Patient-Reported Outcomes (PROs) in CAR T-Cell Therapy

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PROs: Definition

"Reports of the status of a patient's health that come directly from the patient, with interpretation of the patient's response by a physician or anyone else"

https://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

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Benefits of PROs in the Research Setting

- Provides complementary information to physician-rated adverse events
- In Phase I-III clinical trials, can help to assess:
  - Treatment tolerability
  - Therapeutic benefit (e.g., symptom palliation, quality of life)
  - Value of treatments (e.g., quality-adjusted life years)
- Educate patients and family members about what to expect during treatment

Di Maio et al. J Clin Oncol 2015; 33: 910-5
Jim et al. J Clin Oncol 2017; 35: 1133-34

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Cytokine Release Syndrome (CRS) in CAR-T

Event n(%)	Any	Grade ≥ 3
CRS, any	94 (93)	13 (13)
Pyrexia	77 (76)	11 (11)
Hypotension	41 (41)	9 (9)
Hypoxia	22 (22)	9 (9)
Tachycardia	21 (21)	1 (1)
Chills	20 (20)	0
Sinus tachycardia	8 (8)	0
Headache	5 (5)	0

Event n(%)	Any	Grade ≥ 3
Neurologic, any	65 (64)	28 (28)
Encephalopathy	34 (34)	21 (21)
Confusion	29 (29)	9 (9)
Tremor	29 (29)	1 (1)
Aphasia	18 (18)	7 (7)
Somnolence	15 (15)	7 (7)
Agitation	9 (9)	4 (4)
Memory impairment	7 (7)	1 (1)
Mental status change	6 (6)	2 (2)

Neelapu et al. NEJM 2017; 377: 2531-44

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Current Challenges of PROs in CAR-T

- PRO measures developed in the era of chemotherapy
  - Existing measures do not assess important PROs in CAR-T
  - All PROs relevant to CAR-T not yet identified
- Not clear when to measure PROs
  - PRO assessment during CRS may not be feasible
- No consensus on most appropriate comparison group

Known PRO Studies in CAR-T

Sponsor	CAR-T	Patients	Measures	Time points	Status
Fred Hutchison Cancer Research Center	Any	On institutional clinical trials	PROMIS-29 PROMIS Global	Annual for 15 years	Not yet enrolling
Mayo Clinic, MN	Any	Commercial or on trial	FACT-G, PRO-CTCAE	Biweekly for 1 month, monthly for 6 months	Enrolling
Memorial Sloan Kettering Cancer Center	Any	Commercial only	PROMIS-29	Weekly through day 30, days 60, 90	Enrolling
Moffitt Cancer Center	Any	Commercial or on trial	SF-36, PRO-CTCAE	Baseline, days 14, 30, 60, 90, 180, 360	Enrolling
NCI (intramural)	Anti-CD22	On trial	Neurotoxicity checklist	Baseline, day 14, day 21-28	Enrolling
Novartis	Kymriah	On trials ELENA, ELIANA, BELINDA, or CART19-BE-01	SF-36, FACT-Lym, PedsQL, EQ-VAS	Varies	Enrolling or not yet open

Recommendations to MEDCAC

- More mature data are needed on PROs
  - Not enough data to base payer reimbursement decisions
- Harmonization of patient-level data from existing studies should be undertaken
  - Increase statistical power, improve generalizability
  - Identify PRO measures most sensitive to change
  - Evaluate frequency CAR-T specific symptomatic toxicities
- A working group should be convened

Recommendations for Working Group

- Goals:
  - Conduct data harmonization, disseminate results
  - Provide recommendations on optimal study design and selection of PRO measures for CAR-T in research and clinical care
- Members:
  - Experts in clinical care of CAR-T patients
  - Experts in research on CAR-T, PROs in cancer, cancer care delivery
  - Patient and family advocates
- Timeline: one year