

EVALUATION OF PATIENT REPORTED OUTCOME INSTRUMENTS IN IMMUNE-CHECKPOINT INHIBITOR CLINICAL TRIALS

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Background

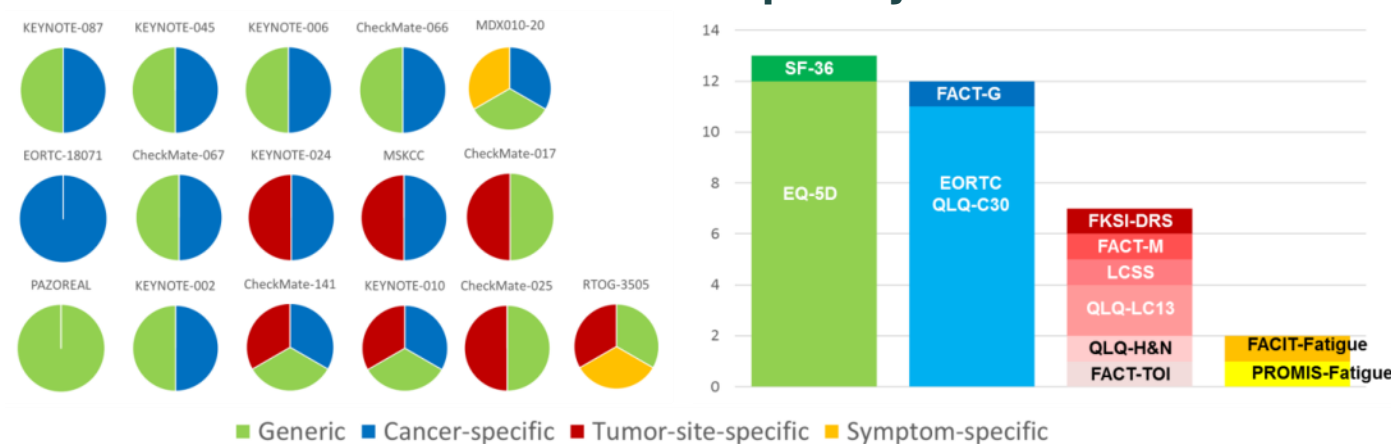
Immune checkpoint inhibitors (ICI) have shown significant clinical benefit in various cancer types. However, linked to their mechanisms of action, these treatments exhibit **specific toxicities that impact patients' quality of life (QoL)**. Patient-reported outcome (PRO) instruments are used in clinical trials (CT) to collect symptoms, functional status, and QoL. **The question remains whether these instruments capture ICI-specific symptoms and symptomatic AEs.**

We therefore conducted a systematic review of published literature to identify and categorize PRO instruments and to evaluate their utility in the context of ICI-CTs.

Literature search

Literature was searched using PubMed, Embase, PsycINFO, Medline and CINAHL databases (June 2017). Search terms included controlled vocabulary and specific keywords related to: (1) Food and Drug Administration (FDA) approved ICI, (2) PRO, and (3) Oncology. 16 articles were identified from the literature search. Symptoms were extracted from PRO instruments and compared to the most frequent AEs reported for the corresponding cohort.

Frequency of use and combinations of PROs used in ICI-CTs



From the 16 studies (including 13 ICI-CTs, 2 study protocols RTOG-3505 and PAZOREAL, and the qualitative study -MSKCC), 13 used a generic QoL questionnaire (12 EQ-5D and 1 SF-36) and 12 used a cancer-specific one (11 EORTC-QLQ-C30 and 1 FACT-G). Whereas in 8 cases only cancer-specific and/or generic questionnaires were used, 7 studies combined them with tumor-site-specific modules, and 2 included a symptom-specific questionnaire.

Comparison of PRO instruments' symptom-related content and AEs reported in ICI-CTs

