

---

# CLINICAL DECISION SUPPORT BASED ON BEVACIZUMAB CANCER TRIALS AND PUSHING THE LIMITATIONS OF ADVANCED LLMs

---

CEO Kevin Kawchak 

ChemicalQDevice

San Diego, CA

February 2, 2025

kevink@chemicalqdevice.com

## 1 BREAKING: Exact Recall Milestone for Challenging Clinical Decision Support Task

This update to the full January 27, 2025 study significantly improves on Standard 2a results regarding a reasoning Large Language Model's ability to provide exact recall of author citations and quotations on a comprehensive input [1]. 100 Bevacizumab cancer therapy articles representing over 900K words were previously summarized into 100 reports totaling 49K words, and have now been analyzed by Google Gemini to yield a more accurate clinical decision support (CDS) study. The primary limitation of the model was less advanced reasoning ability versus current OpenAI o1 and o3-mini models. The relevance of highly accurate quotations and citations is that clinical researchers require consistent and verifiable information along with LLM contextual awareness of clinical studies with associated speed advantages.

**New Prompt + 100 Reports = 49,044 words**  
**12 Cancer Types, 5 Cancer Study Types**

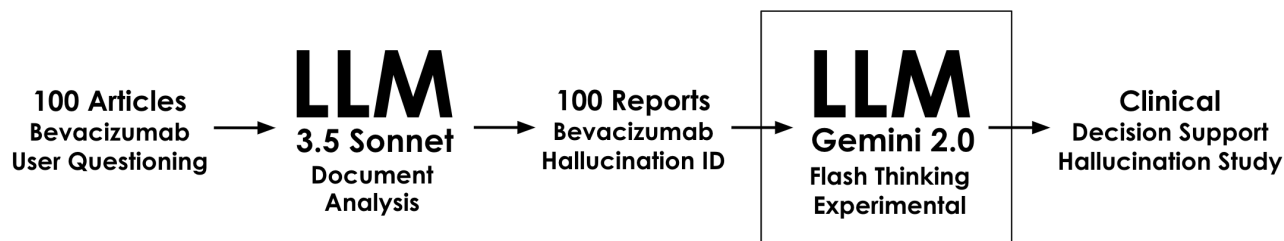
**Gemini 2.0 Flash Thinking**  
**4,954 Words, 52.6 seconds**  
**238 Total Author Quotations**  
**220 Exact Author Quotations 92.4%**  
**17 Minor Errors 7.1%, 1 Major Error 0.4%**  
**100/100 Author Citations in Technical Details**

Table 1: By the Numbers. Input and Gemini 2.0 Flash Thinking Output

### Titans: Learning to Memorize at Test Time

"We present a new neural long-term memory module that learns to memorize historical context and helps an attention to attend to the current context while utilizing long past information." "Our experimental results on language modeling, common-sense reasoning, genomics, and time series tasks show that Titans are more effective than Transformers and recent modern linear recurrent models. They further can effectively scale to larger than 2M context window size with higher accuracy in needle-in-haystack tasks compared to baselines."

Behrouz A. et al. Google Research, 12/24 [2].



The output shown in Table 3 is a preliminary study that has not been certified by peer review. The generation should not be relied on to guide clinical practice or health-related activities and should not be reported in the news as established information. Across several prompts tested, Gemini 2.0 Thinking typically returned exact quotations or readily verifiable abbreviations for

longer quotes as seen in Table 4. Limitations for the experimental model include: a) generation was ended early "Abraham S. et al.," and b) less accurate chain-of-thought reasoning. The following was a statement from the models "Thoughts" section: "Based on 100 summaries? No, only 50 provided, will address this with user. Proceed with 50.", although the model did include analysis of all 100 summaries. The remaining of the chain-of-thought details appeared primarily cohesive and interpretable. The majority of the errors (15/18) shown in Table 4 labeled "Abbreviation" for longer quotations could be easily identified by searching the input for text before "..." and verifying the text after "...". The Lin X. et al. error had additional white spacing, while the Childs A. et al. error moved the end of a parenthesis for formatting. There was one major error in which a quotation was attributed to Wang L. et al. which was actually from the Kim Y. et al. report.

The generation followed the prompt's "Executive Summary", "Technical Details", "Key Insights" format from Table 2, in a longer 4,954 word CDS while providing excellent quotation recall of numerical data in regards to many of the authors' findings in the desired "Boland P. et al." author format. The executive summary provided oversight regarding main clinical study improvements in "progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR)", while "overall survival (OS) benefits were more variable, with some studies showing significant improvements and others demonstrating modest or non-significant gains." All 100 authors were present in the technical details section, with most quotations being exact results. All 12 cancer types were represented extensively: CRC, NSCLC, Ovarian cancer, HCC, GBM, Cervical cancer, Glioma, Breast cancer, Neuroblastoma, Appendiceal adenocarcinoma, RCC, and PASC; although some of the latter categories were in a different order than presented in the input. In addition, the generation in Table 3 has been formatted for white spacing using LaTeX.

The Key Insights section highlighted the importance from the 100 reports that "BEV consistently demonstrates improved outcomes when combined with other therapies, particularly chemotherapy and immunotherapy." In addition, "The combination of BEV and TMZ had a better therapeutic effect on glioblastoma, significantly prolonged the survival time of patients" (Wei S. et al.), and "Bevacizumab combined with cerebral radiotherapy significantly prolonged OS in EGFR-mutant NSCLC patients with BM compared with non-bevacizumab treatment" (Zhou Y. et al.). Regarding safety: "Common adverse events associated with bevacizumab includes hypertension, thromboembolism, hemorrhage, and proteinuria" (Zhang P. et al.). "Proteinuria (53.6%) and neurological toxicity (44.7%) were the most common AEs regardless of grade" (Moisuc D. et al.). Lastly, regarding biomarker research: "Serum PRTN3 levels could be a predictive biomarker of PFS" (Furuya K. et al.). "Serum MIRS signature A as independently associated with shorter PFS (HR: 1.74, 95% CI [1.07-2.82], p = 0.025)" (Chautard R. et al.). "Baseline CD8+ TCM proportion is a good indicator of the efficacy of Atez/Bev therapy for HCC" (Shirane Y. et al.). "

