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Patient Reported Outcome (PRO) Usage in Early Phase Dose Selection Solid Tumor Clinical Trials

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OBJECTIVE

To characterize the use of patient reported outcomes (PROs) in early phase dose selection of solid tumor clinical trials, and to examine differences in PRO administration across relevant clinical trials through a systematic review of the literature

CONCLUSIONS

PROs have been utilized in dose finding clinical trials but are not reported to directly inform dose selection

Reporting of PRO analyses and results is often nontransparent

More research is needed to determine how PROs can be used in dose selection and to understand the limitations of current PRO analysis recommendations

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AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Gabriel Jensen, PhD, of AbbVie.

Author conflict of interest disclosures: L Perez completed this research as a participant in the AMCP Foundation/AbbVie, Inc. Specialized Summer Internship Program in Health Outcomes. Q Xu and R Sen are employees of AbbVie and may own stock or options.

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Remaining references can be found in the Supplemental Material (scan QR code).

Presented at the 2022 Academy of Managed Care Pharmacy (AMCP) Nexus Meeting; October 11-14, 2022

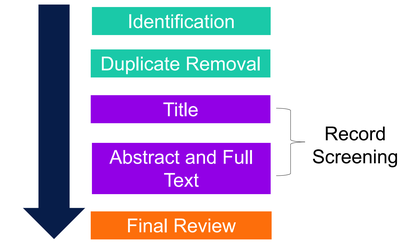
INTRODUCTION

- Traditional early phase drug development in oncology defines the maximum tolerated dose (MTD) in phase 1 and then evaluates the MTD in phase 2 trials; this toxicity-based dose finding approach needs to evolve with the advent of targeted therapies
- The FDA-initiated Project Optimus aims to reform anticancer drug development and approval using new methods for dose selection that prioritize efficacy, safety, and tolerability[1]
- Patient reported outcomes (PROs) may be a useful nonclinical tool to inform understanding of safety and tolerability from the patient perspective

METHODS

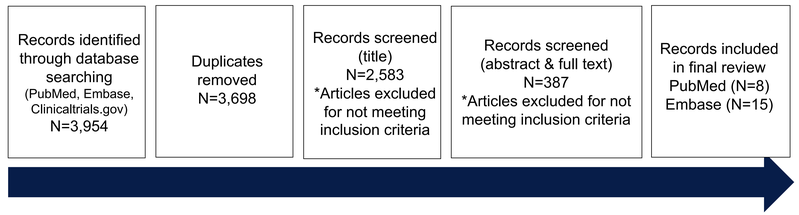
- Clinical trials that met the following criteria were included:
  - Phase 1 or 2 trial in solid tumors (colorectal, pancreatic, lung, and/or gastroesophageal)
  - Tested at least 2 dosages
  - Included a PRO endpoint
  - Published between 2012 and 2022
  - Published in English

Study Design – Record Screening

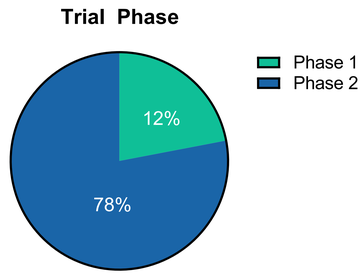


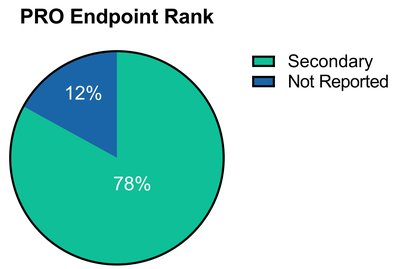
RESULTS

Record screening resulted in 23 clinical trials for analysis

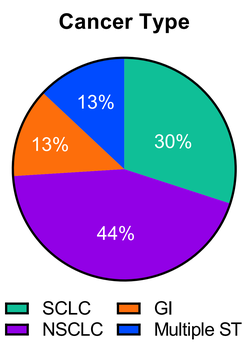


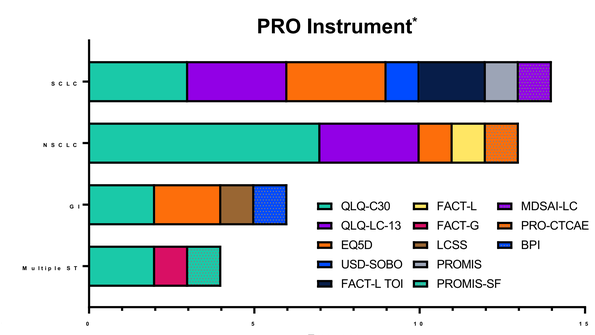
PROs are often a secondary endpoint in phase 2 trials





PRO testing is utilized most often in lung cancer trials, and various PROs are used across solid tumor trials





GI = gastrointestinal, NSCLC = non-small cell lung cancer, PRO = patient reported outcome, SCLC = small cell lung cancer, ST = solid tumor. *Some studies utilized multiple PRO instruments. A PRO instrument abbreviation key is included in the Supplemental Material (scan QR code).

