The Value of PROs in Cancer Clinical Trials

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Value of PROs in Cancer Clinical Trials

Assist in selecting the best treatment by measuring benefits and harms from the patient perspective

- Symptom intervention trial where the primary outcome is a PRO
- Non-inferiority cancer tx trial where PRO (secondary outcome) can guide treatment selection
- Superiority cancer tx trial where PRO can describe (confirm) tolerability
- Superiority cancer tx trial where effectiveness is heterogeneous and a PRO (secondary endpoint) can guide treatment selection

Unique information that for certain domains is not well measured by other biomedical outcomes

- Pain, fatigue, nausea, peripheral neuropathy, etc.

Advancement of clinical trial methods

- Development/validation of measures
- Testing of administration approaches
- Development of analysis & reporting methods

Au HJ, et al. Expert Rev Pharm Out Res, 2010.

N0574: PhIII Randomized Trial of Stereotactic Radiosurgery (SRS) +/- Whole Brain Radiation Therapy (WBRT) in Patients with 1-3 Cerebral Metastases

Adult patients (≥18 years of age) with 1 to 3 brain metastases, all smaller than 3 cm in diameter.

RANDOMIZE (1:1)

- SRS
- SRS + WBRT

Stratified by age (<60 vs ≥60 years), duration of extracranial disease control (≤3 vs >3 months), number of brain metastases (1 vs 2 vs 3), and treatment center

Outcomes (as of Addendum 3):

Primary:
Neurocognitive progression @ 3-months (based on cognitive testing)

Secondary:
Overall survival*
Time to CNS failure
QOL (FACT-Br)

*original primary endpoint at time of trial activation

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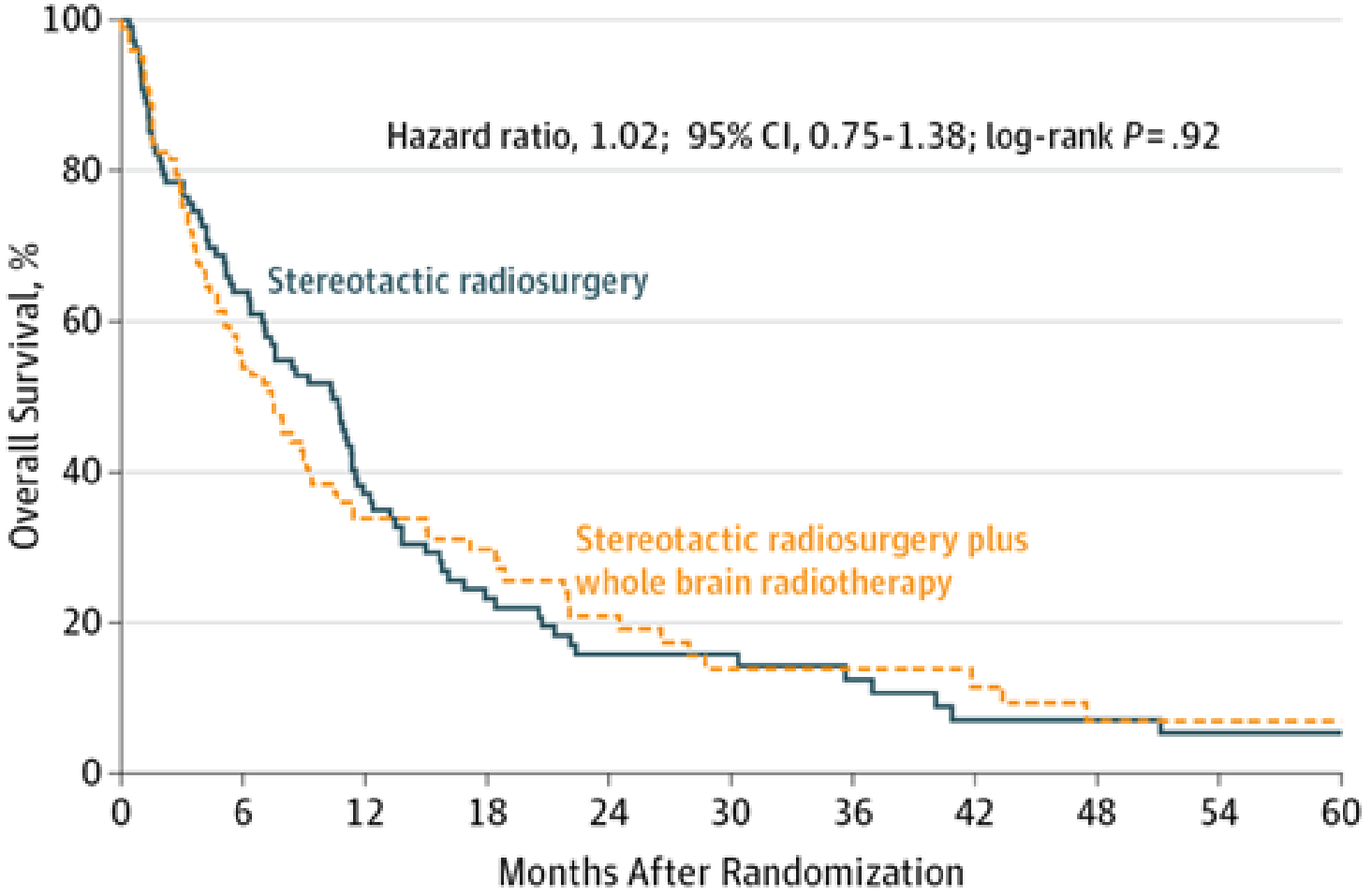
Alliance for Clinical Trials in Oncology

Brown PD, et al. JAMA. 2016; 316(4):401-409.



