al. 2024"). Meanwhile, evaluations in Peru showed that fixed-dose combination pertuzumab–trastuzumab for HER2-positive breast cancer reduced non-drug consumable costs by "\$999" per patient annually and yielded total annual savings of "\$5,727" while also saving significant healthcare professional time ("Figallo M. et al. 2024"). In Iran, a Markov model comparing trastuzumab–emtansine to trastuzumab revealed an incremental cost of "\$1,408" with an incremental cost-effectiveness ratio of "\$886" per quality-adjusted life year gained ("Hemati H. et al. 2024"). In a complementary analysis at a Peruvian reference cancer center, subcutaneous administration of trastuzumab was found to reduce overall treatment costs by "\$4,071.72" per complete treatment course compared to intravenous administration ("Otoya I. et al. 2024").

Cost-based pricing models for innovative mAbs have also been developed. One study estimated cost-justified prices for pembrolizumab and daratumumab that were substantially lower than current list prices, highlighting the role of patient population size, research and development, and manufacturing costs in pricing strategies ("Heine R. et al. 2024"). In the United States, financial analyses of high-revenue mAb therapies—such as pembrolizumab, which has generated annual revenues of "\$17.321 billion" and costs of approximately "\$175,000" per patient per year—underscore the challenges of balancing high development costs, regulatory incentives, and patient access ("Whitacre R. et al. 2024"). Finally, an Italian study comparing healthcare costs in metastatic non-small cell lung cancer showed that first-line pembrolizumab increased per-patient costs by roughly "\$12,647" (converted from "€11,497") compared to chemotherapy, though monthly costs remained similar when adjusted for survival benefits ("Gentili N. et al. 2024").

Technical Details

Study Designs and Data Sources:

- **Retrospective Claims Analysis:** One study analyzed over 1.7 million claims from commercially insured patients to assess out-of-pocket spending using two-part regression modeling ("Feng K. et al. 2024").
- **Interrupted Time Series:** Pharmaceutical sales data from 57 countries were used to measure immediate and sustained pricing changes after biosimilar introduction ("Chen H. et al. 2024").
- **Quasi-Experimental Methods:** Comparative analyses using generalized synthetic control methods evaluated the impact of financial incentives on biosimilar adoption in Japan ("Itoshima H. et al. 2024").
- **Market Share and Cost Analysis:** Hospital-level data were examined to assess the effects of an evergreening strategy for trastuzumab, with key cost metrics converted from euros (using an approximate conversion factor of 1€ ≈ \$1.10) resulting in treatment cost estimates of approximately "\$1,889" for intravenous and "\$1,783" for subcutaneous formulations compared to "\$1,087" for biosimilars ("Kirshner G. et al. 2024").
- **Retrospective Consumption and Time Series Modeling:** Analysis of monthly consumption data from over 2,200 hospitals in China provided insights into biosimilar uptake and price negotiations for trastuzumab ("Wu Q. et al. 2024").
- **Propensity Score Matching:** A Canadian study matched patients to compare total treatment costs and outcomes between bevacizumab biosimilars and the originator, identifying per-patient savings of "\$6,379" over one year ("Lu B. et al. 2024").
- **Mixed Quantitative–Qualitative Cost Minimization:** An 18-cycle treatment analysis in Peru compared fixed-dose combination pertuzumab–trastuzumab to separate intravenous infusions, quantifying savings in consumables, professional time, and indirect costs ("Figallo M. et al. 2024").
- **Markov Modeling:** A lifetime horizon model was used in Iran to compare the cost–utility of trastuzumab–emtansine versus trastuzumab, yielding an incremental cost of "\$1,408" and an ICER of "\$886" per QALY ("Hemati H. et al. 2024").
- **Cost Component and Time Requirement Analysis:** A real-world study from a Peruvian cancer center compared subcutaneous versus intravenous administration of trastuzumab and documented an overall cost saving of "\$4,071.72" per treatment course ("Otoya I. et al. 2024").
- **Cost-Based Pricing Modeling:** Inputs such as R&D, manufacturing expenses, and profit margins were integrated to derive cost-based price ranges for pembrolizumab and daratumumab, with estimated per-vial prices ranging from "\$52" to "\$885" for pembrolizumab and a comparable range for daratumumab ("Heine R. et al. 2024").
- **Revenue and Clinical Trial Economic Analysis:** Longitudinal revenue data and clinical trial timelines provided insight into how cost pressures and regulatory strategies affect pricing and patient access, as demonstrated by therapies such as pembrolizumab ("Whitacre R. et al. 2024").
- **Retrospective Healthcare Resource Utilization:** An Italian study compared healthcare costs for metastatic non-small cell lung cancer patients, revealing that first-line pembrolizumab increased per-patient costs by approximately "\$12,647" (converted from "€11,497") while demonstrating improved survival outcomes ("Gentili N. et al. 2024").

Key Insights

1. **Biosimilar Competition and Cost Savings:** Biosimilar entry has driven immediate dose-level price reductions—such as decreases of "\$110" per dose for bevacizumab and "\$438" per dose for trastuzumab ("Chen H. et al. 2024")—and has yielded patient cost reductions in certain products. However, product-specific differences exist; for instance, biosimilar claims for bevacizumab may incur higher out-of-pocket expenses compared to the reference product, whereas rituximab and trastuzumab biosimilars tend to lower costs ("Feng K. et al. 2024").
2. **Impact of Financial Incentives and Regulatory Strategies:** Financial incentives, even modest amounts like "\$10.4" per patient monthly, can effectively shift prescribing toward biosimilars, thereby potentially lowering overall expenditure ("Itoshima H. et al. 2024"). In contrast, evergreening strategies—such as the introduction of a subcutaneous formulation of trastuzumab—may temporarily preserve market share and higher pricing, though biosimilar competition ultimately results in lower treatment costs (with biosimilar trastuzumab averaging approximately "\$1,087" compared to higher costs for proprietary formulations; "Kirshner G. et al. 2024").
3. **Cost-Effectiveness and Resource Optimization:** Real-world evidence supports the cost-effectiveness of biosimilar mAbs, as demonstrated by savings of "\$6,379" per patient in metastatic colorectal cancer when using bevacizumab biosimilars ("Lu B. et al. 2024"). Similarly, fixed-dose combination therapies and subcutaneous formulations have been shown to reduce both direct and indirect costs, with savings ranging from "\$999" in consumables to a total of "\$5,727" annually per patient and overall treatment course savings of "\$4,071.72" ("Figallo M. et al. 2024; "Otoya I. et al. 2024").
4. **Pricing Models and Market Dynamics:** Cost-based pricing models indicate that current list prices for innovative mAbs such as pembrolizumab and daratumumab may be significantly above cost-justified levels. The analyses underscore that factors such as patient population size, R&D, and manufacturing costs are critical in establishing sustainable pricing ("Heine R. et al. 2024"). Concurrently, high annual revenues—as seen with pembrolizumab generating "\$17.321 billion" and incurring costs of around "\$175,000" per patient—illustrate the financial pressures that can impede patient access ("Whitacre R. et al. 2024").
5. **Overall Healthcare System Implications:** Although the introduction of innovative therapies such as pembrolizumab has raised per-patient treatment costs, analyses from Italy indicate that improved survival outcomes and reductions in hospitalization may help balance the monthly cost burden ("Gentili N. et al. 2024"). Collectively, these findings highlight the complexity of mAb therapy economics, where lower biosimilar prices and efficient administration strategies must be weighed against high development costs and market exclusivity measures.

