Beyond RECIST 1.1: The need for alternative disease measurement criteria for clinical trials in ovarian cancer

Shirley Pepke[1] and Trudy Rucker[2]

Background

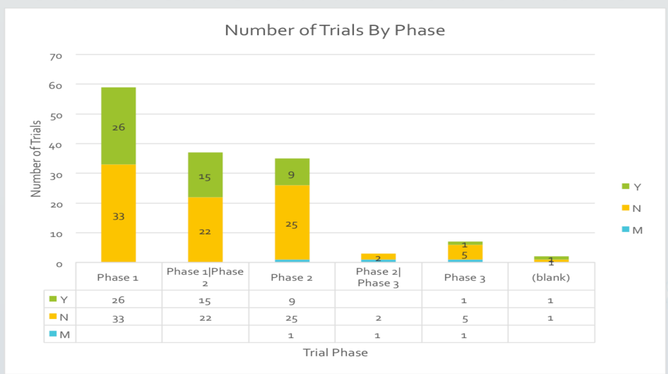
- Upon ovarian cancer recurrence, there is a high level of interest in participation in clinical trials of novel treatments.
- However, most patients with recurrent disease present with "non-measurable" disease by RECIST solid tumor response criteria.
- Patients with non-measurable disease are currently excluded from most ovarian cancer clinical trials.

RECIST1.1

Response **E**valuation **C**riteria **I**n **S**olid **T**umors:

- Guidelines for determining **change in tumor size by imaging** via X-ray, CT or MRI. FDG-PET allowed for determination of progression only. (Eisenhauer et al., *European Journal of Cancer,* 2009)
- Requires visible solid tumor lesion > 10 mm
- Standard for measuring response in clinical trials, but limiting and not clear it is an appropriate measure in the context of targeted therapies. (Friedlander and Thigpen in Controversies in the Management of Gynecological Cancers, eds. Ledermann et al., 2014)

Current clinical trials



Only 36% of all trials accept non-measurable disease. Of these, only 11 out of 54 are Phase 2 or Phase 3.

Prevalence of non-measurable disease

Pattern in Recurrence

About 50% of recurrent ovarian cancer patients will present with non-measurable disease. (Ferrandina et al., *European Journal of Cancer,* Sep 2006.)

Further, studies indicate that angiogenesis inhibitors such as bevacizumab may increase the likelihood of non-measurable recurrent disease. (Petrillo et al., *Gynecologic Oncology,* Aug 2016.)

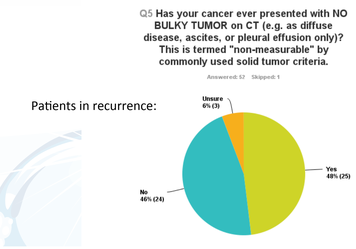
Treatment effects

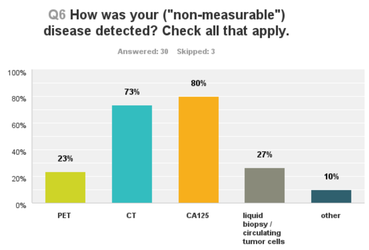
Primary tumor debulking to microscopic disease is standard of care and secondary debulkings are common. Thus disease that presents as measurable will not remain so prior to systemic therapy.

Patient experience

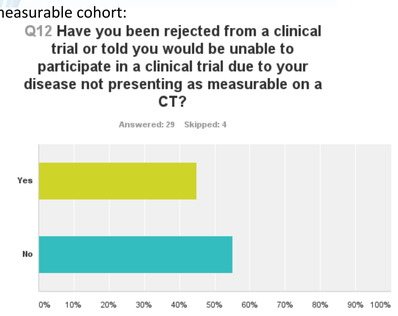
Survey results

Non-measurable disease affected approximately half of women in recurrence, despite the majority having disease that is visible using traditional imaging (CT or PET). Surprisingly, nearly a third of respondents have utilized liquid biopsies.

