Considerations on How to Incorporate PROs in NCTN Clinical Trials

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THE UNIVERSITY OF KANSAS
CANCER CENTER

NCI Designated Cancer Center

BEST HOSPITALS U.S.News CANCER 2021-22

NCTN Early Career Faculty Leadership Series Lecture, 3-17-26

A Little About Myself

- Research focused on PROs for 15+ years
- NRG and Alliance, designed PROs for >10 trials
  - NRG Chair for Patient Centered Outcomes Research Committee
- Co-Chair, Prostate Cancer Task Force
- PI: NRG GU008, NRG CC007CD

Disclosures

- Consulting and research relationships with: Janssen, Vir Biotechnology, Astellas – not related to content of this talk

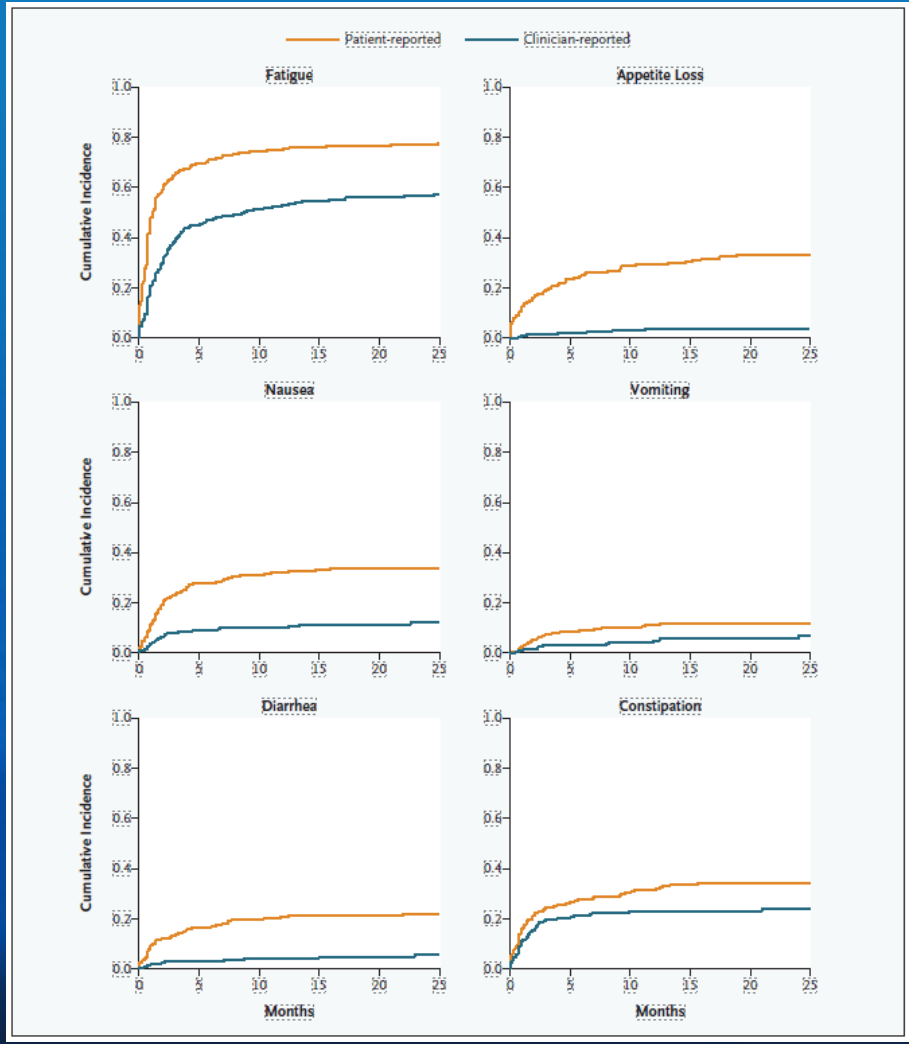
Topics

1) Why
2) NCTN trial review process
3) Types of NCTN trials to have PRO
4) Key components of PRO section of protocol
5) Design considerations
6) PRO is more than just toxicity assessment
7) Maximize data completion
8) Interpreting PRO data

PROs collected for 467 patients over 4034 clinical visits at MSKCC

CTCAE toxicity collected by physicians/nurses at the same visit

Cumulative incidence of moderate/severe symptoms:



Basch E. NEJM 362(10):865-9, 2010.

