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GCIG Criteria, Programming Makes It Easy

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ABSTRACT

Ovarian cancer is a heterogeneous and genomically unstable cancer and as technologies advance, there is a great potential to incorporate biomarkers into ovarian cancer diagnosis, prognosis, and therapy choices. Carcinoma antigen-125 (CA-125) is the most commonly used biomarker in ovarian cancer and has been examined in many pivotal clinical trials for drug approval in ovarian cancer. The Gynecological Cancer Intergroup (GCIG) proposes the criteria for CA-125 response and progression and specified the situations which criteria could be used in. In addition to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, GCIG CA-125 response and progression criteria have become more and more popular in clinical trials of ovarian cancer and usually serves as one of the secondary endpoints. However, GCIG criteria are more complicated than RECIST criteria and not programming-friendly, especially when combined with RECIST criteria Version 1.1. Thus, we would like to share our experience and developed tools on implementing GCIG CA-125 response and progression criteria, and propose a reliable solution from programming point of view.

INTRODUCTION

Ovarian cancer, a heterogeneous and genomically unstable cancer, is the fifth most common cause of death from cancer in women in the United States (US) and the tenth most common cancer in women in China. As our understanding of it evolves and as technologies advance, there is a great potential to incorporate biomarkers into ovarian cancer diagnosis, prognosis, and therapy choices. Carcinoma antigen-125 (CA-125) is the most commonly used biomarker in ovarian cancer and has been used as a secondary endpoint in pivotal clinical trials for drug approval in ovarian cancer.

The Gynecological Cancer Intergroup (GCIG) proposes the criteria (Table 1) for CA-125 response and progression and specified the situations which criteria could be used in. In addition to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, GCIG CA-125 response and progression criteria have become more and more popular in clinical trials of ovarian cancer and usually serves as one of the secondary endpoints.

However, GCIG criteria are much more complicated than RECIST criteria and not programming-friendly, especially when combined with RECIST criteria Version 1.1.

Thus, we would like to share the experience on implementing GCIG criteria, such as evaluation of CA-125 response and progression, and propose a reliable solution from programming point of view. This paper focuses on the concept maps and the SAS tools for evaluation of CA-125 response and progression.

Table 1. GCIG recommendations for CA-125 criteria for response and progression in various clinical situations

	Use Recommended by GCIG	Not Standard and Needs Further Validation	Not Recommended by GCIG
First-line trials	CA-125 progression		CA-125 response
Maintenance or consolidation trials		CA-125 response and progression	
Relapse trials	CA-125 response and progression		

Source: Rustin GJS, Thigpen T, Eisenhauer EA, et al. “Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG)”. Int J Gynecol Cancer 2011; 21: 419-423.

EVALUATION OF CA-125 RESPONSE AND PROGRESSION

DEFINITIONS

CA-125 response: defined as at least a 50% reduction in CA-125 levels from a pretreatment sample, which must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment.

CA-125 complete responders (response and normalized): defined as evaluable patients who have a CA-125 response and whose CA-125 level falls to within the reference range. But patients without initial CA-125 less than twice the upper limit of the reference range who have a fall of CA-125 to within the reference range a CA-125 response cannot therefore be classified as CA-125 complete responders.

Date of the CA-125 response: defined as the date when the first CA-125 response occurs.

The rules must be followed to calculate CA-125 responses accurately:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (e.g., paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (e.g., surgery and chemotherapy), any CA-125 response results from both treatment modalities. CA-125 cannot distinguish between the effects of the 2 treatments.

To calculate response rate, an intent-to-treat analysis should be used that includes all patients with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable.

EVALUATION OF CA-125 RESPONSE IN PATIENTS RECEIVING FIRST-LINE THERAPY

The CA-125 response definition was developed to evaluate response to chemotherapy in patients with recurrent ovarian cancer. If the patient has had combined modality therapy as part of their first-line therapy (e.g., surgery and chemotherapy), CA-125 response may be due to both or either treatments, and it should be clearly stated that CA-125 cannot distinguish between the effects of the 2 treatments. It should be also noted that for a patient to be classified as a complete responder according to RECIST, tumor marker levels such as CA-125 must be within the reference range.

