Patient Reported Outcomes in an Era of Immunotherapy Drug Development

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Disclosures

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Treatment Benefit

May be measured as:

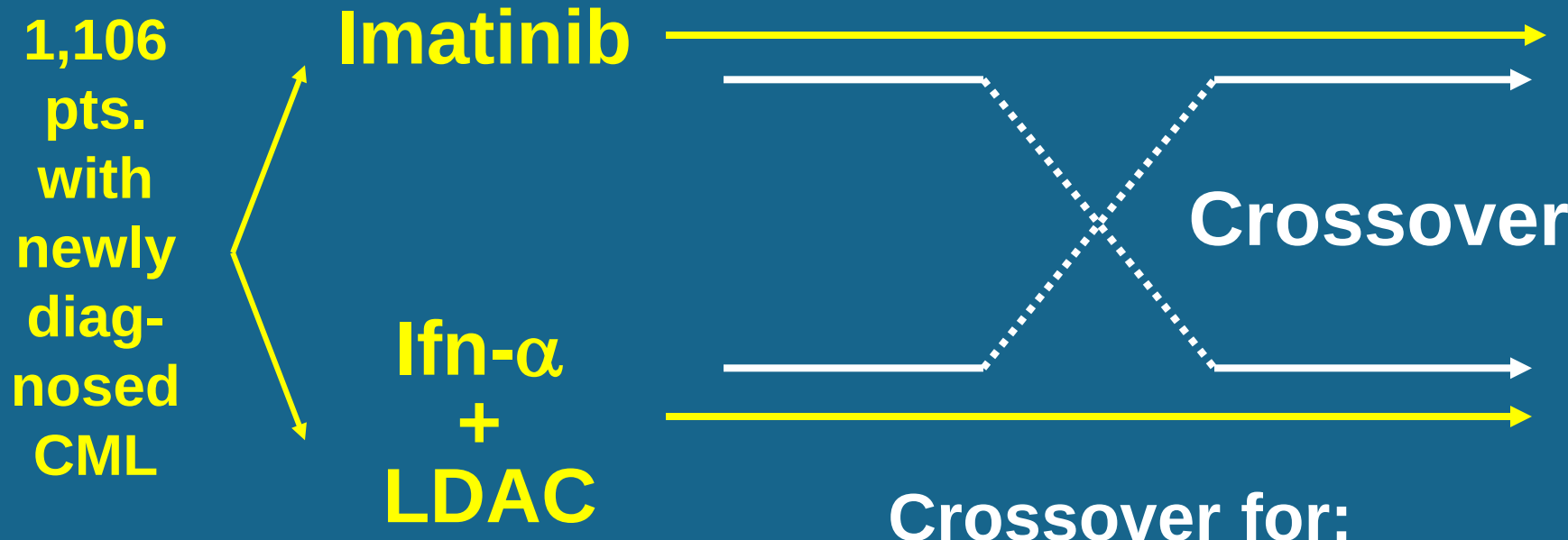
- Comparative efficacy

  An improvement or delay in the development of symptoms or decrements in function compared to placebo or an active comparator

- Comparative safety

  Reduction or delay in treatment-related toxicity compared to placebo or an active comparator

