Patient Reported Outcomes

-In the Benefit Risk Assessment

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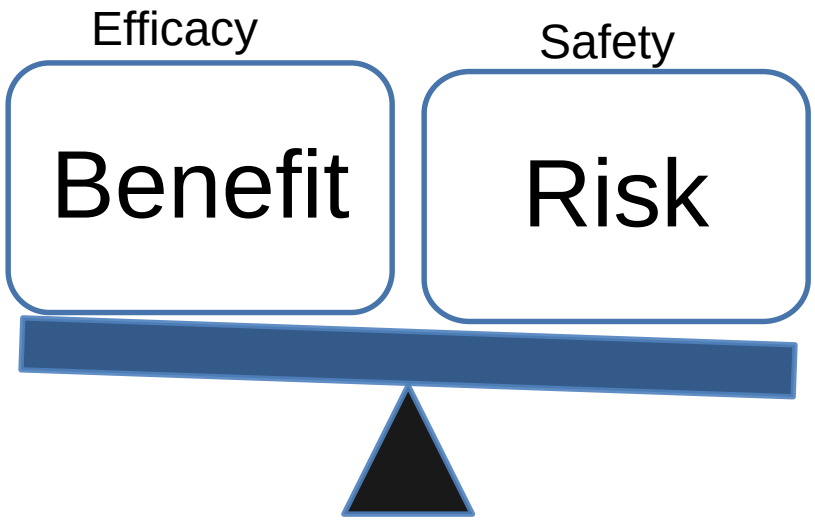
2019 OCE Partners in Progress