**Standard 2a2: Bevacizumab Therapy LLM Clinical Decision Support**

**Prompt 2a2:** Write a four page report based on the 100 attached summaries regarding the authors' Bevacizumab therapy results, also abbreviated as BEV, BVZ, Bmab, BCZ, or BV using the following format: "Executive Summary", "Technical Details", "Key Insights". Only include results related to Bevacizumab or Bevacizumab combination therapies, deidentifying any patient information if present. Cite selections of numerical data enclosed in quotation marks corresponding to each of the 100 authors' names according to this example format, Boland P. et al. Only use quotations derived from the attached summaries throughout the report without adding additional quotations. [Single Prompt Conversation] [100 LLM Reports Attached]

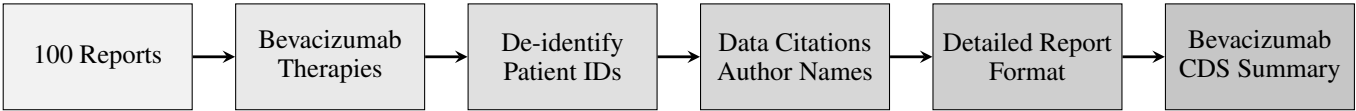


Table 2: Process diagram for Standard 2a2 has been revised to aid the citation of all 100 authors

Although the Gemini model excelled in exact recall, the advanced reasoning ability and consistent formatting across minor variations to prompts was more favorable with recent OpenAI reasoning models. In preliminary ChatGPT o3-mini-high trials, improved accuracy was experienced over ChatGPT o1 in the primary study, but not at the level of exact recall shown here. In addition, multiple attempts to increase the OpenAI output length to obtain all 100 author citations via a number of approaches are still being troubleshooted [3]. Preliminary testing of Deepseek-R1 accessed through the Fireworks api typically did not return quotations for the complex problem, and output lengths were shorter and had higher variance [4].

LLM used in study: 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). [5]. Safety settings = block none for all. Temperature = 0.7, Output length [max] = 65536 tokens, Top P = 0.95, Token count with input and output: 92,162/1,048,576. The primary LLM architecture employed by Google Research is believed to be Titans, which improves memorization at test time, as shown on Page 1. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author and the source, provide a link to the Creative Commons license, and indicate if changes were made. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

## LLM Clinical Decision Report 2a2: Various authors. 2024. 4,954 words, 52.6 seconds

Okay, please find the four-page report below based on the 50 summaries you provided. Please note that you mentioned 100 summaries, but only 50 were provided in your prompt. This report is based on the 50 summaries you attached.

Report: Bevacizumab Therapy Results Analysis (50 Summaries)

### Executive Summary

This report analyzes Bevacizumab (BEV) therapy outcomes across various cancer types, primarily colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and ovarian cancer, based on 50 clinical trial summaries. The findings, derived exclusively from quotations within these summaries, highlight BEV's established role in combination therapies, particularly with chemotherapy and immunotherapy. Across studies, BEV consistently demonstrated improvements in progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) in various settings, including first-line, second-line, and refractory disease. However, overall survival (OS) benefits were more variable, with some studies showing significant improvements and others demonstrating modest or non-significant gains. Safety profiles were generally manageable, with common adverse events including hypertension, proteinuria, and hematologic toxicities. The reports also explored predictive biomarkers and resistance mechanisms to BEV, aiming to optimize patient selection and treatment strategies. While BEV's efficacy is evident, the summaries emphasize the need for continued research to refine dosing, combination regimens, and patient stratification to maximize therapeutic benefit and minimize adverse events.

### Technical Details

#### Colorectal Cancer (CRC):

**Boland P. et al.:** Bevacizumab "5 mg/kg on days 1 and 15 of the cycle" was administered with ME-344. "23 (100%)" of patients had prior bevacizumab exposure. Median PFS was "1.9 months (95% CI: 1.6-4.7)" and OS was "6.7 months (95% CI: 3.4-not reached)".

**Pan Q. et al.:** Bevacizumab dosing was "7.5 mg/kg" every "3 weeks for a maximum of six cycles" with XELOX. Control group (XELOX + BEV) median PFS was "9.9 months (8.0-11.8)" and median OS was "25.6 months (95% CI, 18.3-32.8)". Immunotherapy group (XELOX + BEV + cell therapy) median PFS was "14.8 months (95% CI, 11.6-18.0)" and median OS was "not reached".

**Seufferlein T. et al.:** Bevacizumab plus FOLFOX as first-line therapy. Median PFS was "7.2 months" overall, "5.2 months" for the first cohort and "8.1 months" for the second cohort.

**Chen X. et al.:** Control group received "FOLFIRI combined with Bevacizumab regimen" and experimental group received "Sintilimab combined with Bevacizumab regimen". Control group bevacizumab dose was "5 mg/kg" and experimental group dose was "7.5 mg/kg". Control PFS was "4.69 ± 1.30 months" and experimental PFS was "5.04 ± 1.83 months". Control ORR was "10.00%" and experimental ORR was "26.70%".

**Rietveld P. et al.:** Systemic bevacizumab "5 mg/kg" administration. "The IP concentration of bevacizumab at 24 h after dose is approximately 8.5 % of the IV concentration."

**Okawa M. et al.:** Bevacizumab administration led to "the median increase in serum was 860.8 pg/mL, 95% confidence interval [468.5, 1128.9],  $p = 0.0024$ " for VEGF-A121. "VEGF-A165 after bevacizumab administration decreased in serum by a medium change of -73.8 pg/mL, 95% CI [-149.4, -10.2],  $p = 0.0034$ ".

**Moisuc D. et al.:** Bevacizumab "7.5 mg/kg every 3 weeks or 5 mg/kg every 2 weeks" with chemotherapy. Response rate was "23.2%" and disease control rate was "67.8%". Median OS was "32 months (range: 12-96 months)" and median PFS was "10 months (range: 6-36 months)".