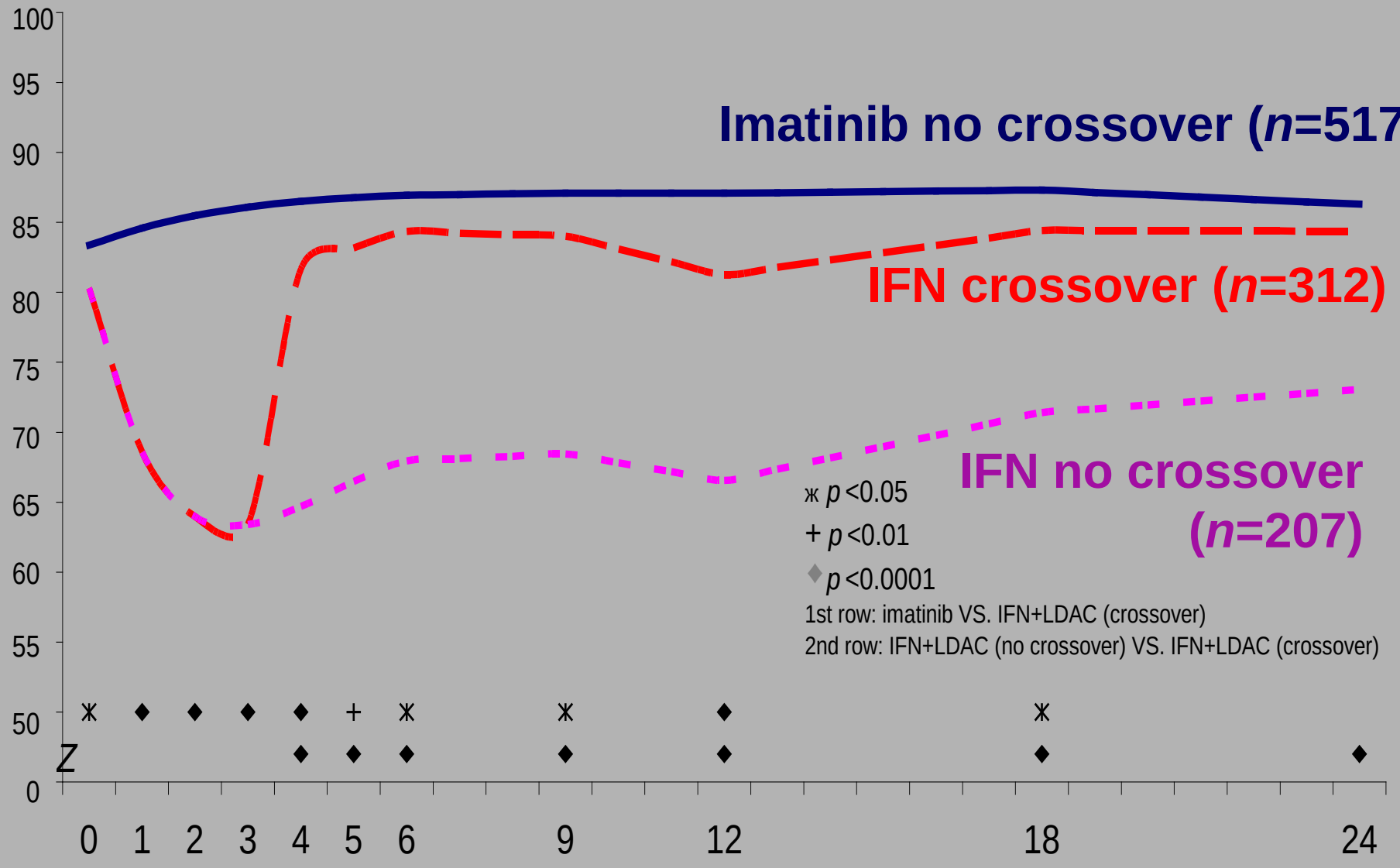
Imatinib (Glivec) Registration Trial (Phase III, Multicenter, Open Label)



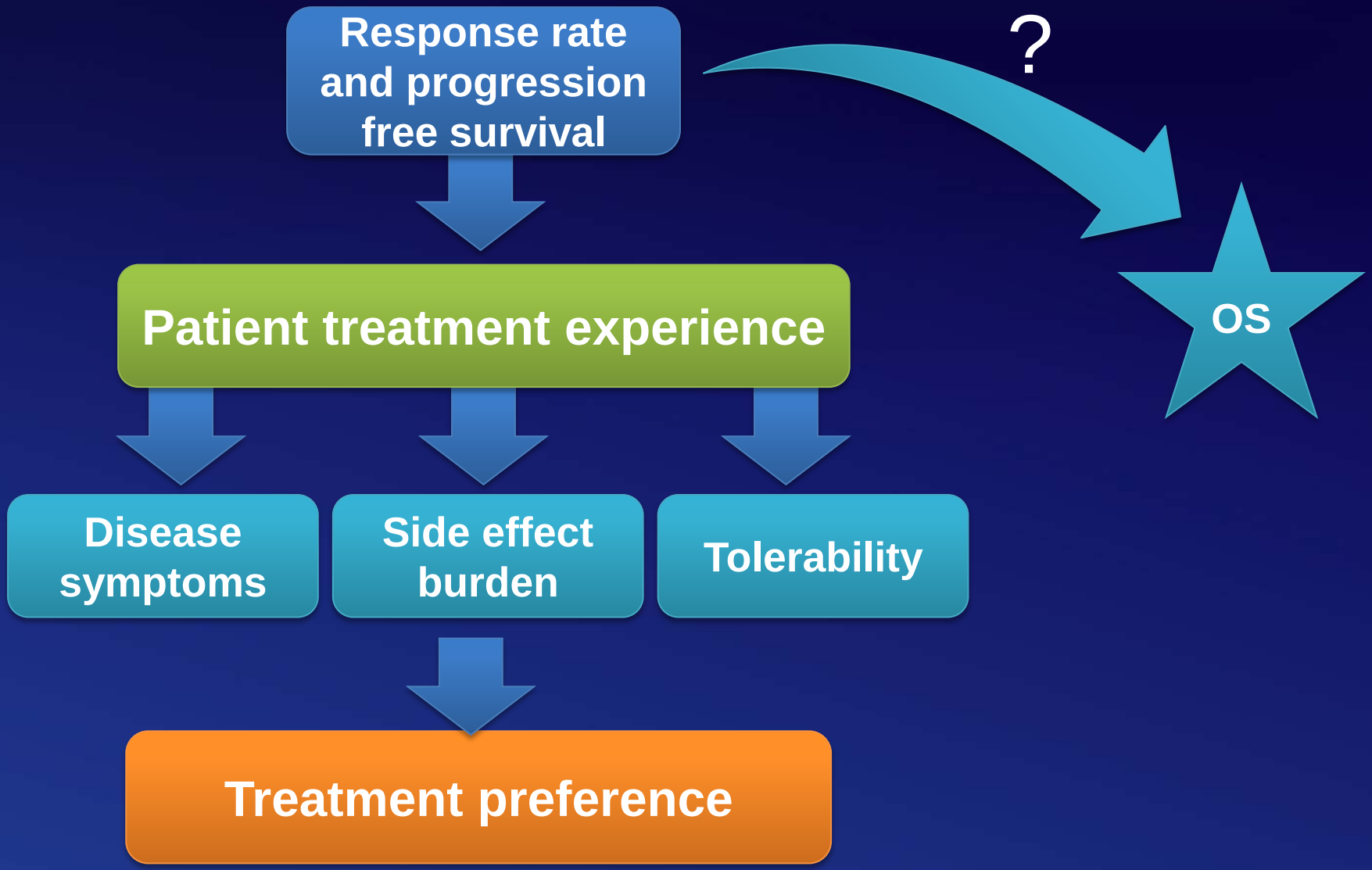
Crossover for:

- Lack of response
- Loss of response
- Intolerance of treatment

Estimated Mean FACT-BRM (with crossover)



Patient reported outcomes in oncology



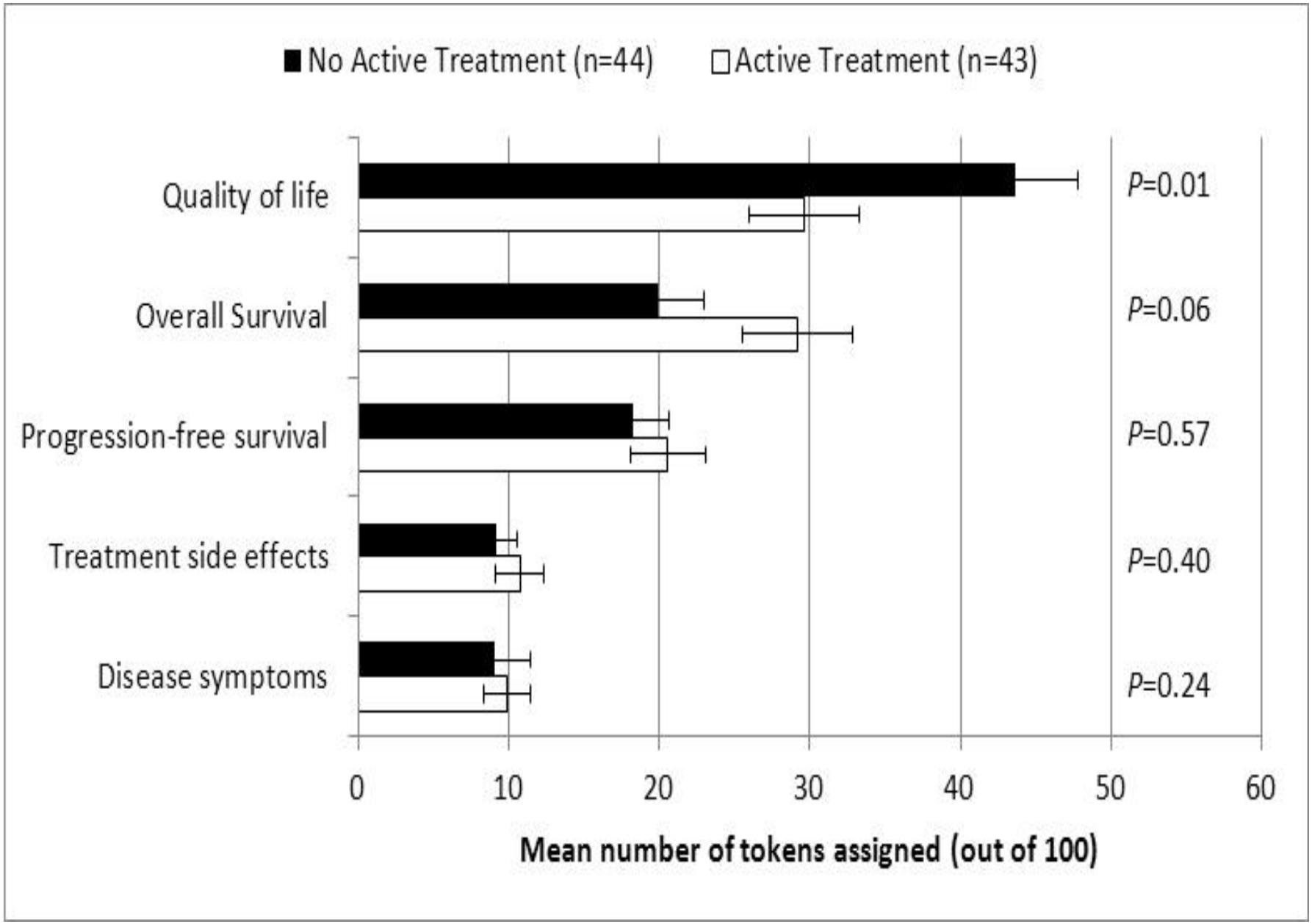
Cella D. *J Community Support Oncol.* 2014;12:265–266.