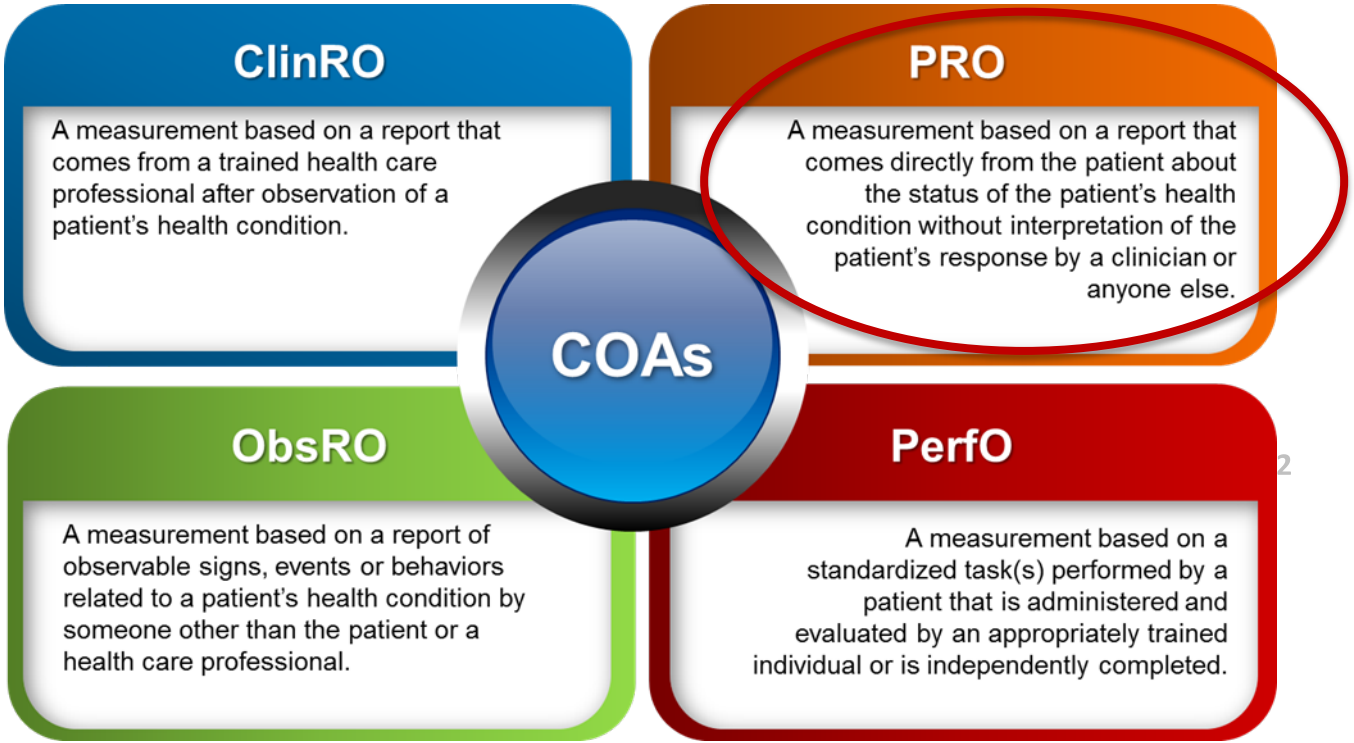
Benefit-Risk Assessment



Traditional approval

- Substantial evidence of Safety and Efficacy
- Well-controlled clinical trials
- Prolongation of life, a better life or an established surrogate for either of the above

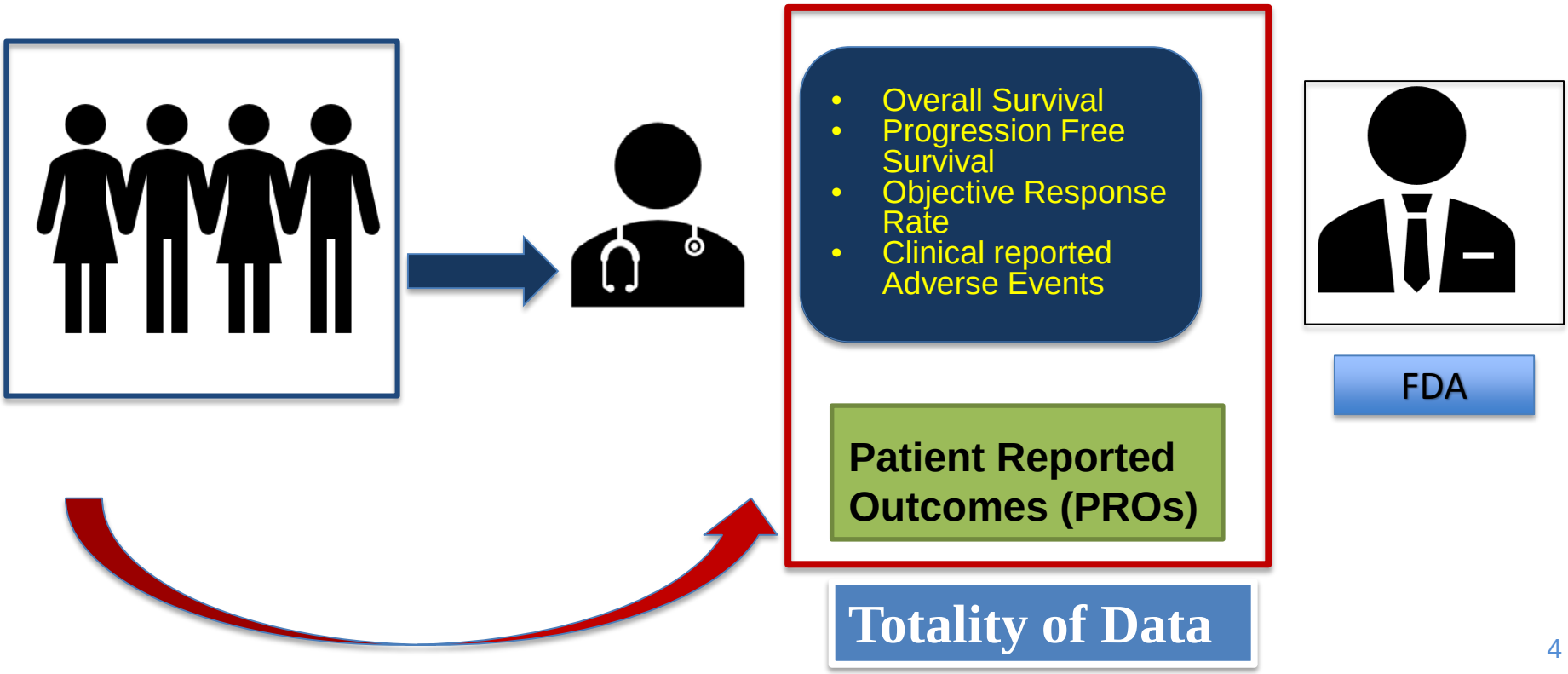
Clinical Outcome Assessments (COAs)



