

Supplementary Material

Multi-targeted TKIs in Patients with Advanced Ewing Sarcoma: A Systematic Review and Single-Arm Meta-Analysis

Michelon *et al.*

Table of Contents

Table S1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Checklist for the Manuscript (A), and for the Abstract (B).	3
(A) Manuscript Prisma Checklist	3
(B) Abstract Prisma Checklist	6
Table S2: Full search used in each database.	7
Table S3: Outcomes definition and assessment criteria used across studies.....	8
Table S4: List of excluded studies after full read.....	10
Table S5: Adverse events according to each study.	11
Table S6: Adverse events of studies with data available exclusively for patients with Ewing sarcoma.	13
Table S7: Tools and criteria used to assess the quality of studies included in this meta-analysis.	14
Table S8: Risk of bias assessment.....	16
Table S9: Leave-one-out for overall ORR and DCR.....	18
Figure S1: Response analyses according to the TKI used.....	19
Figure S2: Response analyses including only studies on single-agent TKI.	20
Figure S3: Responses stratified per studies on single-agent TKI versus TKI-combined regimens.	21
Figure S4: Median progression-free survival (mPFS) per TKI agent used.	22
Figure S5: Meta-regression on the impact of the median number of prior lines of therapy on the ORR.	23

Tables

Table S1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Checklist for the Manuscript (A), and for the Abstract (B).

(A) Manuscript Prisma Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Table S1B
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 4, 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5, 6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6

Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages 6, 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pages 6, 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Table S3
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S4

Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 2, 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table S4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 2, 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9
	23b	Discuss any limitations of the evidence included in the review.	Page 12
	23c	Discuss any limitations of the review processes used.	Page 12
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 14
Competing interests	26	Declare any competing interests of review authors.	Page 14

Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 14
---	-----------	--	----------------

NA: not available

(B) Abstract Prisma Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	No
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesise results.	No
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

Table S2: Full search used in each database.

PubMed	Ewing AND ("tyrosine kinase inhibitor" OR TKI OR regorafenib OR cabozantinib OR anlotinib OR sorafenib OR lenvatinib OR fruquintinib OR sunitinib OR apatinib OR imatinib OR pazopanib)
Cochrane	Ewing AND ("tyrosine kinase inhibitor" OR TKI OR regorafenib OR cabozantinib OR anlotinib OR sorafenib OR lenvatinib OR fruquintinib OR sunitinib OR apatinib OR imatinib OR pazopanib)
Embase	ewing:ab,ti AND ('tyrosine kinase inhibitor':ab,ti OR tki:ab,ti OR regorafenib:ab,ti OR cabozantinib:ab,ti OR anlotinib:ab,ti OR sorafenib:ab,ti OR lenvatinib:ab,ti OR fruquintinib:ab,ti OR sunitinib:ab,ti OR apatinib:ab,ti OR imatinib:ab,ti OR pazopanib:ab,ti)

Table S3: Outcomes definition and assessment criteria used across studies.

Study	ORR definition	DCR definition	PFS definition	Scale
Attita 2023 (SARC024)	percentage of patients whose cancer shrinks or disappears after treatment	percentage of patients who achieved ORR or stable disease on treatment	time to treatment start to progression or death	RECIST version 1.1
Duffaud 2023 (REGOBONE)	CR or PR as best response from randomisation	NA	date of randomisation to confirmed radiological progression or death	RECIST version 1.1
Italiano 2020 (CABONE)	PR as best response within 6 months, assessed by RECIST v1.1, based on blinded central radiological review	best overall response defined as CR, PR, or SD, assessed from treatment start until progression, per RECIST v1.1, central review	time from treatment onset to progression or death from any cause, whichever occurred first; censored at last follow-up	RECIST version 1.1
Kokkali 2023	CR or PR, assessed according to RECIST v1.1	SD as best response; among evaluable ES patients	time from cabozantinib initiation to disease progression or death from any cause, assessed per RECIST v1.1.	RECIST v1.1
Soroka 2023	CR or PR, assessed by local investigators	CR + PR + SD lasting > 3 months	time from TKI initiation to disease progression or death, assessed by local investigators	NA
Liu 2021	proportion of patients achieving CR or PR, assessed using RECIST v1.1	proportion of patients achieving CR, PR or SD, assessed using RECIST v1.1.	time from treatment initiation to disease progression or death, assessed using RECIST v1.1	RECIST v1.1
Xie 2018	CR + PR, assessed according to RECIST v1.1.	proportion of patients achieving CR or PR or SD, assessed using RECIST v1.1.	time from start of apatinib to disease progression or death, whichever occurred first	RECIST v1.1
Xu 2021	proportion of patients with CR or PR at 12 weeks, assessed by RECIST v1.1.	proportion of patients with CR or PR or SD at 12 weeks, assessed by RECIST v1.1.	time from study entry until documented progression, protocol violation at investigator discretion, serious	RECIST v1.1