The integrated evidence from these analyses emphasizes that while advances in biosimilar adoption, alternative administration routes, and cost-based pricing models offer promising avenues for reducing expenditures, market dynamics and regulatory policies continue to shape the overall economic landscape of mAb cancer therapies. Stakeholders are encouraged to consider these findings when designing policies that aim to improve both affordability and access to life-saving treatments.

Table 6: ChatGPT o3-mini Generation B1, Plain Text: Supplementary B14G, Full Input Context: B15

Global mAb Cancer Cost Solutions. Generation B2, Various authors. 2024. 496 words, 21.85 seconds

Below are several solutions derived from the previous analysis that address Global mAb Cancer economics. These solutions focus on lowering costs and improving access while ensuring that all financial figures are de-identified and properly converted as needed.

- **Promote Biosimilar Adoption through Financial Incentives**
 - Implement modest incentive payments—such as a "\$10.4" per patient monthly payment (up to "\$31.2" per patient)—to encourage providers to prescribe biosimilars.
 - Increase uptake of biosimilars that are priced 40–60% lower than their reference products (for example, a bevacizumab biosimilar priced at "\$377.3" versus a reference product priced at "\$843.4"). (Itoshima H. et al. 2024)
- **Adopt Cost-Based Pricing Reviews for Innovative mAbs**
 - Introduce periodic reviews that calculate prices using actual R&D and manufacturing costs plus a reasonable profit margin.
 - Use cost-based pricing models that have estimated prices for products such as pembrolizumab to range from "\$52" to "\$885" per vial, contrasting with current list prices that reach levels like "\$2,861" to "\$5,350." (Heine R. et al. 2024)
- **Optimize Administration Methods to Reduce Resource Use**
 - Transition from intravenous (IV) to subcutaneous (SC) administration for therapies when clinical efficacy is maintained.
 - Emphasize fixed-dose combination therapies—for instance, using a fixed-dose combination of pertuzumab–trastuzumab, which has demonstrated annual savings of "\$5,727" per patient—and SC administration of trastuzumab that reduces total treatment course costs by "\$4,071.72." (Figallo M. et al. 2024; Otoyá I. et al. 2024)
- **Revise Reimbursement and Cost-Sharing Policies**
 - Reassess current patient cost-sharing arrangements so that the benefits of biosimilar competition are passed on to patients.
 - Adjust policies so that when biosimilar entry reduces mean out-of-pocket costs from "\$911" to "\$707," the savings are reflected in reduced patient expenditures. (Feng K. et al. 2024)
- **Address Evergreening Strategies to Enhance Market Competition**
 - Develop regulatory measures to limit evergreening practices that use alternative formulations to delay biosimilar competition.
 - Support policies that promote a competitive market—for example, by ensuring that biosimilar trastuzumab, which averages a treatment cost of "\$1,087," can compete effectively against higher-priced subcutaneous and IV formulations. (Kirshner G. et al. 2024)
- **Support and Expand Real-World Cost-Effectiveness Research**
 - Fund additional studies using real-world data to continuously monitor and compare the economic impact of biosimilars versus originator mAbs.
 - Use findings such as per-patient savings of "\$6,379" with bevacizumab biosimilars in metastatic colorectal cancer to guide policy and reimbursement decisions. (Lu B. et al. 2024)
- **Encourage Alternative Dosing Strategies**
 - Implement weight-based dosing protocols in place of fixed dosing for certain mAbs to reduce drug overuse and waste, thereby lowering costs.
 - Leverage alternative dosing strategies that not only decrease pharmaceutical usage but also reduce environmental impacts, as evidenced by reductions of up to 21–26% in emissions for pembrolizumab. (Malmberg R. et al. 2024)

Each of these solutions has been derived directly from the previously analyzed data, ensuring that Global mAb Cancer economics benefit from enhanced competition, cost efficiency, and improved access while maintaining clinical effectiveness.

Table 7: ChatGPT o3-mini Generation B2, Plain Text: Supplementary B14G, Full Input Context: B15

Global mAb Table Cost Solutions. Generation B3, Various authors. 2024. 463 words, 22.04 seconds

Solution Strategy	Intervention Description	Key Financial Metrics/Targets	Expected Economic Impact	Source
Promote Biosimilar Adoption through Financial Incentives	Implement incentive payments and provider education to encourage biosimilar prescribing.	Incentive payment of "\$10.4" per patient monthly (up to "\$31.2" per patient); biosimilars offered at 40–60% lower prices (e.g., a bevacizumab biosimilar priced at "\$377.3" versus a reference product priced at "\$843.4").	Increased biosimilar uptake leading to reduced drug acquisition costs and improved patient affordability.	Itoshima H. et al. 2024
Adopt Cost-Based Pricing Reviews for Innovative mAbs	Establish periodic pricing reviews using cost-based models that incorporate actual R&D and manufacturing costs plus a reasonable profit margin.	Cost-based pricing estimates for pembrolizumab range from "\$52" to "\$885" per vial compared to current list prices ranging from "\$2,861" to "\$5,350."	More sustainable pricing structures that align with actual production expenses and lower overall treatment costs.	Heine R. et al. 2024
Optimize Administration Methods to Reduce Resource Use	Transition from intravenous (IV) to subcutaneous (SC) administration and adopt fixed-dose combination therapies where clinical efficacy is maintained.	Fixed-dose combination pertuzumab–trastuzumab results in annual savings of "\$5,727" per patient; SC administration of trastuzumab reduces the total treatment course cost by "\$4,071.72."	Lower overall treatment costs through reduced consumable usage, decreased personnel time, and improved resource utilization.	Figallo M. et al. 2024; Otoy I. et al. 2024
Revise Reimbursement and Cost-Sharing Policies	Adjust patient cost-sharing and reimbursement frameworks to ensure that savings from biosimilar competition are passed on to patients.	Mean out-of-pocket costs reduced from "\$911" to "\$707" after biosimilar entry.	Reduced patient financial burden and improved treatment affordability, leading to broader access.	Feng K. et al. 2024
Address Evergreening Strategies to Enhance Market Competition	Develop regulatory measures to limit evergreening practices that use alternative formulations to delay biosimilar competition.	Biosimilar trastuzumab averages a treatment cost of "\$1,087" compared to higher prices for alternative subcutaneous and IV formulations.	A more competitive market that drives down treatment costs and promotes greater biosimilar market share.	Kirshner G. et al. 2024
Support and Expand Real-World Cost-Effectiveness Research	Fund and support additional studies using real-world data to compare economic impacts between biosimilar and originator mAb therapies.	Observed per-patient savings of "\$6,379" with bevacizumab biosimilars in metastatic colorectal cancer.	Evidence-based policy adjustments and reimbursement decisions that further reduce treatment expenditures while maintaining clinical effectiveness.	Lu B. et al. 2024
Encourage Alternative Dosing Strategies	Implement weight-based dosing protocols and alternative dosing strategies for mAbs to reduce drug overuse and waste while maintaining therapeutic efficacy.	Alternative dosing strategies for pembrolizumab can lead to emission reductions of 21–26%, indirectly reducing drug usage and associated costs.	Lower pharmaceutical consumption costs and environmental benefits that contribute to overall system sustainability and cost efficiency.	Malmberg R. et al. 2024

