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Cost Effectiveness of Treatment Optimization with Biomarkers for Immunotherapy in Solid Tumors: A Systematic Review Protocol

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5 6	1	Cost Effectiveness of Treatment Optimization with Biomarkers for
7 8 9	2	Immunotherapy in Solid Tumors: A Systematic Review Protocol
10 11 12	3	Sara Mucherino ¹ , Valentina Lorenzoni ² , Valentina Orlando ¹ , Isotta Triulzi ² , Marzia Del Re ³ , Annalisa
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53 54 55 56 57 58 59 60	24	Keywords: Immunotherapy; Biomarkers; Cost effectiveness; Economic evaluation; Quality of life

ABSTRACT

identify what further research needs.

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Introduction: The combination of biomarkers and drugs is the subject of growing interest both

from regulators, physicians and companies. This study protocol of a systematic review is aimed to

describe available literature evidences about the cost-effectiveness, cost-utility or net-monetary

Methods and analysis: A systematic review of the literature will be carried out according to the

PRISMA statement guidelines. PubMed and Embase will be queried from June 2010 to June 2020.

immunotherapy; the interventions (I) will be the use of predictive biomarkers; the comparator (C)

cost-utility, net-monetary benefit, life years gained and quality of life. The quality of the evidence

Ethics and dissemination: This systematic review will assess the cost effectiveness implications of

using blood-based biomarkers in the immunotherapy, which may help to understand whether this

approach is widespread in real clinical practice. This research is exempt from ethics approval

because the work is carried out on published documents. We will disseminate this protocol in a

was graded according to GRADE (Grading of Recommendations Assessment, Development and

will be any other strategies; the outcomes (O) will be expressed in terms of cost-effectiveness,

The PICO Model will be applied: the patients target will be with solid tumours treated with

benefit of the use of biomarkers in solid tumour as tools for customizing immunotherapy to

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Evaluation).

related peer-reviewed journal.

PROSPERO registration number: CRD42020201549

ARTICLE SUMMARY

Strengths and limitations of this study

- The use of predictive biomarkers in the immunotherapy can help target therapy in some solid tumors, hence, the combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies.
- This is the first systematic review which will specifically describe and synthetize available • 18 52 literature evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumor as tools for customizing immunotherapy to identify what further research needs. 23 54
- An in-depth search strategy will be applied to two major scientific databases, without • 28 56 geographic or language restrictions, and conducted by a multidisciplinary team with expertise in the field.
 - The literature will be carefully assessed for quality using the GRADE (Grading of • Recommendations Assessment, Development and Evaluation) tool.

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Introduction

In recent years, the pharmaceutical industry has seen a shift from the blockbuster model, in which drugs are developed for an ideal patient, to a nichebuster model, in which drugs developed specifically for specific patient groups ^{1,2}. In this context, the combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies ³⁻⁷. The US Food and Drug Administration (FDA) publishes and updates a list of drugs for which it is suggested or mandatory to associate a genetic-molecular test⁸. The importance of predictive biomarkers is related to optimizing patient benefits, reducing the risk of toxicity and leading combined approaches ⁹. Particularly, for some drugs the test result defines whether or not to administer, for others it establishes the most appropriate dosage of therapy. Only in 29% of cases (48 combinations) the use of the biomarker has an impact on the doctor's choice to prescribe or not prescribe a specific drug ¹⁰. In Italy, 34 of the 48 combinations are approved for use and of these, about 80% find application in oncology particularly for solid tumors treatment ¹⁰. The clinical development of checkpoint inhibitor-based immunotherapy has ushered in an exciting era of anticancer therapy. The importance of predictive biomarkers is related to the optimization of benefits in patients treated with immunotherapy, by reducing the risk of toxicity and leading combined approaches. Durable responses have been observed in patients with various malignant neoplasms ¹¹. This study protocol is part of a funded Italian National Research Project based on the hypothesis that the identification of predictive biomarkers can improve the understanding of the mechanisms

underlying the complex interactions between the immune system and cancer, and can help
 clinicians optimize therapy with monoclonal anti-PD-1 and anti-PD-L1 antibodies. Hence, among
 the already known biomarkers, the overexpression of PD-L1 is an important and widely explored
 predictive biomarker for the response to PD-1/PD-L1 antibodies ^{4,12}. Direct assessment of PD-L1

expression on tumor cells is a logical biomarker for the prediction of treatment response to anti-PD-1 or anti-PD-L1 therapies ^{13,14}. The use of PD-1 and PDL-1 as predictive biomarkers can help target therapy in some solid tumors, including renal and non-small cell lung cancer (NSCLC) ¹⁵⁻¹⁷. Nivolumab and pembrolizumab (two PD-1 inhibitors) and an PD-L1 inhibitor, atezolizumab, have been approved by the Italian Medicines Agency (AIFA), for the treatment of patients with NSCLC 18-20. A targeted approach to treatment using predictive biomarkers has the potential not only to maximize clinical benefit, but also to improve cost-effectiveness and reduce the economic burden of the disease ²¹. As the global impact of these types of cancers continues to grow, the implementation of new and more effective therapies becomes important but also overly expensive ²². Therefore, the analysis of the cost-effectiveness and economic impact of the use of biomarkers upstream of the choice of the specific therapy represents an imperative to validate its effectiveness, the eventual relationship with the quality of life and patient reported outcomes (PROMs), and sustainability ²³. However, there is no existing peer-reviewed or published synthesis assessing the impact in terms of cost-effectiveness and quality of life of predictive biomarkers use in oncological treatment. This is the protocol of a systematic review aimed to describe and synthetize available literature evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumor as tools for customizing immunotherapy to identify what further research needs. **Methods and Analysis** Information sources A systematic review of the literature will be carried out according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement guidelines ²⁴. For the