No. at risk											
Stereotactic radiosurgery	111	64	35	19	13	10	7	4	4	2	2
Stereotactic radiosurgery plus whole brain radiotherapy	102	50	28	22	13	8	8	5	3	1	1

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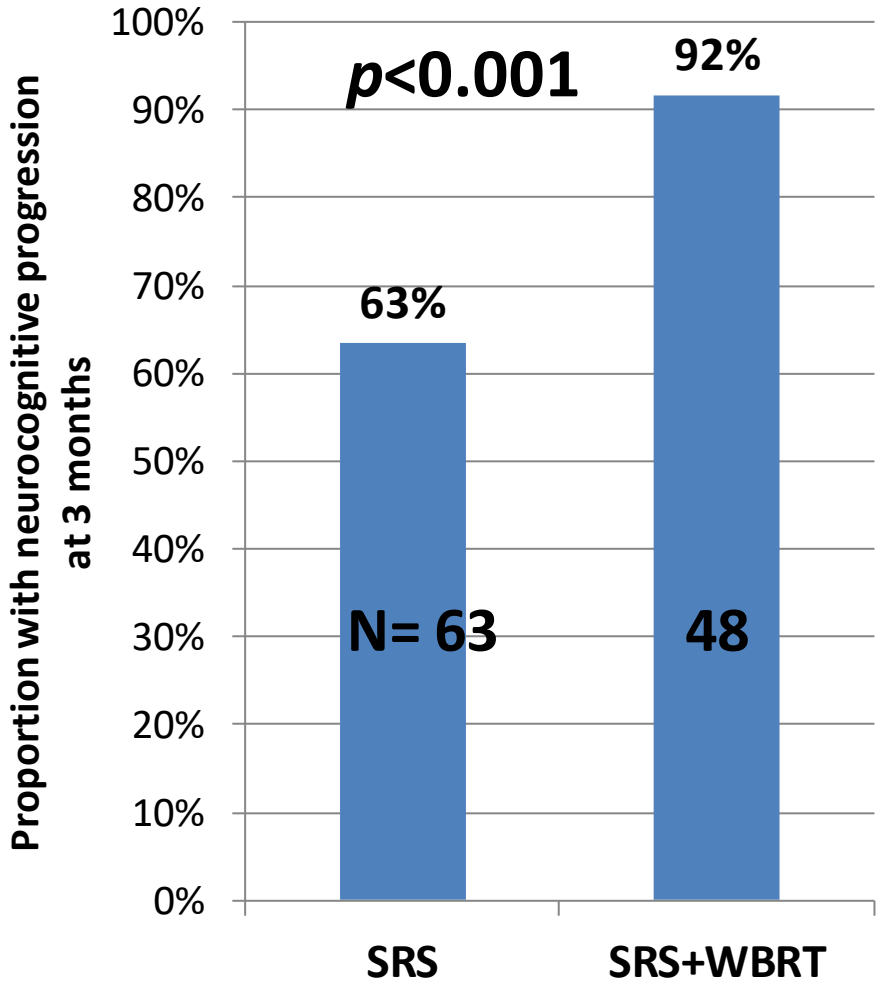
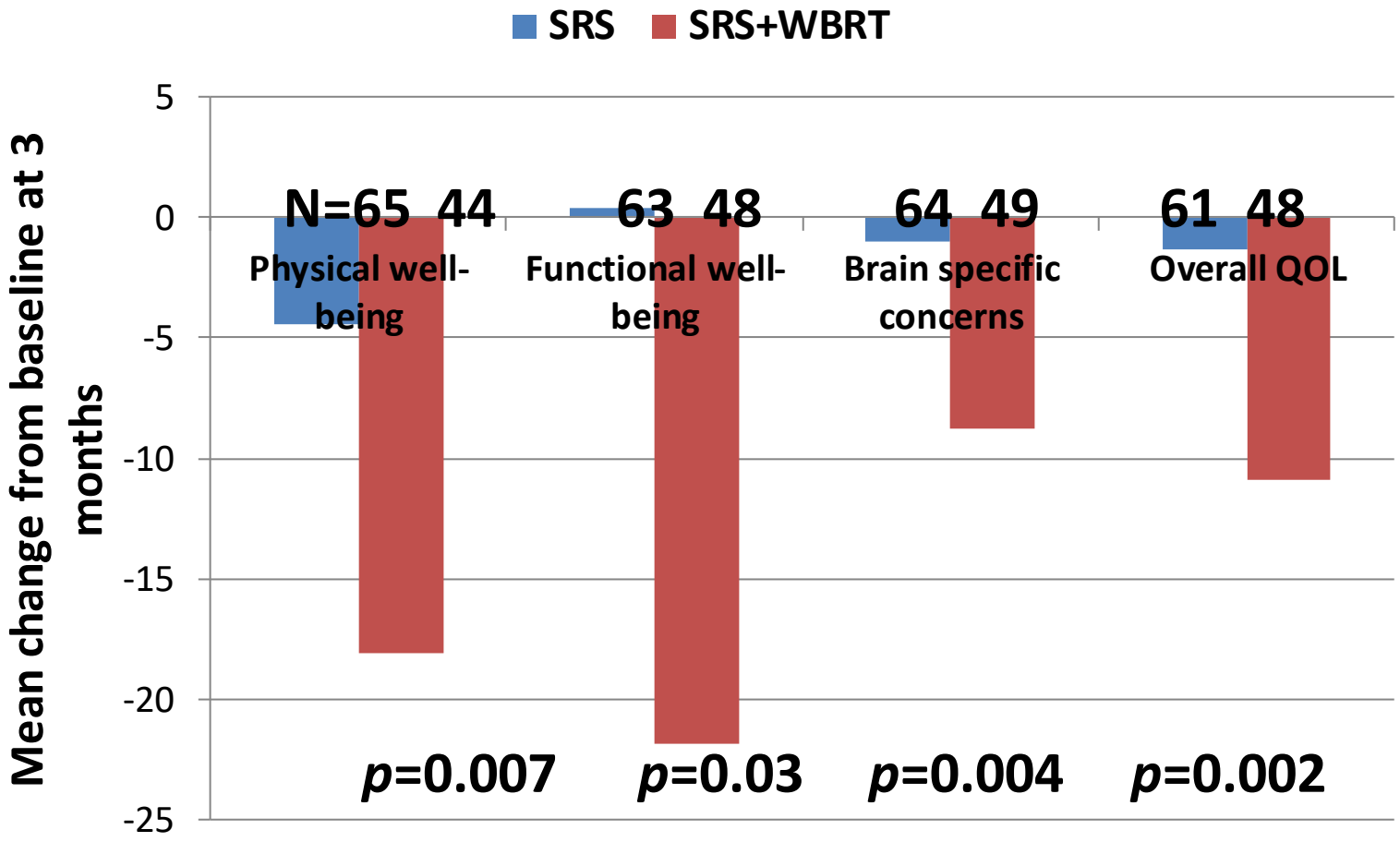
Brown PD, et al. JAMA. 2016; 316(4):401-409.

