

Using Shortfall Metrics to Prioritize Therapeutic Innovation in Oncology

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Background

- Oncology drug development requires strategic prioritization across an increasingly diverse set of indications, biomarkers, and lines of therapy under constrained research and development (R&D) resources.
- Conventional frameworks often rely on clinical endpoints or commercial considerations, which may not fully capture disease burden or societal unmet need.
- Life-years (LYs) and quality-adjusted life-years (QALYs) provide standardized measures of health by capturing survival and, for QALYs, quality of life, enabling comparisons across diseases.
- LY and QALY shortfall extends this framework by quantifying the gap between expected lifetime health in the general population and outcomes achievable under current standard of care (SoC), aligning with health technology assessment (HTA) approaches to assessing severity and unmet need.
- In this analysis, SoC is defined as a clinically relevant, guideline-recommended or benchmark therapy representative of current practice and the competitive landscape, and does not necessarily reflect the most commonly used treatment.

Objectives

- To apply a LY and QALY shortfall-based portfolio modeling approach across oncology indications to quantify unmet need and assess potential health gains of hypothetical future interventions across cancers, disease stages, and lines of therapy relative to SoC.

Methods

Approach

- A LY and QALY shortfall-based portfolio model was applied to a hypothetical set of oncology indications spanning solid tumors and hematologic malignancies. The selected indications were designed to represent a balanced portfolio, capturing diversity in disease biology, treatment paradigms, lines of therapy, and market dynamics. The included indications and their key characteristics are summarized in **Table 1**.
- LY and QALY shortfall was estimated using two measures: absolute shortfall, defined as the difference between outcomes under current SoC and those expected in an age- and sex-matched general population; and proportional shortfall, defined as the percentage of total expected LYs or QALYs lost.

Table 1. Oncology indications included in the portfolio model

Category	Cancer Type	Indication	Stage/Line	Market Characteristics
Solid tumors	Breast	TNBC	Metastatic, 1L	High-growth, innovation-driven
	Breast	HR+/HER2-breast cancer	Metastatic, 3L+	Large, heterogeneous market
	Lung	NSCLC	Metastatic, 2L+ (post-IO)	Large market, post-IO treatment gap
	Prostate	HSPC	Metastatic, 1L	Large, rapidly evolving
	Skin	cSCC	Perioperative	Curative-intent expansion opportunity
Hematologic malignancies	Lymphoid	CLL	1L	Large market, targeted chronic therapy
	Lymphoid	MCL	R/R, 3L+	Niche, high-value segment
	Myeloid	AML	R/R, 2L+	Poor prognosis population
	Plasma cell	MM	Newly diagnosed, 1L	Large, high-volume market
	Plasma cell	MM	R/R, 2L+	Crowded, innovation-driven sequencing landscape

Abbreviations: 1L = first line; 2L+ = second line or later; 3L+ = third line or later; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; cSCC = cutaneous squamous cell carcinoma; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor-positive; HSPC = hormone-sensitive prostate cancer; IO = immuno-oncology; MCL = mantle cell lymphoma; MM = multiple myeloma; NSCLC = non-small cell lung cancer; R/R = relapsed/refractory; TNBC = triple-negative breast cancer

Inputs

- Clinical inputs for SoC were derived from published Kaplan-Meier survival data from pivotal trials, supplemented with evidence from HTA reports and clinical guidelines to inform survival and health-related quality of life estimates. Overall survival was capped by age- and sex-matched general population mortality, and health outcomes were discounted at an annual rate of 3%.
- Health state utility values for each indication were sourced from relevant literature corresponding to SoC and were assumed to be non-treatment specific, with identical utilities applied to both SoC and hypothetical future interventions within each health state.
- To ensure consistency with general population norms, utilities were capped at age-matched population values. When literature-based utility estimates exceeded general population norms, the event-free (EF) utility was set equal to the population value, and the corresponding progressed disease (PD) utility was derived by applying the EF-PD decrement reported in the literature.

Methods (cont'd)

- Hypothetical future interventions were modeled by applying assumed hazard ratios (HRs) to extrapolated SoC survival curves. For demonstration purposes, a constant HR of 0.8 was applied across all endpoints. In practice, HR assumptions can be informed by target product profiles, reflecting anticipated improvements in median or landmark survival outcomes.

- Table 2** summarizes the key model inputs.