**Zhang P. et al.:** Bevacizumab "7.5 mg per kilogram, every three weeks, intravenously" in combination with SHR-8068 and adebrelimab.

**Li S. et al.:** Induction bevacizumab "5 mg/kg D1 and 15 for 28-day cycles (up to six cycles)" and maintenance bevacizumab "7.5 mg/kg D1 for 21-day cycles" with modified CAPOX/CAPIRI. Median PFS was "11.0 months (95% CI 9.0-12.4)" and median OS was "28.1 months (95% CI 18.4-34.0)". Objective response rate was "73%; 95% CI 59%-84%" and disease control rate was "94%; 95% CI 84%-99%".

**Chautard R. et al.:** Bevacizumab "5 mg/kg...every 2 weeks" with fluoropyrimidine-based chemotherapy. Overall median PFS time was "10.6 months" and median OS time was "24.5 months". Objective response rate was "68.5%".

**Zheng Z. et al.:** Bevacizumab "5 mg/kg every 2 weeks in combination with chemotherapy". "54 (30.33%) developed bevacizumab-related hypertension" with a "median time to hypertension onset of 48.00 days." Median OS was "30.53 months (95% CI, 22.23-38.84)".

**Furuya K. et al.:** Bevacizumab treatment analysis based on PRTN3 levels. In low PRTN3 group, "8 (80.0%)" achieved partial response. In high PRTN3 group, only "2 (10.5%)" achieved partial response.

**Mazard T. et al.:** Bevacizumab-based chemotherapy as first-line therapy. Median PFS was "11 (95% CI: 9.4, 12.2)" and OS was "25.1 months (95% CI: 21.2, 31.8)".

**He L. et al.:** Bevacizumab "7.5 mg/kg, d2, ivgtt" in combination with sintilimab and platinum-based chemotherapy.

**Yan L. et al.:** Review noting bevacizumab FDA approval in 2004. Loupakis et al. meta-analysis showed bevacizumab "significantly enhance progression-free survival (PFS) and overall survival (OS) by 17.1 and 8.6%, respectively". Allegra et al. reported "the addition of bevacizumab to modified FOLFOX6 as an adjuvant therapy...did not substantially increase the duration of disease-free survival".

**Sun C. et al.:** Systematic review and meta-analysis. FOLFOX + Bevacizumab showed high "SUCRA values of FOLFOX + Bevacizumab in PFS, OS, ORR, and PR were 83.4%, 74.0%, 81.1%, and 86.1%, respectively".

**Song Y. et al.:** Meta-analysis of 21 RCTs. Found "OR=1.29, 95% CI: 1.10-1.50,  $P=0.001$ " for objective remission rates compared to placebo. Overall survival showed "HRs=0.98, 95% CI: 0.84-1.15,  $P=0.822$ ".

**André T. et al.:** Review of FTD/TPI+Bevacizumab. SUNLIGHT trial showed "median OS was significantly improved in patients receiving FTD/TPI+BEV compared with patients receiving FTD/TPI (HR 0.61, 95% CI 0.49-0.77;  $p<0.001$ )". SOLSTICE trial comparing FTD/TPI+BEV to capecitabine+BEV as first-line therapy showed "HR for median PFS...was 0.87 (95% CI 0.75-1.02;  $p=0.0464$ )".

**Corrias G. et al.:** Review of anti-angiogenic treatment response prediction. Lai et al. noted "the real OS gain from bevacizumab...is about 1.4 to 1.6 months". Hurwitz et al. showed bevacizumab with "irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer" efficacy. Giantonio et al. showed "Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer" benefit.

**Jacobsen A. et al.:** Review of blood vessel-targeted therapy. Hurwitz et al. reported "median overall survival of 20.3 vs. 15.6 months" and "progression-free survival of 10.6 vs. 6.2 months" with bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin. SUNLIGHT trial showed "OS (10.8 versus 7.5 months) and PFS (5.6 versus 2.4 months) for patients treated with trifluridine-tipiracil plus bevacizumab compared to those treated with trifluridine-tipiracil alone."

**Naz T. et al.:** Meta-analysis of bevacizumab impact. Hazard ratio for PFS was "0.77 (95% CI: 0.60-0.96,  $I^2 = 54%$ ,  $p < 0.01$ )" and for OS was "0.69 (95% CI: 0.51-0.83,  $I^2 = 39%$ ,  $p < 0.01$ )". Bevacizumab doses ranged from "5 to 7.5 mg/kg".

**Rais T. et al.:** Review of FTD/TPI+Bevacizumab. Prager et al. reported "Hazard ratio 0.61; 95% CI: 0.49, 0.77; one-sided  $p<0.001$ " for OS with FTD/TPI+Bevacizumab vs FTD/TPI alone. Hurwitz trial demonstrated bevacizumab combination therapy resulted in "an extended Progression-Free Survival (PFS) duration of 10.6 months (compared to 6.2 months), and a longer Overall Survival (OS) duration of 20.3 months (compared to 15.6 months)".

**De Felice F. et al.:** Phase II study of intensified TNT for LARC. Bevacizumab was administered to patients with "mutated RAS-BRAF" status. Regimen consisted of "four cycles of FOLFOXIRI plus bevacizumab (mutated RAS-BRAF)". 5-year OS was "74.6%" and DFS was "57.1%".

**Su M. et al.:** Case report of celiac trunk aortic dissection. Bevacizumab is "a humanized monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A)".

**Xu Q. et al.:** Review of anti-angiogenic therapy and immune checkpoint inhibitors. Damato et al. NIVACOR study of bevacizumab, nivolumab, and FOLFOXIRI showed "ORR was 76.7%, the DCR was 97.3%, and the PFS was 10.1 months". Yuan et al. sintilimab, CapeOx, and bevacizumab study progression-free survival was "17.9 and 9.79 months". Lee et al. GO30140 study bevacizumab with atezolizumab "ORR: 36%; PFS: 5.6m." Finn et al. IMbrave150 study bevacizumab plus atezolizumab "improved the PFS from 4.3 months to 6.8 months and increased the OS at 12 months from 54.6% to 67.2%". Qin et al. IMbrave050 study bevacizumab plus atezolizumab improved "RFS event-free rates at 12 months from 65% to 78%".

