"Me, too" Tumor Marker Submission Criteria

Development of Industry Recommendations – Issues and Suggestions for FDA-OIR

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08 October 2015
2015 AMDM IVD Focus Meeting

Background – 1 of 2

1. What are “Me, too” tumor marker tests?
   - CA 125 (ovarian cancer), Total PSA (prostate cancer), CA 19-9 (pancreatic cancer), CA 15-3 (breast cancer), *etc*.

2. What is their use?
   - To monitor patients diagnosed previously with a given primary cancer. Historically, “Monitoring” = Serial Sets. How to demonstrate performance without assessment of time series?

3. Down classified from Class III (PMA) to Class II (510(k) in the mid-1990’s.

4. Many manufacturers and instruments hosting these tests that have been, are, and will be cleared for this use in the USA

Background – 2 of 2

- Some of these tests have been used as standard of care since the 1980's, most since the 1990's
- Used in conjunction with other clinical signs and symptoms, imaging studies, *etc*. to inform the managing health care provider regarding status of patient (NOTE: managing HCP takes all available information into account to decide what/how/when to start/stop/change treatment (or not))
- Practice Guidelines are well-established (*e.g.*, RECIST, *etc.*) in standard of care clinical practice and in therapeutic trials for "biochemical recurrence" *et al.*

CA 125 as an Example

Rustin GJ, Vergote I., Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA125 agreed by the Gynecologic Cancer Intergroup (GCIG) Intl. J. Gynecol Cancer. 2011

The GCIG previously has reached consensus regarding the criteria for use of serum CA125 in clinical trial protocols and has summarized the criteria and definitions and specified situations where these criteria should be used outlined in Table 1 below. The GCIG updated these criteria to accommodate the new version 1.1 of the RECIST. The GCIG requests that the definitions and recommendations are followed for use of serum CA125 in all clinical trials to ensure consistency of results.

TABLE 2. Evaluation of best overall response in patients *without* initial measurable disease and who are evaluable by CA 125

CA 125	Nontarget Lesions*	New Lesions	Overall Serological Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD†	Yes or No	PD	
Any	Any	Yes	PD	

*Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.
†Unequivocal progression in nontarget lesions may be accepted as disease progression.
CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease.

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"Traditional" Requirements for 510(k) Clearance of "Me, too" Tumor Marker Tests

1. All the standard CLSI analytical/technical assessments

2. Method Comparison – testing of clinical specimens with IUO test versus chosen predicate test
   a. Reference Interval – age, sex, smoking, other
   b. Benign Disease – primary organ and not
   c. Cancer – single point primary organ and not
   d. Cancer – serial specimens by stage and status of primary cancer *
      – 60 – 150 sets with an average of four draws per subject
      – approx. 1/3 = RESP, 1/3 = STAB-NED, 1/3 = PROG-RECUR

* - THIS IS WHERE THE RUBBER HITS THE ROAD!

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Important Issues

- ***SERIAL SETS obtained from subjects diagnosed with low incidence rate primary cancers (ovarian, pancreatic, liver)***
- **Recently (since early 2000's) collected serial sets for these primary cancers are increasingly difficult to obtain (rare) and *very* expensive**
- **"QUESTIONS or CONSEQUENCES"**
  1. **Does the ROI for placing the "Me, too" tumor marker tests on GEN IV instrument? Does this delay or prevent introduction of new instruments/tests in the USA?**
  2. **If all the very rare and expensive serial sets are used to place "Me, too" tumor marker tests on GEN IV instruments, will there be enough sets available for "never ever" new tumor marker tests?**

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Sentiment of IVD Industry – 1 of 2

- Where all the critical reagents (antibodies and antibodies) are long-established and previously cleared by FDA on technologically similar instruments (same family) the following should continue:
  - Very robust analytical studies (CLSI) – precision (EP-05-A3), linearity (EP-06-A), and LoB/LoD/LoQ (EP-17-A2)
  - Method Comparison (CLSI – EP-09-A3)
- The following studies can be "transferable" if data are the same:
  - Estimation of reference interval (CLSI EP-28-A3)
  - Hook Effect
  - Stability Studies (reagent and specimen)
  - Malignant and non-malignant cohorts if not performed as part of Method Comparison testing

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Sentiment of IVD Industry – 2 of 2

- **Eliminate Requirement for testing of serial specimens for well-established "Me, too" tumor marker tests (hosted on new versions of previously cleared instrument family members)**
  Recall: How to demonstrate performance without assessment of time series?

- **Benefits:**
  - **Save as much as several hundred thousand dollars per "Me, too" tumor marker assay 510(k) submission**
  - **Easier to justify launch next generation of instrument(s) in USA**
  - **Preserve precious serial sets of specimens for evaluation of novel ("never ever" – not reviewed previously by FDA) tumor marker tests proposed to monitor patients**

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WHAT ARE YOUR THOUGHTS/COMMENTS?