			adverse effect, or death from any cause.	
Wang 2018	CR or PR, assessed according to RECIST v1.1	CR + PR + SD, assessed according to RECIST v1.1.	time from apatinib initiation to disease progression or death	RECIST v1.1
Bodea 2022	Objective response assessed using RECIST v1.1 (CR or PR as best response)	DCR corresponds to CR + PR + SD	NA	RECIST v1.1
Yang 2024	proportion of patients with best overall response of CR or PR, assessed by RECIST v1.1	proportion of patients with best overall response of CR, PR, or SD, assessed by RECIST v1.1	time from first fruquintinib administration to documented progression or death, whichever occurred first	RECIST v1.1
Palmerini 2024	CR + PR per RECIST v1.1 (central radiology review)	CR + PR + SD per RECIST v1.1	time from enrollment to progression or death, assessed by RECIST v1.1 with central review	RECIST v1.1
Chugh 2009	CR or PR by radiologic assessment	NA	time from treatment initiation to disease progression or death	NA
Dela Cruz 2024	CR + PR per RECIST v1.1, assessed at Week 16	CR + PR + stable disease lasting ≥ 7 weeks from first dose.	NA	RECIST v1.1

CR: complete response, DCR: disease control rate; ORR: objective response rate; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

Table S4: List of excluded studies after full read.

Author	TKI	Exclusion reason
Akshintala 2021	Cabozantinib	Unpublished (abstract only available). No Ewing subgroup analysis.
Campbell 2023	Cabozantinib	Phase I trial.
Geoerger 2021	Regorafenib	Phase I trial. No Ewing subgroup analysis.
Bond 2008	Imatinib	No outcomes of interest. No Ewing sarcoma subgroup analysis.
Tang 2022	Anlotinib	<5 Ewing sarcoma patients.
Chuk 2018	Cabozantinib	Phase I trial. <5 Ewing sarcoma patients.
Garnier 2016	Targeted therapies	No targeted therapies subgroup analysis. No Ewing subgroup analysis.
Geller 2018	Axitinib	Phase I trial. <5 Ewing sarcoma patients.
Chen 2018	Apatinib	Unpublished (abstract only available). <5 Ewing sarcoma patients.
Raciborska 2018	Sorafenib	<5 Ewing sarcoma patients.
Gaspar 2017	Lenvatinib	No Ewing subgroup analysis.
Aggerholm 2020	Pazopanib	<5 Ewing sarcoma patients.
Seto 2019	Pazopanib	<5 Ewing sarcoma patients.
Subbiah 2017	Pazopanib	<5 Ewing sarcoma patients.
Wang 2020	Anlotinib	No Ewing subgroup analysis.

Table S5: Adverse events according to each study.