EVALUATION OF CA-125 RESPONSE IN PATIENTS RECEIVING MAINTENANCE OR CONSOLIDATION THERAPY

Patients whose CA-125 is greater than twice the upper limit of the reference range when they start maintenance or consolidation therapy can be evaluated using the GCIG CA-125 response definition. However, it should be noted that there are no data to validate the implications of achieving CA-125 response in this setting with respect to progression-free or overall survival. To prevent the prior therapy from interfering with the response assessment, 2 pretreatment samples no more than 8 weeks apart are required if test treatment is given as part of maintenance or consolidation therapy. For the test treatment to be evaluable according to CA-125, there should be no more than a 10% fall in CA-125 between the 2 pretreatment samples. The sample closest in time to the test therapy should be considered the pretreatment sample.

EVALUATION OF OVERALL RESPONSE IN PATIENTS WITH OR WITHOUT INITIAL MEASURABLE DISEASE AND EVALUABLE BY CA-125

Patients with or without initial measurable disease can be enrolled into ovarian cancer clinical trials. In the combined assessment of CA-125 and RECIST 1.1 response, the following algorithm (table 2, table 3) applies when determining the overall response for the patients with or without initial measurable disease. Table 2 shows the evaluation of overall response in patients without initial measurable disease, because either no measurable disease is evident on radiological imaging or appropriate imaging has not been performed.

Table 2. Evaluation of overall response in patients without initial measurable disease and who are evaluable by CA-125

CA-125	Non-target Lesions [1]	New Lesions	Overall Serological Response	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-response/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD [2]	Yes or No	PD	
Any	Any	Yes	PD	

[1] Non-target lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.

[2] Unequivocal progression in non-target lesions may be accepted as disease progression.

CR, Complete response; PR, partial response; PD, progressive disease; SD, stable disease.

Source: Rustin GJS, Thigpen T, Eisenhauer EA, et al. “Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG)”. Int J Gynecol Cancer 2011; 21: 419-423.

Table 3 shows the evaluation of overall response in patients who are measurable by one or both criteria and who may have events at different time points. In patients who have measurable disease by both criteria, the date of response will be the date of the earlier of the 2 events if this approach to combined response reporting is to be used. If patients have progressive disease (PD) according to RECIST 1.1 within 28 days of CA-125 response, they are classified as PD. If the PD according to RECIST 1.1 is longer than 28 days before or after the CA-125 response, they are classified as partial response (PR). Patients whose overall response according to RECIST 1.1 is stable disease but who have a CA-125 response are classified as CA-125 responders.

Table 3. Evaluation of overall response in patients with measurable disease and who are also evaluable by CA-125

Target Lesion [1]	Non-target Lesions [2]	New Lesions	CA-125	Overall Serological Response	
CR	CR	No	Response and Normalized	CR	Best RECIST 1.1 response for CR and PR also requires it to be confirmed and maintained for at least 28 days if response is primary end point
CR	Non-CR/Non-PD	No	Non-PD	PR	
CR	CR	No	Response	PR	
CR	NE	No	Response	PR	
PR	Non-PD or NAE	No	Non-PD	PR	
NAE	Non-PD	No	Response	PR	
PD > 28 days from CA-125 Response [3]			Response	PR	
SD [4]	Non-PD	No	Response	PR	

Table 3. Evaluation of overall response in patients with measurable disease and who are also evaluable by CA-125

SD [4]	Non-PD or NAE	No	Non-response /non-PD	SD
PD ≤ 28 days from CA-125 Response [3]			Response	PD
PD	Any	Yes or No	Any	PD
Any	PD	Yes or No	Any	PD
Any	Any	Yes	Any	PD
Any	Any	Yes or No	PD	PD

[1] Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1.