Cognitive Testing & QOL Outcomes





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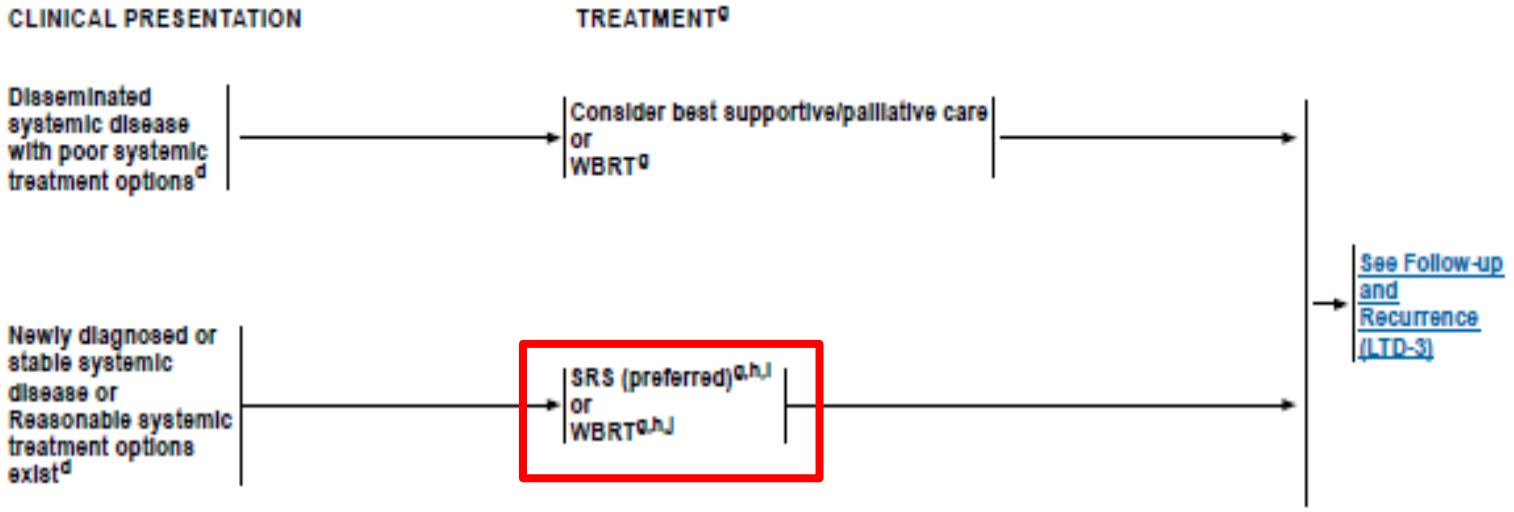
Brown PD, et al. JAMA. 2016; 316(4):401-409.

NCCN Guidelines Version 1.2018
Limited Brain Metastases
NCCN Evidence Blocks™



[d]For secondary CNS lymphoma treatment may include systemic treatment, whole-brain or focal RT, or combination.

[g]If an active agent exists (eg, cytotoxic, targeted, or immune modulating), trial of systemic therapy with good CNS penetration may be considered in select patients (eg, for patients with small asymptomatic brain metastases from melanoma or ALK rearrangement positive NSCLC); it is reasonable to hold on treating with radiation to see if systemic therapy can control the brain metastases. See Principles of Brain and Spinal cord Tumor Systemic Therapy (BRAIN-D).

[h]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

[i]SRS is preferred when safe, especially for low tumor volume, to both the resection cavity and any other non-resected brain metastases. WBRT is generally not recommended but may be appropriate in some rare clinical circumstances (eg, ventricle is violated, cerebellar lesions, risk of meningeal disease, need for complete CNS control before going on protocol, not good SRS candidate for technical reasons, poor PS, advanced age).

[j]For brain metastases not managed with resection, SRS + WBRT is generally not recomended but may be appropriate in some rare clinical circumstances. Brown 2016 showed that for tumors <3 cm, SRS + WBRT improved local control compared with SRS alone, but did not significantly improve survival, and was associated with greater cognitive decline and poorer quality of life. (Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA 2016;316:401-409).

All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

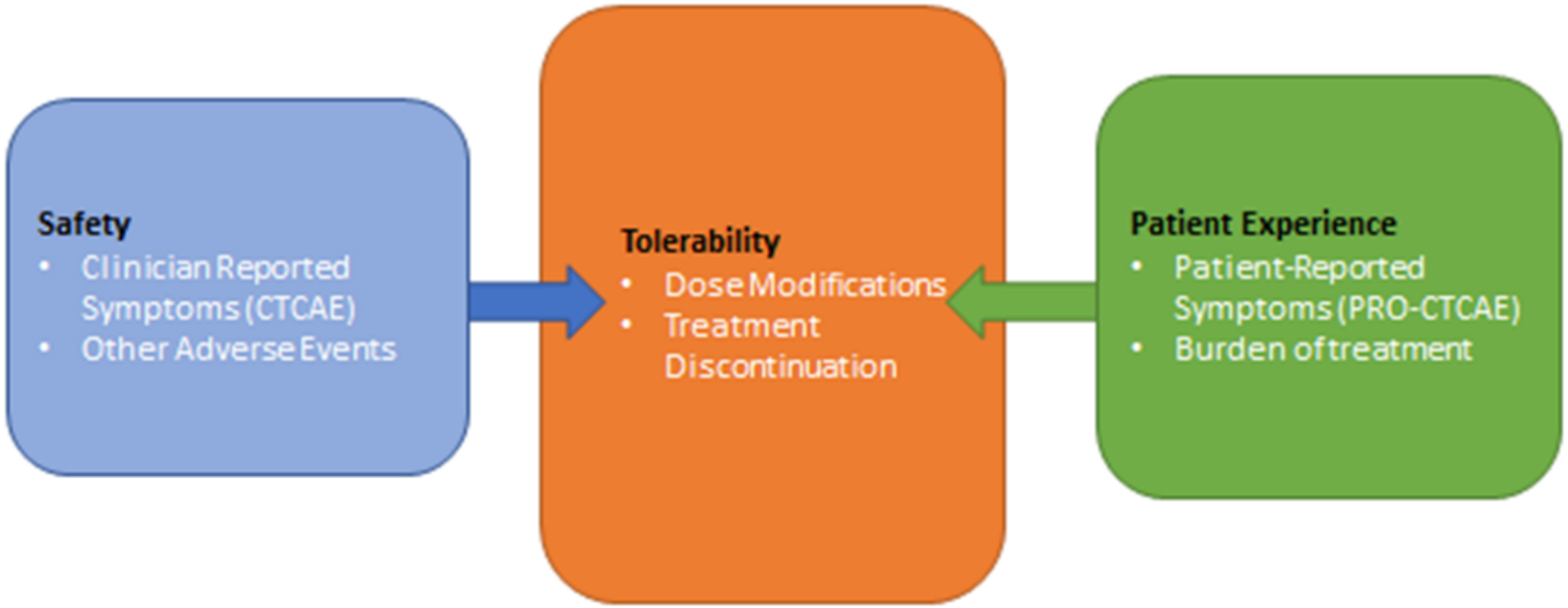
NRG/RTOG 0415: Ph III trial of Hypofractionated vs Conventional Radiotherapy for Patients with Low-Risk Prostate Cancer

- Hypofractionation non-inferior to conventional RT wrt DFS
  - Lee WR, et al. J Clin Oncol. 2016 Jul 10;34(20):2325-32.