Study	TKI	Toxicity assessment criteria	N	Most common AEs	Grade 1-2 N (%)	Grade 3-4 N (%)	Dose reductions N (%)	Treatment discontinuation N (%)			
Attia 2023/SARC024	Regorafenib	CTCAE v4.03	30	Hypophosphatemia	0	6 (20%)	16 (53.3%)	2 (6.6%)			
				Hypertension	3 (10%)	2 (6.7%)					
				Transaminasemia	0	2 (6.7%)					
Bodea 2022*	Sorafenib	CTCAE	37	Lymphopenia	NA	NA	33 (63.9%)	2 (5.1%)			
				Leucopenia							
				Palmar-plantar erythrodysesthesia							
Chugh 2009	Imatinib	CTCAE v2.0	13	NA	NA	NA	NA	NA			
Dela Cruz 2024	Fruquitinib	CTCAE v4.03	10	Leucopenia	5 (50%)	1 (10%)	NA	3 (7.3%)			
				Proteinuria	5 (50%)	1 (10%)					
				Lymphopenia	2 (20%)	3 (30%)					
Duffaud 2023 (REGOBONE)	Regorafenib	CTCAE v4.0	23	Pain	12 (52.2%)	5 (27.1%)	9 (39.1%)	NA			
				Asthenia	12 (52.2%)	4 (17.4%)					
				Diarrhea	11 (47.8%)	3 (13%)					
Italiano 2020 (CABONE)	Cabozantinib	CTCAE v4.0	45	Fatigue	26 (57.8%)	3 (6.7%)	19 (21%)	12 (14.0%)			
				Diarrhea	23 (51.1%)	2 (4.4%)					
				Mucositis oral	24 (53.3%)	1 (2.2%)					
Kokkali 2023*	Cabozantinib	NA	16	Fatigue	5 (31.3%)	NA	5 (31.3%)	2 (12.5%)			
				Anorexia	3 (18.8%)						
				Transaminasemia	3 (18.8%)						
Liu 2021*	Anlotinib	CTCAE v4.0	48	Hand-foot syndrome	28 (58.3%)	2 (4.2%)	8 (16.7%)	2 (4.2%)			
				Cholesterol elevation	20 (41.6%)	1 (2.1%)					
				Hypertriglyceridemia	18 (37.5%)	1 (2.1%)					
Palmerini 2024*	Sunitinib	CTCAE v4.0	40	Hypertension	19 (47.5%)	6 (15.0%)	1 (2.5%)	7 (17.0%)			
				Fatigue	22 (55.0%)	3 (7.5%)					
				Diarrhea	28 (45.0%)	0					
Soroka 2023 (CanSaRCC)	Regorafenib	CTCAE v5.0	29	NA	NA	NA	13 (44.8%)	NA			
									Mucositis	16 (40.0%)	2 (5.0%)
Soroka 2023 (CanSaRCC)	Cabozantinib	CTCAE v5.0	37	NA	NA	NA	15 (40.5%)	NA			
Wang 2018	Apatinib	CTCAE	10	Hand-foot syndrome	5 (50%)	1 (10%)	NA	1 (10.0%)			
				Oral ulcers	4 (40%)	0					
				Gastrointestinal discomfort	4 (40%)	0					

Xie 2018*	Apatinib	CTCAE	45	Hypertension	30 (67.7%)	5 (11.1%)	NA	10 (18.0%)
				Rash	24 (53.3%)	2 (0.4%)		
				Hair hypopigmentation	25 (55.6%)	0		
Xu 2021	Anlotinib	CTCAE v4.0	60	NA	NA	NA	NA	NA
Yang 2024*	Fruquitinib	CTCAE v5.0	124	Pneumothorax	0	18 (14.5%)	NA	NA
				Diarrhea	1 (0.8%)	7 (5.6%)		
				Thrombocytopenia	1 (0.8%)	6 (4.8%)		

*Data available only for the total population of the study and does not refer exclusively to Ewing sarcoma patients. CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TKI: tyrosine kinase inhibitor.

Table S6: Adverse events of studies with data available exclusively for patients with Ewing sarcoma.