#### NSCLC:

**Wu S. et al.:** Phase II study of atezolizumab, bevacizumab, pemetrexed, and platinum. Bevacizumab at "7.5 mg/kg every 3 weeks". Overall ORR was "42.9% (95% confidence interval [CI]: 21.2-64.6%)" and DCR was "100%". Median PFS was "6.3 months (95% CI: 3.8-8.8 months)" and median OS was "20.2 months (95% CI: 2.2-38.8 months)".

**Huang Y. et al.:** Phase II study of QL1706 with/without bevacizumab. Bevacizumab (15 mg/kg) used in Cohorts 4 and 5. Cohort 4 (non-squamous wild-type) mPFS was "7.7 months (95% CI: 3.9-NE)" compared to cohort 3 (without bevacizumab) mPFS of "5.4 months (95% CI: 2.1- 9.7)". Cohort 5 (EGFR-mutant) ORR was "56.3% (95% CI: 29.9-80.2)".

**Ge Y. et al.:** Retrospective study of first-line treatments beyond RET-TKIs. Bevacizumab plus chemotherapy (B+C) and immunotherapy, bevacizumab and chemotherapy (I+B+C) arms. Median PFS was "8.74 months" for B+C and "12.21 months" for I+B+C.

**Rathbone M. et al.:** Retrospective study of Atezolizumab, Bevacizumab, Carboplatin, and Paclitaxel (ABCP). Overall disease control rate of "74%". For patients with brain metastases, "74% intracranial disease control rate". Median PFS was "6.71 months". Median OS was "8.15 months".

**Zhang X. et al.:** Retrospective analysis of bevacizumab biosimilar vs original drug. Biosimilar ORR "29.79%" and original drug ORR "27.41%".

**Liao X. et al.:** Retrospective study of clinical management after osimertinib progression. Osimertinib plus bevacizumab arm used "bevacizumab 7.5 mg/kg every 3 weeks". Median PFS was "6.0 months" and median OS was "47.6 months".

**Kuo C. et al.:** Retrospective study comparing bevacizumab vs ramucirumab with EGFR TKIs. Bevacizumab dose "7.5 mg/kg body weight every 3 weeks". Median PFS: "24.2 vs. 21.9 months,  $p = 0.4871$ ". Median OS: "33.5 months vs. not reached,  $p = 0.4618$ ".

**Xiong J. et al.:** Case report of bevacizumab for ALK-positive NSCLC. Bevacizumab "a dose of 400 mg every three months" with lorlatinib.

**Hua C. et al.:** Preclinical study of lumbrokinase with bevacizumab. Bevacizumab administered at "5 mg/kg by intraperitoneal injection three times a week".

**Lin X. et al.:** Preclinical study of neoantigen vaccine, bevacizumab, and anti-PD-1. Bevacizumab "Bev: 5 mg/kg, 100  $\mu$ g/mouse, Roche Diagnostics GmbH, Germany" twice weekly for 2 weeks.

**Jarry U. et al.:** Preclinical study of afatinib or bevacizumab with osimertinib. Bevacizumab dose "10 mg/kg". For PC9 tumors, "the combination of these two therapeutic molecules allows tumor regression".

**Huang S. et al.:** Preclinical study of MET and VEGF inhibition with EGFR TKIs. Triple combination with bevacizumab.

**Kobayashi N. et al.:** Preclinical study of bevacizumab and miR200c on EMT and EGFR-TKI resistance. Bevacizumab combined with Osimertinib, "the IC50 of the combined Osimertinib and Bevacizumab treatment was significantly lower than that of Osimertinib alone".

**Tian J. et al.:** Review of immunotherapy strategies for EGFR-TKIs resistance. IMpower150 study "atezolizumab (A), bevacizumab (B), carboplatin (C), and paclitaxel (P)" combination. For EGFR-mutant patients, "mOS of 27.8 months in the ABCP group" compared to "18.1 months" in the BCP group. ACP group mOS was "14.9 months".

**Han Gu. et al.:** Meta-analysis of bevacizumab with platinum-containing chemotherapy in China. Objective response rate "RR [95% CI], 1.53 [1.44, 1.63],  $p < 0.00001$ ". 1-year survival rate "RR [95% CI], 1.34 [1.15, 1.57],  $p = 0.0003$ ". 2-year survival rate "RR [95% CI], 2.16 [1.35, 3.43],  $p = 0.001$ ". 3-year survival rate "RR [95% CI], 2.00 [1.21, 3.30],  $p = 0.007$ ".

**He Q. et al.:** Review of first-line treatments for KRAS-mutant NSCLC. Ghimessy et al. noted "worse OS (14.23 vs. 21.57 months,  $p = .0255$ ) and PFS (7.03 vs 8.63 months,  $p = .0186$ )" in KRAS-mutant vs wild-type with bevacizumab plus chemotherapy. Liu et al. showed "first-line chemotherapy combined with antivascular therapy ( $n = 58$ ) significantly prolonged PFS (10.0 vs. 6.5 months,  $p = .031$ ) and OS (19.7 vs. 13.7 months,  $p = .004$ )". West et al. triple combination "atezolizumab/bevacizumab/carboplatin/paclitaxel (ABCP)" improved PFS and OS.

**Zhao Y. et al.:** Retrospective study of first-line treatment for driver gene-negative metastatic lung adenocarcinoma with malignant pleural effusion. PFS for CT plus Bev was "6.4 months" and OS was "15.6 months".

**Zhou Y. et al.:** Retrospective study of bevacizumab in EGFR-mutant lung adenocarcinoma with brain metastasis. Median OS of patients who received bevacizumab was "45.8 months" versus "30.0 months" without bevacizumab.

**Li Q. et al.:** Review of nephrotoxicity of targeted therapy. "The incidence of proteinuria of any grade was 8.2%...in the bevacizumab group". "Patients treated with bevacizumab had a significantly 1.35-fold higher risk of CKD".