GENERIC	CANCER SPECIFIC	TUMOR SITE SPECIFIC	SYMPTOM SPECIFIC	STUDY	TREATMENT ARM	MOST FREQUENT AEs REPORTED													
SF-36 Asthenia / Fatigue Anxiety / Depression Pain				MDX010-20 Melanoma	Ipi_3mg/kg	Fatigue	Nausea	Diarrhea	Dec. Appet.	Pruritus	Vomiting	Constipation	Rash	Cough	Abdominal pain	Dyspnea	Headache		
	EORTC-QLQ-C30			EORTC-18071 Melanoma	Ipi_10mg/kg	Diarrhea	Pruritus	Fatigue	Rash	Headache	Weight loss	Nausea	Inc. ALT	Inc. liver function	Hypophysitis	Pyrexia	Inc. AST		
		QLQ-LC13 Cough		KEYNOTE-024 NSCLC	Pem_200mg	Diarrhea	Fatigue	Pyrexia	Nausea	Dec. Appet.	Hypothy.	Hyperthy.	Pneumonitis	Anemia	Infusion reaction	Constipation	Severe skin reactions		
			QLQ-H&N Pain mouth/throat Swallowing Soreness mouth Dry mouth	KEYNOTE-010 NSCLC	Pem_2mg/kg	Dec. Appet.	Fatigue	Nausea	Rash	Hypothy.	Diarrhea	Asthenia	Pneumonitis	Stomatitis	Hyperthy.	Anemia	Colitis		
EQ-5D				CheckMate-141 Head & Neck	Pem_10mg/kg	Fatigue	Rash	Dec. Appet.	Nausea	Hypothy.	Diarrhea	Hyperthy.	Asthenia	Pneumonitis	Anemia	Stomatitis	Severe skin reactions		
Mobility				CheckMate-141 Head & Neck	Niv_2mg/kg	Fatigue	Nausea	Rash	Dec. Appet.	Pruritus	Diarrhea	Anemia	Asthenia	Vomiting	Dry skin	Stomatitis	Weight loss		
Self-Care				KEYNOTE-006 Melanoma	Ipi_3mg/kg	Pruritus	Diarrhea	Fatigue	Rash	Nausea	Colitis	Asthenia	Arthralgia	Hyperthy.	Hypophysitis	Hypothy.	Vitiligo		
Pain / Discomfort				KEYNOTE-006 Melanoma	Pem_10mg/kg/2w	Fatigue	Diarrhea	Rash	Pruritus	Asthenia	Hypothy.	Nausea	Arthralgia	Vitiligo	Hyperthy.	Colitis	Hepatitis		
Anxiety / Depression				KEYNOTE-006 Melanoma	Pem_10mg/kg/3w	Fatigue	Diarrhea	Pruritus	Rash	Arthralgia	Asthenia	Nausea	Vitiligo	Hypothy.	Colitis	Hyperthy.	Hepatitis		
				KEYNOTE-045 Urothelial	Pem_200mg	Pruritus	Fatigue	Nausea	Diarrhea	Dec. Appet.	Hypothy.	Asthenia	Pneumonitis	Hyperthy.	Anemia	Colitis	Constipation		
				CheckMate-066 Melanoma	Niv_3mg/kg	Fatigue	Pruritus	Nausea	Diarrhea	Rash	Constipation	Vitiligo	Asthenia	Vomiting					
				KEYNOTE-087 Clas. Hod. Lymph.	Pem_200mg	Hypothy.	Pyrexia	Fatigue	Rash	Diarrhea	Headache	Cough	Nausea	Neutropenia	Arthralgia	Muscle spasms	Pruritus		
				KEYNOTE-002 Melanoma	Pem_2mg/kg	Fatigue	Pruritus	Rash	Diarrhea	Arthralgia	Vitiligo	Dry skin	Hypothy.	Myalgia	Dec. Appet.	Nausea	Asthenia		
				CheckMate-067 Melanoma	Pem_10mg/kg	Fatigue	Pruritus	Diarrhea	Rash	Dec. Appet.	Nausea	Hypothy.	Arthralgia	Maculo. rash	Vomiting	Vitiligo	Dry skin		
		FCSI-DRS Asthenia / lack of energy Pain Weight loss Bone pain Fatigue Dyspnea Cough Fever Hematuria		CheckMate-025 Renal	Niv_3mg/kg	Pruritus	Diarrhea	Rash	Fatigue	Nausea	Dec. Appet.	Colitis	Headache	Vomiting	Pyrexia	Arthralgia	Hypothy.		
				CheckMate-017 NSCLC	Niv_3mg/kg	Diarrhea	Rash	Fatigue	Pruritus	Nausea	Pyrexia	Dec. Appet.	Inc. ALT	Vomiting	Inc. AST	Hypothy.	Colitis		
			LCSS Appetite Fatigue Cough Dyspnea Hemoptysis Pain	CheckMate-017 NSCLC	Niv_3mg/kg	Fatigue	Dec. Appet.	Asthenia	Nausea	Diarrhea	Arthralgia	Pneumonitis	Pyrexia	Rash	Mucosal inflammation	Anemia	Myalgia		

Ipi.: Ipilimumab; Niv.: Nivolumab; Pem.: Pembrolizumab; Inc.: increase; Dec.: decrease.

Symptom-related content from each PRO instrument was compared to the AEs in the corresponding cohort. Color bars on the left relate to PRO instruments used in each study.

In the table, the most frequent AE (any grade) are shown for the 13 ICI-CTs. AE frequency (most common to least common) is depicted from left to right respectively.

Symptomatic AEs covered by the content of the PRO instrument(s) are shown in green (44%); multi-symptom AEs and items related to a specific type of pain (headache, arthralgia, myalgia) that are partially covered, in yellow (25%); and AEs/symptoms not present in the PRO instruments in red (31%).

From the non-covered AEs, 66% refer to the dermatologic system (rash, pruritus, vitiligo, dry skin). Of the partially covered AEs, 39% relate to endocrine alterations (hyper-, hypothyroidism, hypophysitis) and 28% to the musculoskeletal or nervous system (dashed yellow).

Conclusion

Cancer-specific or generic QoL questionnaires are the most widely used PRO instruments in ICI-CTs. As ICI therapies exhibit unique characteristics different from conventional cancer therapies, such **broad PRO instruments do not capture the specific ICI-related symptomatic toxicities**. Dermatological, endocrine and musculoskeletal-related AEs are among the most common problems reported with the use of these therapies, independent of cancer type. Despite their high frequency, they are not or only partially covered by the currently used PRO instruments. Hence, the adaptation or development of ICI-specific PRO tools should be further investigated in the context of ICI therapies.

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