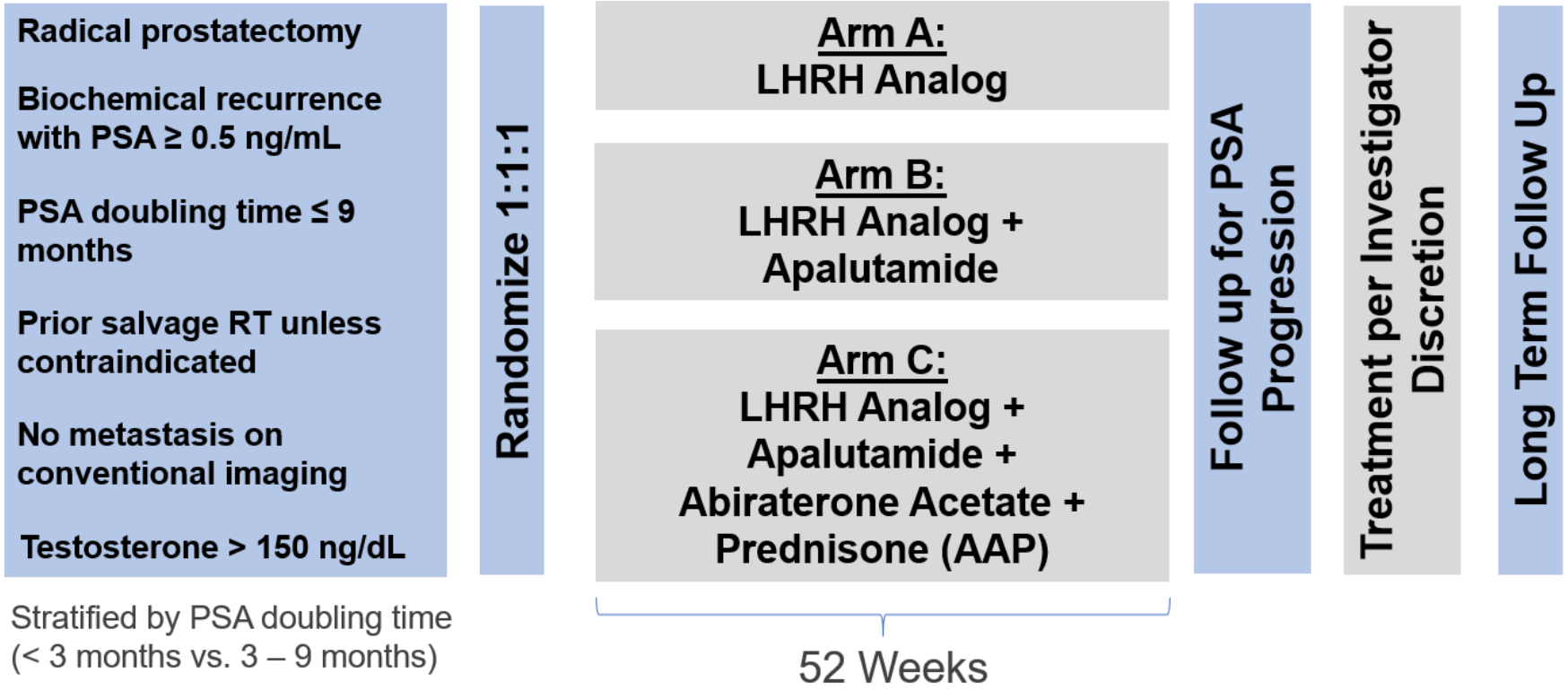
2024 ASCO ANNUAL MEETING

Health-related quality of life (HRQOL) results from PRESTO (AFT-19), a phase 3 randomized trial of intensification of androgen blockade in patients with high-risk biochemically relapsed castration sensitive prostate cancer

Ronald C Chen, Gina L Mazza, Briant F Fruth, Han Xiao, Joel Picus, Mary-Ellen Taplin, Tanya Dorff, Leonard Appleman, Douglas Weckstein, Akash Patnaik, Alan Bryce, Daniel Shevrin, James L Mohler, Daniel Anderson, Arpit Rao, Alan Tan, Charles J Ryan, Scott E Eggener, Michael J Morris, Rahul R Aggarwal

PRESENTED BY: Ronald Chen, MD MPH

Study Schema (N=504)