Study	TKI	N	Most common AEs	Grade 1-2 N (%)	Grade 3-4 N (%)	Dose reductions N (%)	Treatment discontinuation N (%)
Attia 2023/SARC024	Regorafenib	30	Hypophosphatemia (n=6/30; 20%)	0	6 (20%)	16 (53.3%)	2 (6.6%)
			Hypertension (n=5/30)	3 (10%)	2 (6.7%)		
			Transaminasemia (n=2/30)	0	2 (6.7%)		
Dela Cruz 2024	Fruquitinib	10	Leucopenia (n=6/10; 60%)	5 (50%)	1 (10%)	NA	3 (7.3%)
			Proteinuria (n=6/10; 60%)	5 (50%)	1 (10%)		
			Lymphopenia (n=5/10; 50%)	2 (20%)	3 (30%)		
Duffaud 2023 (REGOBONE)	Regorafenib	23	Pain (n=17/23; 73.9%)	12 (52.2%)	5 (27.1%)	9 (39.1%)	NA
			Asthenia (n=16/23; 69.9%)	12 (52.2%)	4 (17.4%)		
			Diarrhea (n=14/23; 60.9%)	11 (47.8%)	3 (13%)		
Italiano 2020 (CABONE)	Cabozantinib	45	Fatigue (n=29/45; 64.4%)	26 (57.8%)	3 (6.7%)	19 (21%)	12 (14.0%)
			Diarrhea (n=25/45; 55.5%)	23 (51.1%)	2 (4.4%)		
			Mucositis oral (n=25/45; 55.5%)	24 (53.3%)	1 (2.2%)		
Wang 2018	Apatinib	10	Hand-foot syndrome	5 (50%)	1 (10%)	NA	1 (10.0%)
			Oral ulcers	4 (40%)	0		
			Gastrointestinal discomfort	4 (40%)	0		

CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TKI: tyrosine kinase inhibitor.

Table S7: Tools and criteria used to assess the quality of studies included in this meta-analysis.

(A) Methodological items for non-randomized studies (MINORS) tool:

I. A clearly stated aim: Is the research question clear, precise, and relevant?
II. Inclusion of consecutive patients: Have all eligible patients been included during the study period?
III. Prospective collection of data: Was data collected according to prespecified criteria described in the protocol?
IV. Endpoints appropriate to the aim of the study: Were endpoints and definitions clearly defined and presented per protocol?
V. Unbiased assessment of the study endpoint: Were outcomes evaluated through blind assessment of objective endpoints? If not, were reasons provided?
VI. Follow-up appropriate to the aim of the study: Was the follow-up time adequate?
VII. Loss to follow-up less than 5%: Were all patients included in the follow-up? Otherwise, the proportion lost to follow-up should not exceed the proportion experiencing the major endpoint.
VIII. Prospective calculation of study size: Has the calculation of sample size been adequately explained and conducted using adequate statistical methods?

Items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate).

- Good quality/low risk of bias – 15-16 points
- Moderate quality and risk of bias – 9-14 points
- Poor quality and high risk of bias – ≤ 8

(B) Joanna Briggs Institute Critical Appraisal Tool for Cohort Studies adapted for non-comparative cohort studies

1. Were all participants recruited according to clear, pre-specified eligibility criteria from a well-defined (and representative) source population?
2. Was the intervention/exposure (e.g. TKI treatment) defined and measured in a consistent, reliable way for every participant?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient?
9. Was follow-up complete, and if not, were reasons for loss described?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

Questions are answered as "yes", "no" or "unclear"

- Low risk – If 'yes' to all questions
- Moderate risk – If 'no' for one of the questions 4, 5, and/or 6
- High risk – If 'no' for more than one of the questions 4, 5, and/or 6, or if 'no' for one of these questions and any other

Table S8: Risk of bias assessment

(A) MINORS

MINORS Index for included prospective non-randomized studies									
Study	I	II	III	IV	V	VI	VII	VIII	Total
Attia 2023 (SARC024)	2	2	2	2	1	2	2	2	15 - low risk
Chugh 2009	2	2	2	2	0	2	2	2	14 - moderate risk
Dela Cruz 2025	2	2	2	2	0	2	2	2	14 - moderate risk
Duffaud 2023 (REGOBONE)	2	2	2	2	2	2	2	2	16 - low risk
Italiano 2020 (CABONE)	2	2	2	2	2	2	2	2	16 - low risk
Palmerini 2024	2	2	2	2	0	2	2	2	14 - moderate risk
Xu 2021	2	2	2	2	0	2	2	2	14 - moderate risk

(B) JBI

JBI Critical Appraisal Checklist for Cohort Studies												
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Overall Appraisal
Bodea 2022	NA	NA	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Moderate risk
Kokkali 2023	NA	NA	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Moderate risk
Liu 2021	NA	NA	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Moderate risk
Soroka 2023	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate risk
Wang 2018	NA	NA	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Moderate risk
Xie 2018	NA	NA	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Moderate risk
Yang 2024	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate risk

Table S9: Leave-one-out for overall ORR and DCR.