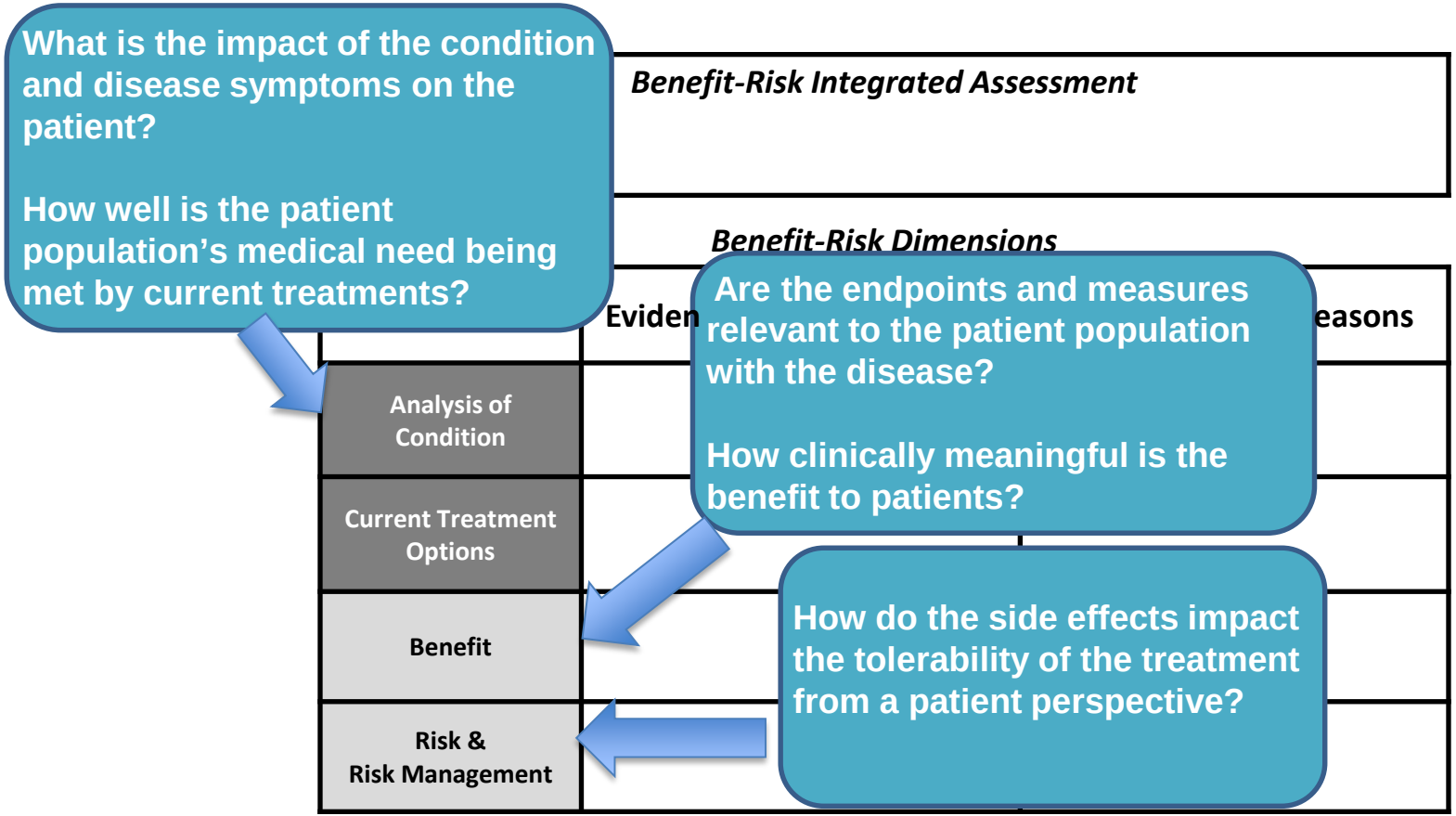
COA: Assessment of a clinical outcome made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment

Slide Courtesy of Selena Daniels, FDA Clinical Outcome Assessment Staff.

PROs in the Benefit-Risk Assessment



Patient Focused Benefit Risk Assessment



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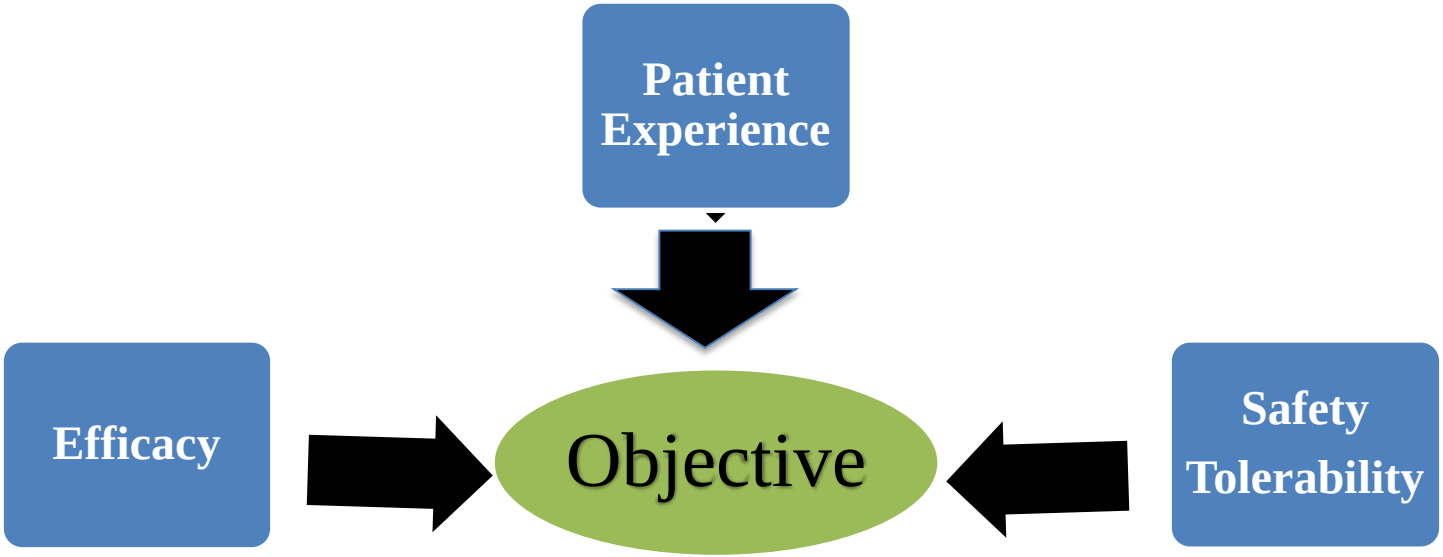
Patient-reported Outcome Measures

Measures in adequate and well-controlled trials:

- Clear statement of objectives
- Distinguish effect of the drug from other influences
- Well-defined and reliable assessments