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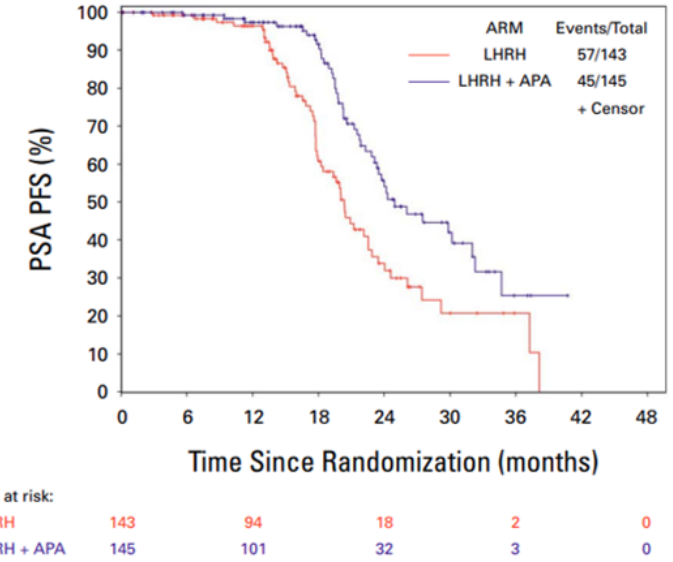
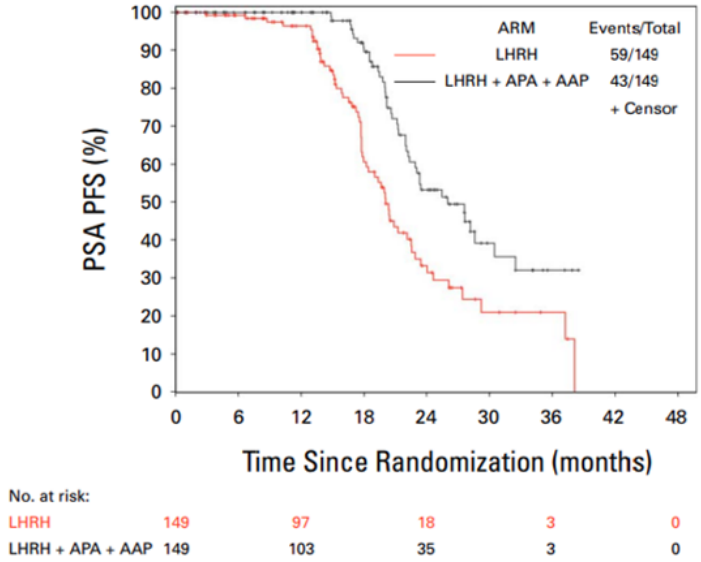
PRESTO (AFT-19): PSA-PFS





Median PSA-PFS

ADT: 20.3 months
ADT + apa: 24.9 months

ADT: 20.0 months
ADT + apa + AAP: 26.0 months

Aggarwal R, et al. JCO 42:1114-23, 2024.

1) Why

- Modern clinical trials feel incomplete without PROs
- No longer do patients and physicians just care about cancer-related outcomes
  - Balance with quality of life
  - To inform treatment decision-making

1) Why

- Extra funding: additional $1000/patient to participating site for doing PROs
- Extra data
  - It's a lot of work to do a large clinical trial → PRO provides opportunity for additional high-impact publications

2) NCTN Trial Review Process

- NRG: in-person meeting twice a year
  - GU Committee: monthly meeting
    - Propose trial ideas (concept template 10 pages)
  - Patient-Centered Outcomes Committee
    - Help design PRO components
- Trial concept approved by NRG
- Prostate Cancer Task Force review (2 chances)
- GU Steering Committee review (2 chances)

2) NCTN Trial Review Process

- GU Steering approved! NCI CTEP trial.
  - Start protocol writing
  - PRO component reviewed by NCI DCP → separate review, additional funding $1000/pt

3) Types of Trials where PRO Can Be Included

- Phase III trials (classic)
  - Why are PRO data important? How do PRO data, together with primary disease/survival outcomes, impact clinical care and clinical decisions?
- Randomized phase II trials (less common)
  - If PRO is (co-)primary endpoint
  - If PRO results will inform whether trial will progress to Phase III
  - Rare tumors with limited PRO data available