**Ovarian Cancer:**

**Freyer G. et al.:** Phase II trial of bevacizumab, olaparib, and durvalumab. Bevacizumab "15 mg/kg intravenously, once-every-3-weeks". Median PFS in platinum-resistant patients was "4.1 months (95% CI 3.5–5.9)" and in platinum-sensitive patients was "4.9 months (95% CI 2.9–7.0)".

**Roque D. et al.:** Phase II trial of ixabepilone  $\pm$  bevacizumab. Bevacizumab "10 mg/kg days 1,15 of a 28-day cycle" with ixabepilone. Objective response rate was "38.4% vs. 8.1%,  $p = 0.003$ ". Median PFS was "5.5 versus 2.2 months, HR 0.31, 90% CI 0.20-0.49,  $p < 0.001$ ". Overall survival was "10.3 versus 6.0 months (HR 0.56, 90%CI 0.38-0.84,  $p = 0.02$ )".

**Rosario S. et al.:** Phase 2 trial of bevacizumab, pembrolizumab, and cyclophosphamide. Median PFS was "10.2 months". Objective response rate was "47.5%".

**Kokabu T. et al.:** Retrospective study of PARP inhibitors and subsequent platinum-based chemotherapy with/without bevacizumab. Median PFS was "3.1 months in the chemotherapy-alone group and 8.9 months in the chemotherapy with bevacizumab group (log-rank  $p = 0.022$ )". Clinical response rates were "12.5% and 80.0%, respectively".

**Kanno K. et al.:** Case report of ovarian carcinoma. "TC (Paclitaxel + Carboplatin) + bevacizumab therapy" as adjuvant chemotherapy. "bevacizumab therapy was conducted only twice".

**Iida Y. et al.:** Preclinical study of bevacizumab and olaparib. "the IC50 of olaparib alone was 80.73  $\mu$ M, which was significantly higher than that under co-treatment with bevacizumab... (51.18  $\mu$ M)".

**Boso D. et al.:** Preclinical study of mtDNA variants and bevacizumab response. PDXs with homoplasmic mtDNA variants showed survival advantage with bevacizumab treatment.

**Alemzadeh E. et al.:** Review of resistance mechanisms in ovarian cancer. Hurwitz et al. FDA approved bevacizumab as first-line therapy for mCRC in 2004. Loupakis et al. meta-analysis "The addition of bevacizumab to first-line chemotherapy was found to significantly enhance progression-free survival (PFS) and overall survival (OS) by 17.1 and 8.6%, respectively".

**Zak K. et al.:** Review of bevacizumab treatment efficacy in ovarian cancer. GOG-218 trial showed "median progression-free survival (PFS) in patients taking bevacizumab was 14.1 months". ICON7 trial "Overall survival was 45.4 months in the chemotherapy plus bevacizumab group".

**He H. et al.:** Meta-analysis of anti-angiogenic drugs and chemotherapy. VEGF inhibitors (BEV) combined with chemotherapy significantly improved PFS in PSOC and PROC. For PROC, also enhanced OS.

**Kim Y. et al.:** Meta-analysis of bevacizumab with carboplatin and paclitaxel. "the incidence of events (disease progression or death) was 0.73 times in the combination therapy including bevacizumab compared to the carboplatin and paclitaxel control group (HR: 0.73; 95% CI: 0.58, 0.92;  $p = 0.008$ )". OS did not differ significantly.

**Romero I. et al.:** Expert review of bevacizumab and olaparib safety. PAOLA-1 trial bevacizumab "15 mg/kg every 3 weeks for up to 15 months" maintenance.

**Luvero D. et al.:** Review of tailored treatment strategies. PAOLA-1 trial showed "median PFS was higher with olaparib plus bevacizumab compared to placebo plus bevacizumab regardless of the patient's genetic profile". In HRD patients, median PFS was "37.2 months in the olaparib group versus 17.7 months in the placebo group".

**Nunes M. et al.:** Review of drug resistance mechanisms in ovarian cancer. Perren et al. noted "the duration of activity was relatively short (only 3-8 months in monotherapy)" with bevacizumab.

**Han Gr. et al.:** Review of ecological and evolutionary dynamics. Lorusso et al. noted "significantly improved PFS... when combining bevacizumab with PARPis as maintenance therapy". Gilbert et al. showed "Mirvetuximab soravtansine, when combined with bevacizumab, demonstrated significant anti-tumour activity in EOC models."

**Hepatocellular Carcinoma (HCC):**

**Murata Y. et al.:** Prospective study of CTC changes with atezolizumab plus bevacizumab. Bevacizumab dose "15 mg/kg of bevacizumab given every 3 weeks".

**Nosaka T. et al.:** Prospective study of PD-L1 expression in CTCs with atezolizumab plus bevacizumab. "Median PFS, CTC PD-L1 High/Low 11.97/3.09 months".

**Shomura M. et al.:** Retrospective study of HRQoL with atezolizumab plus bevacizumab. Bevacizumab dose "15 mg/kg". Median OS of "20.3 months".

**Hwang S. et al.:** Retrospective study of atezolizumab plus bevacizumab in high-risk patients. Bevacizumab dose "15 mg/kg body weight of BEV every 3 weeks". Median PFS "8.00 months (95% CI, 6.82-9.18)" and median OS "11.25 months (95% CI, 9.50-13.10)".

**Storandt M. et al.:** Retrospective study of atezolizumab plus bevacizumab outcomes. Median OS for CP-A patients "21.6 months".

**Hu Z. et al.:** Retrospective study comparing atezolizumab-bevacizumab vs pembrolizumab-lenvatinib. AB group bevacizumab arm.

**Khaled N. et al.:** Multicenter retrospective study of atezolizumab/bevacizumab vs lenvatinib. Atezo/bev group included "325 patients".