Record screening of clinical trials

	First author	N	PRO Instrument	PRO Schedule	PRO Outcomes	Operationalization
SCLC	Simone[2]	21	UCSD-SOBQ, FACT-L TOI, swallowing diary	0-, 13-, 26- and 56-weeks post-RT	QOL	Not available
	Mok[3]	89	QLQ-C30, QLQ-LC13	Baseline, day 1 of each cycle, end of treatment	QOL	Change from baseline in QLQ-C30 and QLQ-LC13
	Higgins[4]	506	FACT-TOI, EQ5D, PROMIS	Up to 15 months after the end of the 4th cycle of chemotherapy (FACT-TOI), up to 2 years (EQ5D, PROMIS)	QOL	Not available
	Gronberg[5]	160	QLQ-C30, QLQ-LC13	Weeks 0, 4 (before TRT), 8 (end of TRT), 12 (response evaluation), 16 (end of PCI), 22, 32, 42 and 52. Baseline, 1, 2, 3, 4,	HRQOL	Change from baseline in QLQ-C30 and QLQ-LC13
	Killingberg[6]	170	QLQ-C30, QLQ-LC13	Weeks 0, 4, 8, 12 and 16, then every 10 weeks year one, and every 3 months year two	HRQOL	Change from baseline in QLQ-C30 and QLQ-LC13
	Woll[7]	220	EQ5D	Baseline, every treatment cycle for first 6 months	QOL	Quality-adjusted life weeks within 6 months of trial entry
	Siva[8]	90	MDASI-LC, EQ5D	24 months	QOL	Change from baseline in MDASI-LC and EQ-5D
NSCLC	Smit[9]	Ongoing	QLQ-C30, QLQ-LC13	Day 1 of every cycle (each cycle is 21 days), and at end of treatment visit 40-day follow-up visit	GHRQOL	Change from baseline in QLQ-C30 and QLQ-LC13, time to deterioration in QLQ-C30
	Solomon[10]	180	QLQ-C30, QLQ-LC13	44 months	QOL	Not available
	Kim[11]	18	QLQ-C30, QLQ-LC13	Baseline, 3rd, 6th, 9th to 13th, and 14th or 16th visit	Symptoms, ADL difficulty, HRQOL	Change from baseline in QLQ-C30 and QLQ-LC13
	Metzenmacher[12]	130	QLQ-C30	Baseline, on day 1 of each cycle, and after the completion of therapy	QOL	Change from baseline in QLQ-C30
	Lenderking[13]	270	QLQ-C30	Baseline and at each 28-day cycle up to end of the study	QOL, GHS	Responder definition threshold for the minimum individual pt change in QLQ-C30 GHS/QOL, representing treatment benefit
	Capelletto[14]	170	LCSS	First 12 treatment cycles	QOL	Not available
	Camerini[15]	167	QLQ-C30	Before randomization, before cycle 2 and then every two cycles and at the end of treatment evaluation	QOL	Change from baseline in QLQ-C30
	Raman[16]	78	FACT-L, EQ5D	Week 13, 26, 39, 52, 78, 104	QOL	Not available
	Von Reibnitz[17]	9	PRO-CTCAE	Not available	AE	MTD from PRO-CTCAE
	Hong[18]	16	QLQ-C30	Baseline, 8 weeks	QOL	Change from baseline in QLQ-C30
GI	Choi[19]	60	QLQ-C30, BPI	Baseline, weeks 4, 13, and 26	QOL, pain intensity	Change from baseline in QLQ-C30 and BPI
	Shitara[20]	101	EQ5D	Baseline, week 4 and week 8	QOL	Change from baseline in EQ5D
	Yamaue[21]	190	QLQ-C30, EQ5D	Not available	QOL	Change from baseline in QLQ-C30 and EQ5D
Multiple ST	Chawla[22]	29	QLQ-C30	Through study completion, average 1 year	HRQOL	Change from baseline in QLQ-C30
	Bitting[23]	23	FACT-G, PROMIS-SF	Baseline, every 4 weeks	QOL, fatigue	Change from baseline in FACT-G, PROMIS-SF
	Ishihara[24]	26	QLQ-C30	Baseline and on treatment phase course 3 day 1, treatment phase course 5 day 1, and treatment phase course 6 day 15	QOL	Change from baseline in QLQ-C30

ADL = activities of daily life, GI = gastrointestinal, HRQOL = health-related quality of life, NSCLC = non-small cell lung cancer, MCC = Merkel cell carcinoma, PRO = patient reported outcome, QOL = quality of life, SCLC = small cell lung cancer.

Summary

- PRO assessment has been completed most often in phase 2 clinical trials
- The most frequently used generic PRO instruments include EORTC QLQ-C30 and the EQ5D
- PRO assessment schedule varies between trials and treatment delivery, but occurs most consistently at baseline and at end of treatment and some interval between those times
- PRO endpoint assessed most frequently are changes from baseline in PRO scores (eg, QOL, VAS score)
- No trials included in the review mentioned whether PRO usage has helped to inform dose selection