4) Key Components of PRO Section

- Background section: including rationale for including PRO
  - Importance of PROs as part of the final results for the trial in helping inform treatment decisions
- Describe each PRO measure
  - Validated and reliable
  - Ideally, available in multiple languages
  - Each included measure should be justified scientifically
  - Choose consistent PRO instruments for possible future data pool
- Clearly stated objective and endpoints
  - Need clear hypotheses to be tested, not just describe QOL
  - Hypothesis for each PRO instrument

5) Key Considerations

- Be aware of patient burden
  - Total number of questions (~6 questions/min), ≤15 min survey
  - Number of time points
- Baseline (pre-treatment)
  - Time points aligned with clinical visits
  - Final time point aligned to expected median survival
- Sample size: enough to test PRO hypotheses (maybe not the entire trial sample size)

6) More Than Just Side Effects

- Common question: should PROs continued to be collected after disease progression or metastasis or treatment cessation?

6) More Than Just Side Effects

- Common question: should PROs continued to be collected after disease progression or metastasis or treatment cessation?

- Answer: absolutely YES.

6) More Than Just Side Effects

- Observation: no short-term side effects

- Treatment A: short-term side effects

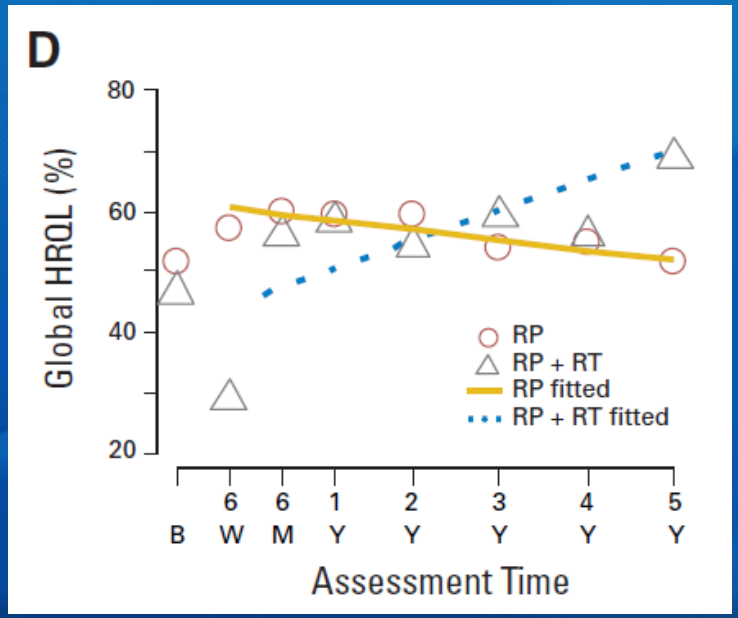
6) More Than Just Side Effects

- Observation: no short-term side effects
  - More disease progression, metastasis, salvage chemotherapy, pain meds/steroids, etc.
- Treatment A: short-term side effects
  - Long-term disease control

SWOG 8794

Post-prostatectomy, patients with high-risk features:

- Observation
- Adjuvant RT



Moinpour CM, et al. JCO 26:112-20, 2008.

7) Maximize Data Completion

- PRO data more likely to be missing than disease/survival endpoints
- Attention to survey burden: survey length and number of time points
  - Max 15 minutes
  - Time points coincide with clinical visits
- Incentivize PRO completion at every time point if possible (not currently possible in NCTN trials)