OS, overall survival.

Clinical Benefit in Hematology-Oncology

- Overall survival considered gold standard
  - Surrogate endpoints like progression-free survival often used
- Traditional endpoints do not fully address treatment responses experienced by the patient
  - Symptom relief, functional improvement
- *Patient-reported outcomes* can complement traditional efficacy measures
- Once we know the patient-reported outcomes, how do we incorporate them into risk-benefit analysis

Markman M. *Current Oncology Reports.* 2009;11:1-2.
Knox J. *The Lancet*. 2008;372(9637):427-429.
Bukowski R, et al. *American Journal of Clinical Oncology*. 2007;3:220-227.
Lipscomb J, et al. *CA Cancer J Clin.* 2007;57:278-300.



Havrilesky LJ SGO abstract 2013

Starting with the end in mind: Possible messages from trial results

- PFS benefit of “x” relative to “y” was associated with:
  - Disease-related symptom benefit (efficacy)
  - Improved physical function (efficacy)
  - Improved quality of life (efficacy)
  - Reduced toxicity (safety)

- Relative to “y,” “x” provided superior CBR. That is:
  - Longer PFS, reduced symptoms, and comparable safety
  - Longer PFS, no difference in symptoms, better safety
  - No difference in PFS with better symptom control
  - etc

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Composite endpoints can be intuitive or conceptually appealing

- Takes into account multiple traditional endpoints:
  - Response rate
  - Survival
  - Toxicity
  - PROs
- Help health-care providers, patients, and decision-makers to understand the total clinical benefit of a particular intervention.
- When survival or QOL measures alone do not adequately define the clinical effects of treatment

Symptom Indexing

- Nesting of tumor-specific or treatment-specific symptoms within larger, often multidimensional questionnaires creates opportunity to derive targeted symptom scales:
  - EORTC; FACT/FACIT; etc
  - PRO-CTCAE
  - PROMIS
- Functional status reported by patient) can offer cross-cutting information
  - Physical Functioning (EORTC; SF-36; FACT PWB; FACT FWB; PROMIS PF)