- Changes in bowel, bladder, and sexual functioning; QOL; anxiety; and depression were comparable between arms
  - Bruner DW, et al. JAMA Oncol. 2019; 5(5):664-670.

- Led to changes in multiple practice guidelines

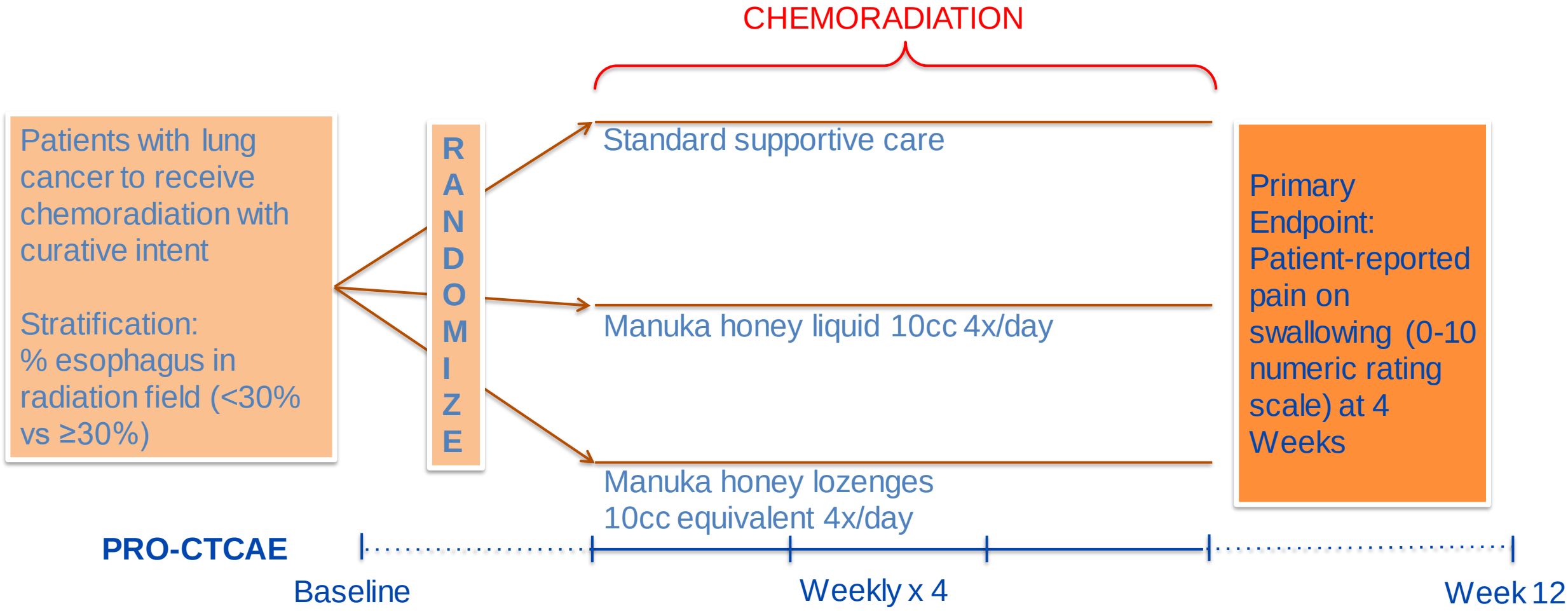
Safety, **tolerability**, and the **patient experience** of AEs in the current landscape of haematology therapies



Thanarajasingam G, et al. Lancet Haematol. 2018 Nov;5(11):e563-e598.

Figure courtesy of Lori Minasian, MD (National Cancer Institute, Bethesda, MD, USA)

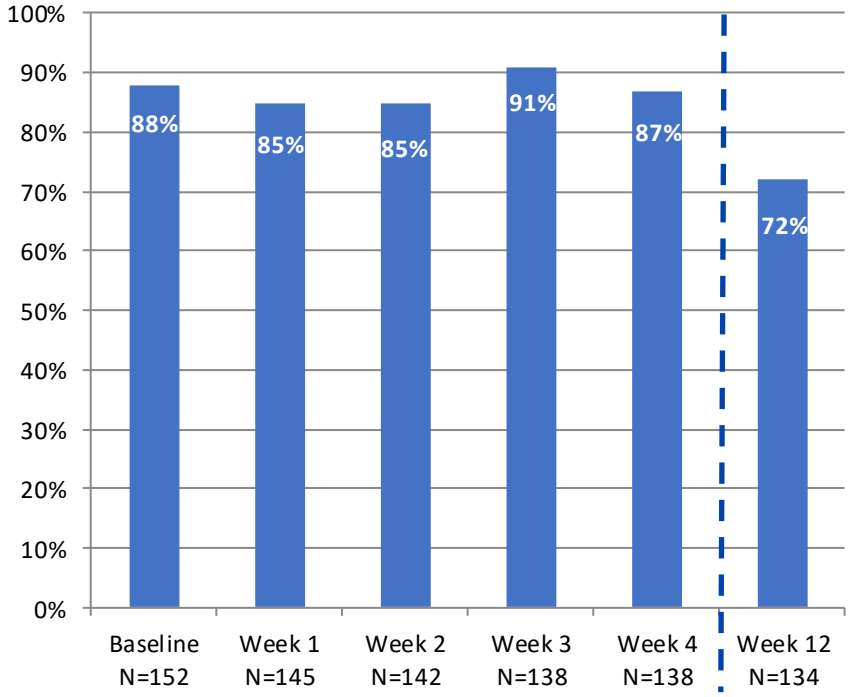
NRG/RTOG 1012



31 symptomatic AEs (53 items) by web system (in-clinic reporting)