[2] Non-target lesions include ascites and peritoneal thickening, which are not measurable according to RECIST 1.1.

[3] Patients who have a CA-125 response that occurs more than 28 days before PD according to RECIST 1.1 are considered a PR, but PD if the RECIST 1.1 PD is within 28 days of CA-125 response.

[4] The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.

NE, Not evaluated; NAE, not all evaluated.

Source: Rustin GJS, Thigpen T, Eisenhauer EA, et al. "Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG)". Int J Gynecol Cancer 2011; 21: 419-423.

Table 4 shows an example of the best overall response reported separately for both RECIST 1.1 and CA-125 response.

Table 4. Example of reporting RECIST, CA-125, and combined response

	CA-125 Response			
RECIST	**Yes**	**No**	**NE**	**Total RECIST**
CR [1]	***4***	0	0	*4*
PR	***3***	1	1	*5*
SD	**3**	12	1	16
PD	**0**	8	2	10
NE	**3**	5	2	10
Total CA-125	**13**	26	6	Total entered = 45

In the above example, the RECIST 1.1 response rate is 9 (25.7%) of 35 RECIST 1.1 evaluable patients, the CA-125 response rate is 13 (33%) of 39 CA-125 evaluable patients, and the combined overall response rate (either RECIST or CA-125 response) is 15 (35%) of 43.

[1] RECIST 1.1 includes normalization of CA-125 to achieve CR (Table 3).

Bolded numbers, CA-125 responders; bolded and italicized numbers, both RECIST and CA-125 responders; italicized numbers, RECIST responders.

Source: Rustin GJS, Thigpen T, Eisenhauer EA, et al. "Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG)". Int J Gynecol Cancer 2011; 21: 419-423.

EVALUATION OF CA-125 PROGRESSION

CA-125 progression is defined according to the following criteria and Table 5:

A. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1

week apart or

B. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart or

C. Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.

Date of CA-125 progression is assigned as the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura (e.g., paracentesis) during the previous 28 days.

A patient may be declared to have PD based on either the objective RECIST 1.1 criteria or the GCIG CA-125 criteria. The date of progression is the earlier date of the 2 events if both are documented.

Table 5. Definition of progression after first-line therapy in ovarian cancer as proposed by the GCIG

GCIG Subcategorized Group	RECIST Measurable/Non-measurable Disease		GCIG CA-125
A	≥ a 20% increase in the sum of diameters of target lesions and an absolute increase of ≥ 5 mm, taking as reference the smallest sum on study or Unequivocal progression of existing non-target lesions or Any unequivocal new lesions Date of PD: date of documentation of progression	and/or	CA-125 ≥ 2 x ULRR documented on 2 occasions* Date of PD: first date of the CA-125 elevation to ≥ 2 x ULRR
B	As for A	and/or	CA-125 ≥ 2 x nadir value on 2 occasions* Date of PD: first date of the CA-125 elevation to ≥ 2 x nadir value
C	As for A	and/or	As for A

GCIG groups A, B, and C defined above.

CA-125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by human Anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days should not be taken into account.

*Repeat CA-125 any time but normally not less than 1 week after the first elevated CA-125 level.

ULRR, upper limit of reference range.

Source: Rustin GJS, Thigpen T, Eisenhauer EA, et al. “Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG)”. Int J Gynecol Cancer 2011; 21: 419-423.

A SAS TOOL TO EVALUATE CA-125 RESPONSE AND PROGRESSION, OVERALL RESPONSE

FLOWCHART

Figure 1. Flowchart for evaluation of CA-125 response with GCIG criteria alone:

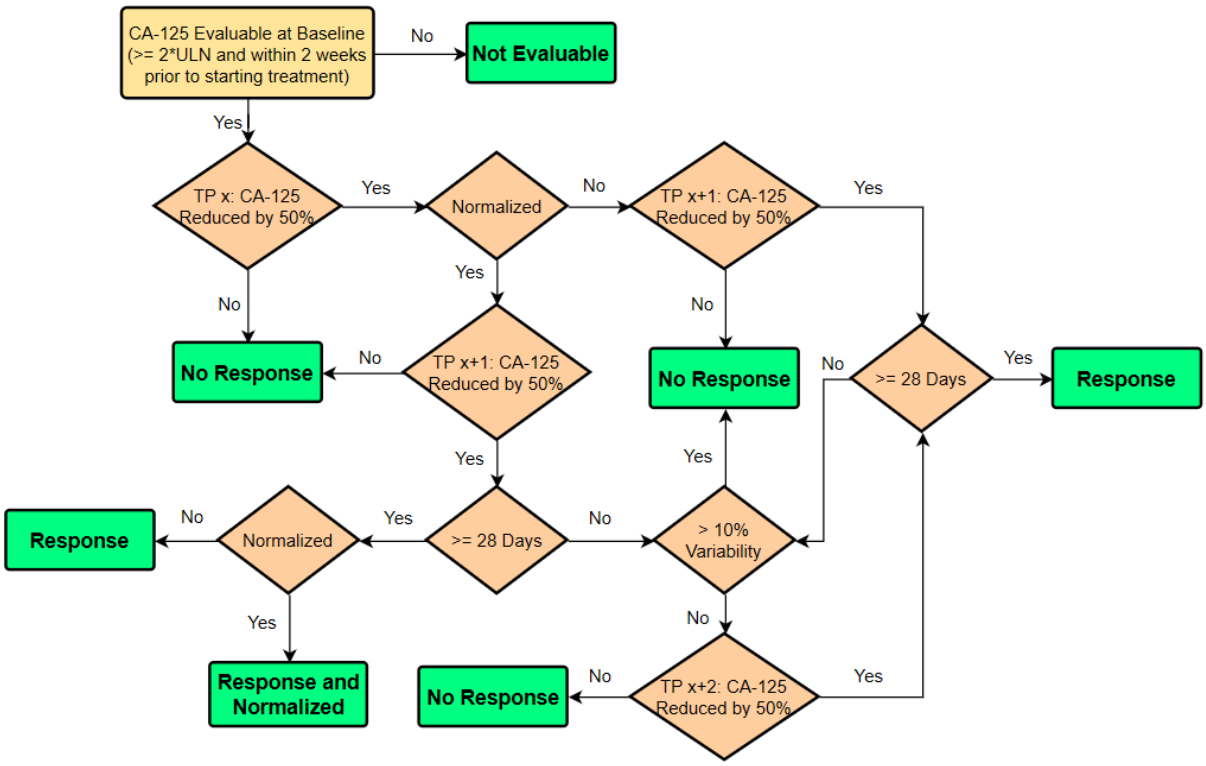


Figure 2. Flowchart for evaluation of CA-125 progression with GCIG criteria alone:

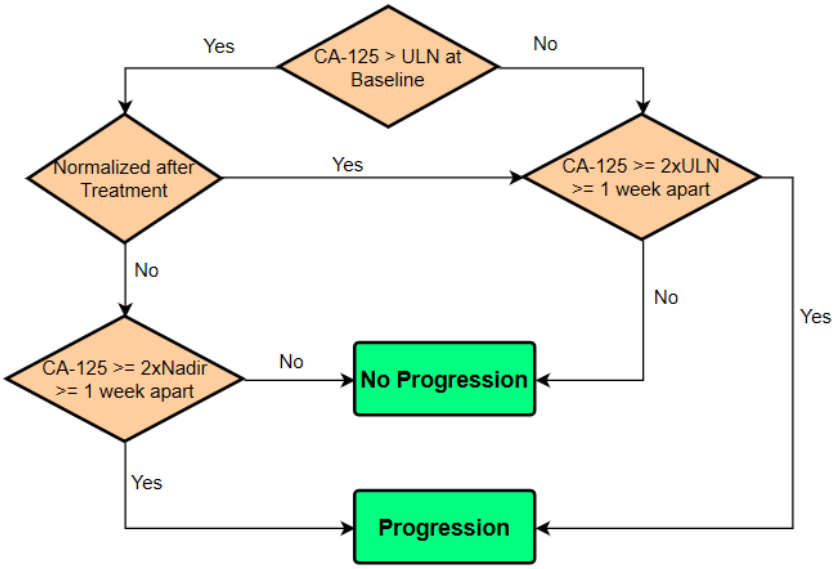


Figure 3. Flowchart for evaluation of overall response with combined RECIST and GCIG criteria in patients without initial measurable disease and who are evaluable by CA-125:

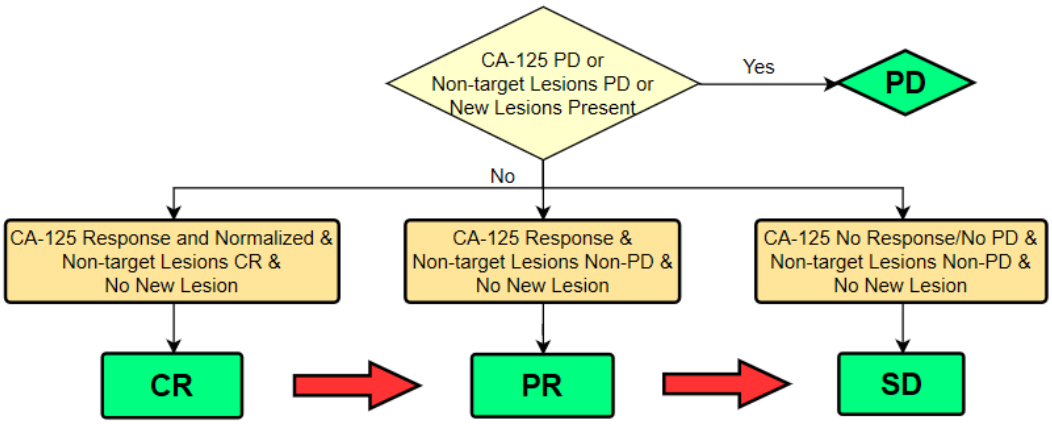
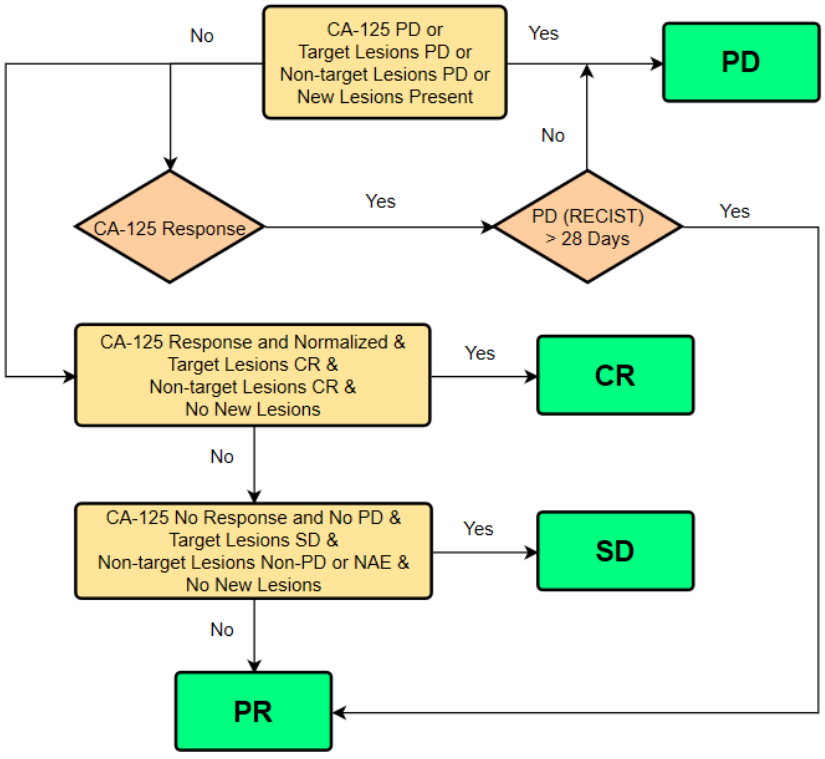


