
Report of the Independent Review of radiologic responses of HERACLES trial

Product Code:	Kadcyla [®] (trastuzumab-emtansine) Perjeta [®] (pertuzumab)
Report of the peer review for study:	HERACLES 004-IRCC-10IIS-12 (cohort B)
EudraCT:	2012-002128-33
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Development Phase of Study:	II

APPROVAL SIGNATURES

I have read the report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.



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29/07/2019

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1. ABBREVIATIONS AND DEFINITION OF TERMS

CR	Complete Response
CRF	Case Report Form
DOR	Duration of Response
FPI	First patient in
LD	Longest Diameter
NE	Not Evaluable
ORR	Objective Response Rate
PR	Partial Response
SD	Stable Disease
PFS	Progression free survival

2. OVERALL REVIEW CONDUCT

The review was conducted by two independent reviewers with the support of the mintLesion™ software. The final reconciliation was performed *de visu* at the Fondazione del Piemonte per l'Oncologia - IRCCS – Candiolo, Italy (FPO) – on July 29, 2019.

The reviewers were: Prof. Daniele Regge, Director of the FPO Department of Radiodiagnostics; Dr. Angelo Vanzulli, Head of the Struttura complessa Radiologia, Ospedale Niguarda Ca'Granda- Milan, Italy.

Copies of CT-Scan of all evaluable patients were collected from each participating center and up loaded on the mintLesion™ suite for evaluation.

Tumor assessments by protocol were required at baseline (within 4 weeks from study drug administration), at cycle 1 and then every 3 cycle thereafter until progressive disease was noted. Methods used to detect tumor lesions at study entry were to be used to follow the same lesion throughout the study. The RECIST 1.1 criteria were used for tumor response evaluation by the Investigators and both Reviewers.

3. REVIEW PROCESS

3.1. Blind independent revision

All CT-scans for all patients in trials were reviewed by both review radiologists, independently. Each reviewer, in blind from both the investigator and each other assessment, recorded his evaluation by RECIST 1.1 criteria of all CT-scans of each patient in the mintLesion™ software.

3.2. Reconciliation process

The study Project Manager downloaded from the system all cases flagged by the mintLesion™ software as discordant in either assessment of response, and or differences in the length of time dependent variables (time to response; progression free survival; duration of response). Cases requiring reconciliation were discussed collegially *de visu* by the two reviewers.

3.3. Blind independent revision

In Table 1 are reported the details of the discrepancies flagged by the mintLesion™ software. Thirteen patients were selected for the reconciliation process due to discrepancies in the assessment of best response (N 2), or length of time dependent variable (N 11); two patients (121064, 123065) were included in both series.

4. REVIEW RESULTS

Patients 121042, 121044, 121059, 121066 were not included in this revision due to impossibility of collection of the baseline CD performed elsewhere, and not in the participating center. For those patients we considered the investigator evaluation only.

After reconciliation, reviewers downgrades two RECIST best responses assigned by the investigators, while anticipated the date of progression - leading to the shortening of the individual patients time dependent variables - in 13 (50%) cases for PFS and 1 (4%) cases

for DOR, as summarized in the Tables 2 and 3, respectively. A short summary of the reconciliation results for each of the 13 reviewed cases is also reported in section 4.1.

Table 1: Discrepancies in the evaluation of response and dates for time-dependent variables calculation

	Assessment			Type of discrepancy	Patient ID #	ACTION
	INV	REV A	REV B			
RESPONSE (RECIST 1.1)	PD	PD	PD	NONE (full concordance)	125037, 125048, 121050, 121057, 121060, 121063,	None
	SD	SD	SD	NONE (full concordance)	122040, 122041, 122047, 122061, 124058, 125046, 125054, 125062, 121039, 121043, 121045, 121051, 121052, 121056, 121064,	None
	PR	PR	PR	NONE (full concordance)	123065, 125055, 121036,	None
	PR	SD	SD	Reviewer A and B discordant with Investigator	122038, 121049,	To be reconciled
	SD	NE	NE	Baseline images not available for revision	121042, 121044, 121059, 121069	Not Revised
TIME DEPENDENT VARIABLES	Time to best response	shorter	shorter	Both Reviewers discordant with Investigator	123065	To be reconciled
		same	same	NONE (full concordance)	121036, 125055	None
TIME DEPENDENT VARIABLES	Progression free survival	same	same	NONE (full concordance)	121050, 121056, 121057, 121060, 121063, 121064, 122040, 125037, 125046, 125048, 125054, 125055, 125062	None
		shorter	shorter	Both Reviewers discordant with Investigator	121036, 121039, 121043, 121045, 121049, 121051, 121052, 122038, 122041, 122047, 122061, 123065, 124058,	To be reconciled
		NE	NE	Baseline images not available for revision	121042, 121044, 121059, 121069	Not Revised

Table 2: Reconciliation results – Objective response by RECIST

Revised Patients N 26		OBJECTIVE RESPONSE POST REVISION		
		PD	SD	PR
OBJECTIVE RESPONSE PRE REVISION	PD	N=6		
	SD		N=15	
	PR		N=2	N=3

Table 3 : Reconciliation results – Time-dependent variables

TTP after review			
Patients N 27	shorter	same	longer
TTP before review	N=13	N=13	None
DOR after review			
Patients N 8	shorter	same	longer
DOR before review	N=1	N=2	None

4.1. Summary of the reconciliation results by patient

Patient 122038

Discrepancy: Best response and Date of progression

INV: PR on 24/04/2017 and PD on 02/10/2017 (clinical progression).