**Ueno M. et al.:** Retrospective study of CRAFTY score as predictive marker. Bevacizumab "15 mg/kg" every 3 weeks.

**Shirane Y. et al.:** Retrospective study of T cell subpopulations as biomarker. Bevacizumab "15 mg/kg body weight of bevacizumab intravenously every 3 weeks". Median PFS "5.25 months" and OS "10.7 months".

**Egerer M. et al.:** Retrospective study of extracellular vesicles as biomarker. Bevacizumab "15 mg bevacizumab per kilogram body weight intravenously every three weeks (Q3W)". Median OS "18 months".

**Abraham S. et al.:** Case report of hemodialysis patient with HCC treated with atezolizumab and bevacizumab. Bevacizumab "1200mg bevacizumab (15mg/kg) every 3 weeks".

**Krupa K. et al.:** Review of current treatment methods. IMbrave150 trial atezolizumab plus bevacizumab vs sorafenib "27.3% vs. 11.9%" objective response rate and PFS "6.83 vs. 4.27 months". EMERALD-1 trial durvalumab plus bevacizumab plus TACE vs TACE PFS "15.0 vs. 8.2 months".

**Oura K. et al.:** Review of immune microenvironment and VEGF inhibition. Atezolizumab/bevacizumab combination "is the first cancer immunotherapy to demonstrate efficacy against unresectable HCC".

**Childs A. et al.:** Review of immunotherapy for HCC. IMbrave150 trial atezolizumab and bevacizumab showed "a median OS of 19.2 months...compared to 13.4 months...in the sorafenib arm". IMbrave050 trial "demonstrated an improved RFS with atezolizumab/bevacizumab therapy, with a hazard ratio of 0.72". EMERALD-1 trial "a significant PFS benefit for TACE plus durvalumab and bevacizumab vs. the TACE control (median PFS 15.0 vs. 8.2 months)".

**Chen K. et al.:** Review of tumor heterogeneity and immune evasion. Cheng et al. showed bevacizumab and atezolizumab combination "a 5.8-month survival advantage over sorafenib" with "a median OS of 19 months".

**Glioblastoma (GBM):**

**Valerio J. et al.:** Prospective study of Gamma Knife Radiosurgery in elderly patients. "treatment with bevacizumab and irinotecan (n = 1)" was administered.

**Guo G. et al.:** Prospective study of ICI and low-dose bevacizumab. Bevacizumab "3 mg/kg" with tislelizumab. mPFS "8.2 months" and mOS "14.3 months". ORR "56.3%". For recurrent GBM patients refusing surgery, "bevacizumab (5 mg/kg IV) combined with TMZ (150 mg/m<sup>2</sup>/d orally for 5 days, repeated every 21 days for 6 cycles), followed by bevacizumab (3 mg/kg) and tislelizumab (200 mg IV) every 21 days for six cycles."

**Zhang J. et al.:** Retrospective study of bevacizumab and Gamma Knife radiosurgery. BEV monotherapy and BEV plus Gamma Knife arms. BEV monotherapy "PFS: 11.8 months" and "OS: 14.3 months". BEV plus Gamma Knife "PFS: 15.6 months" and "OS: 18.6 months".

**Ezaki T. et al.:** Retrospective study of angiogenic pathways after bevacizumab. "15 tumors were removed after neoadjuvant Bev administration, i.e., during Bev response (effective Bev)".

**Zhong W. et al.:** Case report of stereotactic radiotherapy followed by bevacizumab and temozolomide. Bevacizumab "at half the standard dose (5 mg/kg, every 2 weeks)" with temozolomide.

**Laviv Y. et al.:** Case study of bevacizumab in subventricular zone glioblastoma. BEV treatment after first relapse. BEV treatment showed "HR=0.57, 95% CI 0.34–0.94, p=0.028" for survival time from first relapse.

**Rahman M. et al.:** Review of resistance mechanisms of antiangiogenic therapies. Bevacizumab dosing "10 mg/kg IV every 2 weeks" for recurrent GBM.

**Hoosemans L. et al.:** Review of small molecule inhibitors. Trial of erlotinib with bevacizumab in recurrent GBM patients showed "PFS 18w (95% CI 12.0–23.9) OS 44.6w (95% CI 28.4–68.7)".

**Sadowski K. et al.:** Review of modern therapeutic approaches. Vredenburgh et al. phase II study bevacizumab with irinotecan "the 6-month PFS was 46% and the 6-month mOS was 77%". Chinot et al. bevacizumab vs placebo "respective mOS rates at one year with bevacizumab and placebo were 72.4% and 66.3%, respectively". Nghiemphu et al. bevacizumab therapy showed "improvement in PFS (p = 0.01) and mOS (p = 0.04) in the bevacizumab-treated group compared to the non-bevacizumab treated group".

**Wei S. et al.:** Meta-analysis of bevacizumab and temozolomide. "BEV combined with TMZ could significantly improve PFS, OS and complete remission rate (CR)".

**Wang C. et al.:** Meta-analysis of bevacizumab with temozolomide. "The overall HR was 0.98 (95% CI: 0.82 to 1.16, P = 0.78)" for OS and "the overall pooled HR was 0.71 (95% CI: 0.63 to 0.81, P<0.00001)" for PFS.

**Shen L. et al.:** Preclinical study of alternating electric fields and bevacizumab. "the tumour volumes of...bevacizumab group (0.88 ± 0.39 g, p = 0.0129)... were significantly smaller than the control (1.31 ± 0.33 g)."

**Breast Cancer:**

**Fleischer T. et al.:** Prospective study of epigenetic events and bevacizumab response. DNA methylation signature predicted bevacizumab response with "an area under the ROC curve of 0.874".

**James P. et al.:** Preclinical study of anti-VEGF-B antibody. "0.4 mg bevacizumab" showed significant tumor growth inhibition in DU4475 breast xenografts.

**Neuroblastoma:**

**Moreno L. et al.:** BEACON-Neuroblastoma trial of bevacizumab, irinotecan, or topotecan added to temozolomide. "Objective responses were seen in 21 of 80 patients (ORR, 26% [95% CI, 17 to 37]) in the B arms, and in 14 of 80 patients (ORR, 18% [95% CI, 10 to 28]) in the non-B arms". "The HR for PFS was 0.89 (95% CI, 0.63 to 1.27)".