Table 8: ChatGPT o3-mini Generation B3, Plain Text: Supplementary B14G, Full Input Context: B15

Global mAb Table Cost Forecasts. Generation B4, Various authors. 2024. 450 words, 39.56 seconds

Solution Strategy	Forecast Metric	Baseline Value	Forecasted Value/Target	Forecasted Savings/Change	Time Horizon	Source	Notes
Promote Biosimilar Adoption through Financial Incentives	Acquisition cost for bevacizumab per dose	"\$843.4" per dose (reference product price)	"\$377.3" per dose (biosimilar price)	Reduction of 40–60% in acquisition cost	Per dose	Itoshima H. et al. 2024	Incentive payments of "\$10.4" per patient monthly (up to "\$31.2" per patient) support increased biosimilar uptake.
Adopt Cost-Based Pricing Reviews for Innovative mAbs	Price per vial for pembrolizumab	"\$2,861" to "\$5,350" per vial (list price)	"\$52" to "\$885" per vial (cost-based forecast)	Significant reduction from current list prices	Ongoing	Heine R. et al. 2024	Cost-based pricing reviews aim to realign prices with actual R&D and manufacturing costs.
Optimize Administration Methods (Fixed-Dose Combination)	Annual cost savings per patient using fixed-dose combination	Not explicitly provided (separate IV higher)	Annual savings of "\$5,727" per patient	Savings of "\$5,727" per patient per year	Annual	Figallo M. et al. 2024	Savings driven by reduced consumable usage, healthcare professional time, and resource utilization.
Optimize Administration Methods (SC Administration of Trastuzumab)	Treatment course cost reduction for SC trastuzumab administration	Higher cost with IV administration	Reduction of "\$4,071.72" per treatment course	"\$4,071.72" saved per treatment course	Per treatment course	Otoya I. et al. 2024	Savings result from reduced drug preparation, administration, and resource utilization compared to IV dosing.
Revise Reimbursement and Cost-Sharing Policies	Mean patient out-of-pocket cost per claim	"\$911" per claim	"\$707" per claim	Reduction of "\$204" per claim	Per claim	Feng K. et al. 2024	Policy revisions are intended to better pass biosimilar cost reductions on to patients, reducing their financial burden.
Address Evergreening Strategies to Enhance Market Competition	Competitive treatment cost for trastuzumab	Higher cost with alternative formulations	Biosimilar trastuzumab at "\$1,087" per treatment	Benchmark target for cost competitiveness	Ongoing	Kirshner G. et al. 2024	Limiting evergreening practices may force market prices toward the lower biosimilar level, enhancing overall competition.
Support and Expand Real-World Cost-Effectiveness Research	Per-patient cost savings using bevacizumab biosimilars in mCRC	Higher cost with originator product	Savings of "\$6,379" per patient annually	"\$6,379" per patient per year	Annual	Lu B. et al. 2024	Real-world cost-effectiveness studies provide evidence to support policy and reimbursement decisions that favor biosimilar adoption.
Encourage Alternative Dosing Strategies	Reduction in pharmaceutical consumption (proxy via emissions reduction)	Standard fixed dosing with higher consumption	21–26% reduction in emissions (indirect cost proxy)	Indirect savings via reduced drug usage (exact \$ not specified)	Over 2-year treatment course	Malmberg R. et al. 2024	Although exact dollar savings are not provided, the 21–26% emission reduction indicates a potential decrease in drug consumption and associated costs over time.

Table 9: ChatGPT o3-mini Generation B4, Plain Text: Supplementary B14G, Full Input Context: B15

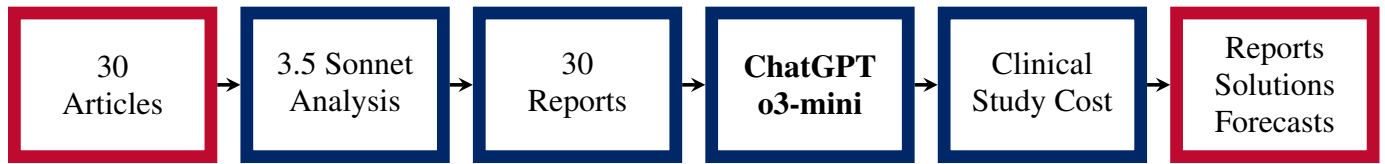


Figure 8: Standard C ChatGPT o3-mini Process Diagram

Standard C: Clinical mAb Cancer Cost Containment

Prompt C1: Write a four page report based only on the 30 attached summaries under “Clinical mAb Cancer Cost” regarding the authors’ Monoclonal antibody cancer cost analysis using the following format: “Executive Summary”, “Technical Details”, “Key Insights”. Only include results affecting Clinical mAb therapy and mAb combination therapy cancer economics, de-identifying any patient information if present. Cite financial information in \$ signs using no abbreviations enclosed in quotation marks corresponding to the authors’ names in this format, Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the 30 attached summaries under “Clinical mAb Cancer Cost” throughout the report without adding additional quotations. [30 Reports Attached] [First Prompt in Conversation]

Prompt C2: Provide solutions based only on the previous generation in this conversation regarding the Clinical mAb Cancer Cost problem. Only include solutions affecting Clinical mAb Cancer economics, de-identifying any patient information if present. Cite financial information in \$ signs using no abbreviations enclosed in quotation marks corresponding to the authors’ names in this format, Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the previous generation in this conversation throughout the solutions without adding additional quotations. [Second Prompt]

Prompt C3: Construct a very large and comprehensive table based only on the previous generation in this conversation regarding the Clinical mAb Cancer Cost problem solutions. Only include results affecting Clinical mAb Cancer Cost problem solution economics, de-identifying any patient information if present. Cite financial information in \$ signs using no abbreviations enclosed in quotation marks corresponding to the authors’ names in this format, Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the previous generation in this conversation throughout the table without adding additional quotations. [Third Prompt in Conversation]

Prompt C4: Construct a very large and comprehensive table of financial forecasts based only on the two previous generations in this conversation regarding the Clinical mAb Cancer Cost problem solutions. Only include results affecting Clinical mAb Cancer Cost problem financial forecasts, de-identifying any patient information if present. Cite financial information in \$ signs using no abbreviations enclosed in quotation marks corresponding to the authors’ names in this format, Feng K. et al. Convert other currencies into USD in \$ signs if present, and only use exact details derived from the two previous generations in this conversation throughout the table without adding additional quotations. [Fourth Prompt in Conversation]