AXIS Trial and FKSI

Advanced Kidney Cancer Symptom Index – Long Form

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

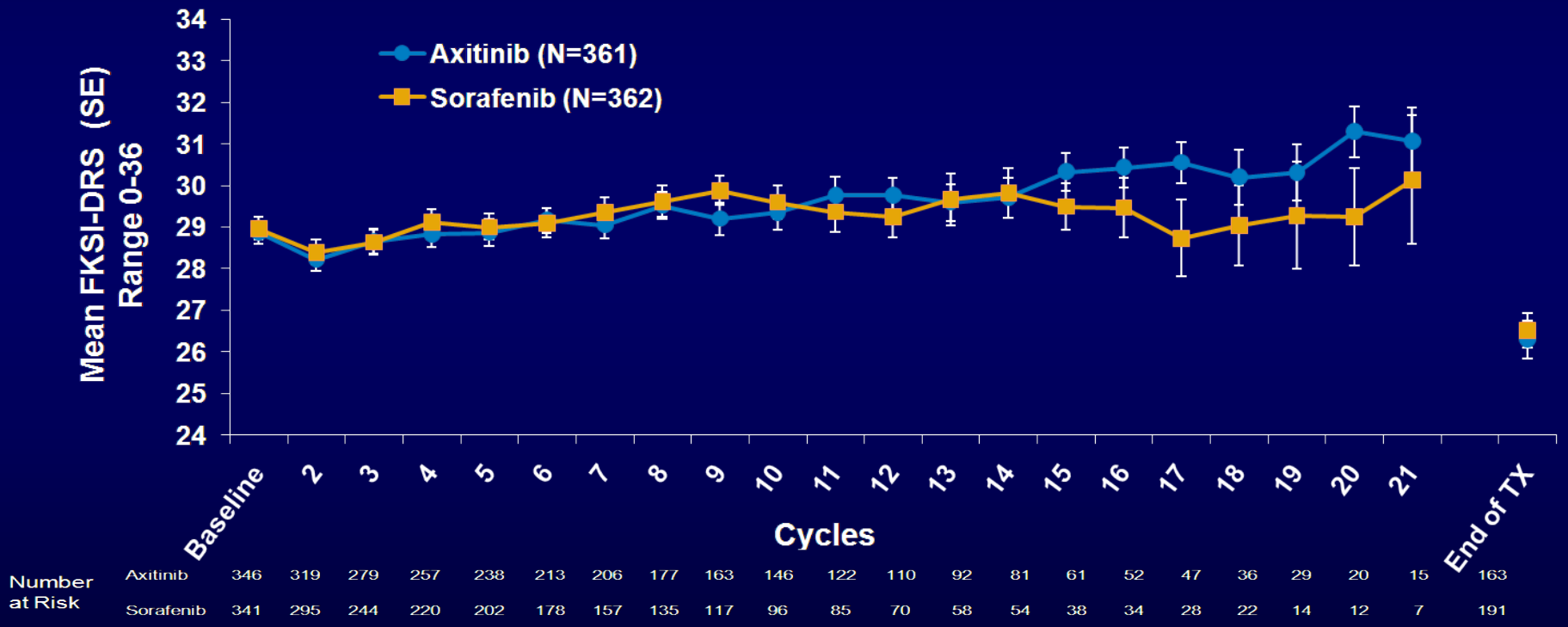
	Not at all	A little bit	Some-what	Quite a bit	Very much
I have a lack of energy	0	1	2	3	4
I am bothered by side effects of treatment	0	1	2	3	4
I have pain	0	1	2	3	4
I am losing weight	0	1	2	3	4
I have bone pain	0	1	2	3	4
I feel fatigued	0	1	2	3	4
I am able to enjoy life	0	1	2	3	4
I have been short of breath	0	1	2	3	4
I worry that my condition will get worse	0	1	2	3	4
I have a good appetite	0	1	2	3	4
I have been coughing	0	1	2	3	4
I am bothered by fevers	0	1	2	3	4
I am able to work (includes work from home)	0	1	2	3	4
I am bothered by blood in my urine	0	1	2	3	4
I am sleeping well	0	1	2	3	4

Cella D, et al. *Supportive Oncology*. 2006;4:191-199.

AXIS Trial: Disease-related symptoms

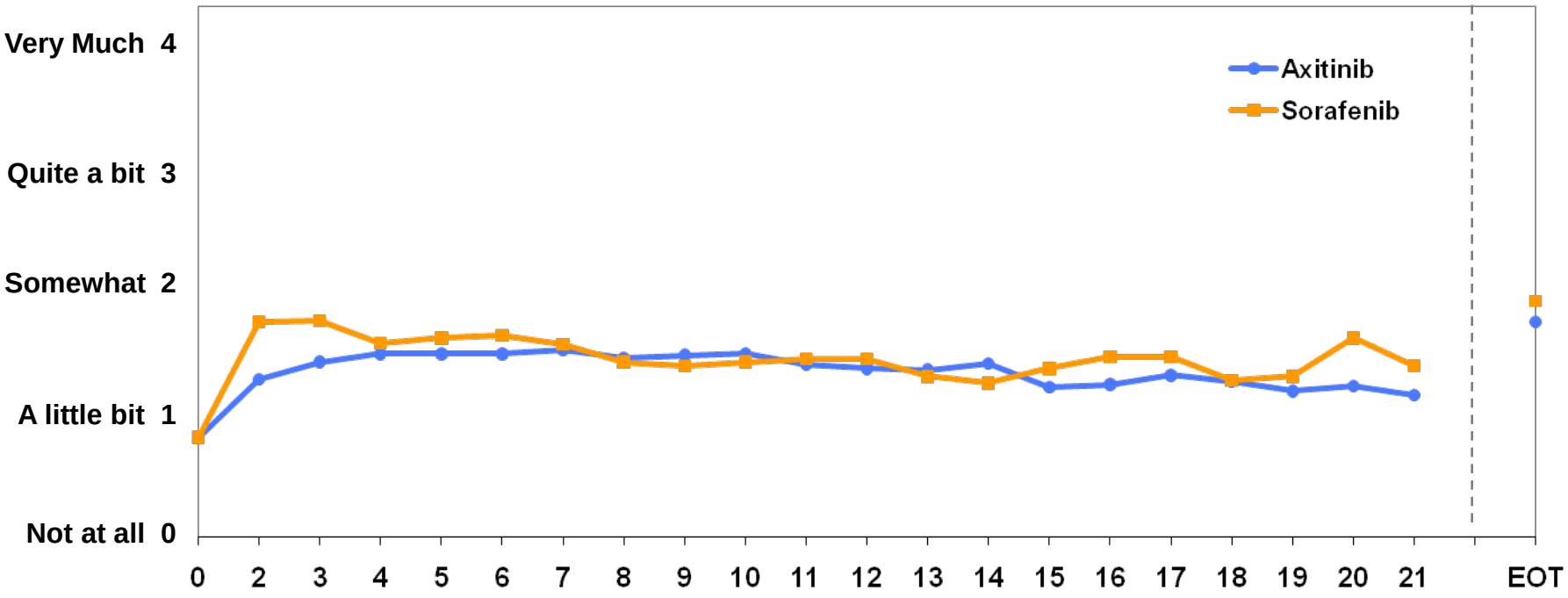
Overall, disease-related symptoms did not change while on treatment