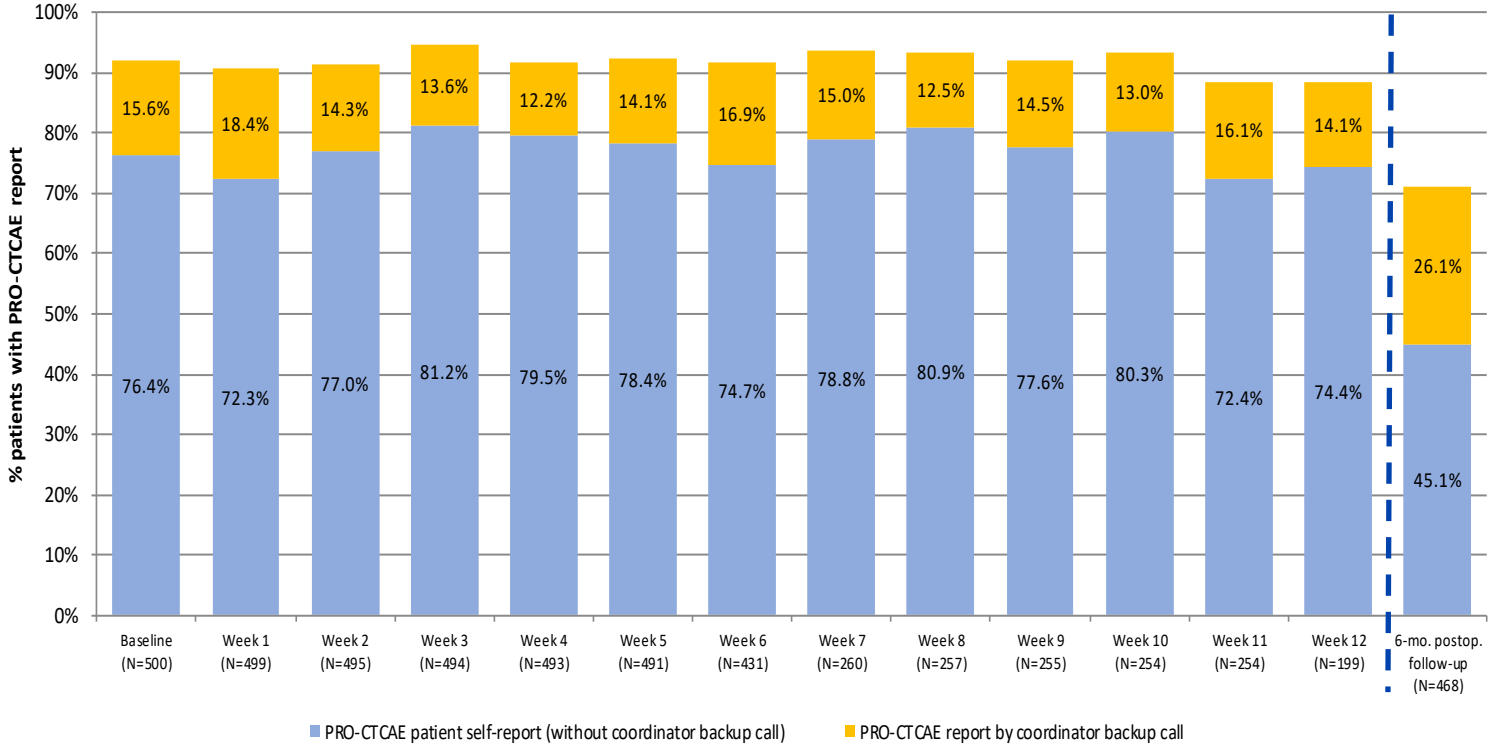
NRG/RTOG 1012: **in-clinic** reporting

- 86% overall compliance



N1048 PROSPECT: **at-home** reporting

- 92% overall compliance
  - 77% compliance (automated reminders only)
  - 15% data captured by human backup calls
- Lower compliance associated with worse ECOG PS (p=0.03), lower educational level (p=0.03), and Hispanic or Latino ethnicity (p=0.01)
- Patients were able to report within 7 days for 18/26 (69%) clinician reported CTCAE grade 4 AEs and 27/40 (68%) hospitalizations



Basch E, Pugh SL, Dueck AC, et al. Int J Radiat Oncol Biol Phys. 2017; 98(2):409-418.

Basch E, Dueck AC, Rogak LJ, et al. J Clin Oncol. 2018; 36(31):3120-3125.

NRG/RTOG 1012: Manuka liquid honey vs manuka lozenge vs supportive care for chemoradiation induced esophagitis in lung cancer

- Fogh SE, et al. Int J Radiat Oncol Biol Phys. 2017; 97(4):786-796.
- Maximum score per item per patient across treatment and follow-up

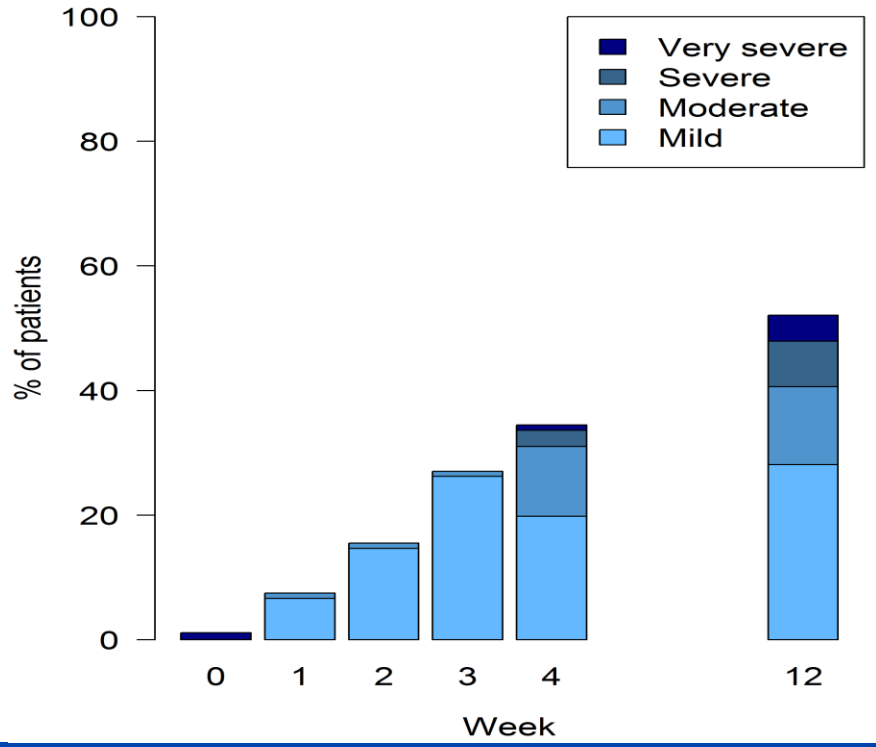
Symptomatic Adverse Event†			Any Level (CTCAE Grade or PRO-CTCAE Score ≥1) [N (%)]			High Level (CTCAE Grade or PRO-CTCAE Score* ≥3) [N (%)]		
			Supportive Care (n=46)	Liquid Honey (n=47)	Lozenge Honey (n=47)	Supportive Care (n=46)	Liquid Honey (n=47)	Lozenge Honey (n=47)
Anorexia	CTCAE:		11 (23.9%)	15 (31.9%)	5 (10.6%)	1 (2.2%)	--	1 (2.1%)
	PRO-CTCAE:	Severity	35 (76.1%)	42 (89.4%)	42 (89.4%)	12 (26.1%)	11 (23.4%)	14 (29.8%)
		Interference	25 (54.3%)	36 (76.6%)	34 (72.3%)	9 (19.6%)	12 (25.5%)	13 (27.7%)
Anxiety	CTCAE:		4 (8.7%)	4 (8.5%)	2 (4.3%)	--	--	--
	PRO-CTCAE:	Frequency	34 (73.9%)	41 (87.2%)	44 (93.6%)	10 (21.7%)	12 (25.5%)	13 (27.7%)
		Severity	33 (71.7%)	40 (85.1%)	44 (93.6%)	9 (19.6%)	10 (21.3%)	9 (19.1%)
		Interference	23 (50%)	29 (61.7%)	26 (55.3%)	7 (15.2%)	8 (17%)	9 (19.1%)
Cough	CTCAE:		14 (30.4%)	21 (44.7%)	11 (23.4%)	--	1 (2.1%)	--
	PRO-CTCAE:	Severity	43 (93.5%)	44 (93.6%)	44 (93.6%)	12 (26.1%)	12 (25.5%)	5 (10.6%)
		Interference	28 (60.9%)	34 (72.3%)	33 (70.2%)	9 (19.6%)	11 (23.4%)	4 (8.5%)