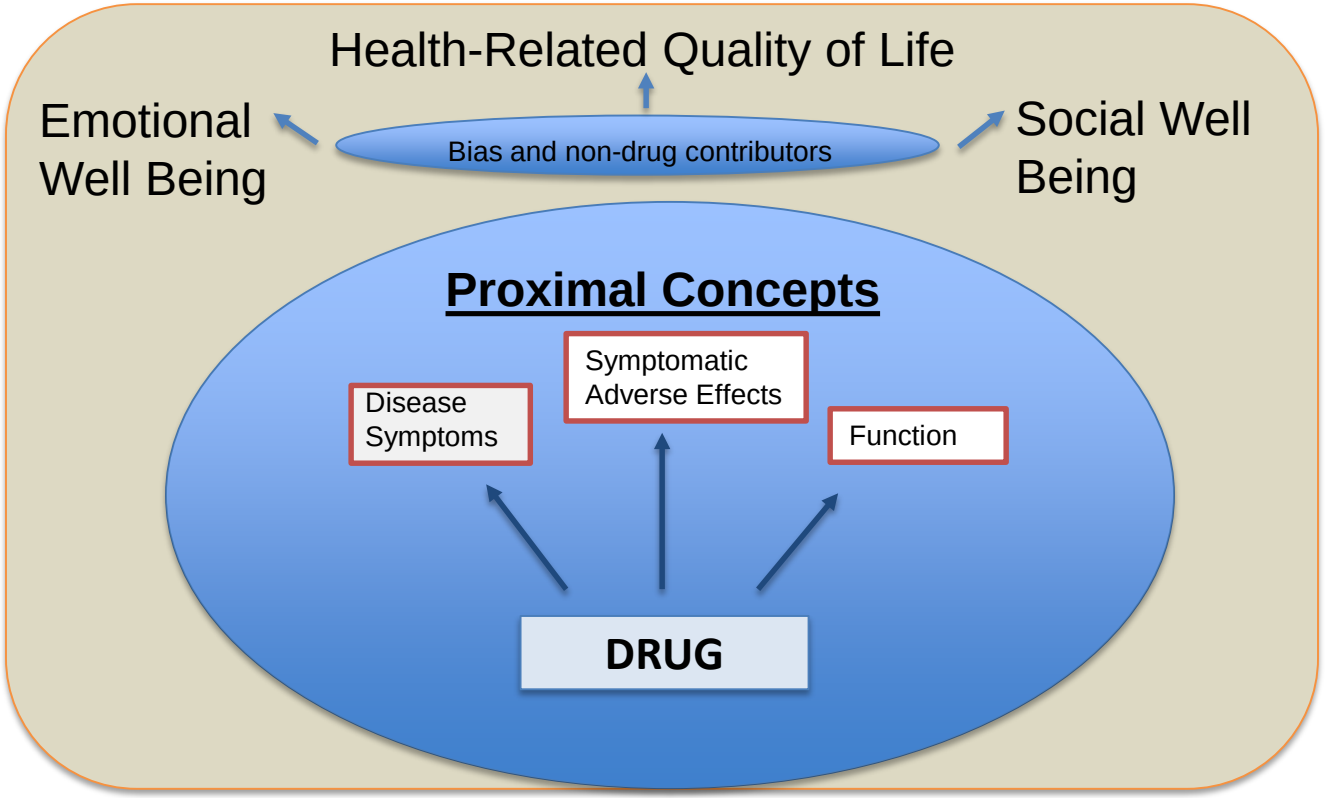
Reference 21 CFR 314.126, 21 CFR 201.57(c)(7)

PRO measures can address many trial objectives



Regulatory goal for the PRO data may be different

Focus on Core PRO Concepts



Proximal concepts may not be the only PRO data to assess or measure in a clinical trial

Adapted from Kluetz et al *Clin Can Res* 22.7 (2016): 1553-1558.

What is a “Fit For Purpose” PRO Instrument?