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3 4 5	108	present review, the identification of relevant studies will be achieved by searching electronic
5 6 7	109	databases of the published literature, which will include the following: Medical Literature Analysis
8 9	110	and Retrieval System Online (via PubMed/MEDLINE) and Embase (via Ovid), queried from June
10 11 12	111	2010 to June 2020.
	112	Search strategy
15 16	113	First, the search strategy will be developed and completed in PubMed, and then the same strategy
17 18 19	114	will be applied to Embase. More in detail, the search strategy will combine headings and keywords
20 21	115	identifying according to the PICO Model. They will be searched as Mesh Term (PubMed) or Emtree
22 23 24	116	(Embase) and in title and abstract (antibodies, immunotherapy, nivolumab, durvalumab,
25 26	117	avelumab, atezolizumab, nivolumab, pembrolizumab, neoplasms, cancer, carcinoma, biomarkers,
27 28 29	118	PD-1, programmed death 1, PD-L1, programmed death ligand 1, IL-6, interleukin-6; cost benefit
	119	analysis; cost effectiveness; cost utility; economic evaluation; quality of life). The Boolean
32 33 34	120	operators used will be AND/OR. The full search strategy that will be used is reported in Table 1.
	121	More in detail, the search syntax for the two databases are presented in the online Supplementary
37 38	122	Appendix 1.
39 40 41	123	Elegibility criteria
42 43	124	The inclusion criteria are based on compliance with the PICO. Particularly, we will identify:
44 45 46	125	- the patients target (P) will be with solid tumors treated with immunotherapy;
47 48	126	- the interventions (I) will be related to the use of predictive biomarkers before the choice
49 50 51	127	of therapeutic approach;
52 53	128	- the comparator (C) will be any other strategies;
54 55 56	129	- the outcomes (O) will be expressed in terms of cost-effectiveness, cost-utility, net-
	130	monetary benefit, life years gained and quality of life.
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2 3 All studies responding to the PICO will be included in the research. Hence, peer-reviewed original 131 4 5 articles, published between June 2010 to June 2020, will be included. Particularly, all studies about 132 6 7 8 health economics evaluation performed within clinical trials or observational studies related to 133 9 10 biomarkers use published will be included (inclusion criteria). 134 11 12 13 135 On the other hand, conference proceedings, rationale and/or design, letters, editorials, 14 15 136 commentaries, case reports, case study, case series, review, consensus, guidelines, expert 16 17 18 137 opinions will be not included (exclusion criteria). Any identified literature reviews will be used as a 19 20 138 source for finding additional articles not present in our dataset. Moreover, no language restriction 21 22 will be applied to the research, but, fundamental to the eligibility of the study will be the 23 139 24 ²⁵ 140 availability of the papers' full text published in English. 26 27 28 141 Selection and data process 29 30 142 The references will be collected using the software program Reference Manager, ver. 12 (Institute 31 32 for Scientific Information, Berkeley, CA). All references will be screened for relevance and, those 143 33 34 35 144 potentially eligible will be assessed, according the inclusion/exclusion criteria, accepted or 36 37 145 rejected, as appropriate. 38 39 Four researchers will screen titles and abstract to discard irrelevant ones in the first screening 40 146 41 ⁴² 147 phase, then they will assess full texts for eligibility defining which references to include in the 43 44 45 148 qualitative analysis. The references obtained will be validated by expert researchers in the fields of 46 ⁴⁷ 149 pharmacology, immunotherapy, pharmacovigilance, pharmacoeconomic. Reference lists from 48 49 ₅₀ 150 included records will be also screened to identify additional papers. Full texts of relevant studies 51 52 151 will be retrieved and reviewed for eligibility in accordance with the inclusion criteria. 53 54 152 From each reference included in the qualitative analysis information which will be extracted in an 55 56 Excel file are reported in Table 2. Finally, the quality of the evidence was graded according to 57 153 58 59 60

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2 3 <u>^</u> 4	154	GRADE (Grading of Recommendations Assessment, Development and Evaluation) system ²⁵ ,
5 6 ⁻ 7	155	assessing heterogeneity, consistency and risk of bias. Quality of evidence and recommendation for
-	156	All studies and their individual elements will be graded in terms of adequacy of the study
10 11 12	157	regarding the research question, risk of selection bias, measurement of exposure and assessment
13 <u>1</u> 14	158	of outcomes. Disagreements will be resolved by third reviewers.
15 16 17	159	Study registration
18 1 19	160	The study is prospectively registered in PROSPERO, the International Prospective Register of
20 / 21 22	161	Systematic Reviews (CRD42020201549).
23 1 24	162	Ethics and dissemination
25 26 27	163	This review will systematically describe the extent of available evidences investigating the
28 <u>1</u> 29	164	predictive biomarkers used in immunotherapy and their health-economic impact. The use of
30 31 32	165	biomarkers to monitor the clinical outcome of patients treated with immune check-point
33 1 34	166	inhibitors may help to reduce the incidence of adverse events related to the immune system thus
35 36 37	167	also improving quality of life. Furthermore, from the pharmaco-economic evaluations already
38 1 39		conducted on these immune biomarkers we expect to find that their use is associated with better
40 <u>4</u> 1 42	169	cost/effectiveness (or cost-utility, net-monetary benefit) ratio due to their improved ability to
43 ² 44		predict clinical outcome and to redirect non-reactive patients towards alternative and more
45 <u>1</u> 46 47		effective and cost/effective therapeutic approaches.
48 ² 49		Accordingly, main strength of the present work will consist in having an overview on what is
50 <u>1</u> 51 52 ,		already know on blood-based immune biomarkers use to realize treatment personalization of
53 ⁻ 54	174	cancer patients. Also, we will try to gather considerations about the diffusion of their real use
55 1 56		through economic evaluations that report their outcomes in terms of cost effectiveness ratio or
57 58 59 60	176	cost utility ratio and patients' health related quality of life.

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4	177	Other systematic reviews on biomarkers were already published evaluating cost-related aspects
5 6 7	178	but they are specifically focused on a cancer condition and the pertaining biomarker ²⁶⁻²⁹ . To the
-	179	best of our knowledge this is the first systematic review published broadly exploring the health-
10 11	180	economic impact of biomarkers.
12 13 14	181	A potential limitation relates to the heterogeneity associated to the study conducted on
15 16	182	biomarkers. Accordingly, between-study heterogeneity may not support the conduct of
	183	quantitative meta-analysis.
19 20 21	184	Results of the systematic review will be published in a peer-reviewed journal and disseminated at
22 23 24	185	a range of health research conferences. The systematic review is part of a larger project funded by
	186	PRIN 2017 whose aims include the identification of biomarkers able to predict
27 28 29	187	immunotherapeutic-related adverse drug reactions and the potential cost-effectiveness and
	188	quality of life of personalized therapies based on advanced tools.
32 33	189	Finally, this systematic review will assess the cost effectiveness implications of using blood-based
34 35 36	190	biomarkers is in the immunotherapy, which may help to understand whether or not this approach
37 38	191	is widespread in real clinical practice and how the customization of therapy, can actually affect a
39 40 41	192	decrease in costs for the health care systems.
41 42 43	193	
44 45	194	Author contributions
46 47		E.M. designed and concentualized this review C.M. V.O. V.L. LT. drafted the protocol All outbors
48 49	195	E.M. designed and conceptualised this review. S.M., V.O., V.L., I.T. drafted the protocol. All authors
50 51 52	196	were involved in checking various steps of the search strategy, including keywords, as well as the
	197	final version of the protocol. S.M, V.L. and I.T. were involved in the statistical strategy for data
55 56	198	analysis. M.D.R., A.C., R.D. and G.T. were involved in establishing eligibility criteria and data
57 58 50	199	extraction forms. G.T. and E.M. supervised all work stages. R.D. was the funding acquisition

⁶⁰ 200 supervisor. All authors reviewed and agreed the final version of the manuscript.