*PRO-CTCAE score of 3 or 4 represents an adverse event frequency of “frequently” or “almost constantly”; severity of “severe” or “very severe”; or interference with usual or daily activities of “quite a bit” or “very much”.
†Maximum grades occurring during and post treatment are included.

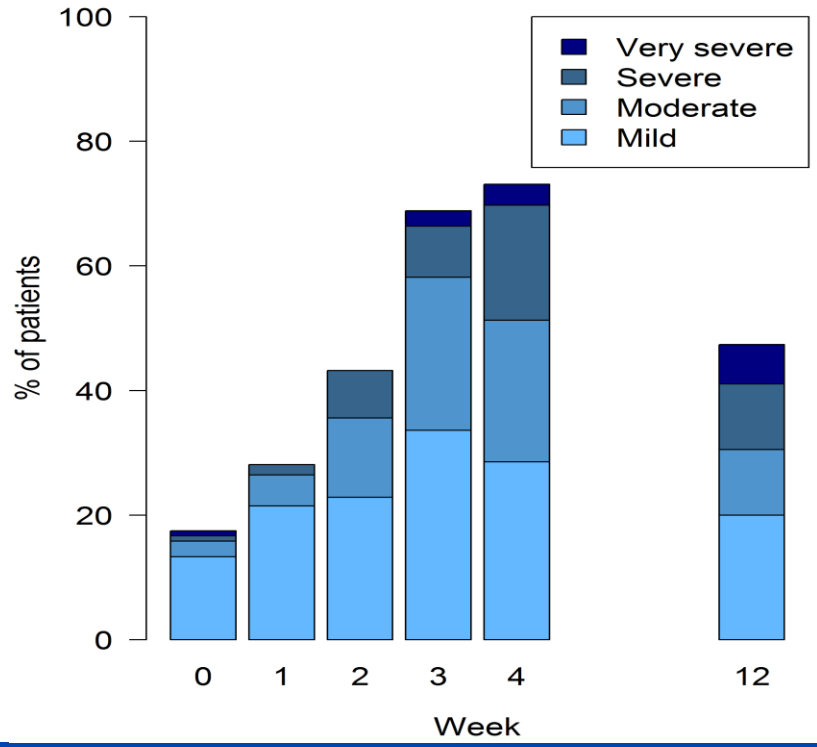
NRG/RTOG 1012: Manuka liquid honey vs manuka lozenge vs supportive care for chemoradiation induced esophagitis in lung cancer

- Basch E, et al. Int J Radiat Oncol Biol Phys. 2017; 98(2):409-418.
- PRO-CTCAE score frequencies at each time point (all arms combined)