Table 2. Key model inputs

Indication	SoC	Model Structure	Median OS/PFS (months ^a)	Utility Input	Sources
mTNBC, 1L (PD-L1 positive)	Pembrolizumab + chemotherapy	Three-state partitioned survival	Median OS: 17.1 Median PFS: 7.5	PF: 0.81 PD: 0.73	[1, 2]
HR+/HER2-mBC, 3L+	Sacituzumab govitecan	Three-state partitioned survival	Median OS: 14.4 Median PFS: 5.1	PF: 0.73 PD: 0.69	[3, 4]
mNSCLC, 2L+ (post-IO)	Docetaxel	Three-state partitioned survival	Median OS: 11.1 Median PFS: 3.5	PF: 0.76 PD: 0.69	[5, 6]
mHSPC, 1L	AAP + ADT	Three-state partitioned survival	Median OS: 53.9 Median PFS: 32.9	PF: 0.76 PD: 0.66	[7, 8]
cSCC, perioperative	Cemiplimab + surgery + cemiplimab	Three-state partitioned survival	Median OS: 106.6 Median PFS: 82.0	PF: 0.76 PD: 0.60	[9]
CLL, 1L	Acalabrutinib + obinutuzumab	Three-state transition model	Median OS: 175.9 Median FS: 142.0	EF: 0.75 PD: 0.60	[10, 11]
MCL, 3L+	Brexu-cel	Three-state partitioned survival	Median OS: 44.0 Median PFS: 22.2	PF: 0.76 PD: 0.66	[12, 13]
AML, R/R (FLT3+)	Gilteritinib	Three-state partitioned survival	Median OS: 9.9 Median PFS: 4.4	PF: 0.78 PD: 0.71	[14 - 16]
MM, 1L (transplant-eligible)	Daratumumab combination	Three-state partitioned survival	Median OS: 265.1 Median PFS: 204.0	PF: 0.73 PD: 0.69	[17, 18]
MM, R/R	Cilta-cel	Three-state partitioned survival	Median OS: 172.2 Median PFS: 51.4	PF: 0.78 PD: 0.61	[19, 20]

Abbreviations: 1L = first line; 2L+ = second line or later; 3L+ = third line or later; AAP = abiraterone acetate plus prednisone; ADT = androgen deprivation therapy; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; cSCC = cutaneous squamous cell carcinoma; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor-positive; IO = immuno-oncology; mBC = metastatic breast cancer; MCL = mantle cell lymphoma; mHSPC = metastatic hormone-sensitive prostate cancer; MM = multiple myeloma; mNSCLC = metastatic non-small cell lung cancer; mTNBC = metastatic triple negative breast cancer; OS = overall survival; PD = progressed disease; PD-L1 = programmed death ligand 1; PF = progression free; PFS = progression-free survival; R/R = relapsed/refractory; SoC = standard of care

^aMedian OS and PFS were derived from long-term extrapolation of survival data by fitting parametric distributions to published Kaplan-Meier curves.

Outputs

- Outcomes included comparative estimates of LY and QALY shortfall under SoC as measures of unmet need, as well as the potential incremental health gains from hypothetical future interventions across indications.

Results

- The analysis demonstrates substantial variation in both LY and QALY shortfall across oncology indications, with the highest unmet need observed in advanced and late-line settings.
- Indications such as metastatic non-small cell lung cancer (mNSCLC; second line or later [2L+] post-immuno-oncology [IO]), hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (mBC; third line or later [3L+]), metastatic triple negative breast cancer (mTNBC; first line [1L], programmed death ligand-1 positive [PD-L1+]), and relapsed/refractory (R/R) acute myeloid leukemia (AML) exhibit very high proportional LY and QALY shortfall (approximately 87%–92%), indicating limited survival benefit with current SoC treatments.
- Intermediate shortfall is observed in metastatic hormone-sensitive prostate cancer (mHSPC; 1L) and mantle cell lymphoma (MCL; 3L+), reflecting meaningful but non-curative gains. In contrast, early-stage or chronic disease settings, including perioperative cutaneous squamous cell carcinoma (cSCC), newly diagnosed multiple myeloma (MM), and frontline chronic lymphocytic leukemia (CLL), demonstrate low LY and QALY shortfall ($\leq 19\%$), consistent with improved long-term outcomes.
- Overall, proportional LY and QALY shortfall ranges from 1%–92% and is highest in aggressive diseases with limited effective treatment options, highlighting areas of greatest unmet need and potential for meaningful health gains from new interventions. Detailed LY and QALY outcomes are presented in **Table 3**, and **Figure 1** and **Figure 2** illustrate the decomposition of outcomes into achieved benefit, potential gains with a hypothetical intervention, and remaining shortfall.