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10 11 204 12	
13 14 205 15	Conflicts of interest
16 17 206	The authors have no conflicts of interest to declare.
18 19 207 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 60	

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292 Tables

293 Table 1. Search strategy

Query	Keywords (MeshTerms/Emtree OR Title and Abstract)
#1	Antibodies, monoclonal
#2	Immunotherapy
#3	(nivolumab/ipilimumab[Title/Abstract]) OR ipilimumab[Title/Abstract]) OR durvalumab[Title/Abstract]) OR atezolizumab[Title/Abstract]) OR nivolumab[Title/Abstract]) O pembrolizumab[Title/Abstract]) OR "Ipilimumab"[Mesh]) OR "durvalumab" [Supplementary Concept]) OR "avelumab" [Supplementary Concept]) OR "atezolizumab" [Supplementary Concept]) OR "Nivolumab"[Mesh]) OR "pembrolizumab" [Supplementary Concept]
#4	Neoplasms
#5	Cancer
#6	Carcinoma
#7	Biomarkers OR PD1 OR Programmed Death 1 OR PD-L1 OR Programmed Death Ligand 1 OR IL OR Interleukin-6
#8	Cost benefit analysis
#9	Cost effectiveness
#10	Cost utility
#11	Economic evaluation
#12	Quality of life
#13	1 AND 2 AND 3
#14	4 OR 5 OR 6
#15	8 OR 9 OR 10 OR 11 OR 12
#16	13 AND 14
#17	16 AND 7
#18	17 AND 15

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Data extraction	Description
Reference	All paper identification details
Year	Year of publication of the paper
Study design	In the case of economic evaluations, specific technique used and source of the clinica data, e.g. RCT, expert panel
Analysis perspective	National health service, society, government, patient
Type of costs	Direct healthcare costs, direct non-health costs, indirect costs, intangible costs
Reference year of costs	Specific year of reference of costs if reported
Patient Diagnosis	Type of solid tumor studied
Patient (P)	Solid tumors treated with immunotherapy
Intervention (I)	The use of predictive biomarkers before the choice of therapeutic approach
Comparator (C)	Any other strategies
Outcomes (O)	Cost-effectiveness, cost-utility, net-monetary benefit, life years gained (LYG) and qua of life (QALY)

Appendix 1

Search syntax in different databases

PubMed

((((((Antibodies, monoclonal[MeSH Terms]) OR (Antibodies, monoclonal[Title/Abstract])) AND ((immunotherapy[MeSH Terms]) OR (immunotherapy[Title/Abstract]))) AND ((nivolumab/ipilimumab[Title/Abstract]) OR ipilimumab[Title/Abstract]) OR durvalumab[Title/Abstract]) OR atezolizumab[Title/Abstract]) OR nivolumab[Title/Abstract]) OR pembrolizumab[Title/Abstract]) OR "Ipilimumab"[Mesh]) OR "durvalumab" [Supplementary Concept]) OR "avelumab" [Supplementary Concept]) OR "atezolizumab" [Supplementary Concept]) OR "Nivolumab" [Mesh]) OR "pembrolizumab" [Supplementary Concept])) AND ((((cancer[Title/Abstract]) OR (cancer[MeSH Terms])) OR ((carcinoma[Title/Abstract]) OR (carcinoma[MeSH Terms]))) OR ((neoplasm[Title/Abstract]) OR (neoplasm[MeSH Terms])))) AND ((((((((PD1[Title/Abstract]) OR (PD1[MeSH Terms])) OR (Programmed Death 1[MeSH Terms])) OR (Programmed Death 1[Title/Abstract])) OR (PD-L1[Title/Abstract])) OR (PD-L1[MeSH Terms])) OR (Programmed Death Ligand 1[MeSH Terms])) OR (Programmed Death Ligand 1[Title/Abstract])) OR (IL-6[Title/Abstract])) OR (IL-6[MeSH Terms])) OR ((biomarker[Title/Abstract]) OR (biomarker[MeSH Terms])))) AND ((((((cost benefit analysis[Title/Abstract]) OR (cost benefit analysis[MeSH Terms])) OR ((cost effectiveness[MeSH Terms]) OR (cost effectiveness[Title/Abstract]))) OR ((cost utility[Title/Abstract]) OR (cost utility[MeSH Terms]))) OR ((economic evaluation[Title/Abstract]) OR (economic evaluation[MeSH Terms]))) OR ((quality of life[Title/Abstract]) OR (quality of life[MeSH Terms]))) Sort by: Publication Date

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Embase

(('cost benefit analysis':ti,ab,kw OR 'cost benefit analysis'/exp) AND [embase]/lim OR (('cost effectiveness':ti,ab,kw OR 'cost effectiveness'/exp) AND [embase]/lim) OR (('cost utility':ti,ab,kw OR 'cost utility'/exp) AND [embase]/lim) OR (('economic evaluation':ti,ab,kw OR 'economic evaluation'/exp) AND [embase]/lim) OR (('quality of life':ti,ab,kw OR 'quality of life'/exp) AND [embase]/lim)) AND ('biomarkers':ti,ab,kw OR 'biomarkers'/exp OR 'pd1':ti,ab,kw OR 'pd1'/exp OR 'programmed death 1':ti,ab,kw OR 'programmed death 1'/exp OR 'pd-11':ti,ab,kw OR 'pd-11' OR 'programmed death ligand 1':ti,ab,kw OR 'programmed death ligand 1'/exp OR 'il-6':ti,ab,kw OR 'il-6'/exp OR 'interleukin-6':ti,ab,kw OR 'interleukin-6'/exp) AND ('antibodies monoclonal':ti,ab,kw OR 'antibodies monoclonal'/exp) AND ('immunotherapy':ti,ab,kw OR 'immunotherapy'/exp) AND ('pembrolizumab':ti,ab,kw OR 'nivolumab/ipilimumab' OR 'ipilimumab' OR 'durvalumab' OR 'avelumab' OR 'atezolizumab' OR 'nivolumab' OR 'pembrolizumab'/exp) AND [embase]/lim AND (('neoplasms':ti,ab,kw OR 'neoplasms'/exp) AND [embase]/lim OR (('cancer':ti,ab,kw OR 'cancer'/exp) AND [embase]/lim) OR (('carcinoma':ti,ab,kw OR 'carcinoma'/exp) AND [embase]/lim))

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
Title			
Identification	<u>#1a</u>	Identify the report as a protocol of a systematic review	1
Update	<u>#1b</u>	If the protocol is for an update of a previous systematic	1
		review, identify as such	
	For pee	er review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2 3	Registration			
4 5		<u>#2</u>	If registered, provide the name of the registry (such as	2
6 7			PROSPERO) and registration number	
8 9 10 11	Authors			
12 13 14	Contact	<u>#3a</u>	Provide name, institutional affiliation, e-mail address of all	1
14 15 16			protocol authors; provide physical mailing address of	
17 18			corresponding author	
19 20	Contribution	#3b	Describe contributions of protocol authors and identify the	9
21 22 23	Contribution	<u></u>	guarantor of the review	0
24 25			guaranter of the review	
26 27	Amendments			
28 29		<u>#4</u>	If the protocol represents an amendment of a previously	5-6
30 31 32			completed or published protocol, identify as such and list	
33 34			changes; otherwise, state plan for documenting important	
35 36			protocol amendments	
37 38				
39 40 41	Support			
41 42 43	Sources	<u>#5a</u>	Indicate sources of financial or other support for the review	10
44 45 46	Sponsor	<u>#5b</u>	Provide name for the review funder and / or sponsor	10
47 48 49	Role of sponsor or	<u>#5c</u>	Describe roles of funder(s), sponsor(s), and / or	10
50 51	funder		institution(s), if any, in developing the protocol	
52 53 54 55 56	Introduction			
57 58				
59 60		For peer	review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