Figure 4. Flowchart for evaluation of overall response with combined RECIST and GCIG criteria in patients with measurable disease and who are also evaluable by CA-125:



LOGICS

The tool is based on available SDTM domains (LB, TU, RS) and ADaM ADSL dataset, where LB contains the results of CA-125.

Here is the logics:

Step 1 – Get the source data from SDTM domains and ADaM ADSL dataset, identify the records for next step, such as reduced by 50%;

Step 2 – Derive the CA-125 response based on figure 1 for each subject in defined population;

Step 3 – Derive the CA-125 progression based on figure 2 for each subject in defined population;

Step 4 – Derive the overall response combining CA-125 and RECIST criteria based on figure 3/4 for each time point per subject with/without initial measurable disease in defined population;

Step 5 – Merge the datasets from step 2 - 4 and output the final dataset.

SAMPLE DATA AND RESULTS

1. Sample results for evaluation of CA-125 response with GCIG criteria alone:

SUBJID	ADSL.TRTSDT	SDTM.LB.LBDTC	SDTM.LB.LBSTRESN	NORMAL RANGE	EVALUABLE AT BASELINE	CA-125 RESPONSE	NORMALISED	NOTE
GCIG-001	2016-05-11	**2016-05-31**	**58**	0 - 35 kU/L	No	Not Evaluable	Yes	Not evaluable: no sample pre-treatment
		2016-06-21	24				1	
		2016-07-19	15				2	
		2016-08-09	14					
		2016-09-13	11					
GCIG-002	2016-03-30	**2016-03-28**	**34**	0 - 35 kU/L	No	Not Evaluable	Yes	Not evaluable: 1st sample < 2xULRR
		2016-04-19	37					
		2016-05-10	36					
		2016-07-05	30				1	
		2016-08-02	13				2	
GCIG-003	2016-06-22	2016-06-20	217	0 - 35 kU/L	Yes	No Response	No	No response: no 50% reduction
		2016-07-31	220					
		2016-09-01	230					
GCIG-004	2016-07-01	2016-06-18	84	0 - 35 kU/L	Yes	No Response	Yes	Not confirmed: no sample > 28 days after fall
		2016-08-20	45					
		2016-09-21	43					
		2016-10-22	**9**			1	1	
		2016-11-10	**8**					
GCIG-005	2016-05-18	2016-05-18	985	0 - 35 kU/L	Yes	Response and Normalized	Yes	Confirmed response
		2016-06-08	145			1		
		2016-07-19	**16**				1	
		2016-08-09	**15**					Intervening sample variation within 10%
		2016-08-30	**14**				2	
		2016-10-06	17					
		2016-11-02	9					
GCIG-006	2015-09-14	2015-09-12	407	0 - 35 kU/L	Yes	Response	No	Confirmed response
		2015-10-05	360					
		2015-10-26	258					
		2015-11-16	**192**			1		
		2015-12-28	**130**			2		
		2016-01-19	125					