Radiation dermatitis severity

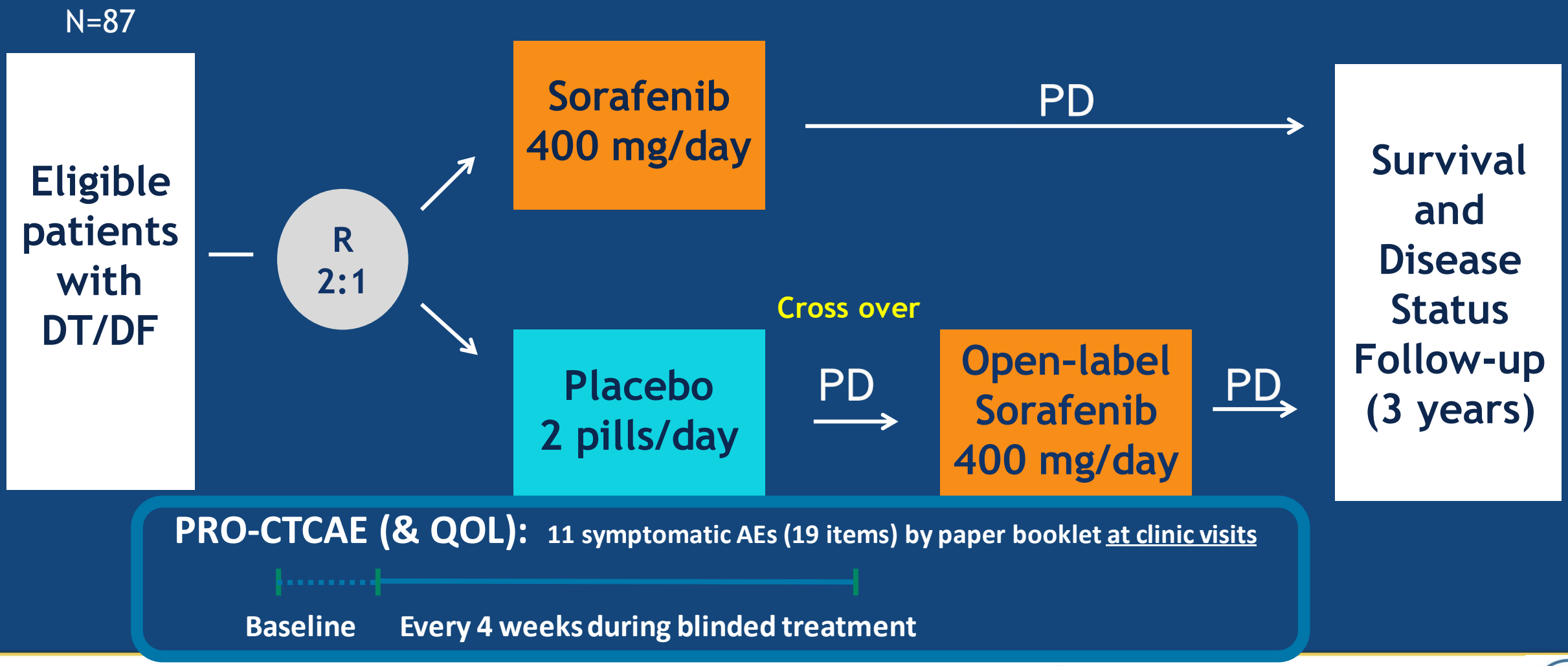


Dysphagia severity



*Denominator at each time point is the number of patients who completed the PRO-CTCAE item

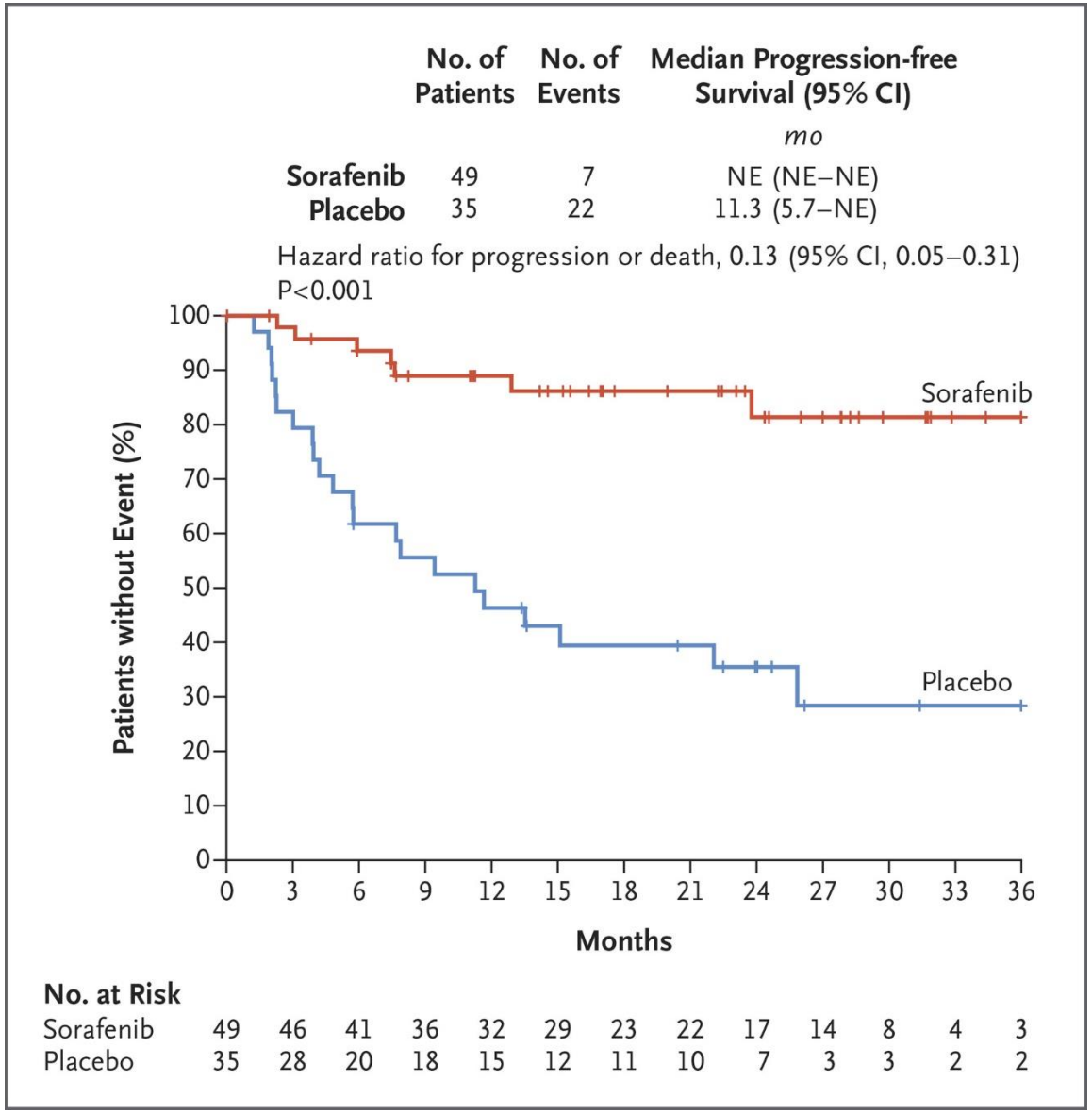
A091105: Phase III, Placebo-Controlled, Double-blind Randomized Design



PRESENTED BY: Mrinal M. Gounder, MD
Memorial Sloan Kettering Cancer Center

A091105

- 87 patients enrolled, 85 started treatment
- PRO-CTCAE/QOL was an **optional** substudy (N=64 consented)
- 64 patients completed PRO-CTCAE at baseline (all started tx)
- 63 patients completed PRO-CTCAE post-baseline (all started tx)
- 63 patients completed PRO-CTCAE at baseline + at least one post-baseline (all started tx)
- **81.3%** completion (baseline-Week 32)



Gounder MM, et al. NEJM. 2018; 379(25):2417-2428.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sorafenib for Advanced and Refractory Desmoid Tumors