Rationale	<u>#6</u>	Describe the rationale for the review in the context of what is already known	4-5
Objectives	<u>#7</u>	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions,	5
		comparators, and outcomes (PICO)	
Methods			
Eligibility criteria	<u>#8</u>	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	<u>#9</u>	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6
Search strategy	<u>#10</u>	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records - data management	<u>#11a</u>	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Study records - selection process	<u>#11b</u>	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
	For peer	review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	Study records -	<u>#11c</u>	Describe planned method of extracting data from reports	7-8
3 4	data collection		(such as piloting forms, done independently, in duplicate),	
5 6	process		any processes for obtaining and confirming data from	
7 8 9			investigators	
10 11 12 13 14	Data items	<u>#12</u>	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned	6-7
15 16			data assumptions and simplifications	
17 18 19	Outcomes and	<u>#13</u>	List and define all outcomes for which data will be sought,	6-7
20 21 22	prioritization		including prioritization of main and additional outcomes, with	
22 23 24 25			rationale	
26 27	Risk of bias in	<u>#14</u>	Describe anticipated methods for assessing risk of bias of	7-8
28 29 30	individual studies		individual studies, including whether this will be done at the	
31 32			outcome or study level, or both; state how this information	
33 34			will be used in data synthesis	
35 36 37	Data synthesis	<u>#15a</u>	Describe criteria under which study data will be	7-8
38 39 40			quantitatively synthesised	
41 42	Data synthesis	<u>#15b</u>	If data are appropriate for quantitative synthesis, describe	7-8
43 44 45			planned summary measures, methods of handling data and	
46 47			methods of combining data from studies, including any	
48 49 50			planned exploration of consistency (such as I2, Kendall's τ)	
51 52	Data synthesis	<u>#15c</u>	Describe any proposed additional analyses (such as	7-8
53 54 55			sensitivity or subgroup analyses, meta-regression)	
56 57				
58 59 60		For peer	review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2	Data synthesis	<u>#15d</u>	If quantitative synthesis is not appropriate, describe the type	7-8
3 4 5			of summary planned	
6 7 8	Meta-bias(es)	<u>#16</u>	Specify any planned assessment of meta-bias(es) (such as	7-8
9			publication bias across studies, selective reporting within	
10 11 12 13			studies)	
14 15	Confidence in	<u>#17</u>	Describe how the strength of the body of evidence will be	7-8
16 17	cumulative		assessed (such as GRADE)	
18 19 20	evidence			
21 22 23	The PRISMA-P che	cklist is (distributed under the terms of the Creative Commons Attribution Licer	ise
24 25	CC-BY 4.0. This che	ecklist w	as completed on 17. December 2020 using <u>https://www.goodreports.c</u>	org/,
26 27 28	a tool made by the	EQUATO	<u>DR Network</u> in collaboration with <u>Penelope.ai</u>	
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Cost Effectiveness of Treatment Optimization with Biomarkers for Immunotherapy in Solid Tumors: A Systematic Review Protocol

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Keywords:	HEALTH ECONOMICS, ONCOLOGY, Breast tumours < ONCOLOGY, Kidney tumours < ONCOLOGY

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5 6	1	Cost Effectiveness of Treatment Optimization with Biomarkers for
7 8 9	2	Immunotherapy in Solid Tumors: A Systematic Review Protocol
10 11 12	3	Sara Mucherino ¹ , Valentina Lorenzoni ² , Valentina Orlando ¹ , Isotta Triulzi ² , Marzia Del Re ³ , Annalisa
13 14	4	Capuano ⁴ , Romano Danesi ³ , Giuseppe Turchetti ² , Enrica Menditto ^{1,*}
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44 45	19	Email: enrica.menditto@unina.it
46 47	20	
48 49	21	Word count: 2176
50 51	22	
52 53	23	
55 54 55 56 57 58 59 60	24	Keywords: Immunotherapy; Biomarkers; Cost effectiveness; Economic evaluation; Quality of life

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ABSTRACT

Introduction: The combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies. This study protocol of a systematic review is aimed to describe available literature evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumour as tools for customizing immunotherapy to identify what further research needs.

Methods and analysis: A systematic review of the literature will be carried out according to the PRISMA statement guidelines. PubMed and Embase will be queried from June 2010 to June 2021. The PICOS Model will be applied: target population (P) will be patients with solid tumors treated with immune checkpoint inhibitors (ICIs); the interventions (I) will be test of the immune checkpoint predictive biomarkers; the comparator (C) will be any other targeted or non-targeted therapy; outcomes evaluated will be health economic and clinical implications assessed in terms of incremental cost-effectiveness ratio (ICERs), net health benefit, net monetary benefit, life years gained (LYG), quality of life (QALY), etc. (O); study (S) considered will be economic evaluations reporting cost-effectiveness analysis, cost-utility analysis, net-monetary benefit. The quality of the evidence will be graded according to GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Ethics and dissemination: This systematic review will assess the cost effectiveness implications of using biomarkers in the immunotherapy with ICIs, which may help to understand whether this approach is widespread in real clinical practice. This research is exempt from ethics approval because the work is carried out on published documents. We will disseminate this protocol in a related peer-reviewed journal.

47 PROSPERO registration number: CRD42020201549

ARTICLE SUMMARY Strengths and limitations of this study The use of predictive biomarkers in the therapy with immune checkpoint inhibitors can help target therapy in some solid tumors, hence, the combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies. This is the first systematic review which will specifically describe available literature • evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumor as tools for customizing immunotherapy to identify what further research needs. An in-depth search strategy will be applied to two major scientific databases, without • geographic and conducted by a multidisciplinary team with expertise in the field. 28 58 The quality of studies included and related level of evidence will be assessed quality using the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) checklist and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

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In recent years, the pharmaceutical industry has seen a shift from the blockbuster model, in which drugs are developed for an ideal patient, to a nichebuster model, in which drugs developed specifically for specific patient groups ^{1,2}. In this context, the combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies ³⁻⁷. The US Food and Drug Administration (FDA) regularly publishes and updates a list of drugs for

which it is suggested or mandatory to associate a genetic-molecular test⁸. The importance of predictive biomarkers is related to optimizing patient benefits, reducing the risk of toxicity and leading combined approaches ⁹. Particularly, for some drugs the test result defines whether or not to administer, for others it establishes the most appropriate dosage of therapy. Among the 166 biomarker-drug combinations reported by the FDA, in only 29% (48 combinations) of cases, results obtained from biomarker test have an impact on the physician's choice to prescribe or not prescribe a particular drug. ¹⁰. In Italy, 34 of those 48 combinations are approved for use and among these, about 80% find application in oncology particularly for solid tumors treatment ¹⁰. The clinical development of checkpoint inhibitor-based immunotherapy has ushered in an exciting era of anticancer therapy. Since the FDA approval of ipilimumab (human IgG1 k anti-CTLA-4 monoclonal antibody) in 2011, six more immune checkpoint inhibitors (ICIs) have been approved for cancer therapy. Programmed Death-1 (PD-1) inhibitors nivolumab, pembrolizumab, cemiplimab and Programmed Death Ligand-1 (PDL-1) inhibitors atezolizumab, avelumab, and durvalumab are in the current list of the approved agents in addition to ipilimumab ¹¹. The importance of predictive biomarkers is related to the optimization of benefits in patients treated with immunotherapy, by reducing the risk of toxicity and leading combined approaches. Durable responses have been observed in patients with various malignant neoplasms ¹².