7) Maximize Data Completion

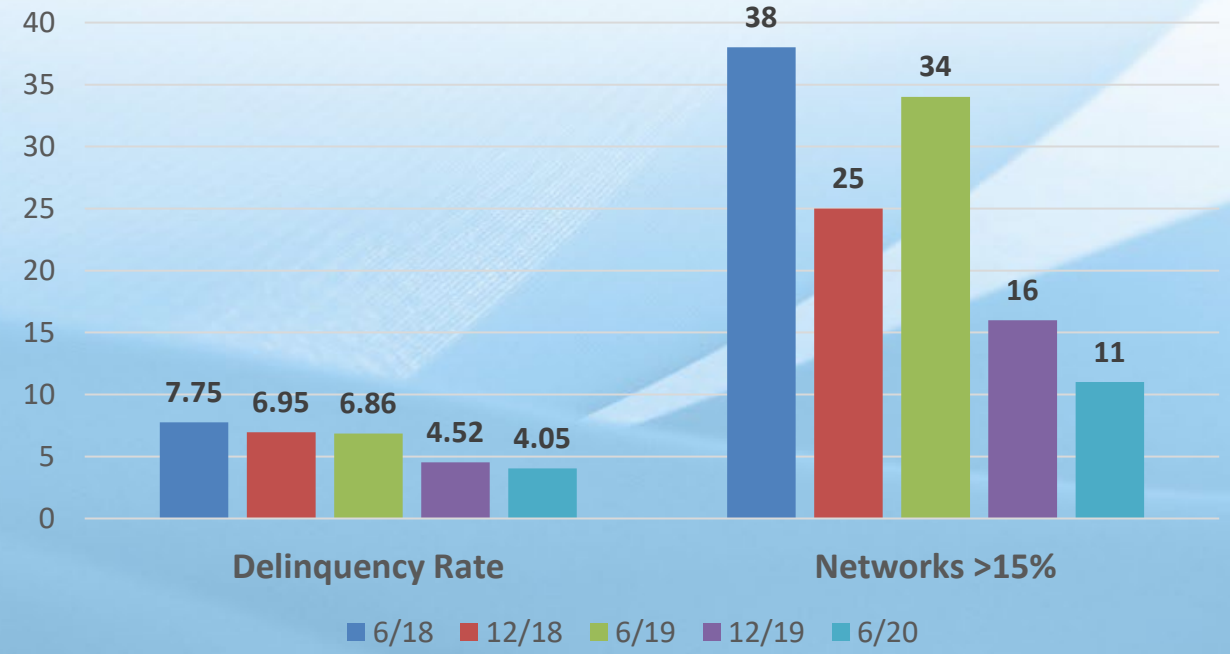
Trial 1	Baseline **6.6%**	Cycle 3 **8.7.%**	Cycle 6 **14.2%**	6 months **16.4%**	12 months **19.4%**
Trial 2	**Baseline** **10.0%**	**12 weeks** **15.5%**	**24 weeks** **25.3%**	**36 weeks** **31.5%**	**48 weeks** **36.6%**
Trial 3	**Baseline** **4.9%**	**12 weeks** **27.9%**	**24 weeks** **37.6%**	**36 weeks** **46.2%**	**48 weeks** **53.4%**

- Unfortunately, some CRAs/physicians/PIs consider collecting PRO data to be optional, and less important than disease outcomes

Multi-Pronged Approach

- Auditing completion rates prospectively
- Increase awareness: NRG meetings, newsletter articles, discuss % missing PRO data for each trial at disease committees
- Decrease PRO burden
- Contacting poor-performing sites (ask for corrective action)

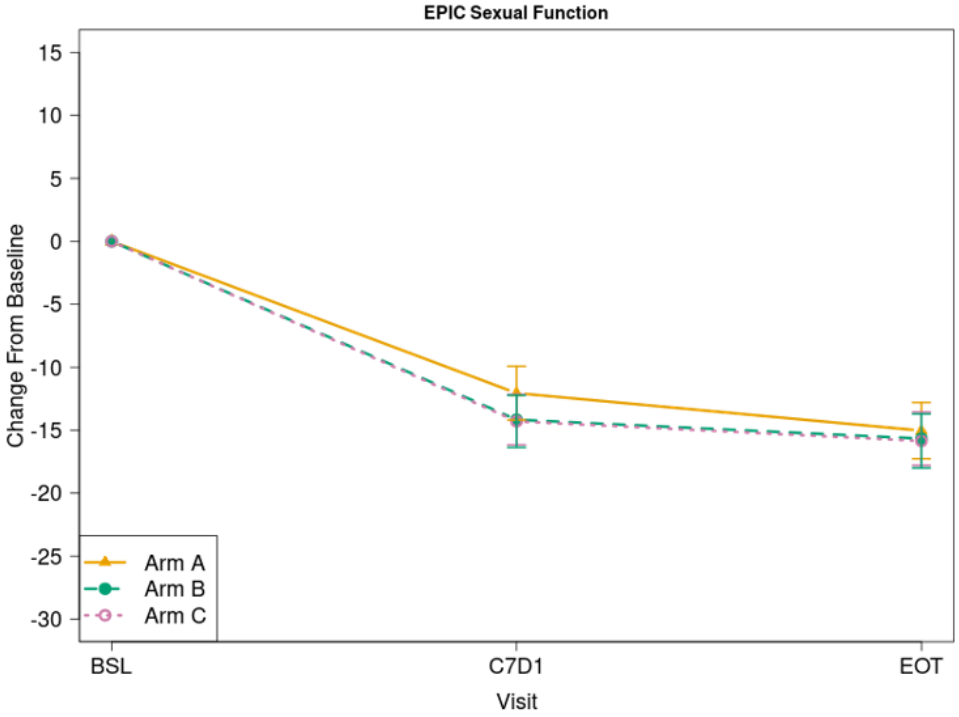
Progress over time



8) Interpreting PRO Data

- Important for physicians and patients to understand what PRO data mean
  - Statistical significance vs clinical significance
  - How to describe scores in the clinic?

