

**Clinical trial results:****Immunomodulatory effect of esomeprazole antitumoral and high-dose under neoadjuvant and adjuvant in patients with melanoma in stage III. Randomized pilot study treatment vs control****Summary**

EudraCT number	2014-000334-30
Trial protocol	IT
Global end of trial date	29 November 2016

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information**Trial identification**

Sponsor protocol code	INT27/14
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione IRCCS "Istituto Nazionale dei Tumori"
Sponsor organisation address	via G. Venezian 1, Milano, Italy, 20133
Public contact	Segreteria Tecnico Scientifica, Fondazione IRCCS "Istituto Nazionale dei Tumori" , etico@istitutotumori.mi.it
Scientific contact	PI: Licia Rivoltini (licia.rivoltini@istitutotumori.mi.it) Project Manager: Paola Frati, Fondazione IRCCS "Istituto Nazionale dei Tumori" , paola.frati@istitutotumori.mi.it

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2016
Global end of trial reached?	Yes
Global end of trial date	29 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of immunomodulatory and anti-tumor effect of treatment with high doses of esomeprazole in patients with metastatic melanoma

Protection of trial subjects:

Each patient will be informed about the study and, if accepted, must sign the consent to participate. Patients will be informed of the contingencies associated with the Protocol procedures in order to provide adequate information about potential risks. However, through the adverse events monitoring, the protection of the interests and safety of the participants will be guaranteed.

Background therapy:

None

Evidence for comparator:

Not Applicable

Actual start date of recruitment	03 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 109
Worldwide total number of subjects	109
EEA total number of subjects	109

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	84
From 65 to 84 years	23

Subject disposition

Recruitment

Recruitment details:

As for the phase A of the study, 23 stage III melanoma patients, received oral treatment with Esom prior to surgery (5-7 weeks, mean: 5,7). A control group of 86 patients receiving no Esom treatment for logistic reasons (interval to surgery \leq 5 weeks) was also included (9 DO/failure). Phase B was never activated to the rapidly evolving scenario of melanoma therapy

Pre-assignment

Screening details:

Clinical data have been collected to ascertain patient eligibility; signed ICF has been obtained & blood sample for immunological studies was withdrawn. In case surgery was scheduled at \geq 5 weeks interval, enrolment into the ESOM pre-surgery treatment study arm was proposed. For surgery planned before 5 weeks, pts were offered to enter the Control Group

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Esom Group (treatment)

Arm description:

The Esom treatment arm foresees the administration of Esom to stage III melanoma patients undergoing lymph node surgical dissection. The treatment was given in the interval prior to surgery for a period ranging from 5 to 7 weeks, depending on the individual patients' waiting list. Patients enrolled in this group were 23, 20 of which completed the whole treatment program.

Arm type	Experimental
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	034972416/M(40mg)
Other name	Nexium
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients enrolled in the Esom arm received Esom orally according to an intermittent schedule which provided a dose of 2,5 mg/kg/die for three days, followed by a maintenance dose (20 mg/die) for four days. This weekly schedule was repeated for a mean of 5-7 weeks, up to 24 h prior to surgical intervention.

Arm title	Control Group (Control)
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Arm description:

A group of stage III melanoma patients (not entering the Esom group for logistic reasons, i.e. surgery scheduled before 5 weeks) was included in the study as controls to gain parallel information about blood and LN immune status in the absence of ESOM administration

Arm type	No intervention
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No investigational medicinal product assigned in this arm

Number of subjects in period 1	Esom Group (treatment)	Control Group (Control)
Started	23	86
Completed	20	80
Not completed	3	6
Physician decision	-	6
no treatment compliance	3	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
Reporting group description:	
<p>Esom Group (treatment): Esomeprazole was administrated orally according to an intermittent schedule which provided a dose of 2,5 mg/kg/die for three days, followed by a maintenance dose (20 mg/die) for four days. This weekly schedule was repeated up to 24 h before the surgical intervention.</p> <p>Control Group (Control): A group of stage, gender and age-matched melanoma patients (not entering the tratment group for logistic reasons) included in the study as controls to gain parallel information about blood and LN immune status in the absence of ESOM administration</p>	

Reporting group values	Overall Trial	Total	
Number of subjects	109	109	
Age categorical			
Age > 18 years			
Units: Subjects			
Adults (18-64 years)	84	84	
From 65-84 years	23	23	
85 years and over	2	2	
Age continuous			
Age > 18			
Units: years			
arithmetic mean	52		
full range (min-max)	20 to 86	-	
Gender categorical			
Units: Subjects			
Female	35	35	
Male	74	74	

End points

End points reporting groups

Reporting group title	Esom Group (treatment)
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Reporting group description:

The Esom treatment arm foreseen the administration of Esom to stage III melanoma patients undergoing lymph node surgical dissection. The treatment was given in the interval prior to surgery for a period ranging from 5 to 7 weeks, depending on the individual patients' waiting list. Patients enrolled in this group were 23, 20 of which completed the whole treatment program.