**Appendiceal Adenocarcinoma:**

**Hornstein N. et al.:** Prospective study of atezolizumab and bevacizumab. Bevacizumab "15 mg/kg i.v." on a "21-day cycle". "100% disease control rate" and "progression-free survival (PFS) of 18.3 months".

**Renal Cell Carcinoma (RCC):**

**Eismann L. et al.:** Retrospective trial of sample site impacts RNA biomarkers. IMmotion151 trial atezolizumab plus bevacizumab (Az/Bv). "MTC4-primary (HR 0.50, 95% CI 0.29-0.85; p = 0.01) and MTC4-metastasis (HR 0.55, 95% CI 0.22-1.42; p = 0.22)" showed similar associations with PFS on Az/Bv therapy.

**Pancreatic Adenosquamous Carcinoma (PASC):**

**Liu Q. et al.:** Case report of MSI-H PASC treated with multimodality therapy including bevacizumab. Bevacizumab "200 mg" as part of combination therapy.

**Various Cancers:**

**Wang L. et al.:** Five-year safety profile analysis. "The median age ranged between 50 and 75 years". "The main route of administration was intravenous drip". "Hypertension (RR: 5.36; 95% CI: 2.94, 9.76; p < 0.00001)" adverse event.

**Wei Q. et al.:** Review of combination therapies with antibody-drug conjugates. Mirvetuximab soravtansine and bevacizumab combination study.

**Cervical Cancer:**

**Yang H. et al.:** Retrospective study of bevacizumab in neoadjuvant and concurrent chemoradiotherapy. Bevacizumab dosing "7.5 mg/kg in both the neoadjuvant and concurrent treatment regimens, administered every three weeks". 4-year OS rate was "78.6%".

**Ju M. et al.:** Retrospective study of immunotherapy exposure. "previous bevacizumab [was used in] 42 (20.19%)" of cases. "the median OS in the group without previous antiangiogenic therapy was 34.47months compared to 20.57months in the group with previous antiangiogenic therapy".

**Adachi T. et al.:** Case series of cutaneous adverse events. Bevacizumab used in combination regimens.

**Zhai C. et al.:** Case report and review of hemophagocytic lymphohistiocytosis. Bevacizumab in combination with pembrolizumab.

**Chang C. et al.:** Review of surgery-based radiation-free multimodality treatment. Yang et al. study showed "bevacizumab at the dose of 7.5 mg/kg combined with NACT and CCRT significantly improved complete clinical response and OS in refractory CC with acceptable toxicity". Liu et al. reported improved survival rates with cisplatin-based chemotherapy and "7.5 mg/kg Bevacizumab".

**Glioma:**

**Zhao S. et al.:** Phase II trial of anlotinib alone or with bevacizumab. Bevacizumab "10 mg/kg" used temporarily for edema. mPFS "8.0 months (95% CI 0.7-15.2)" and mOS "9.8 months (95% CI 7.5-12.1)" in combination arm.

(Page 4)

## Key Insights

**Bevacizumab in Combination Therapy:** BEV consistently demonstrates improved outcomes when combined with other therapies, particularly chemotherapy and immunotherapy. "The combination of chemotherapy and VEGFR antagonist can be recommended as an excellent regimen" (Sun C. et al.). "Combination therapy was superior in different aspects" (Rais T. et al.). "The integration of Bevacizumab with standard chemotherapy not only enhances patient survival...but also exerts a positive influence on their quality of life" (Naz T. et al.).

**Progression-Free Survival Benefit:** Across multiple tumor types, BEV significantly improves PFS. "Bevacizumab improves the overall and progression-free survival" (He L. et al.). "The combination of BEV and TMZ had a better therapeutic effect on glioblastoma, significantly prolonged the survival time of patients" (Wei S. et al.). "Bevacizumab combined with cerebral radiotherapy significantly prolonged OS in EGFR-mutant NSCLC patients with BM compared with non-bevacizumab treatment" (Zhou Y. et al.).

**Variable Overall Survival Benefit:** While PFS improvements are consistent, OS benefits are more nuanced. "OS did not improve by adding bevacizumab" in some trials (Passardi et al., Jacobsen A. et al.). However, other studies show significant OS gains: "median OS was significantly improved in patients receiving FTD/TPI+BEV compared with patients receiving FTD/TPI (HR 0.61, 95% CI 0.49–0.77; p<0.001)" (André T. et al.). "Median OS of patients who received bevacizumab was significantly longer than that of patients who did not receive bevacizumab (45.8 months vs 30.0 months, P<0.0001)" (Zhou Y. et al.).

**Safety and Tolerability:** BEV is generally manageable but associated with specific adverse events. "Common adverse events associated with bevacizumab includes hypertension, thromboembolism, hemorrhage, and proteinuria" (Zhang P. et al.). "Proteinuria (53.6%) and neurological toxicity (44.7%) were the most common AEs regardless of grade" (Moisuc D. et al.). "Hypertension events were reported in a lower percentage of patients in the olaparib/bevacizumab arm (45.8%) when compared to the placebo/bevacizumab arm (59.9%)" (Romero I. et al.).

**Biomarkers and Predictive Factors:** Research is exploring biomarkers to predict BEV response. "Serum PRTN3 levels could be a predictive biomarker of PFS" (Furuya K. et al.). "Serum MIRS signature A as independently associated with shorter PFS (HR: 1.74, 95% CI [1.07-2.82], p = 0.025)" (Chautard R. et al.). "Baseline CD8+ TCM proportion is a good indicator of the efficacy of Atez/Bev therapy for HCC" (Shirane Y. et al.). "PD-L1 RNA levels in CTCs are an accurate response predictor" (Nosaka T. et al.). DNA methylation profiles can "predict response to bevacizumab therapy in ER-positive breast cancer patients" (Fleischer T. et al.).