2. Sample results for evaluation of CA-125 progression with GCIG criteria alone:

SUBJID	ADSL.TRTSDT	SDTM.LB.LBDTC	SDTM.LB.LBSTRESN	NORMAL RANGE	EVALUABLE AT BASELINE	CA-125 PROGRESSION	NORMALISED	NOTE
GCIG-007	2016-07-01	2016-06-18	84	0 - 35 kU/L	Yes	No Progression	Yes	No progression: no sample > 2xULRR
		2016-08-20	45					
		2016-09-21	43					
		2016-10-22	9				1	
		2016-11-10	8					
GCIG-008	2016-05-18	2016-05-18	30	0 - 35 kU/L	No	Progression	Yes	Progression: ≥ 2xULRR, ≥ 1 weeks apart
		2016-06-08	45					
		2016-07-10	16				1	
		2016-08-09	15					
		2016-09-05	14					
		2016-10-06	**75**			1		
		2016-11-02	**80**			2		
GCIG-009	2015-09-12	2015-09-12	407	0 - 35 kU/L	Yes	Progression	No	Progression: ≥ 2xNadir, ≥ 1 weeks apart
		2015-10-05	360					
		2015-10-26	100					Nadir value
		2015-11-16	132					
		2015-12-28	**210**			1		
		2016-01-19	**216**			2		

3. Sample results for evaluation of overall response with combined RECIST and GCIG criteria in patients with measurable disease and who are also evaluable by CA-125:

SUBJID	ADSL.TRTSDT	SDTM.LB.LBDTC	SDTM.LB.LBSTRESN	NORMAL RANGE	EVALUABLE AT BASELINE	CA-125 RESPONSE	TARGET LESIONS RESPONSE	NON-TARGET LESIONS RESPONSE	NEW LESIONS	OVERALL SEROLOGICAL RESPONSE
GCIG-010	2016-07-01	2016-06-18	84	0 - 35 kU/L	Yes	NA	NA	NA	NA	NA
		2016-08-20	45			*No Response*	*SD*	*Non-CR/Non-PD*	*No*	***SD***
		2016-09-21	43			No Response	PR	Non-CR/Non-PD	No	PR
		2016-10-22	9			No Response	PR	Non-CR/Non-PD	No	PR
		2016-11-10	8			No Response	CR	CR	No	PR
GCIG-011	2016-05-18	2016-05-18	985	0 - 35 kU/L	Yes	NA	NA	NA	NA	NA
		2016-06-08	145			*Response*	*SD*	*Non-CR/Non-PD*	*No*	***PR***
		2016-07-07	46			Response	PR	Non-CR/Non-PD	No	PR
		2016-08-06	40			Response	PR	Non-CR/Non-PD	No	PR
		2016-09-05	50			Response	PR	Non-CR/Non-PD	No	PR
		2016-10-06	37			**Response**	**PR**	**Non-CR/Non-PD**	**No**	**PD**
		2016-10-30	39			Response	PR	Non-CR/Non-PD	**Yes**	**PD**
GCIG-012	2015-09-14	2015-09-12	407	0 - 35 kU/L	Yes	NA	NA	NA	NA	NA
		2015-10-05	360			No Response	NA	Non-CR/Non-PD	No	SD
		2015-10-26	258			No Response	NA	Non-CR/Non-PD	No	SD
		2015-11-16	192			Response	NA	Non-CR/Non-PD	No	PR
		2015-12-28	130			Response	NA	Non-CR/Non-PD	No	PR
		2016-01-28	125			*Response*	*NA*	*CR*	*No*	***PR***

CONCLUSION

GCIG CA-125 response and progression criteria are much more complicated than RECIST criteria due to varies of reasons, such as limited source of publications, no fully detailed elaboration of algorithms in references. Thus, we share our experience on implementing the criteria in clinical trials expecting to provide a reliable solution from programming point of view.

REFERENCES

Rustin GJS, Thigpen T, Eisenhauer EA, et al. “Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG)”. Int J Gynecol Cancer 2011; 21: 419-423.

Vergote I, Rustin GJS, Eisenhauer EA, et al. “Re: new guidelines to evaluate the response to treatment in solid tumours (ovarian cancer)”. J Natl Cancer Inst. 2000; 92: 1534-1535.

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Thanks to our managers (Leo Li, Cindy Song and Tony Guo) for their great support on the conference and medical colleagues for their detailed clarification on the criteria.

RECOMMENDED READING

- *Base SAS® Procedures Guide*
- *CA-125 Response Definition (https://gciggroup.com/content/ca-125-response-definition)*

CONTACT INFORMATION

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