This study protocol is part of a funded Italian National Research Project based on the hypothesis that the identification of predictive biomarkers can improve the understanding of the mechanisms underlying the complex interactions between the immune system and cancer thus guiding clinicians to optimize therapy with monoclonal anti-PD-1 and anti-PD-L1 antibodies. Hence, among the already known biomarkers, the overexpression of PD-L1 is an important and widely explored predictive biomarker for the response to PD-1/PD-L1 antibodies ^{4,13}. Direct assessment of PD-L1 expression on tumor cells is a logical biomarker for the prediction of treatment response to anti-PD-1 or anti-PD-L1 therapies ^{14,15}. The use of PD-1 and PDL-1 as predictive biomarkers can help target therapy in some solid tumors, including renal and non-small cell lung cancer (NSCLC) ¹⁶⁻¹⁸. Nivolumab and pembrolizumab and an PD-L1 inhibitor, atezolizumab, have also been approved by the Italian Medicines Agency (AIFA), for the treatment of patients with NSCLC ¹⁹⁻²¹. A targeted approach to treatment using predictive biomarkers has the potential not only to maximize clinical benefit in respect to not-targeted therapy, but also to improve cost-effectiveness and reduce the economic burden of the disease ²². As the global impact of these types of cancers continues to grow, the implementation of new and more effective therapies becomes important but also overly expensive ²³. Therefore, the analysis of the cost-effectiveness and economic impact of the use of biomarkers upstream of the choice of the specific therapy represents an imperative to validate its effectiveness, the eventual relationship with the quality of life, patient reported outcomes (PROMs), and sustainability ²⁴. However, there is no existing peer-reviewed or published synthesis summarizing the impact of predictive biomarkers use in oncological treatment in healtheconomics terms. This is the protocol of a systematic review aimed at describing available literature about the costeffectiveness, cost-utility or net-monetary benefit of the use of predictive biomarkers in solid

tumor treated with ICIs as tools for customizing immunotherapy; the final goal of the study is to

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3 109 4 5	help decision-makers and clinicians identify the most effective and sustainable options and
6 110 7	identify further research needs.
8 111 9 10	Methods and Analysis
11 112 12	The PRISMA-P 2015 (Preferred Reporting Items for Systematic Review and Meta-Analysis
¹³ 113 14 15	Protocols) checklist was used to develop the present study protocol. Modifications in the item
16 114 17	sequencies were done where appropriate ²⁵ .
¹⁸ 115 19 20	Information sources
₂₁ 116 22	A systematic review of the literature will be carried out according to the PRISMA 2020 (Preferred
23 117 24 25	Reporting Items for Systematic reviews and Meta-Analyses) statement guidelines ²⁶ . For the
26 118 27	present review, the identification of relevant studies will be achieved by searching electronic
28 119 29	databases of the published literature. In details Medical Literature Analysis and Retrieval System
³⁰ 31 32	Online (via PubMed/MEDLINE) and Embase (via Ovid) were queried from June 2010 to June 2021.
52	
33 121 34	Search strategy
33 121 34 35 122 36	Search strategy First, the search strategy will be developed and completed in PubMed, and then the same strategy
33 121 34 35 122 36 37 38 123 39	
33 121 34 35 122 36 37 38 123 39 40 124 41	First, the search strategy will be developed and completed in PubMed, and then the same strategy
33 121 34 35 122 36 123 37 38 123 39 40 124 41 42 43 125 44	First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to Embase. The search strategy was developed according to the PICOS model and
33 121 34 35 122 36 122 37 38 123 39 40 124 41 42 43 125 44 45 126 46 47	First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to Embase. The search strategy was developed according to the PICOS model and based on the existing literature and finally revised by clinicians. More in detail, the search strategy
33 121 34 35 122 36 37 38 123 39 40 124 41 42 43 125 44 45 126	First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to Embase. The search strategy was developed according to the PICOS model and based on the existing literature and finally revised by clinicians. More in detail, the search strategy will combine headings and keywords listed in Table 1 answering each questions of the PICOS
33 121 34 122 36 122 37 123 38 123 39 124 40 124 41 125 44 125 44 125 45 126 46 47 49 50 128 51 126	First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to Embase. The search strategy was developed according to the PICOS model and based on the existing literature and finally revised by clinicians. More in detail, the search strategy will combine headings and keywords listed in Table 1 answering each questions of the PICOS Model. Those terms combined with boolean operators AND/OR will be searched both as Mesh
33 121 34 35 122 36 123 37 38 123 39 40 124 41 42 43 125 44 45 126 46 47 48 127 49 50 128 51 52 129	First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to Embase. The search strategy was developed according to the PICOS model and based on the existing literature and finally revised by clinicians. More in detail, the search strategy will combine headings and keywords listed in Table 1 answering each questions of the PICOS Model. Those terms combined with boolean operators AND/OR will be searched both as Mesh Term (PubMed) or Emtree (Embase) both in title and abstract. The full search strategy that will be
 33 121 34 35 122 36 37 38 123 39 40 124 41 42 43 125 44 45 126 46 47 48 127 49 50 128 51 52 120 	First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to Embase. The search strategy was developed according to the PICOS model and based on the existing literature and finally revised by clinicians. More in detail, the search strategy will combine headings and keywords listed in Table 1 answering each questions of the PICOS Model. Those terms combined with boolean operators AND/OR will be searched both as Mesh Term (PubMed) or Emtree (Embase) both in title and abstract. The full search strategy that will be used is reported in Table 1. More in detail, the search syntax for the two databases are presented

6

1 2	
$\begin{array}{c}3\\4\end{array}$ 132	- Patient (P): Patients with solid tumors treated with immune checkpoint inhibitors
5 6 133 7	(monotherapy or combination therapy): nivolumab, pembrolizumab, ipilimumab,
, 8 134 9	atezolizumab, durvalumab, avelumab, cemiplimab;
10 11 135 12	- Intervention (I): Test of the immune checkpoint predictive biomarkers, such as PD1, PDL-1
¹³ 136 14	CTLA4, IL-6.
15 16 137 17	- Comparator (C): Any other targeted or non-targeted therapy
¹⁸ 138 19	- Outcomes (O): health-economic outcomes (Incremental Cost-effectiveness, ICERs, net
20 21 139 22	health benefit, net monetary benefit, life years,LYs, quality adjusted life years, QALYs, etc.)
23 140 24	will be evaluated between immune checkpoint inhibitors therapy
25 26 141 27	- Study design (S): health-economic evaluations reporting cost-effectiveness analysis, cost-
28 142 29	utility analysis, net-monetary benefit.and conducted within clinical trials or observational
30 31 143 32	studies.
33 144 34	All peer-reviewed original articles about health economics evaluation related to biomarkers use
³⁵ 36 37	published between June 2010 to June 2021 and responding to the PICOS will be considered for
38 146 39	inclusion in the study. On the other hand, conference proceedings, rationale and/or study
40 41 42	protocol, letters, editorials, commentaries, case reports, case study, case series, review,
42 43 148 44	consensus, guidelines, expert opinions and grey literature will be not included (exclusion criteria).
⁴⁵ 149 46	Moreover, language restriction will be applied to the research, as fundamental to the eligibility of
47 48 150 49	the study will be the availability of the papers' full text published in English.
50 151 51	Any identified literature reviews will be used as a source for finding additional articles not present
52 53 54	in our dataset.
55 153 56	Inclusion and exclusion criteria are summarized in Table 2.
57 58 59	The quality of the economic evaluations that will be included in the study will be assessed through
60 155	the CHEERS checklist ²⁷ .