- **However, disease-related symptoms were worse when patients came off treatment due to disease progression or AEs**



Cella et al. British Journal of Cancer. 108 (8):1571–1578, 2013

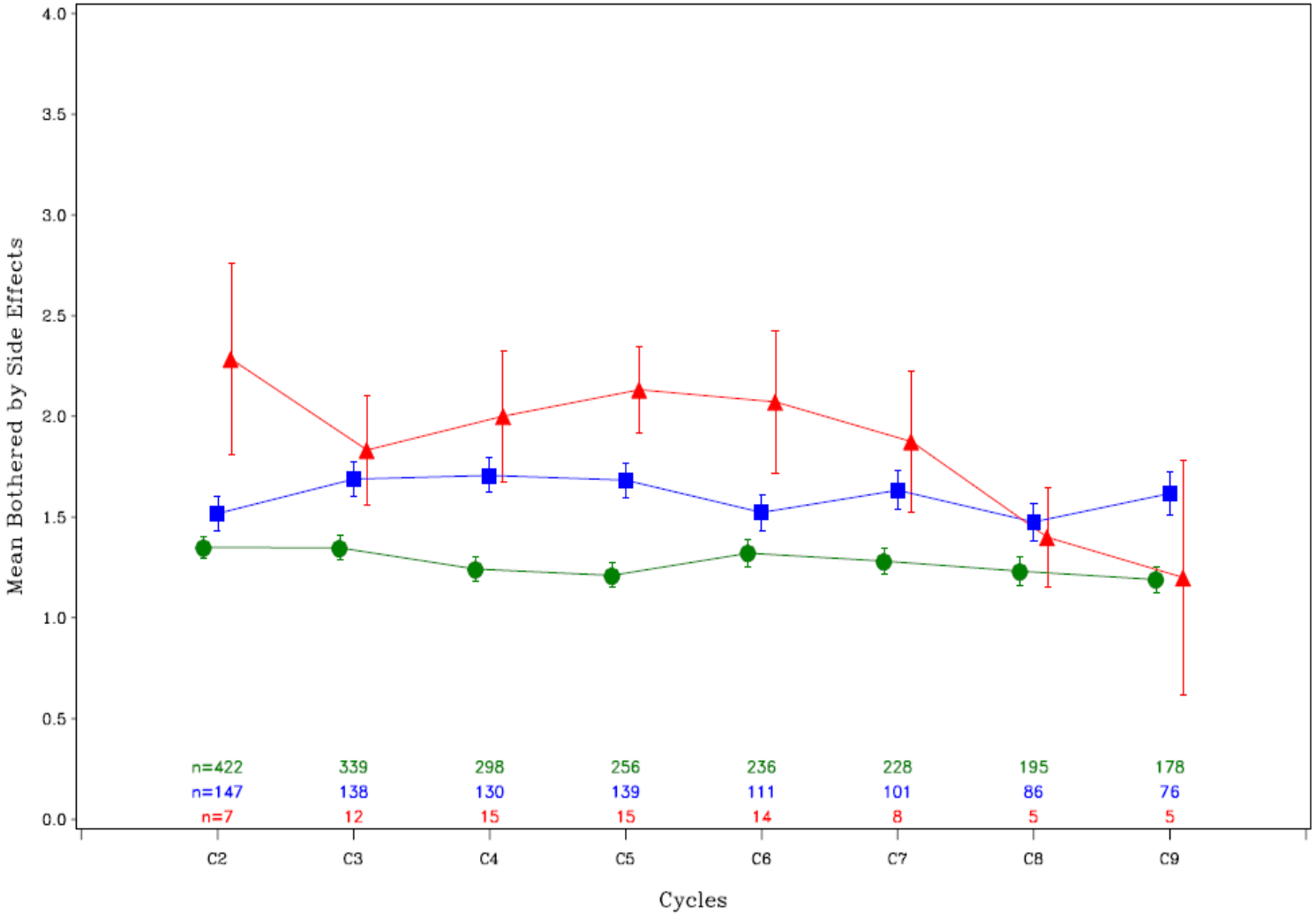
FKSI-15 # 2: I Am Bothered by Side Effects of Treatment