1. Appropriate for its intended use
   - Study design, Patient population, Therapy under study
2. Validly and reliably measures concepts that are:
   - Clinically relevant
   - Important to patients
3. Can be communicated in labeling in a way that is accurate, interpretable, and not misleading (i.e., **well-defined**)

Slide Courtesy Paul Kluetz, Depute Director, Oncology Center of Excellence

PRO for Efficacy

Ruxolitinib for myelofibrosis

- Primary endpoint: Radiographic Surrogate Endpoint
- Reduction in spleen size by (MRI) (Splenic Response Rate)

Is shrinking a patient's spleen clinical benefit?

Key secondary endpoint: PRO

Proportion of patients with a 50% or greater reduction in Total Symptom Score from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary

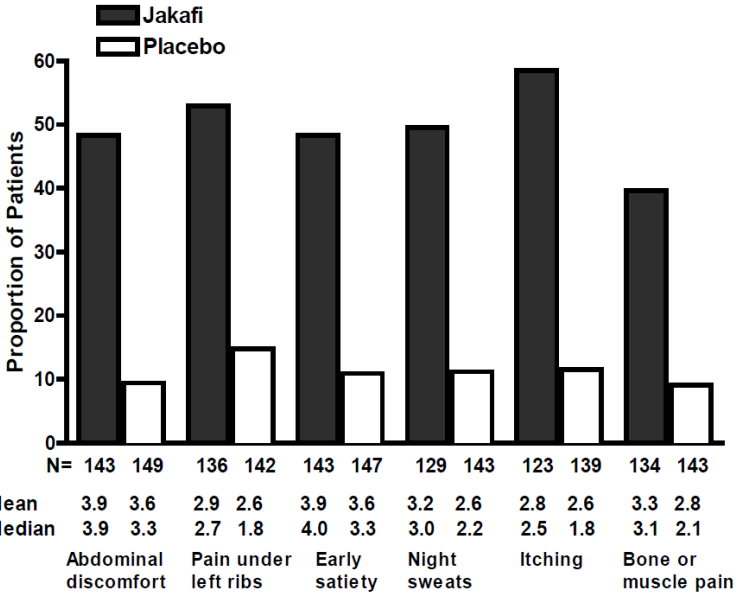
Total Symptom Score

- Abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety

PRO for Efficacy

- ✓ Measure meaningful clinical outcome
- ✓ Fit for purpose instrument
- ✓ Prespecified endpoint definition

Proportion of Patients With Myelofibrosis Achieving 50% or Greater Reduction in Individual Symptom Scores at Week 24



FDA Label for ruxolitinib https://www.accessdata.fda.gov/drugsatfda_

Using PRO for Safety/Tolerability

2013 Crizotinib Visual Symptoms- VSAQ-ALK

- "The majority of patients on the XALKORI arm in Study 1 (> 50%) reported visual disturbances; these visual disturbances occurred at a frequency of 4-7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured in a patient questionnaire."

FDA Label for Crizotinib https://www.accessdata.fda.gov/

Using PRO for Patient Preference

FDA Label for Rituxan Hycela (Subcutaneous delivery)

14.4 Patient Experience

After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire.

FDA Label for Rituxan Hycela https://www.accessdata.fda.gov/

Ideally, PRO labeling would provide strong data on patient outcomes

Efficacy:

- Does the drug provide superior improvement in disease related symptoms or functional deficits?

– Disease Related Symptom Score appropriate for the context (Pain, Total Symptom Score)
– Physical function / Performance status (PROMIS? Domain of existing instrument?)
– Formal statistical analysis

Safety
– Adverse events from therapy

Patient Experience:

- How do patients feel while on therapy?

As we optimize and standardize PRO, we expect more PRO data will be labelled.