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2 3 4	156	Selection and data process
5 6 7	157	The references will be collected using the software program Reference Manager, ver. 12 (Institute
-	158	for Scientific Information, Berkeley, CA). All references will be screened for relevance and, those
	159	potentially eligible will be assessed, according to the inclusion/exclusion criteria, accepted or
12 13 14	160	rejected, as appropriate.
15 16	161	Four researchers will double screen titles and abstract to discard irrelevant ones in the first
17 18 19	162	screening phase. Then, full texts of the records selected from the previous step will be retrieved
20 21	163	and double screened to assess the eligibility for the inclusion in the qualitative analysis. Finally, the
22 23 24	164	references obtained will be validated by clinicians and researchers in the fields of pharmacology,
25 26	165	immunotherapy, pharmacovigilance, pharmacoeconomics. Reference lists from included records
27 28 29	166	will be also screened to identify additional papers (backward reference searching) as for other
	167	studies citing that paper (forward citation searching).
32 33 34	168	The type of information that will be extracted from each reference included in the qualitative
	169	analysis and collected into a dedicated file are reported in Table 3. The structure of the table that
38	170	will be used to describe results obtained is shown in Appendix 2. Changes to the variables in the
39 40 41	171	table could be made in the final revision based on the evidence that emerged. Quality of studies
42 43	172	will be assessed using the Cheers checklist and finally, the quality of the evidence will be graded
44 45 46	173	according to GRADE (Grading of Recommendations Assessment, Development and Evaluation)
	174	system ²⁸ , assessing heterogeneity, consistency and risk of bias.
	175	All studies and their individual elements will be graded in terms of adequacy of the study
51 52 53	176	regarding the research question, risk of selection bias, measurement of exposure and assessment
55	177	of outcomes. Disagreements will be resolved by third reviewers.
56 57 58	178	Study registration
59 60		

1	
2 ³ 179 4	The study is prospectively registere
5 6 180 7	Systematic Reviews (CRD42020201
, 8 181 9	Data description
10 11 182 12	This review will systematically desc
13 183 14	predictive biomarkers used in immu
15 16 17	biomarkers to monitor the clinical o
18 185 19	inhibitors (ICIs) may help to reduce
²⁰ 186 21	thus also improving quality of life. F
22 23 187 24	conducted on these immune bioma
²⁵ 188 26	cost-effectiveness (or cost-utility, n
27 28 189 29	predict clinical outcome and to redi
30 190 31	effective and cost-effective therape
³² 33 191 34	Accordingly, main strength of the p
35 192 36	already know on immune biomarke
³⁷ 193 38 39	cancer patients treated with ICIs. A
40 194 41	their real use through economic eva
42 43	cost effectiveness ratio or cost utili
44 45 196 46	expected from the systematic revie
47 197 48	consider the study design such as c
49 50 198 51	analysis, highlighting first the meth
52 199 53	used in cancer patients their cost-e
54 55 200 56	threshold. Appendix 1 shows the hy
57 201 58	Other systematic reviews on bioma
⁵⁹ 202 60	but they are specifically focused on

The study is prospectively registered in PROSPERO, the International Prospective Register of
 Systematic Reviews (CRD42020201549).

This review will systematically describe the extent of available evidences investigating the predictive biomarkers used in immunotherapy and their health-economic impact. The use of biomarkers to monitor the clinical outcome of patients treated with immune check-point inhibitors (ICIs) may help to reduce the incidence of adverse events related to the immune system thus also improving quality of life. Furthermore, from the pharmaco-economic evaluations already conducted on these immune biomarkers we expect to find that their use is associated with better cost-effectiveness (or cost-utility, net-monetary benefit) ratio due to their improved ability to predict clinical outcome and to redirect non-reactive patients towards alternative and more effective and cost-effective therapeutic approaches.

Accordingly, main strength of the present work will consist in having an overview on what is already know on immune biomarkers use to guide choice and personalization of treatment for cancer patients treated with ICIs. Also, we will try to gather considerations about the diffusion of their real use through economic evaluations that report their outcomes in terms of incremental cost effectiveness ratio or cost utility ratio and patients' health related quality of life. So, results expected from the systematic review will strictly depend on the study design used. We aim to consider the study design such as cost-effectiveness analysis, cost-utility analysis, budget impact analysis, highlighting first the methodology used in the study and to report for each biomarker used in cancer patients their cost-effectiveness, willingness to pay (WTP) with the reference threshold. Appendix 1 shows the hypothetical structure of the data synthesis. Other systematic reviews on biomarkers were already published evaluating cost-related aspects

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1		
4	203	Particularly, our study differs to that of Oosterhoff et al ²⁹ as they aimed to widely investigate the
5 6 7	204	methodological characteristics of economic evaluations on biomarkers and examine economic
	205	aspect. To the best of our knowledge this is the first systematic review published broadly
10 11 12	206	exploring the health-economic impact of predictive biomarkers specifically used in treatment of
13 14	207	solid tumors with ICIs comparing them with other targeted and non-targeted therapeutic
15 16 17	208	strategies that do not include the use of the reference biomarker.
18 19		A potential limitation relates to the heterogeneity associated to the study conducted on
21	210	biomarkers. Accordingly, between-study heterogeneity may not support the conduct of
22 23 24	211	quantitative meta-analysis. Based on the results obtained, any heterogeneity of the studies will be
26	212	managed by grouping, if feasible, the included records into different classes such as solid tumor
27 28 29	213	type (e.g. breast cancer, bladder cancer, cervical cancer, colon cancer, head and neck cancer,
31	214	hodgkin lymphoma, liver cancer, lung cancer, renal cell cancer, skin cancer, stomach cancer, rectal
32 33 34	215	cancer) and study design type (e.g. cost-effectiveness analysis, cost-utility analysis, net-monetary
35 36		benefit). The same variables present in Appendix 2 will be evaluated for each group and subgroup.
37 38	217	Patient and Public Involvement
39 40 41	218	No patients involved.
42	219	Ethics and dissemination
43 44 45	220	Ethics and dissemination
46 47 48	221	Results of the systematic review will be published in a peer-reviewed journal and disseminated at
49 50	222	a range of health research conferences. The systematic review is part of a larger project funded by
51 52 53	223	PRIN 2017 whose aims include the identification of biomarkers able to predict
54 55	224	immunotherapeutic-related adverse drug reactions and the potential cost-effectiveness and
56 57 58	225	quality of life of personalized therapies based on advanced tools.
59 60		

Finally, this systematic review will assess the cost effectiveness implications of using biomarkers in
in cancer patients treated with ICIs compared to any other target therapy or conventional therapy
without the use of biomarkers. This review may help to understand if this approach may be costeffective in clinical practice and how the customization of therapy, can actually affect a decrease in
costs for the health care systems.