Axitinib	327	327	285	260	246	219	212	179	166	148	127	112	93	82	63	54	48	37	30	21	15	164
Sorafenib	317	302	249	226	206	181	162	139	121	98	89	73	61	57	41	36	28	22	14	12	7	193

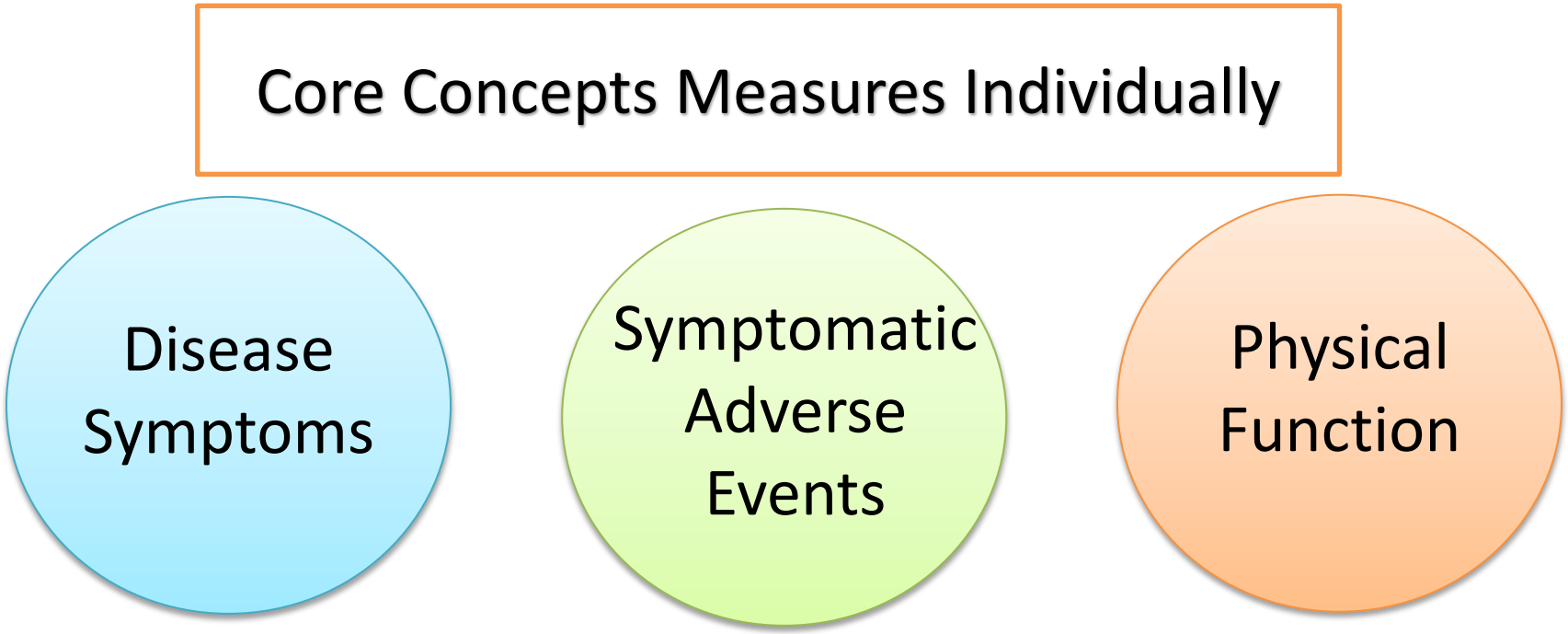
Cella et al, Br J Cancer (2013) 108, 1571–1578

Side effect bother by diarrhea grade, combined Treatments



Cella et al, Br J Cancer (2013) 108, 1571–1578

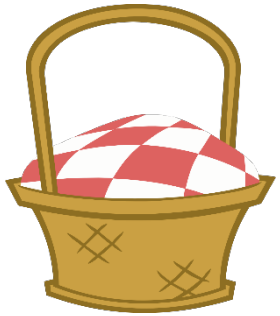
FDA Perspective: Key contributors to Quality of Life



