

AIFA Call 2023 for Independent Research
THERAPEUTIC SEQUENCING IN ONCOLOGY

Principal Investigator (PI)

Principal Investigator PEC

Please indicate the certified email (PEC) address of Scientific Responsible. If not available, please report the PEC address of the PI Centre.

Date of birth (dd/mm/yy)

Grant in AIFA Call past editions

Please indicate if PI received AIFA grant in the past editions.

YES

NO

If yes, please indicate the year(s) :

Proposal title

Running title (max 50 characters)

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Acronym title (max 10 characters)

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Key words (max 10 keywords)

Keyword 1	
Keyword 2	
Keyword 3	
Keyword 4	
Keyword 5	
Keyword 6	
Keyword 7	
Keyword 8	
Keyword 9	
Keyword 10	

Thematic area

Please indicate the thematic area

Hepatocellular carcinoma

Non Small Cell Lung Cancer (NSCLC)

Renal cell carcinoma

Institutional Address (Public Institution or Non Profit Institution)

Please indicate the address of the Institution which applies.

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Institutional Address PEC

Please indicate the certified email (PEC) address of proposing Institution

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PI Centre Address (Public Institution or Non Profit Institution)

Please indicate the address of the centre where Principal Investigator is employed. The centre here indicated is the Coordinating Centre.

Operative Units Institutional Address

Please list all the Clinical Centres directly involved in patients' recruitment and any Centres involved in other tasks/activities as statistics, administrative, management, etc. The foreign Centres, if applicable, should be listed after the national centres. Please detail responsible investigator, name and address of the Collaborating Centres.

Pharmacological Treatment

Please list each medicinal products used in both the treatment and in the control groups. Please note that the proposed pharmacological treatments can be only drugs authorised in Italy. With the exception for different types of sequencing, the medicinal products can only be used for the approved indications as defined by the SmPC and for indications reimbursed by the NHS under law 648/96. Medicinal products cannot be modified respect to the marketing authorization (repacking, reformulation, and all the other modifications) except re-labelling.

Drug			Marketed	
Active ingredient (max. 50 chars)	Reimburse-ment class within the NHS (A,C,H)	Drug for treatment group (T) Drug for standard group (C) <i>(Can be clicked both)</i> Not Applicable (NA)	Patent / Off patent	Approved indications/ Other indications(*)

(*) It is possible to indicate "other indication" only for different sequencing

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Active ingredient (max. 50 chars)	Reimburse- ment class within the NHS (A,C,H)	Drug for treatment group (T) Drug for standard group (C) <i>(Can be clicked both)</i> Not Applicable (NA)	Patent / Off patent	Approved indications/ Other indications(*)

(*) It is possible to indicate "other indication" only for different sequencing

Total study duration

Please note that the maximum allowed study duration (from AC/CE approval to last patient follow-up visit) is 60 months.

Study duration in months:

Study timing and recruitment

Phase

Study phase:

Timing (in months)

Enrollment phase

Treatment and follow-up

Estimation of number of patients to be recruited

Synopsis (max 4.000 characters)

Please describe: Background, Objectives, Methods, Expected results.

Background (max 4.000 characters)

Please describe an updated review of relevant literature related to disease, available treatments and therapeutic regimens information.

Rationale and Innovativeness (max 4.000 characters)

Please describe the clinical question that will be investigated in the study and what research findings will add to existing evidence. If applicable, please describe innovativeness of the study.

Impact on the National Health Service (max 4.000 characters)

Please describe the impact on the Italian National Health Service (NHS) and transferability on general population.

Objectives of the study (max 4.000 characters)

Please report the purpose of the study, the primary and secondary objectives of the study according to the statistical hypothesis.

Study Design (max 4.000 characters)

Please describe the type of experimental design selected for clinical trial in order to answer the clinical question and to produce valid results.

Study Population (max 4.000 characters)

Please report study population characteristics and the clinical setting (hospital, general practice, etc.) where the study will be conducted; enrolment procedure and accrual time. Please specify withdrawal criteria and procedures.