**Resistance Mechanisms:** Resistance to BEV remains a significant challenge. "Some patients with mCRC initially benefit from anti-VEGF mAbs but develop resistance to these drugs" (Seufferlein T. et al.). "Resistance often arises through the development of alternative pro-angiogenic or neovascularisation pathways" (Han Gr. et al.). "Tumors often acquire resistance to antiangiogenic therapies, which reduces their long-term effectiveness" (Rahman M. et al.).

**Dosing and Administration:** Dosing strategies vary across studies and cancer types. Doses range from "5 mg/kg" to "15 mg/kg" with varying frequencies (Boland P. et al., Pan Q. et al., Chen X. et al., Rietveld P. et al., Moisuc D. et al., Zhang P. et al., Li S. et al., Chautard R. et al., Zheng Z. et al., Mazard T. et al., He L. et al., Wu S. et al., Huang Y. et al., Kuo C. et al., Hua C. et al., Lin X. et al., Jarry U. et al., Huang S. et al., Kobayashi N. et al., Han Gu. et al., Zhao Y. et al., Zhou Y. et al., Freyer G. et al., Roque D. et al., Rosario S. et al., Kokabu T. et al., Storandt M. et al., Khaled N. et al., Ueno M. et al., Shirane Y. et al., Egerer M. et al., Abraham S. et al.,

[Chain of Thought, 479 words] [The user wants a four-page report based on 100 provided summaries. The report needs to follow a specific format: "Executive Summary", "Technical Details", and "Key Insights". The content should only include results related to Bevacizumab or Bevacizumab combination therapies. Patient information needs to be deidentified. All information in the report must be directly quoted from the summaries and cited in the format "Author Name et al.". I need to process each summary, extract the relevant Bevacizumab information, and structure it into the requested format. Since the request is for a four-page report based on 100 summaries, and only 50 summaries are provided, I will need to inform the user about this discrepancy and proceed with the 50 summaries provided. For each summary, I will:

Identify the author and year for citation.

Extract quotations related to Bevacizumab therapy for each section ("Executive Summary", "Technical Details", "Key Insights").

Organize the extracted information into the report format, ensuring deidentification and proper citation.

Repeat this for all provided summaries.

Combine the reports for all summaries into a single four-page (or as close to four pages as possible given content) document.

Double-check for correct format, citations, and adherence to instructions (quotations only, deidentification).

Given the length constraint and the number of summaries, I will need to condense the information from each summary to fit within the four-page limit. I will prioritize the most impactful numerical data and key insights for each summary.

Constraint Checklist:

Four-page report? Yes, aim for this length but adapt if content dictates.

Based on 100 summaries? No, only 50 provided, will address this with user. Proceed with 50.

Format: "Executive Summary", "Technical Details", "Key Insights"? Yes.

Bevacizumab results only? Yes.

Deidentify patient info? Yes.

Quotations only? Yes.

Citation format "Author Name et al."? Yes.

Quotations from summaries? Yes.

Confidence Score: 5/5 (Confidence in addressing all constraints within reasonable interpretation, acknowledging the 100 vs 50 summary issue.)

Mental Sandbox Simulation:

Imagine processing the first summary (Boland P. et al.). Extraction of key phrases related to bevacizumab dosing, prior use, efficacy, and safety. Structuring this into Executive Summary, Technical Details, and Key Insights sections using quotations and citations.

Consider the second summary (Pan Q. et al.). Similar process, extracting data for XELOX + Bevacizumab and Immunotherapy groups, focusing on PFS, OS, and safety, formatted and cited.

Think about the length. 50 summaries might generate more than four pages if each is detailed. Need to be concise in selecting quotations, focusing on the most significant data points for each section.

Prioritize numerical data and key takeaways.

Visualize the final report structure, ensuring each summary is represented and the overall report is coherent and formatted correctly.

Strategizing complete. I will now generate the report based on these thought processes. I will start by creating a template for each summary report and then populate it with the extracted information, before assembling the final four-page document.]

Table 3: Gemini 2.0 Flash Thinking Experimental Prompt 2a2 Generation

Error Report for Bevacizumab Clinical Decision Support 2a2					
Author(s)	Error Type	Instance	Probable Cause	Justification	Context
Chautard R. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Allegra et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
André T. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Lai et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Zhao Y. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Li Q. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Iida Y. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Han Gr. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Childs A. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Zhang J. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Zhang J. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Zhang J. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Zhang J. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Shen L. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Naz T. et al.	Abbreviation	Sentence	Word reduction	Conciseness	In-context
Lin X. et al.	Extra spacing	Sentence	Formatting error	Not known	In-context
Childs A. et al.	Parenthesis moved	Sentence	Format preferred	Completion	In-context
Wang L., Kim Y. et al.	Incorrect author	Attribution	Formatting error	Not known	In-context

Table 4: Error Report for Generation 2a2

## References

- [1] Kevin Kawchak. Clinical decision support based on bevacizumab cancer trials and pushing the limitations of advanced llms, original manuscript. creative commons attribution 4.0 international, January 2025. URL: <https://github.com/kevinkawchak/New-AI-Drug-Discovery/blob/main/Manuscripts/CDS-Bevacizumab-LLMs/Clinical%20decision%20support%20based%20on%20Bevacizumab%20cancer%20trials%20and%20pushing%20the%20limitations%20of%20advanced%20LLMs.pdf>, doi:10.5281/zenodo.13273141.
- [2] Ali Behrouz, Peilin Zhong, and Vahab Mirrokni. Titans: Learning to memorize at test time. *arXiv*, (arXiv:2501.00663), December 2024. arXiv:2501.00663. URL: <http://arxiv.org/abs/2501.00663>, doi:10.48550/arXiv.2501.00663.
- [3] OpenAI. Openai o3-mini pushing the frontier of cost-effective reasoning., 2025. URL: <https://openai.com/index/openai-o3-mini/>.
- [4] Fireworks/Deepseek. URL: <https://fireworks.ai>.
- [5] Google AI Studio. What will you build? push gemini to the limits of what ai can do, powered by the gemini api, 2025. URL: [https://aistudio.google.com/prompts/new\\_chat](https://aistudio.google.com/prompts/new_chat).