Author contributions

21 233 E.M. designed and conceptualised this review. S.M., V.O., V.L., I.T. drafted the protocol. All authors were involved in checking various steps of the search strategy, including keywords, as well as the 26 235 final version of the protocol. S.M, V.L. and I.T. were involved in the definition of specific criteria for the extraction of information from studies included and in the development of the strategy for the qualitative data analysis. M.D.R., A.C., R.D. and G.T. were involved in establishing eligibility criteria 31 237 and data extraction forms. G.T. and E.M. supervised all work stages. R.D. was the funding acquisition supervisor. All authors reviewed and agreed the final version of the manuscript. 36 239 Funding 41 241 This research is funded by Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) in the framework of the PRIN Project 2017, grant number 2017NR7W5K.

49 244 **Conflicts of interest**

The authors have no conflicts of interest to declare.

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58	
59	
60	

Table 1.	Search strategy
Query	Keywords (MeshTerms/Emtree OR Title and Abstract)
#1	Antibodies, monoclonal
#2	Immunotherapy
#3	(nivolumab/ipilimumab[Title/Abstract]) OR ipilimumab[Title/Abstract]) OR durvalumab[Title/Abstract]) OR atezolizumab[Title/Abstract]) OR nivolumab[Title/Abstract]) O pembrolizumab[Title/Abstract]) OR "Ipilimumab"[Mesh]) OR "durvalumab" [Supplementary Concept]) OR "avelumab" [Supplementary Concept]) OR "atezolizumab" [Supplementary Concept]) OR "Nivolumab"[Mesh]) OR "pembrolizumab" [Supplementary Concept]
#4	Immune checkpoint inhibitor
#5	Neoplasms
#6	Cancer
#7	Carcinoma
#8	Tumor OR Toumor
#9	Target therapy OR Chemotherapy
#10	Biomarkers OR PD-1 OR Programmed Death 1 OR PD-L1 OR Programmed Death Ligand 1 OR II OR Interleukin-6 OR CTLA-4
#11	Cost benefit analysis
#12	Cost effectiveness
#13	Cost utility
#14	Economic evaluation
#15	Quality of life
#16	1 OR 2 OR 3 OR 4
#17	5 OR 6 OR 7 OR 8
#18	11 OR 12 OR 13 OR 14 OR 15
#19	16 AND 17
#20	19 AND 9 AND 10
#21	20 AND 18

Table 2. Synthesis of inclusion and exclusion criteria **Selection Criteria Inclusion Criteria Exclusion Criteria** Non-English Language study type English Time limit (years) < 2010 2010 - 2021 and , comi evalut. Conference proceedings, rationale and/or design, letters, editorials, commentaries, Published and peer-reviewed Study design case reports, case study, case series, review, consensus, guidelines, expert opinions, grey 20 345

Data extraction	Description
Reference	All paper identification details
Publication year	Year of publication of the paper
Perspective of the analysis	National health service, society, government, patient
Type of costs	Direct healthcare costs, direct non-health costs, indirect costs, intangible costs
Reference year of costs	Specific year of reference of costs if reported
Patient Diagnosis	Each status of: breast cancer, bladder cancer, cervical cancer, colon cancer, head and neck cancer, hodgkin lymphoma, liver cancer, lung cancer, renal cell cancer (a type of kidney cancer), skin cancer, stomach cancer, rectal cancer and any solid tumor that i not able to repair errors in its DNA that occur when the DNA is copied.
Patient (P)	Patients with solid tumors treated with immune checkpoint inhibitors (monotherapy o combination therapy): nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, avelumab, cemiplimab
Intervention (I)	Test of the immune checkpoint predictive biomarkers, such as PD1, PDL-1 CTLA4, IL-6.
Comparator (C)	Any other targeted or non-targeted therapy
Outcomes (O)	health-economic outcomes (Incremental cost-effectiveness ratio, ICERs, net health benefit, net monetary benefit, LYs, QALYs)
Study design (S)	Health-economic evaluations reporting cost-effectiveness analysis, cost-utility analysis, net-monetary benefit

Appendix 1

Search syntax in different databases

PubMed

(((((Antibodies, monoclonal[MeSH Terms]) OR (Antibodies, monoclonal[Title/Abstract])) OR ((immunotherapy[MeSH Terms]) OR (immunotherapy[Title/Abstract]))) OR ((nivolumab/ipilimumab[Title/Abstract]) OR ipilimumab[Title/Abstract]) OR durvalumab[Title/Abstract]) OR atezolizumab[Title/Abstract]) OR nivolumab[Title/Abstract]) OR pembrolizumab[Title/Abstract]) OR "Ipilimumab"[Mesh]) OR "durvalumab" [Supplementary Concept]) OR "avelumab" [Supplementary Concept]) OR "atezolizumab" [Supplementary Concept]) OR "Nivolumab"[Mesh]) OR "pembrolizumab" [Supplementary Concept]) OR "immune checkpoint inhibitor[Title/Abstract])) AND ((((cancer[Title/Abstract]) OR (cancer[MeSH Terms])) OR ((carcinoma[Title/Abstract]) OR (carcinoma[MeSH Terms]))) OR ((neoplasm[Title/Abstract]) OR (neoplasm[MeSH Terms]))) OR (((tumor[Title/Abstract]) OR (tumor[MeSH Terms])) OR ((tumour[Title/Abstract]) OR (tumour[MeSH Terms])))) AND ((((((((PD1[Title/Abstract]) OR (PD1[MeSH Terms])) OR (Programmed Death 1[MeSH Terms])) OR (Programmed Death 1[Title/Abstract])) OR (PD-L1[Title/Abstract])) OR (PD-L1[MeSH Terms])) OR (Programmed Death Ligand 1[MeSH Terms])) OR (Programmed Death Ligand 1[Title/Abstract])) OR (IL-6[Title/Abstract])) OR (IL-6[MeSH Terms])) OR ((biomarker[Title/Abstract]) OR (biomarker[MeSH Terms])))) AND (((Target therapy [Title/Abstract]) OR (Target therapy [MeSH Terms])) OR ((Chemotherapy [Title/Abstract]) OR (Chemotherapy [MeSH Terms]))) AND ((((((cost benefit analysis[Title/Abstract]) OR (cost benefit analysis[MeSH Terms])) OR ((cost effectiveness[MeSH Terms]) OR (cost effectiveness[Title/Abstract]))) OR ((cost utility[Title/Abstract]) OR (cost utility[MeSH Terms]))) OR ((economic evaluation[Title/Abstract]) OR (economic evaluation[MeSH

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Terms]))) OR ((quality of life[Title/Abstract]) OR (quality of life[MeSH Terms]))) Sort by: Publication Date