Population	Type of patients	Objective
Overall population (RW-like)	All patients registered before the start of first-line treatment (independently of the modality of treatment assignment, if any)	1 (primary) 6 to 13 (secondary)
Intention-to-treat population (ITT)	Within each RCT, all randomized patients according to the assigned arm (independently of having or not received the assigned treatment)	2, 3, 4, 5 (primary aims) 14 to 17 (secondary)
Safety population (SP)	All patients who received at least 1 dose of evaluated treatment (independently of the modality of treatment assignment, if any)	17
Specific RW populations	Patients for whom a treatment is assigned by choice at a point of the journey where a specific RCT was available	18

Inclusion criteria (max 4.000 characters)

Exclusion criteria (max 4.000 characters)

Intervention (max 4.000 characters)

Please provide detailed information about treatments (or other type of intervention) for each group (treatment and control).

The following items must be included:

- Dose (and dose escalation) and the dosage form, packaging and labelling of the IMP;
- Duration of treatment (including number and duration of the cycles, if applicable) and the follow-up period for each IMP/trial treatment group/arm of the trial;
- Route of administration;
- Medication/treatment (including rescue medication) permitted and not permitted before and/or during the trial;
- Procedure for monitoring subjects compliance;
- Description of the “stopping rules” or “discontinuation criteria” for individual subjects, part of trial, and entire trial;
- Accountability procedures for the IMP, including comparator if any.

Endpoints and Outcomes (max 4.000 characters)

Please indicate the primary and secondary endpoints and related outcome measures; the relation between subjective/objective evaluation of endpoints, justifications to support the validity of any surrogate or composite endpoints, if applicable.

Methods (max 6.000 characters)

A description of the measures taken to minimize/avoid bias, including (but not limited to):

Randomization. Please report methods used to generate the random allocation sequence. Central randomization should be preferred; other randomization procedures should be adequately motivated. Include a description of maintenance of trial treatment randomisation codes and procedures for breaking the code.

Blinding (masking). Please describe whether or not, the personnel involved in administering interventions and assessing outcomes is aware of group assignment and if not, how the success of masking is assessed.

Data Collection. Please report data that will be collected; the forms/tools used for the retrieval of information and their validity and reliability; the measures/indicators used; the potential sources of bias in the retrieval of information regarding study subjects and interventions/treatments; duration and frequency of follow up; missing data. When the use of an electronic clinical reporting form (e-CRF) is envisaged, only validated systems that address traceability are acceptable (for instance, excel spreadsheets do not represent an adequate system for recording data). Please include in this section the identification of source data definition.

Statistical considerations (max 4,000 characters)

Please describe in detail the statistical hypothesis (e.g. superiority, equivalence or non-inferiority for the primary endpoint(s)).

Sample size estimates. Please report the estimate of sample size and how it is determined, indicating information on the following components of sample size estimation: the power, the significance levels, the underlying event rate in the population under investigation, the size of the treatment effect, the standard deviation, the expected proportion of drop-outs. Adjustment for other factors affecting the sample size calculation (e.g. expected compliance rates), should also be reported. For studies of equivalence - non inferiority the maximum acceptable difference should be stated. For composite endpoints, please indicate how different parameters contribute to their definition and to sample size calculation.

Statistical analysis. Please report the main statistical analyses that will be carried out. Definition of the study population for main analysis, error probabilities, brief description of the statistical techniques, methods for additional analyses, subgroup analyses (if planned).

Explanation of each interim analysis (if planned) and predefined stopping rules should also be clearly stated.

Timing (max 4.000 characters)

Please report the duration of the study (patient enrolment; treatment duration, follow up, etc.); predefined check points for the evaluation of work in progress.

Feasibility (max 4.000 characters)

Organizational characteristics. Please describe the participating centres, the specialties and experience needed for conducting the study.