REV A: PD on 23/02/2017 (new lesion: lung)

REV B: PD on 23/02/2017 (target lesions).

Reconciliation: PD 23/02/2017 for progression new lung lesion, best response is SD.

Patient 121049

Discrepancy: Best response and Date of progression

INV: PR on 27/07/2017 and PD on 25/10/2017 (clinical progression).

REV A: PD on 27/07/2017 (new lesion: lung).

REV B: PD on 27/07/2017 (new lesion: lung).

Reconciliation: PD 27/07/2017 for new lung lesion, best response is SD.

Patient 123065

Discrepancy: Date of best response and Date of Progression

INV: PR on 24/05/2018, PD on 30/01/2018

REV A: PR is achieved on 20/03/2018, PD on 28/09/2018 (lung NTL unequivocal progression and new lung lesion)

REV B: PR is achieved on 20/03/2018, PD on 28/09/2018 (lung NTL unequivocal progression and new lung lesion)

Reconciliation: PR is achieved on 20/03/2018, PD on 28/9/2018

Patient 121036

Discrepancy: Date of progression

INV: PD on 01/12/2017 (target lesions).

REV A: PD on 26/05/2017 (new lesion: lung).

REV B: PD on 26/05/2017 (new lesion: lung).

Reconciliation: PD 26/05/2017 for new lung lesion

Patient 121039

Discrepancy: Date of progression

INV: PD on 17/01/2018 (target lesions).

REV A: PD on 21/11/2017 (target and lung NTL unequivocal progression)

REV B: PD on 21/11/2017 (target and lung NTL unequivocal progression)

Reconciliation: PD on 21/11/2017 for target lesion progression and NTL PD.

Patient 121043

Discrepancy: Date of progression

INV: PD on 09/08/2017 (target lesions).

REV A: PD on 12/06/2017 (target lesions).

REV B: PD on 12/06/2017 (target lesions).

Reconciliation: PD on 12/06/2017 for target lesion PD

Patient 121045*Discrepancy: Date of progression*

INV: PD 18/10/2017 (non-target lesions).

REV A: PD on 24/07/2017 (NTL lung unequivocal progression)

REV B: PD on 24/07/2017 (NTL lung unequivocal progression)

*Reconciliation: PD 24/07/2017 for NTL progression***Patient 121051***Discrepancy: Date of progression*

INV: PD 13/03/2018 (target lesions).

REV A: PD 20/12/2017 (new lesion: lung and liver, lung NTL unequivocal PD).

REV B: PD 20/12/2017 (new lesion: lung and liver, lung NTL unequivocal PD).

*Reconciliation: PD 20/12/2017 for multiple new lesions and NTL progression.***Patient 121052***Discrepancy: Date of progression*

INV: PD 22/01/2018 (target lesions).

REV A: PD 13/11/2017 (lung and liver NTL unequivocal PD)

REV B: PD 13/11/2017 (lung and liver NTL unequivocal PD)

*Reconciliation: PD 13/11/2017 for multiple liver and lung NTL progression.***Patient 122041***Discrepancy: Date of progression*

INV: PD 01/08/2017 (target lesions)

REV A: PD 06/06/2017 (target lesions)

REV B: PD 06/06/2017 (target lesions)

*Reconciliation: PD 06/06/2017 for target lesion progression.***Patient 122047***Discrepancy: Date of progression*

INV: PD 30/01/2018 (target lesions)

REV A: PD 22/09/2017 (target lesions and new lung lesion).

REV B: PD 22/09/2017 (new lung lesion).

*Reconciliation: PD 22/09/2017 for target lesion and new lung lesion.***Patient 122061***Discrepancy: Date of progression*

INV: PD 08/11/2018 (target lesions)

REV A: PD 19/07/2018 (lung NTL unequivocal PD and new lung and mediastinal lesions)

REV B: PD 19/07/2018 (lung NTL unequivocal PD and new lung and mediastinal lesions)

*Reconciliation: PD 19/07/2018 for NTL progression and multiple new lesions.***Patient 124058***Discrepancy: Date of progression*

INV: PD 16/07/2018 (target lesions)

REV A: PD 05/03/2018 (target lesions)

REV B: PD 05/03/2018 (target lesions)

Reconciliation: PD 05/03/2018 for target lesion progression.