Table S4: Summary of toxicities reported by patients using PRO-CTCAE								
PRO-CTCAE Item	With adjustment for baseline							
	No. evaluable patients		Score ≥1			Score ≥3		
	Sorafenib N	Placebo N	Sorafenib N (%)	Placebo N (%)	Risk Difference (95% CI)	Sorafenib N (%)	Placebo N (%)	Risk Difference (95% CI)
Insomnia Severity	35	27	18 (51%)	9 (33%)	18.1% (-7.4 - 41.4%)	6 (17%)	2 (7%)	9.7% (-10.2 - 27.5%)
Insomnia Interference	35	26	15 (43%)	11 (42%)	0.5% (-25.4 - 25.4%)	5 (14%)	4 (15%)	-1.1% (-22.2 - 17.8%)
Constipation Severity	35	26	12 (34%)	13 (50%)	-15.7% (-40.6 - 9.6%)	5 (14%)	5 (19%)	-4.9% (-26.7 - 14.6%)
Pain Frequency	35	26	16 (46%)	10 (38%)	7.3% (-19.0 - 31.7%)	13 (37%)	6 (23%)	14.1% (-10.4 - 36.5%)
Pain Severity	35	26	16 (46%)	11 (42%)	3.4% (-22.2 - 28.5%)	9 (26%)	8 (31%)	-5.1% (-28.9 - 18.2%)
Pain Interference	36	26	19 (53%)	12 (46%)	6.6% (-18.9 - 31.6%)	13 (36%)	5 (19%)	16.9% (-7.0 - 38.4%)
Fatigue Severity	36	27	21 (58%)	17 (63%)	-4.6% (-28.7 - 20.2%)	12 (33%)	10 (37%)	-3.7% (-28.1 - 20.2%)
Fatigue Interference	36	26	17 (47%)	13 (50%)	-2.8% (-27.9 - 22.6%)	10 (28%)	7 (27%)	0.9% (-23.0 - 23.4%)
Nausea Frequency	36	27	21 (58%)	6 (22%)	36.1% (8.1 - 57.6%)	5 (14%)	2 (7%)	6.5% (-12.6 - 23.4%)
Nausea Severity	36	27	22 (61%)	8 (30%)	31.5% (4.8 - 54.0%)	4 (11%)	4 (15%)	-3.7% (-23.9 - 13.9%)
Vomiting Frequency	35	27	11 (31%)	6 (22%)	9.2% (-14.1 - 31.5%)	0 (0%)	1 (4%)	-3.7% (-19.7 - 7.0%)
Vomiting Severity	35	27	10 (29%)	5 (19%)	10.1% (-13.4 - 32.0%)	2 (6%)	1 (4%)	2.0% (-13.5 - 16.6%)

Gounder MM, et al. NEJM. 2018; 379(25):2417-2428.

The NEW ENGLAND JOURNAL of MEDICINE

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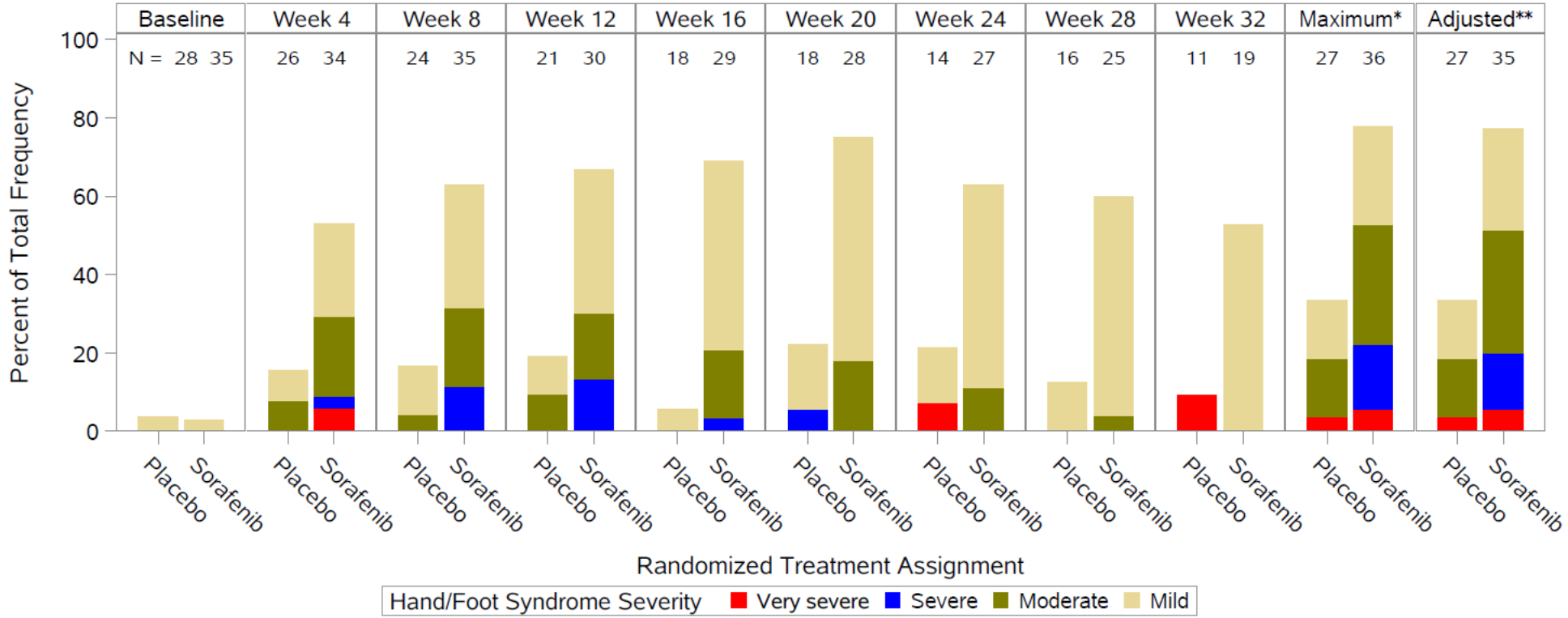
Sorafenib for Advanced and Refractory Desmoid Tumors



*Maximum score reported post-baseline per patient.
**Maximum score reported post-baseline per patient when including only scores which were worse than the patient's baseline score.

Gounder MM, et al. NEJM. 2018; 379(25):2417-2428.

Additional PRO-CTCAE methods development publications based on A091105:

Basch E, et al. Clin Trials. 2021; 18(1)104-114.
Mazza GL, et al. To appear in Qual Life Res. 2021.

+ the foundation of standardized graphics & tables for PRO-CTCAE:
https://cran.r-project.org/web/packages/ProAE/index.html

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PRO-CTCAE uptake in Alliance trials

- 11 NCTN trials
  - 5 randomized ph II, 2 ph II/III, 4 ph III
- 3 NCORP trials
  - 1 ph II/III, 2 ph III

Other guidances, tools

- SPIRIT-PRO – PRO protocol recommendations
- SISAQOL – PRO statistical analysis standards
- CONSORT-PRO – PRO reporting recommendations

PROTEUS

https://more.bham.ac.uk/proteus/

Key issues

- Limited resources, high demand
- Training, knowledge sharing needed
- Multiple modes of administration and enhanced monitoring needed to minimize missing data

Discussion:

What are the issues NCI should think about when considering implementation of the FDAs draft guidance on PROS, particularly around early phase trials?