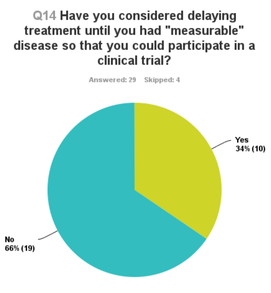




Non-measurable cohort:

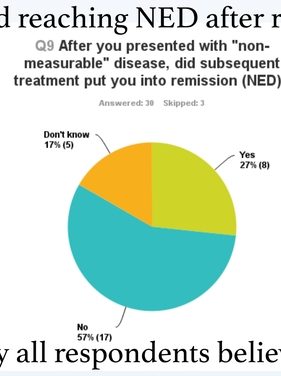


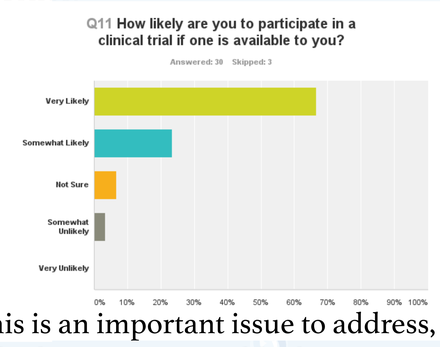
A substantial fraction of patients delay treatment in order to meet measurable disease requirement for trials. Further, some patients are asked to choose between surgical resection or a clinical trial.



"I am currently in screening for an immune therapy trial now that I do have measurable disease. But waiting months for this has made my symptoms worse. It was a cruel choice."

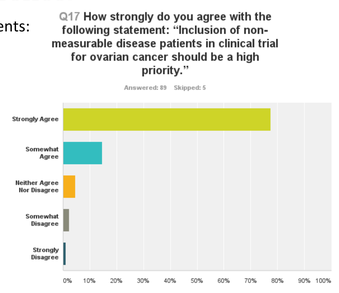
Patients with non-measurable disease are eager to participate in clinical trials. These patients can have good outcomes, with nearly a third reaching NED after recurrence.

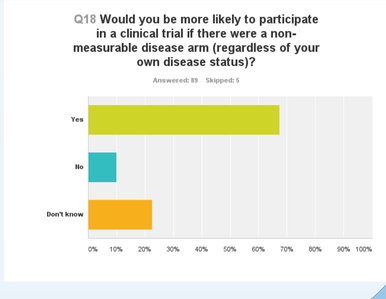




Nearly all respondents believe this is an important issue to address, including those who have never had a non-measurable disease recurrence.

All patients:





Alternatives

Can be implemented by including all patients in regular arms or specifying separate non-measurable disease patient cohort.

- **Tumor markers: CA125** – GCIG published criteria for response and progression, analogous to those for RECIST. (Rustin et al. *International Journal of Gynecologic Oncology,* 2011.)
- **Metabolic response: FDG-PET** – PERCIST criteria (Wahl et al. *The Journal of Nuclear Medicine,* 2009. Also Mustafa et al. in *Nuclear Medicine Communications,* 2016)
- **Laparoscopy** for assessment of peritoneal disease (Rustin et al. *American Journal of Obstetrics and Gynecology,* 2013.)
- **Liquid biopsy: ctDNA** – No specific guidelines yet, but good clinical correlation has been reported for several modalities. E.g.:

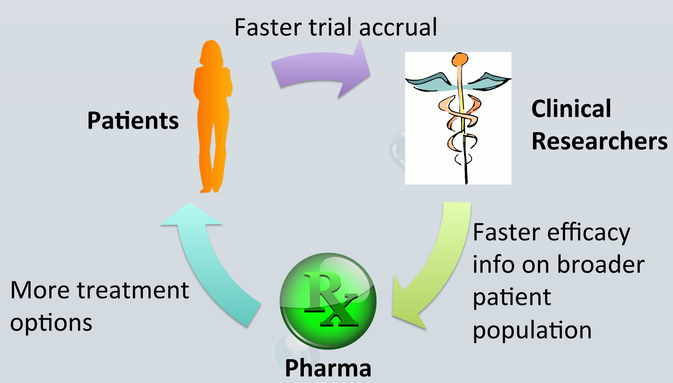
Alteration	Source	Study
TP53 mutations	ctDNA	Piskorz et al., ASCO 2016. (Ariel2 trial)
Copy number instability	ctDNA	Weiss et al., ASCO 2016.
Somatic chromosomal rearrangements	ctDNA	Harris et al., *Scientific Reports,* 2016.
Multiple mutations (whole exome seq)	ctDNA	Murtaza et al., *Nature,* 2013.

Recommendations

- Make every effort to include patients with non-measurable disease through the use of alternative criteria with existing standards.
- Include newer response monitoring techniques into clinical trials in order to obtain validation data.
- Establish separate analysis arms with non-measurable disease patient cohort where feasible.

Impact

Expanding access leads to a virtuous cycle where everyone benefits.



[1]Lyrid, LLC [2]Patient Advocate