EPIC Sexual Domain (MID: 10-12)



	A	B	C
C7D1	-12.3	-14.2	-14.4
EOT	-15.3	-15.8	-16.0

- No statistically significant differences (B vs A, C vs A)
- No differences between arms above MID threshold

EPIC Sexual Domain - Individual Items

% Reported Good or Very Good at EOT

	ADT	ADT + Apa	ADT + Apa + Abi
Erections firm enough for intercourse	5.2	4.6	2.3
Able to reach orgasm	1.8	4.7	2.3

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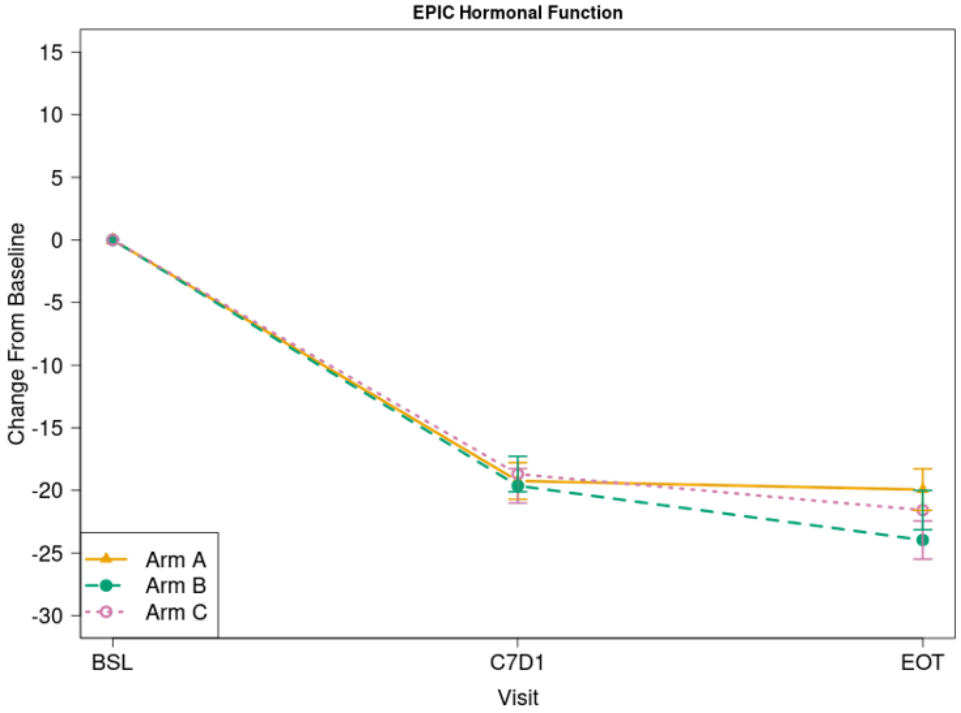
EPIC Hormonal Domain (MID: 4-6)



	A	B	C
C7D1	-19.3	-19.6	-18.9
EOT	-20.2	-23.8	-21.7

- No statistically significant differences (B vs A, C vs A)
- No differences between arms above MID threshold

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EPIC Hormonal Domain - Individual Items

% Reported Big Problem or Moderate Problem at EOT

	ADT	ADT + Apa	ADT + Apa + Abi
Breast tenderness	3.5	3.8	1.6
Depressed	7.1	8.1	6.3
Lack energy	29.8	33.1	35.2
Change in body weight	14.0	19.7	14.4