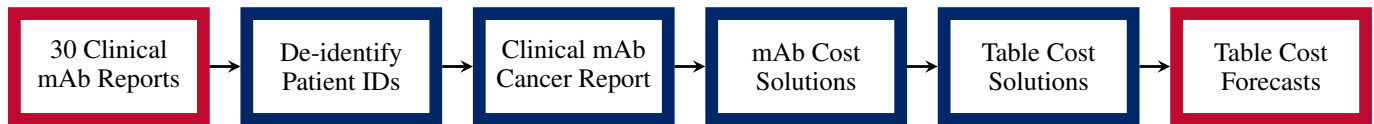


Table 10: Standard C Process Diagram

7 Part C Results: Clinical mAb Cancer Cost

Part C generations had a similar process of reasoning through cost effectiveness data with ChatGPT o3-mini as the prior section, but had 30 reports of clinical trial related data, as shown in Figure 8. The prompts in Table 10 were updated in designating the larger 16,845 word clinical Dataset C30 to yield a detailed report, cost solutions, and two financial tables. Reports typically followed the requested "Feng K. et al." format, returned currencies in quotations, and Generation C1 was in the correct “Executive Summary”, “Technical Details”, “Key Insights” format. The Standard C objectives path in Figure 9 was primarily followed throughout the four prompts, despite a shorter 1,350 word "four page" generation at 45.62 seconds. Generations utilized data from either Dataset C30 or within the conversation which was appropriate, but did not have more fine level control to include information "based only on the two previous generations".

Financial data consistency was achieved based on Clinical mAb therapies for cancer. The incrementally constrained output was followed by a shorter 538 word cost solutions report, 428 word cost solutions table, and a 384 word financial forecast. There were 30 Generation C1 author citations regarding financial information among 14 different authors (Table 11). Generation C2 had 15 author citations regarding financial information among 14 different authors (Table 12). Generation C3 had 14 author citations regarding financial information among 12 different authors (Table 13). Generation C4 had 11 author citations regarding financial information among 9 different authors (Table 14). Traceability across all four generations consisted of 1 partial in-context, incorrect author trace and 5 in-context traces that were within 30 reports where information was appropriate.

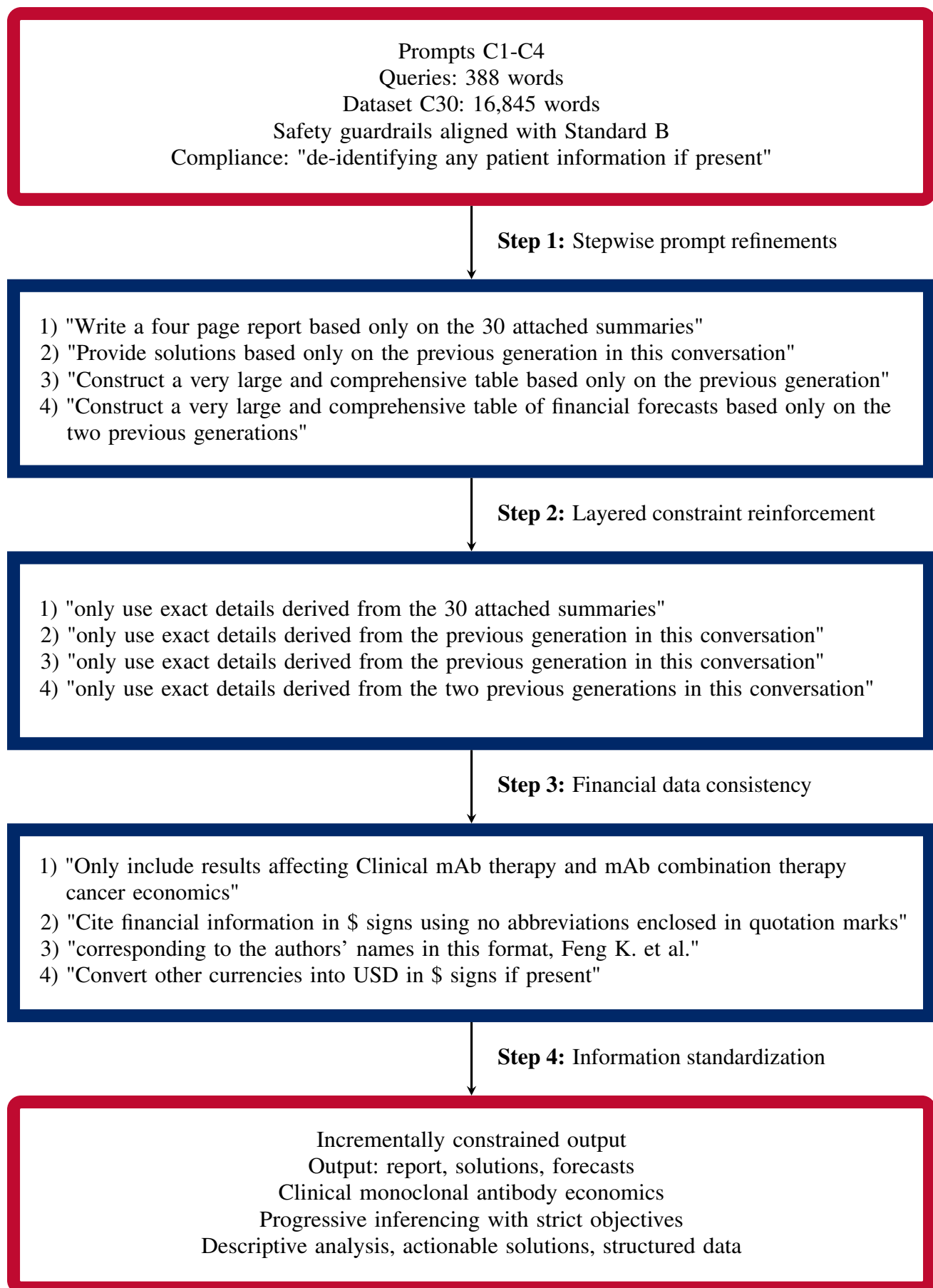


Figure 9: Standard C Objectives

Traceability: Generation C4. Clinical mAb Table Cost Forecasts, Table 14 Various authors. 2024-25

Dataset C30: "A 10% reduction in atezolizumab price would make ABC therapy cost-effective at "\$121,531.24/QALY"" AND "- ABC therapy had an incremental cost-effectiveness ratio (ICER) of "\$193,926.48/QALY" over a 20-year horizon""

Trace 01: "Atezolizumab plus bevacizumab and chemotherapy"10% reduction" AND "Lowers ICER to "\$121,531.24/QALY"" AND "Baseline ICER of "\$193,926.48/QALY""

Dataset C30: "Price reduction of 38% (to "\$1,764" per 1,200mg) would be needed for atezolizumab to achieve cost-effectiveness"

Trace 02: "Atezolizumab plus bevacizumab and chemotherapy" AND "38% reduction" AND "Achieves cost-effectiveness under local threshold"

Dataset C30: "China requires 29.81% nivolumab price reduction (to "\$920.87/100mg") for cost-effectiveness" AND "- Current pricing requires a 72.1% reduction in nivolumab costs to reach cost-effectiveness thresholds"