PRO data, whether labeled or unlabeled, will be integrated into the risk: benefit

PROs in Benefit Risk

Case Study

Patients with recurrent high grade serous ovarian, fallopian tube, or primary peritoneal cancer following response to second line or later platinum based chemotherapy

- Double blind randomized controlled trial
- Two independent cohorts
- Randomized 2:1 to receive maintenance with PARP inhibitor or placebo

Primary Endpoint
Progression Free Survival
Measures: Imaging and clinical signs and symptoms and laboratory markers

Secondary Endpoints
Overall survival, other clinical & **PROs**
PRO Instruments
Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI), EQ-5D-5L, and neuropathy questionnaire

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf

PRO Review Strategy

Instruments being used- Concepts proximal to disease

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
O1	I have swelling in my stomach area	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4

I worry that my condition will get worse

I am content with the quality of my life..

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf

PRO Review strategy

Instruments

-Neuropathy Questionnaire: Limited utility as **drug in study not expected to cause peripheral neuropathy**

Analysis

-**No formal testing of PRO endpoint** so analyses was descriptive

PRO Endpoint

Time to Symptom worsening

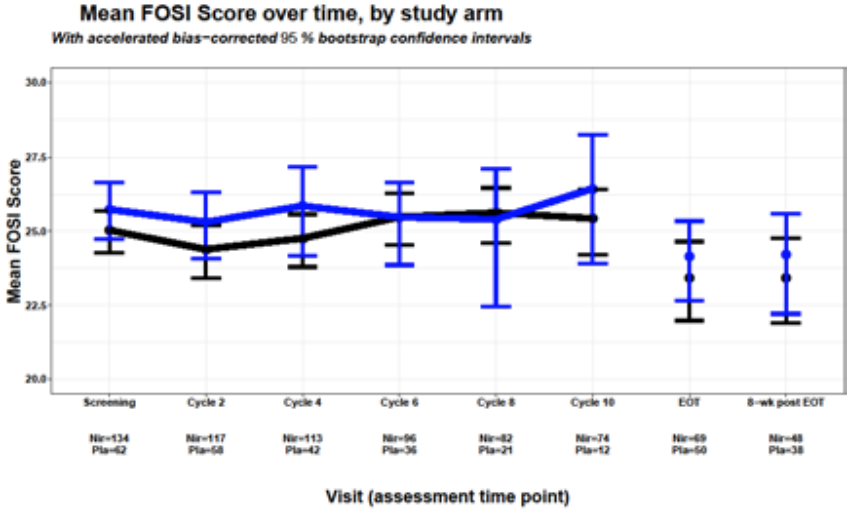
-Analysis of combined total FOSI scores combine disease and treatment symptoms along with worry and HRQOL

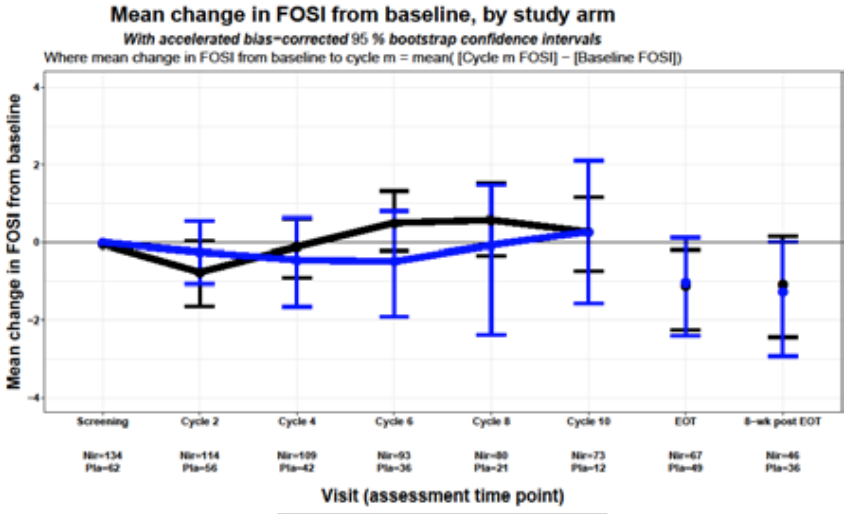
-Potential to **decrease the overall score's responsiveness to changes in symptoms**