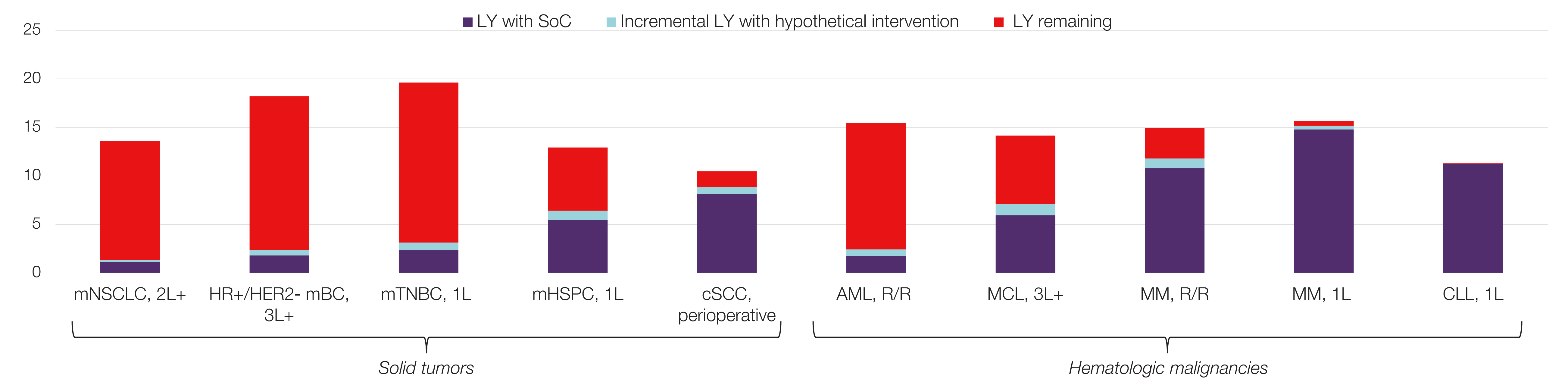
Results (cont'd)

Table 3. Proportional shortfall across oncology indications

Category	Indication	SoC Treatment	LY for General Population	LY with SoC	Proportional LY Shortfall	QALY for General Population	QALY with SoC	Proportional QALY Shortfall
Solid tumors	mNSCLC, 2L+ (post-IO)	Docetaxel	64	13.36	1.12	10.26	0.81	92%
	HR+/HER2- mBC, 3L+	Sacituzumab govitecan	56	17.65	1.81	13.81	1.28	91%
	mTNBC, 1L (PD-L1 positive)	Pembrolizumab + chemotherapy	53	18.86	2.36	14.89	1.82	88%
	mHSPC, 1L	AAP + ADT	67	11.97	5.46	9.17	3.93	57%
	cSCC, perioperative	Cemiplimab + surgery + cemiplimab	73	9.79	8.14	7.42	6.02	19%
Hematologic malignancies	AML, R/R (FLT3+)	Gilteritinib	62	14.75	1.74	11.40	1.33	88%
	MCL, 3L+	Brexu-cel	65	12.99	5.95	9.96	4.32	57%
	MM, R/R	Cilta-cel	61	14.93	10.80	11.57	7.81	32%
	MM, 1L (transplant-eligible)	Daratumumab combination	60	15.29	14.79	11.88	10.71	10%
	CLL, 1L	Acalabrutinib + obinutuzumab	70	11.34	11.25	8.65	8.20	5%