Trace 03: "Nivolumab plus chemotherapy" AND "29.81% reduction" (alternatively up to "72.1% reduction")" AND "Reduces nivolumab cost to "\$920.87/100mg""

Dataset C30: "EV: "\$131.52" per mg" AND "- Reducing EV price to "\$20" per mg would achieve 50% probability of cost-effectiveness" AND "- The incremental cost was "\$962,240.8" per patient" AND "- The incremental cost-effectiveness ratio (ICER) was "\$558,973" per QALY""

Trace 04: "Enfortumab vedotin plus pembrolizumab" AND "Reduce price to "\$20 per mg"" AND "Required to achieve cost-effectiveness; current ICER remains "\$558,973/QALY"" AND "Current price of "\$131.52 per mg" must be reduced"

Dataset C30: "Even with biosimilar versions, bevacizumab would need a 60.75% price reduction from "\$222.88" to "\$87.49" per 100mg to become cost-effective" AND "- The resulting incremental cost-effectiveness ratio (ICER) was "\$188,904.09" per QALY gained, substantially exceeding China's willingness-to-pay threshold of "\$38,201" per QALY"

Trace 05: "Bevacizumab" AND "Approximately "60.75% reduction"" AND "Baseline ICER remains high (e.g., "\$188,904.09/QALY") without reduction"

Dataset C30: "Even with charitable pricing discount of 41.4%, the ICER remained at "\$52,765.69" per QALY" AND "- Resulting incremental cost-effectiveness ratio (ICER) was "\$114,275.67" per QALY"

Trace 06: "Pembrolizumab combination therapies" AND "With a "41.4% charitable pricing discount", ICER reduces to "\$52,765.69/QALY"" AND "Baseline ICER of "\$114,275.67/QALY" reduced through targeted pricing measures"

Dataset C30: "Total pharmaceutical cost avoidance of "\$92,662,609" over the 10-year period"

Trace 07: "Solid tumors across clinical trials" AND "Total drug cost avoidance of "\$92,662,609" over 10 years"

Dataset C30: "Sensitivity Analysis Results:" AND "- Annual discount rate most impactful on ICER"

Trace 08: "Various cancer indications (e.g., mesothelioma, urothelial carcinoma)" AND "Sensitivity analyses show that shorter duration reduces overall treatment costs"

Dataset C30: "showed an incremental cost-effectiveness ratio (ICER) of "\$25,239.29" per quality-adjusted life year (QALY)" AND "- This ICER falls below China's willingness-to-pay threshold of "\$38,223.34""

Trace 09: "Advanced gastric cancer, China" AND "Achieved ICER of "\$25,239.29/QALY"" AND "Favorable relative to local threshold of "\$38,223.34/QALY""

8 Part C Discussion: Clinical mAb Cancer Cost

Generation C1 followed the required report format and the following command "only use exact details derived from the 30 attached summaries" proficiently, as no evidence was found that ChatGPT o3-mini relied on its own training data for the traceable outputs shown. The instruction to "Only include results affecting Clinical mAb therapy and mAb combination therapy cancer economics" also appeared to be followed closely, as seen in "Data from clinical trial cost avoidance analyses (reported by "Carreras M. et al. 2024") reveal that sponsored access to expensive mAb therapies can generate substantial cost savings, with total avoided costs reaching "\$92,662,609" over a 10-year period." As many of ChatGPT o3-mini and prior ChatGPT reasoning models limit word counts to 1,200-2,300 words [66, 67, 30], the 1,350 word output also followed this trend, but the attempt for a "four page report" did not help to increase output length. The 14 unique citations did not include all of the reports in the dataset, but ChatGPT o3-mini does disregard less relevant reports as seen in the Generation C3 chain-of-thought summary in Supplementary C14G. I'll also note references like "Lin Y. et al. 2024,"...but not "Feng K. et al." here."

Overall, generations C1-C4 had more unique authors throughout its conversation, with Generation C4 financial detail being significantly higher than B4. Generation C4 obtained information from a wider selection of quotes per trace, with up to four quotations from Dataset C30. Similar to Part B, the information in this study is most efficiently utilized by first locating specific combination drug therapies, cancer types, and financial information of interest using both Table 13 and Table 14. The following two options represent use cases to utilize the manuscript findings most effectively. **Instruction 1:** Use cost solutions and economic forecasts as an initial screening by following Table 13 and Table 14 guidance, followed by additional context gained from Table 11, Table 12, and supporting Dataset C30 if necessary. **Instruction 2:** Read full reports from Table 11, Table 12 or Dataset B15 for a more extensive understanding of financial synergies.

Clinical mAb Cancer Cost Analysis Report

This report synthesizes findings from thirty economic evaluations of monoclonal antibody (mAb) therapies and combination regimens across various cancer indications. The analyses consistently assess the balance between clinical benefits and economic burden using decision-analytic models. The following sections summarize key results regarding incremental costs, cost-effectiveness ratios, pricing sensitivities, and healthcare system implications for clinical mAb therapy and mAb combination therapy.

Executive Summary

Economic evaluations of mAb-based treatments in oncology consistently demonstrate that, although many combination regimens improve survival outcomes and quality-adjusted life years (QALYs), their high drug acquisition costs often result in incremental cost-effectiveness ratios (ICERs) well above common willingness-to-pay thresholds. For instance, analyses of atezolizumab plus bevacizumab with chemotherapy for cervical cancer reported ICERs of "\$193,926.48/QALY" (reported by "Lin Y. et al. 2024") and "\$73,601.43/QALY" (reported by "Cai H. et al. 2024"), both exceeding local thresholds. Similar challenges have been observed with bevacizumab combinations in glioblastoma and metastatic colorectal cancer, where ICERs of "\$84,071.12/QALY" and "\$188,904.09/QALY" (reported by "Chen Z. et al. 2024" and "Li Y. et al. 2024") indicate that current pricing renders these regimens economically unsustainable in some markets.

Studies of immune checkpoint inhibitors—including pembrolizumab, nivolumab, sintilimab, and others—further highlight that while these agents yield meaningful clinical improvements, their high costs (e.g., "\$114,275.67/QALY" for pembrolizumab combinations in cervical cancer reported by "Lin Y. et al. 2024" and ICERs exceeding "\$150,000/QALY" in other indications) necessitate significant price reductions or innovative reimbursement approaches. In markets such as China, evaluations of nivolumab and other PD-1 inhibitors often require reductions ranging from 29.81% to 72.1% to meet local cost-effectiveness thresholds (as shown by "Xiang G. et al. 2024" and "Meng K. et al. 2024").

Moreover, biosimilar studies reveal that modest price reductions—typically between 40% and 46% in European contexts—offer limited relief, underscoring the need for value-based pricing strategies. Data from clinical trial cost avoidance analyses further illustrate that sponsored access to expensive mAb therapies (with total avoided costs reaching "\$92,662,609" over 10 years, reported by "Carreras M. et al. 2024") can substantially alleviate budget pressures, yet long-term systemic adoption remains contingent on sustained pricing negotiations and targeted patient selection.