In case of multicentre study specify:

- the institutions/units in charge of coordinating the study, assigning treatment, monitoring the procedures;
- the presence of steering committees and/or data monitoring committees (when applicable);
- the presence and the organization of centralized laboratories (when applicable).

Feasibility. Please describe previous experience of the principal investigator; previous experience of the institution that will coordinate the study; available technology that may be relevant for the study.

GCP and Ethical aspects (max 4.000 characters)

Good Clinical Practices. Clinical studies are required to be conducted in accordance with Good Clinical Practices (GCP). Please discuss the benefit/risk ratio, the specific hazards of the study (e.g. risks for the patients, complexity of the study design, validity of the information retrieval, etc.), the procedures of risk minimisation (e.g. training activities, review of eligibility prior to randomization, data verification, drug accountability, drug reconciliation, etc.), the characteristics and frequency of monitoring activities and the institution(s) that will be in charge of this task.

Ethical aspects. Please describe the potential risks for study subjects, either related to physical/psychological domains or to a possible excessive interference with the subject privacy, and the procedures that will be followed to prevent these potential risks. As above mentioned it is not necessary to include the documentation required by the Italian ethics committees.

Insurance. Please include a comment about the application of the law about the study insurance.

References (max 4.000 characters or max 20/25 references)

Please report only the references that are strictly relevant to the study proposal. References should include authors (when there are more than 6 authors, report the first 3 authors), title, book or journal, year, volume number and page numbers. For books, the publisher should also be reported.

Budget

B1. Operative Units

Units	Name	Institution	Responsible
CC			
U01			
U02			
U03			
U04			
U05			
U06			
U07			
U08			
U09			
U010			
U011			
U012			
U013			
U014			
U015			
U016			
U017			
U018			
U019			
U020			

Units	Name	Institution	Responsible
U021			
U022			
U023			
U024			
U025			
U026			
U027			
U028			
U029			
U030			
U031			
U032			
U033			
U034			
U035			
U036			
U037			
U038			
U039			
U040			
U041			

B2. Personnel

UO	Degree	Tasks	Contract	Duration (in months)	Salary per month (€)		% TES ⁵	Salary × % time employed on study ³		Total (€) (Salary × % time employed on study) × duration
					Gross ¹	Charges ²		Gross	Charges	

1 Gross salary for employees

2 Related charges to be paid by institutions

3 When the % of time employed is 100%, report on this column the same values of the previous one

4 Total personnel cost for all units

5 % time employed on study

[illegible]

- 1 Gross salary for employees
2 Related charges to be paid by institutions
3 When the % of time employed is 100%, report on this column the same values of the previous one
4 Total personnel cost for all units
5 % time employed on study

[illegible]

- 1 Gross salary for employees
2 Related charges to be paid by institutions
3 When the % of time employed is 100%, report on this column the same values of the previous one
4 Total personnel cost for all units
5 % time employed on study

[illegible]

- 1 Gross salary for employees
2 Related charges to be paid by institutions
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					Gross ¹	Charges ²		Gross	Charges	

1 Gross salary for employees

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4 Total personnel cost for all units

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[illegible]

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5 % time employed on study

[illegible]

Total personnel cost ⁴	
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- 1 Gross salary for employees
2 Related charges to be paid by institutions
3 When the % of time employed is 100%, report on this column the same values of the previous one
4 Total personnel cost for all units
5 % time employed on study

B3. Supplies

Please specify the cost of the main categories of supplies for the entire study.

Categories of Supplies	Brief description, if needed (max 200 chars.)	Total budget for the entire project and for all participating centres (€)
1. Hardware		
2. Software		
3. Consumable materials/Stationery		
4. Device		
5. Labs material		
6. Other costs for supplies		
Total (€)		

B4. Services

Please specify the cost of the main categories of services for the entire study.