Q-Twist

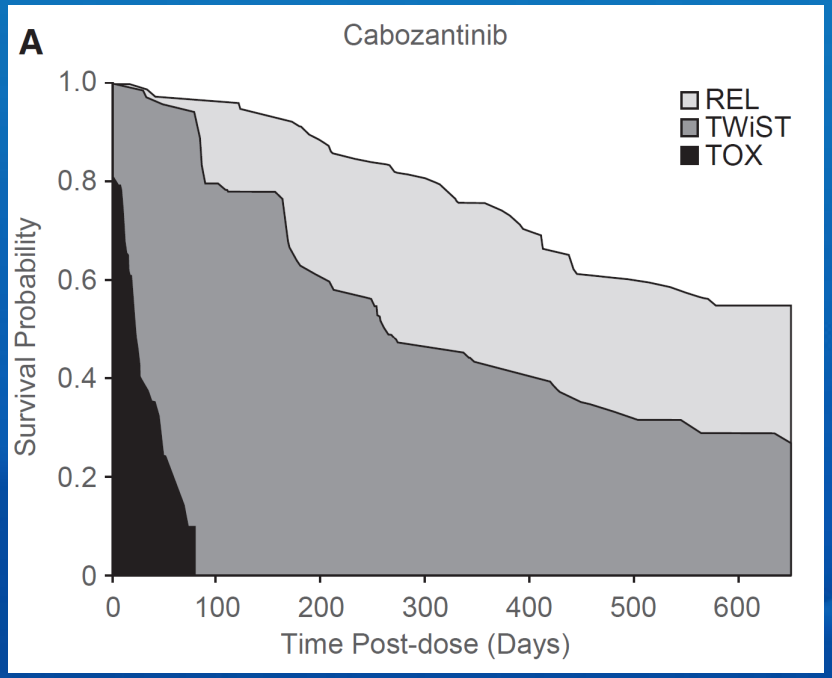
- CABOSUN randomized trial:
  - Metastatic RCC, first line therapy
  - PFS: Cabozantinib (8.6 mo) vs sunitinib (5.3 mo)
  - There are also treatment-relates side effects (>65% grade 3-4 AEs in both arms)
- Can we present a single endpoint that combines survival, disease control and QOL?

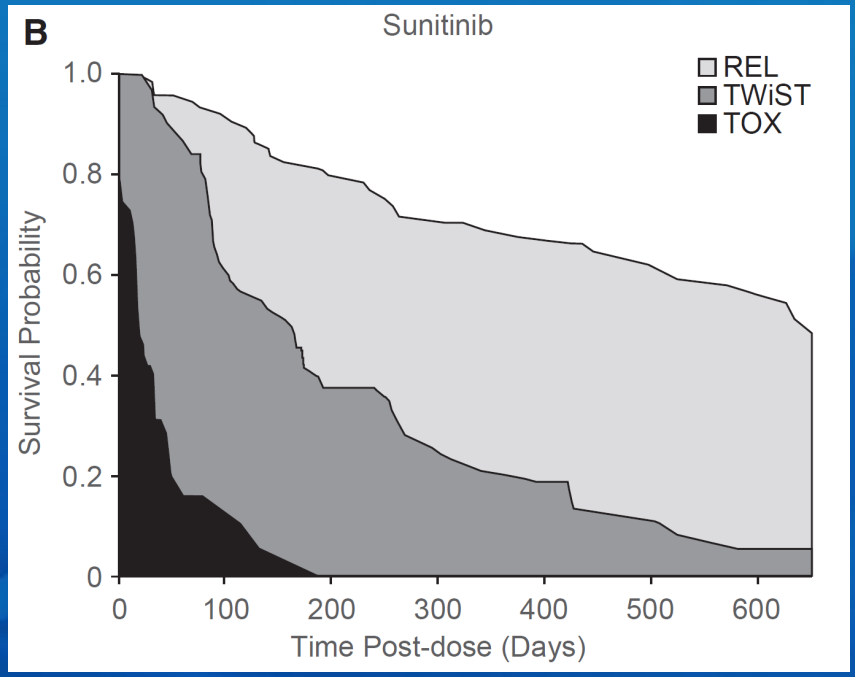
Chen RC. Cancer 126(24):5311-8, 2020.

Q-Twist

- Q-Twist: Quality-adjusted Time Without symptom of disease or Toxicity of treatment
- Three health states:
  - Time without disease progression and without toxicity (ideal)
  - Time before disease progression with toxicity
  - Time after disease progression until death

Q-Twist





Quality-adjusted survival: +24-137 days

Questions: rchen2@kumc.edu

PROTEUS Consortium:
https://theproteusconsortium.org/proteus-trials/study-design/analyzing-data/

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