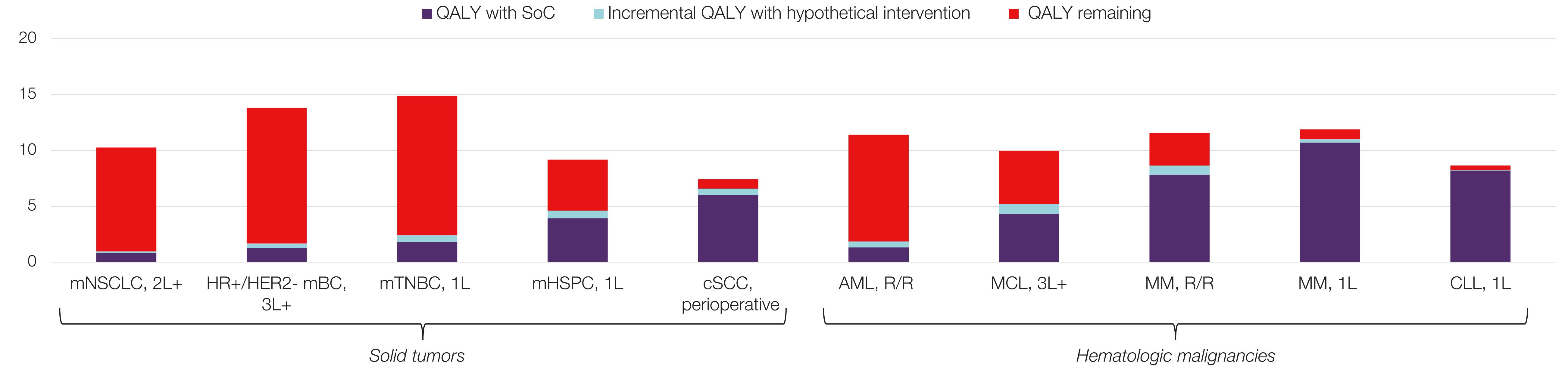
Abbreviations: 1L = first line; 2L+ = second line or later; 3L+ = third line or later; AAP = abiraterone acetate plus prednisone; ADT = androgen deprivation therapy; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; cSCC = cutaneous squamous cell carcinoma; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor-positive; IO = immuno-oncology; LY = life-year; mBC = metastatic breast cancer; MCL = mantle cell lymphoma; mHSPC = metastatic hormone-sensitive prostate cancer; MM = multiple myeloma; mNSCLC = metastatic non-small cell lung cancer; mTNBC = metastatic triple negative breast cancer; PD-L1 = programmed death ligand 1; QALY = quality-adjusted life-year; R/R = relapsed/refractory; SoC = standard of care

Figure 1. LY gains and remaining shortfall



Abbreviations: 1L = first line; 2L+ = second line or later; 3L+ = third line or later; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; cSCC = cutaneous squamous cell carcinoma; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor-positive; LY = life-year; mBC = metastatic breast cancer; MCL = mantle cell lymphoma; mHSPC = metastatic hormone-sensitive prostate cancer; MM = multiple myeloma; mNSCLC = metastatic non-small cell lung cancer; mTNBC = metastatic triple negative breast cancer; QALY = quality-adjusted life-year; R/R = relapsed/refractory; SoC = standard of care

Figure 2. QALY gains and remaining shortfall



Abbreviations: 1L = first line; 2L+ = second line or later; 3L+ = third line or later; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; cSCC = cutaneous squamous cell carcinoma; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor-positive; LY = life-year; mBC = metastatic breast cancer; MCL = mantle cell lymphoma; mHSPC = metastatic hormone-sensitive prostate cancer; MM = multiple myeloma; mNSCLC = metastatic non-small cell lung cancer; mTNBC = metastatic triple negative breast cancer; QALY = quality-adjusted life-year; R/R = relapsed/refractory; SoC = standard of care

Discussion

- This analysis illustrates the application of LY and QALY shortfall metrics within a portfolio modeling framework to systematically compare unmet need across diverse oncology indications. The approach enables consistent cross-indication assessment despite differences in disease biology, prognosis, and treatment paradigms. The results demonstrate that shortfall metrics can differentiate between indications with high disease burden and those where current therapies have substantially reduced the gap to normal life expectancy.
- As a portfolio tool, this framework provides a structured, quantitative basis for evaluating unmet need and supports early-stage prioritization of development opportunities. The analysis has several limitations, including reliance on simplified survival and utility assumptions, use of trial-based inputs that may not reflect real-world populations, and the application of a uniform treatment effect for the hypothetical intervention. Results should be interpreted as comparative estimates intended to inform, rather than replace, detailed indication-level analyses.

Disclosures

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Conclusions

- LY and QALY shortfall-based portfolio modeling provides a quantitative framework to assess unmet need across oncology indications and identify settings where new interventions may deliver the greatest health impact. This approach can support evidence-based prioritization of development opportunities in early portfolio decision making.

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