Reporting group title	Control Group (Control)
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Reporting group description:

A group of stage III melanoma patients (not entering the Esom group for logistic reasons, i.e. surgery scheduled before 5 weeks) was included in the study as controls to gain parallel information about blood and LN immune status in the absence of ESOM administration

Subject analysis set title	Primary Analysis
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Subject analysis set type	Full analysis
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Subject analysis set description:

Patients involved in the immunological analyses were 100, of which 20 in the Esom Group (Treatment Arm) and 80 in the Control Group (Control Arm)

Primary: Primary_1

End point title	Primary_1
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End point description:

The phase A of the study was successfully completed, with a high patient compliance (>90% patients adhered to the full pre-surgery treatment schedule) and good safety profile of the Esom administration (about 10% patients experienced grade 1-2 toxicity). The primary endpoints were to test the modulation of the frequency and/or function of diverse immune cell subset in peripheral blood (PB) and lymph nodes of patients receiving pre-surgery Esom, and to search for signs of reduced tumor viability (decrease in ki67 proliferation marker expression and/or mitosis, and /or increase of apoptosis) in metastatic LN. The immunoprofiling of LN cell suspension and PB immune cells showed a significant increment of cytotoxic and activated T and NK cells, indicating a boost of antitumor immunity. In contrast, cells with inhibitory functions such as monocytes, MDSC and regulatory T cells were reduced, proving a reduction in local and systemic immunosuppression.

End point type	Primary
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End point timeframe:

5-7 weeks

End point values	Esom Group (treatment)	Control Group (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	80		
Units: number	20	80		

Statistical analyses

Statistical analysis title	Statistical analysis
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Statistical analysis description:

The individual tests performed for the variables group were verified with the Hochberg procedure, to consider the multiplicity of the analysis. None of the observed significance are missed because of the adjustment procedures above mentioned.

Comparison groups	Esom Group (treatment) v Control Group (Control)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.05 ^[2]
Method	Hochberg

Notes:

[1] - immunomodulation

[2] - no P-value considered

Primary: Primary_2

End point title	Primary_2 ^[3]
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End point description:

In terms of effects of the treatment on tumor viability, in patients having stage IIIC and receiving pre-surgery Esom (n=8), the expression of melanoma markers (TRP1 and gp100) was significantly lower with respect to the stage IIIC (n=15) patients of the control group, implying a inferior tumor load in metastatic LN in the group receiving Esom, either to the investigational treatment or different distribution in tumor burden among the two groups.

End point type	Primary
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End point timeframe:

5-7 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for the second of the primary end point.

End point values	Esom Group (treatment)	Control Group (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	80		
Units: number	20	80		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

5-7 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	AE_Group
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Reporting group description: -

Serious adverse events	AE_Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	AE_Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Drowning			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Bowel movement irregularity	Additional description: bowel alteration		
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Metabolism and nutrition disorders			

Nausea subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 November 2016	The phase A of the study, testing the safety and immunological effects of Esom administration in pre-surgical regimen was successfully concluded. Instead, the phase B of the study, assessing the same endpoints on the long-term Esom administration in post-surgery setting, was never activated due the rapidly changing scenario of stage III patients clinical management occurring during the Adesom2 trial. Indeed, novel drugs targeting key oncogenic pathways in melanoma (i.e. BRAF and MEK inhibitors for patients bearing BRAF mutation) or stimulating immune responses through the blocking of checkpoint inhibition (anti-CTLA4 and PD-1) were introduced in clinical testing, with multiple multicentric phase II and III trials rapidly activated in our Institution. For reasons related to this clinical competitive landscape, it was substantially impossible to continue the study and activate the phase B of the protocol.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The approval of new therapies for stage III melanoma in adjuvant setting patients completely overwhelmed the field and made any clinical testing of additional new strategies impossible to be performed.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28267587>

<http://www.ncbi.nlm.nih.gov/pubmed/27827921>