In summary, while mAb combination therapies provide demonstrable clinical advantages across diverse tumor types (including cervical, colorectal, lung, urothelial, head and neck, esophageal, and breast cancers), their widespread adoption is constrained by high incremental costs. Strategic interventions—including price negotiations, patient subgroup identification, and alternative financing mechanisms—are critical for aligning clinical innovation with economic sustainability.

Technical Details

Economic evaluations in these studies primarily employed decision-analytic frameworks such as partitioned survival and Markov models. Common methodological parameters include:

- Time Horizon & Cycle Length:** Models ranged from 5-year to lifetime horizons with cycle lengths varying from 1 week to 3 weeks (e.g., a 20-year horizon in "Lin Y. et al. 2024" and a 10-year horizon in "Peng J. et al. 2024").
- Discount Rates:** Annual discount rates for both costs and outcomes typically ranged from 3% to 5%.
- Health States:** The majority of models incorporated three health states—progression-free survival (PFS), progressive disease (PD), and death—to capture disease progression and treatment impact.
- Cost Inputs:** Detailed drug costs were central to the analyses. For example, atezolizumab was priced at "\$10,072.20" per cycle (reported by "Lin Y. et al. 2024"), while bevacizumab costs varied from "\$8,617.84" per cycle (reported by "Lin Y. et al. 2024") to "\$222.88" per 100mg (reported by "Li Y. et al. 2024"). Other mAb therapies such as pembrolizumab, nivolumab, and sintilimab were similarly priced at high acquisition costs (e.g., pembrolizumab at "\$2,458" per 100mg in "Lang W. et al. 2025" and sintilimab at "\$160.57" per 100mg in "Xiang Z. et al. 2024").
- Effectiveness Metrics:** QALYs were the primary measure of effectiveness. Incremental QALY gains ranged from modest increases of 0.09 QALYs (reported by "Nie J. et al. 2024") to improvements exceeding 1.0 QALY in some mAb combination strategies.
- Sensitivity Analyses:** Deterministic and probabilistic sensitivity analyses consistently identified drug acquisition costs as the most influential parameter. Studies reported that even a 10% to 60% reduction in mAb prices could markedly improve cost-effectiveness probabilities, as seen with pembrolizumab, nivolumab, and other agents across different indications.
- Comparative Models:** Several studies compared mAb-based combination therapies to standard chemotherapy (e.g., "Lin Y. et al. 2024", "Lang W. et al. 2025") and to other targeted regimens (e.g., nivolumab plus ipilimumab vs. EXTREME regimen in "Ye D. et al. 2024").

These technical frameworks underpin the economic evaluations and provide a robust basis for comparing clinical outcomes with associated costs, ultimately driving conclusions on cost-effectiveness across various mAb therapies.

Key Insights

- High Drug Acquisition Costs as Primary Barrier:**
 - Across multiple cancer indications, the high cost of mAbs remains the key driver of unfavorable ICERs. For instance, the addition of atezolizumab in cervical cancer resulted in an ICER of "\$193,926.48/QALY" (reported by "Lin Y. et al. 2024"), and pembrolizumab-based combinations exceeded thresholds even after substantial discounts.
 - Sensitivity analyses in several studies (e.g., "Cai H. et al. 2024" and "Meng K. et al. 2024") repeatedly highlighted that even minor changes in drug prices significantly alter cost-effectiveness outcomes.
- Need for Price Reductions and Value-Based Pricing:**
 - Numerous evaluations indicate that mAb combination therapies would only become economically viable with price reductions. For example, in China, nivolumab's cost requires a reduction of up to 72.1% (reported by "Meng K. et al. 2024") and a 29.81% decrease for nivolumab plus chemotherapy to be cost-effective (reported by "Xiang G. et al. 2024").
 - Similar patterns were observed in analyses of biosimilars, where modest price reductions (40–46%) were insufficient to meet cost-effectiveness thresholds, reinforcing the need for innovative pricing strategies.
- Incremental Clinical Benefits Versus Economic Burden:**
 - While mAb therapies such as atezolizumab, pembrolizumab, and nivolumab have shown improvements in progression-free survival and overall survival, these gains are often accompanied by high incremental costs. For example, pembrolizumab plus chemotherapy in pleural mesothelioma increased total treatment costs by "\$18,199.63" with an additional 0.23 QALYs (reported by "Lang W. et al. 2025").
 - In some instances, subgroup analyses revealed that cost-effectiveness improved in patients with favorable biomarker profiles or better performance status, suggesting that targeted patient selection may enhance economic value.
- Economic Impact of Combination Regimens:**
 - mAb combination therapies, particularly those combining immune checkpoint inhibitors with targeted agents or chemotherapy, consistently showed high ICERs. In metastatic urothelial carcinoma, enfortumab vedotin plus pembrolizumab incurred an incremental cost of "\$962,240.8" per patient and an ICER of "\$558,973/QALY" (reported by "Li A. et al. 2024"), underscoring the economic challenge despite improved clinical outcomes.
 - Conversely, some combinations, such as sintilimab plus chemotherapy for advanced gastric cancer, demonstrated favorable cost-effectiveness with an ICER of "\$25,239.29/QALY" (reported by "Xiang Z. et al. 2024"), highlighting regional pricing advantages and potential for broader access.
- Clinical Trial Sponsorship and Cost Avoidance:**
 - Data from clinical trial cost avoidance analyses (reported by "Carreras M. et al. 2024") reveal that sponsored access to expensive mAb therapies can generate substantial cost savings, with total avoided costs reaching "\$92,662,609" over a 10-year period.
 - This mechanism provides a critical pathway for patient access to innovative treatments, even as routine pricing remains a barrier to widespread adoption.
- Healthcare System Implications and Policy Considerations:**
 - The findings consistently emphasize that achieving cost-effectiveness for mAb therapies requires not only drug price reductions but also the implementation of value-based reimbursement models and patient subgroup targeting.
 - Policymakers are urged to consider innovative payment models, such as managed entry agreements and risk-sharing arrangements, to balance the clinical benefits of mAb therapies with the sustainability of healthcare budgets.

In conclusion, the reviewed analyses indicate that while mAb and mAb combination therapies deliver enhanced clinical outcomes across multiple cancer types, their current high costs pose significant economic challenges. The collective evidence underscores an urgent need for strategic pricing reforms, targeted patient selection, and alternative reimbursement models to improve the cost-effectiveness profile of these innovative cancer treatments.