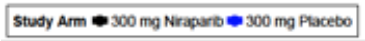
High completion rates of questionnaires

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf

Change in PRO Scores







https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf

Individual items assessed to explore patient experience

Example: Individual FOSI item 'I have nausea"

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=362**	**N=293**		**N=255**		**N=214**		**N=180**	
Severe	13 (4)	20 (7)	4 (1)	13 (5)	1 (<1)	5 (2)	0	4 (2)	0
			10 (3)		6 (2)		4 (2)		2 (1)
			6 (2)		6 (2)		1 (<1)		2 (1)
Moderate	71 (20)	128 (44)	5 (2)	88 (35)	6 (2)	73 (34)	4 (2)	52 (29)	3 (2)
			35 (12)		25 (10)		21 (10)		18 (10)
			88 (30)		57 (22)		48 (22)		31 (17)
None	278 (77)	145 (49)	1 (<1)	156 (61)	3 (1)	136 (64)	3 (1)	124 (69)	4 (2)
			12 (4)		18 (7)		15 (7)		10 (6)
			132 (45)		135 (53)		118 (55)		110 (61)
Placebo	**N=175**	**N=151**		**N=118**		**N=84**		**N=55**	
Severe	3 (2)	5 (3)	1 (<1)	5 (4)	1 (<1)	4 (5)	1 (1)	2 (4)	0
			2 (1)		2 (2)		2 (2)		2 (4)
			2 (1)		2 (2)		1 (1)		0
Moderate	31 (18)	25 (17)	0	15 (13)	1 (<1)	12 (14)	0	7 (13)	0
			14 (9)		8 (7)		6 (7)		4 (7)
			11 (7)		6 (5)		6 (7)		3 (5)
None	141 (81)	121 (80)	1 (<1)	98 (83)	0	68 (81)	0	46 (83)	0
			9 (6)		8 (7)		6 (7)		6 (11)
			111 (74)		90 (76)		62 (74)		40 (73)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

PRO data, whether labeled or unlabeled, will be integrated into the risk: benefit

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PROs in the Benefit Risk Assessment

- Sponsor meeting and discussions
- PRO and PFDD guidance
- Tools and instruments
- Oncology Standard information request for PRO analysis
  - -Completion rates
  - -Disposition
  - -Single item summary
  - -Health Care Utilization

Example: Health Care Utilization

Healthcare Utilization	Baseline		Assessment Period 1		Assessment Period 2		Assessments Period X….	
	Arm A N(%)	Arm B N(%)	Arm A N(%)	Arm B N(%)	Arm A N(%)	Arm B N(%)	Arm A N(%)	Arm B N(%)
ED Visits	n/a	n/a						
Hospitalizations	n/a	n/a						
Opiates								
Antiemetics								
Antidiarrheals								
Oral or IV Steroids								
Transfusions								
- PRBC								
- Platelet								
Growth Factors								
Palliative Procedures (e.g. EBRT, venting g tubes, etc.)								
Other: (describe)								
	N=	N=	N=	N=	N=	N=	N=	N=

Future opportunities

- Evaluate ways to best incorporate patient experience data from available assessments in our benefit-risk assessment
- Obtain additional patient perspectives on representative disease symptoms, treatment effects and endpoints
- FDA is currently exploring how to best communicate patients experience with side effects while on cancer therapy

Conclusion

- There is great momentum to advance the science of PRO measurement, analysis and presentation
- PRO outcomes can complement standard efficacy and safety measures
- Additional data on healthcare utilization, mobile device data, etc. may help support risk: benefit for patients
- Oncology Center of Excellence has prioritized patient-focused drug development as one of its initial programs

We will continue to seek collaboration to advance measurement of the patient experience

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