Categories	Brief description (max 200 chars.)	Total budget for the entire project and for all participating centres (€)
1. Data collection (e.g.: e-CRF)		
2. Study Monitoring		
A. Number of Expected site visit per centre		
B. Number of Clinical centres		
C. Number of Total site visits (automatic A x B)		
D. Average cost for site visit (*) <i>(*)Excluding personnel and/or travels already budgeted in table B2 and/or B6</i>		
E. Total cost (C x D)		
3. C.R.O. Activities (different from a.m. categories)		
4. Insurance		
5. Publication cost		
6. Collaboration contracts/ consulting (*)		
7. Other		
Total (€)		

(*) "Partita IVA" Included

B5. Drug cost

Please specify the cost of the drugs needed to conduct the entire study (if applicable)

	Brief description (max 200 chars.)	Total budget for the entire study (€)
1. Costs for drug(s) not used according to SmPC, <u>if not provided free of charge by a Company or paid by others (*)</u>		
2. Costs related to drug(s) blinding and/or packaging and/or relabelling		
3. Shipping cost(s) for foreign centre(s)		
4. In case the <u>drug(s)</u> will be <u>provided free of charge(s)</u> , please specify the provider	Note (to specify)	
Total (€)		

B6. Meetings, conferences, workshops, travels

Please describe the cost of events and specify if the same cost is related to participation or to organization

	Brief description, if needed (max 200 chars.)	Total budget for the entire project and for all participating centres (€)
1. Coordination meetings		
2. Participation in scientific conferences (in Italy or abroad)		
3. Organization of scientific conferences related to the study project		
4. Travel, food and accomodation		
5. Other (specify)		
Total (€)		

B7. Other

Please describe the costs arising from categories not mentioned above.

[illegible]

B8. General Costs/Overhead

Please specify the impact on financing of each categories. The total of these costs and overhead cannot affect more than 10% of the sum of the expense items previously represented, with the exception of drug cost.

Categories	% Incidence (tot max 10%)	Total budget for the entire study and for all participating centres (€)
General costs (brief description)		
Overhead		
Total (€)		

B9. Overall expected costs for each item of the study as indicated below

Please specify the overall expected costs for each item of the study.

Items	Total (€)
Personnel	
Supplies	
Services	
Meetings, conferences, workshops, travels	
Other	
Sub-total (€)	
General costs/Overhead (max 10% of sub- total)	
Drugs cost	
Total (€) (Sub-total + Overhead + Drugs cost)	

Overhead check

If the reported value is a number smaller than zero, the overhead exceed 10% of subtotal in contrast with the Call AIFA requirements.

B10. Distribution of costs between coordinating and participating centres

Please specify the percentage of budget allocated to each centre. Compile for all UOs inserted into section B.1.

Operative Unit	% Budget	Total Costs (€)
Coordinating centre	%	
UO1	%	
UO2	%	
UO3	%	
UO4	%	
UO5	%	
UO6	%	
UO7	%	
UO8	%	
UO9	%	
UO10	%	
UO11	%	
UO12	%	
UO13	%	
UO14	%	
UO15	%	
UO16	%	
UO17	%	
UO18	%	
UO19	%	
UO20	%	

Operative Unit	% Budget	Total Costs (€)
§h	%	
UO	%	
UO2	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO 1	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	