Clinical mAb Cancer Cost Solutions. Generation C2, Various authors. 2024-2025. 538 words, 23.82 seconds

Below are several solutions—drawn exclusively from the previous analysis—that can improve clinical mAb cancer economics:

1. **Negotiate Significant Price Reductions**
 - For atezolizumab-based combinations in cervical cancer, a "10% reduction" lowers the ICER to "\$121,531.24/QALY" (as reported by "Lin Y. et al. 2024") while in the Chinese setting a "38% reduction" is required (as reported by "Cai H. et al. 2024").
 - For nivolumab plus chemotherapy in advanced urothelial carcinoma, a "29.81% reduction" (to "\$920.87/100mg") is necessary for cost-effectiveness in China (as reported by "Xiang G. et al. 2024"), and in other settings up to "72.1%" reduction is indicated (as reported by "Meng K. et al. 2024").
 - Similar large reductions are needed for enfortumab vedotin; for example, achieving cost-effectiveness may require reducing its price to "\$20" per mg from "\$131.52" per mg (as indicated by "Li A. et al. 2024").
2. **Adopt Value-Based Pricing and Reimbursement Models**
 - Implement managed entry agreements and risk-sharing arrangements that link reimbursement to clinical outcomes. For example, targeting patients with PD-L1 Combined Positive Scores ≥ 10 —where cost-effectiveness improves—can be part of a value-based strategy (as described in "Lin Y. et al. 2024" and "Lang W. et al. 2025").
3. **Promote Biosimilar Adoption**
 - Encourage the use of biosimilars for expensive mAbs such as bevacizumab. Although current biosimilar price reductions (around 40–46%) have shown only modest savings, increasing competition may drive prices lower. In one study, even biosimilar versions required a "60.75%" reduction to become cost-effective (as reported by "Li Y. et al. 2024").
4. **Implement Biomarker-Driven Patient Selection**
 - Focus on treating patient subgroups most likely to benefit from costly mAb therapies. For instance, studies have shown better economic outcomes in patients with high PD-L1 expression or favorable performance status (e.g., "Ye D. et al. 2024", "Li J. et al. 2024", and "Xiang Z. et al. 2024"). Such targeted selection can optimize cost-effectiveness by ensuring that high-cost treatments are reserved for those with the greatest potential benefit.
5. **Leverage Clinical Trial Sponsorship for Cost Avoidance**
 - Expand the use of clinical trial participation and philanthropic programs to achieve cost avoidance. One analysis reported total avoided drug costs of "\$92,662,609" over 10 years due to trial sponsorship (as reported by "Carreras M. et al. 2024"). This model can help offset the high costs of mAb therapies while providing patient access to innovative treatments.
6. **Optimize Treatment Duration**
 - Review and adjust treatment durations where possible to reduce cumulative drug costs. Sensitivity analyses indicate that the length of treatment has a substantial impact on total cost, suggesting that optimizing the duration without compromising efficacy can improve economic outcomes (as noted in "Gan Y. et al. 2024").
7. **Prioritize Cost-Effective Regimens in Specific Markets**
 - In markets with lower willingness-to-pay thresholds, such as China, focus on regimens already demonstrating favorable economics. For example, sintilimab plus chemotherapy, with an ICER of "\$25,239.29/QALY" (as reported by "Xiang Z. et al. 2024"), represents a cost-effective option that could be prioritized in reimbursement and treatment guidelines.

These solutions collectively address the high acquisition costs of mAb therapies by promoting price negotiations, value-based reimbursement, biosimilar adoption, and patient selection strategies—all of which are essential to improving the economic viability of clinical mAb cancer treatments.

Table 12: ChatGPT o3-mini Generation C2, Plain Text: Supplementary C14G, Full Input Context: C30

9 Limitations and Future Work

Preliminary tests of ChatGPT o3-mini-high were limited to smaller generations and yielded less financially detailed tables. Gemini 2.0 Flash Thinking Experimental 01-21 experienced issues with \$ characters, converting text to math despite troubleshooting, and tables were subsequently blank. LLMs run by software manufacturers have inference-time compute, inference-time budget, and output-length limitations to control costs that must be understood to obtain the correct amount of detail for applications. For Part A, 3.5 Sonnet had an inference-time standard deviation that was 20.2x smaller than for output-lengths, which likely indicates the model has strict time limitations, as previously experienced [64]. The Cheng M. et al. 1:1 SEK to USD conversion was likely due to the complexity of multiple RMB ¥, £, and \$ in surrounding context. For Generations B1 and C1, ChatGPT o3-mini had output-length constraints of 1,539 and 1,350 words after attempts of a longer "four page report" did not provide additional words vs. prior studies requesting a "two page report" or "detailed report" [64, 67, 66]. The prompts in the study were effective at grounding outputs to inputs, but it is possible that the number of authors being cited were limited, in other words 14/30 authors for Generation C1.

Scalability issues using these manuscript methods primarily include human-in-the-loop time to obtain new articles through literature review. Given the method of including studies that were directly related to this work, a number of hours were spent searching Google Scholar to obtain the final articles. Although the traceability studies for each of the three parts yielded excellent results regarding LLM inferred fidelity, the time required to manually identify each of the 279 traces for Part A, and 122 traces from generations and reports for Part B and C was significant. Designing, optimizing, and running prompts was also time consuming, but has been improved from recent studies [68, 64, 67]. Future work will likely evaluate the OpenAI Deep Research [69] and Grok 3 DeepSearch [70] web-based agents as a substitute to the human-in-the-loop literature reviews shown here. Some of the technology benefits such as speed and convenience are advantageous; while other areas such as reproducibility, traceability, and the ability to focus on more critical sources will likely require refinements. The standards developed here in using rigorous prompts for report structure, financial data consistency, and traceability will likely transition to automated tasks appropriately.

Clinical mAb Table Cost Solutions. Generation C3, Various authors. 2024-2025. 428 words, 33.95 seconds

Solution Category	Intervention / Strategy	Economic Impact / Metric	Required Adjustment / Target	Financial Detail / Cost Data	Source
Price Reduction Negotiations	Reduce atezolizumab price in ABC therapy for cervical cancer (US)	Lowers ICER to "\$121,531.24/QALY"	"10% reduction"	Baseline ICER reduced from a higher level	"Lin Y. et al. 2024"
Price Reduction Negotiations	Reduce atezolizumab price in ABC therapy for cervical cancer (China)	Achieves cost-effectiveness in the Chinese setting	"38% reduction"	Required reduction for economic viability	"Cai H. et al. 2024"
Price Reduction Negotiations	Reduce nivolumab price in combination with chemotherapy for advanced urothelial carcinoma (China)	Achieve cost-effectiveness; cost reduction to "\$920.87/100mg"	"29.81% reduction" (with up to "72.1%" reduction in alternative analysis)	Current pricing requires reduction to "\$920.87/100mg"	"Xiang G. et al. 2024" and "Meng K. et al. 2024"
Price Reduction Negotiations	Reduce enfortumab vedotin price in combination with pembrolizumab for advanced urothelial carcinoma (US)	Required to achieve cost-effectiveness	Reduce price to "\$20 per mg"	From current price of "\$131.52 per mg"	"Li A. et al. 2024"
Value-Based Pricing & Reimbursement	Implement managed entry agreements and risk-sharing arrangements; target patients with PD-L1 CPS ≥ 10	Improves cost-effectiveness in subgroups	Link reimbursement to clinical outcomes	Enhanced economic value in selected patients	"Lin Y. et al. 2024" and "Lang W. et al. 2025"
Biosimilar Adoption	Promote the use of biosimilars for expensive mAbs such as bevacizumab	Lowers drug costs to improve overall economic profile	Achieve approximately "60.75% reduction" in price	Required biosimilar price reduction for cost-effectiveness	"Li Y. et al. 2024"
Biomarker-Driven Patient Selection	Target treatment to patients with high PD-L1 expression or favorable performance status	Demonstrates improved cost-effectiveness in these subgroups	Employ biomarker testing to select patients	Results in modest QALY gains and improved ICERs (e.g., incremental gains observed)	"Ye D. et al. 2024", "Li J. et al. 2024", and "Xiang Z. et al. 2024"
Clinical Trial Sponsorship	Expand clinical trial participation and philanthropic programs	Achieves substantial cost avoidance	Increase enrollment in sponsored trials	Total cost avoidance of "\$92,662,609" over 10 years	"Carreras M. et al. 2024"
Optimize Treatment Duration	Review and adjust treatment duration without compromising efficacy	Reduces cumulative drug costs and improves cost-effectiveness	Optimize treatment length	Sensitivity analyses show duration is a key cost driver	"Gan Y. et al. 2024"
Prioritize Cost-Effective Regimens	Focus on regimens with favorable economics, e.g., sintilimab plus chemotherapy for advanced gastric cancer	Sintilimab plus chemotherapy achieved an ICER of "\$25,239.29/QALY"	Prioritize adoption in markets with lower willingness-to-pay thresholds	Observed ICER of "\$25,239.29/QALY"	"Xiang Z. et al. 2024"