Embase

(('cost benefit analysis':ti,ab,kw OR 'cost benefit analysis'/exp) AND [embase]/lim OR (('cost effectiveness':ti,ab,kw OR 'cost effectiveness'/exp) AND [embase]/lim) OR (('cost utility':ti,ab,kw OR 'cost utility'/exp) AND [embase]/lim) OR (('economic evaluation':ti,ab,kw OR 'economic evaluation'/exp) AND [embase]/lim) OR (('quality of life':ti,ab,kw OR 'quality of life'/exp) AND [embase]/lim)) AND ('biomarkers':ti,ab,kw OR 'biomarkers'/exp OR 'pd1':ti,ab,kw OR 'pd1'/exp OR 'programmed death 1':ti,ab,kw OR 'programmed death 1'/exp OR 'pd-l1':ti,ab,kw OR 'pd-l1' OR 'programmed death ligand 1':ti,ab,kw OR 'programmed death ligand 1'/exp OR 'il-6':ti,ab,kw OR 'il-6'/exp OR 'interleukin-6':ti,ab,kw OR 'interleukin-6'/exp) OR ('target therapy': ti,ab,kw OR 'target therapy'/exp OR 'chemotherapy': ti,ab,kw OR 'chemotherapy'/exp) AND ('antibodies monoclonal':ti,ab,kw OR 'antibodies monoclonal'/exp) AND ('immunotherapy':ti,ab,kw OR 'immunotherapy'/exp) AND ('pembrolizumab':ti,ab,kw OR 'nivolumab/ipilimumab' OR 'ipilimumab' OR 'durvalumab' OR 'avelumab' OR 'atezolizumab' OR 'nivolumab' OR 'pembrolizumab'/exp) AND ('immune checkpoint inhibitor':ti,ab,kw OR 'immune checkpoint inhibitor'/exp) AND [embase]/lim AND (('neoplasms':ti,ab,kw OR 'neoplasms'/exp) AND [embase]/lim OR (('cancer':ti,ab,kw OR 'cancer'/exp) AND [embase]/lim OR (('tumor':ti,ab,kw OR 'tumor'/exp) AND [embase]/lim OR (('tumour':ti,ab,kw OR 'tumour'/exp) AND [embase]/lim) OR (('carcinoma':ti,ab,kw OR 'carcinoma'/exp) AND [embase]/lim))

Appendix 2

Assumed tables structure for data synthesis

Appendix Table 1. Characteristics of included studies

Study Reference	Publication year	Country	Population	Comparators	Type of biomarker	Health-economic outcomes	Threshold (WTP)	Conclusions

Appendix Table 2. Methodology of the included studies

Study Reference	Study design	Type of Economic evaluation	Perspective used in the analysis	Type of costs included	Reference year of costs	Effectiveness measures

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
Title			
Identification	<u>#1a</u>	Identify the report as a protocol of a systematic review	1
Update	<u>#1b</u>	If the protocol is for an update of a previous systematic	1
		review, identify as such	
	For pee	r review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3	Registration			
4 5		<u>#2</u>	If registered, provide the name of the registry (such as	2
6 7			PROSPERO) and registration number	
8 9 10 11	Authors			
12 13 14	Contact	<u>#3a</u>	Provide name, institutional affiliation, e-mail address of all	1
14 15 16			protocol authors; provide physical mailing address of	
17 18			corresponding author	
19 20		#01-		0
21 22	Contribution	<u>#3b</u>	Describe contributions of protocol authors and identify the	9
23 24			guarantor of the review	
25 26	Amendments			
27 28				5.0
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31 32			completed or published protocol, identify as such and list	
33 34 25			changes; otherwise, state plan for documenting important	
35 36 27			protocol amendments	
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39 40 41	Support			
41 42 43	Sources	<u>#5a</u>	Indicate sources of financial or other support for the review	10
44 45 46 47	Sponsor	<u>#5b</u>	Provide name for the review funder and / or sponsor	10
48 49	Role of sponsor or	<u>#5c</u>	Describe roles of funder(s), sponsor(s), and / or	10
50 51 52	funder		institution(s), if any, in developing the protocol	
52 53 54 55 56 57	Introduction			
57 58 59				
60		For peer	review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	Rationale	<u>#6</u>	Describe the rationale for the review in the context of what is already known	4-5
	Objectives	<u>#7</u>	Provide an explicit statement of the question(s) the review	5
			will address with reference to participants, interventions,	
			comparators, and outcomes (PICO)	
	Methods			
	Eligibility criteria	<u>#8</u>	Specify the study characteristics (such as PICO, study	6-7
			design, setting, time frame) and report characteristics (such	
			as years considered, language, publication status) to be	
			used as criteria for eligibility for the review	
26 27	Information	#9	Describe all intended information sources (such as	5-6
28 29 30	sources		electronic databases, contact with study authors, trial	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60			registers or other grey literature sources) with planned dates	
			of coverage	
	Socrab strategy	#10	Droppet draft of poprohistratory to be used for at least one	6
	Search strategy	<u>#10</u>	Present draft of search strategy to be used for at least one	6
			electronic database, including planned limits, such that it	
			could be repeated	
	Study records -	<u>#11a</u>	Describe the mechanism(s) that will be used to manage	7-8
	data management		records and data throughout the review	
	Study records -	<u>#11b</u>	State the process that will be used for selecting studies	7-8
	selection process		(such as two independent reviewers) through each phase of	
			the review (that is, screening, eligibility and inclusion in	
			meta-analysis)	
		For peer	review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	Study records -	<u>#11c</u>	Describe planned method of extracting data from reports	7-8
	data collection		(such as piloting forms, done independently, in duplicate),	
	process		any processes for obtaining and confirming data from	
			investigators	
	Data items	<u>#12</u>	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned	6-7
			data assumptions and simplifications	
	Outcomes and	<u>#13</u>	List and define all outcomes for which data will be sought,	6-7
	prioritization		including prioritization of main and additional outcomes, with	
			rationale	
26 27	Risk of bias in	<u>#14</u>	Describe anticipated methods for assessing risk of bias of	7-8
28 29 30	individual studies		individual studies, including whether this will be done at the	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55			outcome or study level, or both; state how this information	
			will be used in data synthesis	
	Data synthesis	<u>#15a</u>	Describe criteria under which study data will be	7-8
			quantitatively synthesised	
	Data synthesis	<u>#15b</u>	If data are appropriate for quantitative synthesis, describe	7-8
			planned summary measures, methods of handling data and	
			methods of combining data from studies, including any	
			planned exploration of consistency (such as I2, Kendall's τ)	
	Data synthesis	<u>#15c</u>	Describe any proposed additional analyses (such as	7-8
			sensitivity or subgroup analyses, meta-regression)	
56 57 58				
59 60		For peer	review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	Data synthesis	<u>#15d</u>	If quantitative synthesis is not appropriate, describe the type	7-8
3 4 5			of summary planned	
6 7 8	Meta-bias(es)	<u>#16</u>	Specify any planned assessment of meta-bias(es) (such as	7-8
9 10			publication bias across studies, selective reporting within	
11 12 13			studies)	
14 15	Confidence in	<u>#17</u>	Describe how the strength of the body of evidence will be	7-8
16 17	cumulative		assessed (such as GRADE)	
18 19 20	evidence			
21 22 23	The PRISMA-P ch	ecklist is	distributed under the terms of the Creative Commons Attribution Lice	ense
24 25	CC-BY 4.0. This cl	necklist w	as completed on 17. December 2020 using <u>https://www.goodreports</u>	<u>.org/,</u>
26 27	a tool made by the	EQUAT	<u>DR Network</u> in collaboration with <u>Penelope.ai</u>	
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