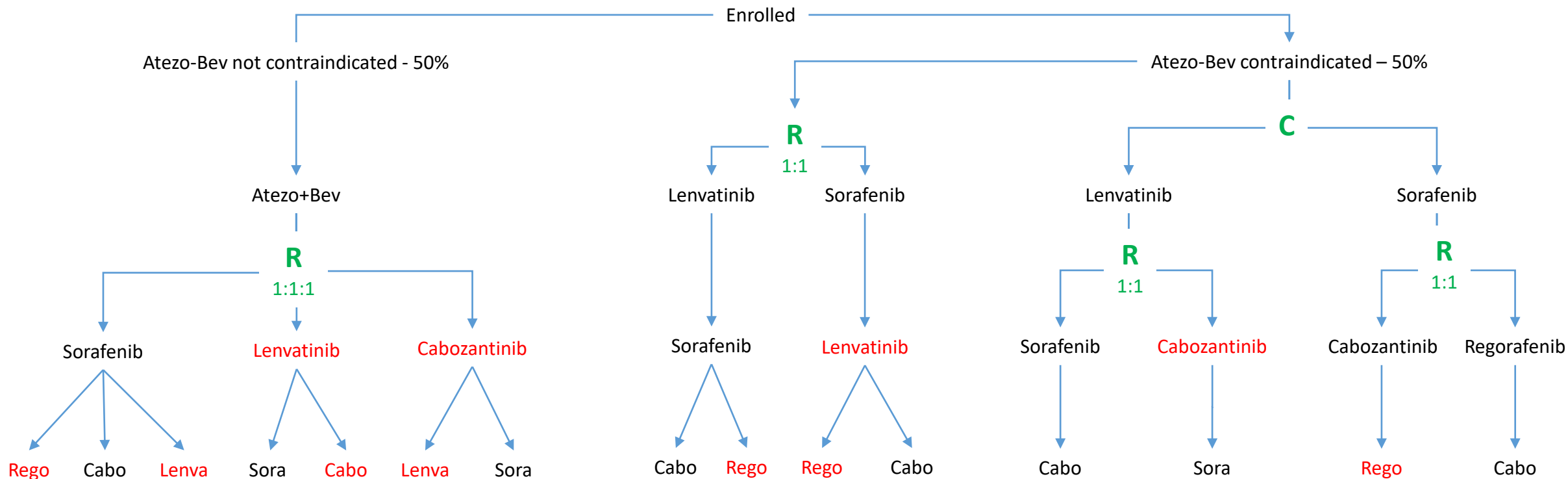
Operative Unit	% Budget	Total Costs (€)
§h	%	
UO	%	
UO	%	
UO	%	
UO4	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO	%	
UO 2	%	
Total (€)	%	

B.11 Budget Annotation (not mandatory)

List of the investigators in charge of the units dedicated to data analysis and to GCP monitoring of the study (max 4.000 characters)

Please report the investigators responsible for the units dedicated to data analysis and GCP monitoring of the study (when applicable). Please be sure to follow applicable monitoring requirements.

Additional documents may be attached in order to explain the study protocol (e.g. reporting form, rating scale, Gantt, etc)



Phase 3 - RCT Question 1. Are lenvatinib or cabozantinib more effective than sorafenib after atezo-bev?

Two independent comparisons
HR 0.70 (from 12 to 17 month): 300 events for each comparison (Alpha 0.025, beta=0.80)

If both winner, alpha 0.05 recycled for lenva vs cabo HR 0.70 (from 17 to 24 months) 247 events

Phase 3 - RCT Question 2. Is the sequence Sorafenib-lenvatinib more effective than the sequence Lenvatinib-Sorafenib?

HR 0.70 (from 12 to 17 months): 247 events
(Alpha 0.05, beta=0.80)

Phase 3 - RCT Question 3. In patients pre-treated with lenvatinib, is the sequence Cabozantinib-Sorafenib more effective than Sorafenib-Cabozantinib?

HR 0.70 (from 9 to 13 months): 247 events
(Alpha 0.05, beta=0.80)

Phase 3 - RCT Question 4. In patients pre-treated with sorafenib, is the sequence Cabozantinib-Regorafenib more effective than Regorafenib-Cabozantinib?

HR 0.70 (from 9 to 13 months): 247 events
(Alpha 0.05, beta=0.80)

I farmaci in nero sono prescrivibili, quindi possono essere scelti

I farmaci in rosso non sono prescrivibili e possono essere assegnati solo in un disegno sperimentale

Possible determinants of the choice

- Age
- ECOG PS
- Comorbidities
- Concomitant medications
- Previous treatment
- Route of administration
- Timing of the schedule
- Expected toxicity
- Patient's refusal
- Other...