Table 13: ChatGPT o3-mini Generation C3, Plain Text: Supplementary C14G, Full Input Context: C30

Clinical mAb Table Cost Forecasts. Generation C4, Various authors. 2024-2025. 384 words, 34.81 seconds

Intervention/ Strategy	Drug/ Therapy	Indication/ Region	Targeted Price Reduction/ Adjustment	Forecasted Financial Outcome	Financial Forecast Metric	Source
Price Reduction Negotiations	Atezolizumab plus bevacizumab and chemotherapy	Cervical cancer, US	"10% reduction"	Lowers ICER to "\$121,531.24/QALY"	Baseline ICER of "\$193,926.48/QALY"	"Lin Y. et al. 2024"
Price Reduction Negotiations	Atezolizumab plus bevacizumab and chemotherapy	Cervical cancer, China	"38% reduction"	Achieves cost-effectiveness under local threshold	Required adjustment from current pricing	"Cai H. et al. 2024"
Price Reduction Negotiations	Nivolumab plus chemotherapy	Advanced urothelial carcinoma, China	"29.81% reduction" (alternatively up to "72.1% reduction")	Reduces nivolumab cost to "\$920.87/100mg"	Meets cost-effectiveness relative to local threshold	"Xiang G. et al. 2024" and "Meng K. et al. 2024"
Price Reduction Negotiations	Enfortumab vedotin plus pembrolizumab	Metastatic urothelial carcinoma, US	Reduce price to "\$20 per mg"	Required to achieve cost-effectiveness; current ICER remains "\$558,973/QALY"	Current price of "\$131.52 per mg" must be reduced	"Li A. et al. 2024"
Biosimilar Adoption	Bevacizumab	Various indications (e.g., metastatic colorectal cancer, glioblas- toma)	Approximately "60.75% reduction"	Makes combination therapy cost-effective by lowering incremental cost	Baseline ICER remains high (e.g., "\$188,904.09/QALY") without reduction	"Li Y. et al. 2024"
Value-Based Pricing & Re- imbursement	Pembrolizumab combination therapies	Cervical cancer and others with PD-L1 CPS ≥10	Implement outcome-linked reimbursement strategies	With a "41.4% charitable pricing discount", ICER reduces to "\$52,765.69/QALY"	Baseline ICER of "\$114,275.67/QALY" reduced through targeted pricing measures	"Lin Y. et al. 2024" and "Lang W. et al. 2025"
Clinical Trial Sponsorship	Various mAb therapies (e.g., pembrolizumab, nivolumab, atezolizumab, bevacizumab)	Solid tumors across clinical trials	N/A	Total drug cost avoidance of "\$92,662,609" over 10 years	Aggregate avoided expenditure	"Carreras M. et al. 2024"
Optimize Treatment Duration	mAb therapies in combination regimens	Various cancer indications (e.g., mesothe- lioma, urothelial carcinoma)	Adjust treatment duration to lower cumulative costs	Sensitivity analyses show that shorter duration reduces overall treatment costs	Key cost driver identified; cumulative cost reduction expected without a specific dollar value	"Gan Y. et al. 2024"
Prioritize Cost- Effective Regimens	Sintilimab plus chemotherapy	Advanced gastric cancer, China	Not applicable (regimen is already cost-effective)	Achieved ICER of "\$25,239.29/QALY"	Favorable relative to local threshold of "\$38,223.34/QALY"	"Xiang Z. et al. 2024"

Table 14: ChatGPT o3-mini Generation C4, Plain Text: Supplementary C14G, Full Input Context: C30

10 Conclusions

The combination of prompt engineering, focused LLM report generation, and reasoning allowed for competitive financial solutions and forecasts that rigorously adhere to 45 source articles in global or clinical monoclonal antibody cancer economics. Instructions were provided for users to quickly screen tables for relevant information prior to utilizing datasets regarding additional context. Users may also gain a more complete understanding of financial synergies through evaluations of abbreviated solutions and full reports. Claude 3.5 Sonnet provided reliable summaries in roughly 20 minutes with a professional format that provided authors' financial figures in quotations, converted most currencies to US Dollar (USD), and limited the insertion of additional quotations. The 15 global mAb cancer economics reports were processed by reasoning model ChatGPT o3-mini in a linear dependency structure within 2.3 minutes to establish a chain of reliance by grounding financial information. The result was a strengthening in ethical AI principles using highly controlled and contextually anchored outputs that yielded an approximate 1,500 word formal cost report, a 500 word cost solution report, and two 450 word tables featuring economic solutions and forecasts with exact sources and dollar amounts. The financial impact for Part B was seen with the Lu B. et al. 2024 bevacizumab biosimilar incremental cost reduction of \$6,379 mean total 1 year cost savings per patient vs. the originator bevacizumab.

ChatGPT o3-mini likewise reasoned through 30 clinical monoclonal antibody cancer cost-effectiveness studies in 2.3 minutes to yield a high quality 1,350 word formal cost report, a 550 word cost solution report, and two 400 word tables featuring cost solutions and cost forecasts. The total run time for all LLM experiments in this study was 24.1 minutes to provide literature studies on 357,000 words and reason through complex financial information that are advantageous to the pharmaceutical industry, and extremely challenging for a human researcher to improve on, especially when time and expense are concerns. Part C included a 10 percent atezolizumab price reduction in a combination treatment that could lower ICER by \$72,000 based on data derived from the BEATcc clinical trial, as calculated by Lin Y. et al. This study brought to life many actual and prospective cancer drug cost cutting measures founded by authors in literature. The divide and conquer approach to obtain several forms of usable financial information across multiple prompts fostered creative expression, and was particularly crucial in avoiding LLM manufacturer inference-time compute, inference-time budget, and output-length constraints associated with single prompts. To the author's best knowledge, this was the first traceable LLM multi-chain cost analysis study of global monoclonal antibody drugs and cancer clinical trial utilities to thoroughly improve AI transparency.

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