– Use existing until something better comes along

Kluetz et al, Clin Cancer Res, published Online Jan 12, 2016; DOI: 10.1158/1078-0432

Umbrellas and Baskets



Umbrella

- Single tumor type or histology
- PRO considerations
  - Small N
  - Single-arms opening and closing
  - Common disease symptoms
  - Physical function unifying endpoint
  - Safety/side effect variability

Basket

- Multiple tumor types
- PRO considerations
  - Small N
  - Single-arms opening and closing
  - Disease symptoms highly variable
  - Physical function unifying endpoint
  - Safety/side effect variability

Some PRO issues with MATCH

- Small N, single-arm searches for efficacy signals among pts with common molecular profile
- Discovery valued over hypothesis testing
- PS = 0/1, variable primary sites, 6 month f/u
  - disease symptom assessment unlikely to be informative
- Variability in patient preferences and tolerability
  - Willingness to undergo testing with unknown benefit
  - Comprehension of testing results, risks and benefits
  - Preferences regarding decision-making… and family impact
- How to measure treatment toxicity
  - "On-target" versus "off-target" and relationship to efficacy
  - Which ones?

Cella & Wagner, J Comm and Supp Onc, 2015

Which Treatment Symptoms? A proposal

Based on available monotherapy data:

- ≥ 40% all grade
- ≥ 2% grade 3/4

Cella & Wagner, J Comm and Supp Onc, 2015

First 4 MATCH Substudies: How might PROs look?

(Cella & Wagner, 2015)

1	2	3	4	5	6	7
MATCH Substudy	Agent	Patient population	Sample size	Key disease symptoms,[1] Functional status and patient preferences	Expected PRO-relevant toxicity[2]	Likely number of questions (minutes per assessment)
F	Crizotinib	ALK translocations, except lung adeno and anaplastic large cell lymphoma	35	Various Physical Function Tolerability /preference	Constipation Diarrhea Nausea Fatigue Dyspnea Visual disturbances	20 (4)
G	Crizotinib	ROS1 translocations, except non small cell lung cancer	35	Various Physical Function Tolerability /preference	Constipation Diarrhea Nausea Fatigue Dyspnea Visual disturbances	20 (4)
H	Dabrafenib and Trametinib	BRAF V600E and V600K mutations, except melanoma and thyroid	35	Various Physical Function Tolerability /preference	Hand foot syndrome Pyrexia Chills Fatigue Rash Nausea Vomiting Back pain Constipation Diarrhea Dehydration	30 (6)
R	Trametinib	BRAF fusions, or non V600E, non V600K BRAF mutations	35	Various Physical Function Tolerability /preference	Nausea Vomiting Fatigue Diarrhea Rash	18 (4)

Attributing and Selecting Symptoms

- Many of the most important symptoms are caused by both disease and treatment
- Treatments induce MANY symptoms
  - Which to select?
  - Who selects?

- A proposal: Use existing questionnaires, supplemented with:
  - Trial-specific, transparent, pre-specified and externally-adjudicated subset of most likely PRO-relevant side effects
  - Careful planning of assessment timing and acuity/chronicity
  - Valuation exercise (within or outside of trial) aimed at providing patient preferences for each of the outcomes in the composite relative to each other

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Some Questions: Where do you stand?

- Can disease symptoms be separated from treatment symptoms?
  - By patients?
  - By investigators or data reviewers?
- Can one "pick and choose" symptoms for use in a precision medicine (or any other) study?
  - If so, how does minimize or remove bias?
  - What validity information is needed?

Potential benefits of successful blinding

- Participants
  - Less likely to have biased psychological or physical responses to intervention
  - More likely to comply with trial regimens
  - Less likely to seek additional adjunct interventions
  - Less likely to leave trial without providing outcome data, leading to lost to follow-up
- Trial investigators
  - Less likely to transfer their inclinations or attitudes to participants
  - Less likely to differentially administer co-interventions
  - Less likely to differentially adjust dose
  - Less likely to differentially withdraw participants
  - Less likely to differentially encourage or discourage participants to continue trial
- Assessors
  - Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest

Schultz & Grimes, THE LANCET, Vol 359: Feb 23, 2002

Impact of Blinding on Trial Results

- Unblinded investigators may report treatment effects not reported by blinded investigators
  - Noseworthy et al, *Neurology* 1994, **44**: 16-20
- More subjective endpoints create greater opportunity for bias
  - Schulz et al, *Ann Intern Med* 2002; **136:** 254–59
- Some studies cannot be fully blinded
  - Lack of blinding does not necessarily make a weak trial
- Those blinded versus unblinded should be explicated for best review and interpretation
  - Beyond single-, double-, triple-blind

Schultz & Grimes, *Lancet*, 2002, **359**: 696-700