(A) Objective response rate (ORR)

Omitted study	Proportion (%)	95% CI (%)	τ^2	τ	I^2
Attia 2023 (SARC024)	24.35	11.46–39.62	0.0618	0.2486	79.4%
Duffaud 2023 (REGOBONE)	23.93	11.05–39.26	0.0634	0.2518	80.3%
Kokkali 2023	24.58	12.26–39.05	0.0585	0.2420	80.4%
Italiano 2020 (CABONE)	22.75	9.67–38.63	0.0700	0.2645	80.8%
Soroka 2023	22.84	10.23–38.01	0.0637	0.2523	80.8%
Xie 2018	20.34	9.18–33.89	0.0521	0.2282	78.0%
Wang 2018	21.97	9.84–36.62	0.0606	0.2461	80.5%
Liu 2021	22.20	10.07–36.82	0.0606	0.2461	80.6%
Xu 2021 (Cohort A)	20.10	9.23–33.24	0.0470	0.2168	75.0%
Xu 2021 (Cohort B)	19.35	9.15–31.64	0.0414	0.2035	73.6%
Bodea 2022	23.70	11.01–38.81	0.0623	0.2496	80.6%
Dela Cruz 2025	25.41	12.95–39.91	0.0551	0.2347	78.9%
Yang 2024	23.46	10.48–39.04	0.0662	0.2572	80.6%
Palmerini 2024	24.90	12.47–39.45	0.0576	0.2400	79.9%
Chugh 2021	25.69	13.31–40.05	0.0528	0.2299	78.0%
Random-effects model (all studies)	23.02	11.17–37.07	0.0580	0.2407	79.3%

(B) Disease control rate (DCR)

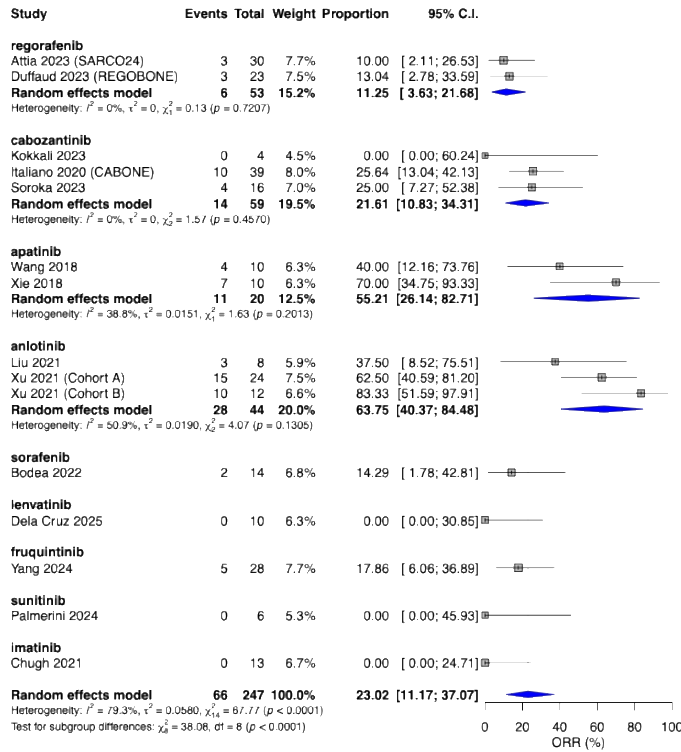
Omitted study	Proportion (%)	95% CI (%)	τ^2	τ	I^2
Attia 2023 (SARC024)	61.22	45.73–75.78	0.0485	0.2203	74.4%
Soroka 2023	62.57	47.92–76.28	0.0427	0.2066	73.2%
Kokkali 2023	60.47	46.22–73.98	0.0426	0.2063	74.3%
Italiano 2020 (CABONE)	59.65	44.46–74.08	0.0456	0.2134	72.4%
Xie 2018	59.70	45.14–73.54	0.0424	0.2059	73.6%
Wang 2018	59.70	45.14–73.54	0.0424	0.2059	73.6%
Xu 2021 (Cohort A)	60.16	44.98–74.53	0.0460	0.2145	73.9%
Liu 2021	60.20	45.64–74.02	0.0430	0.2075	74.1%
Xu 2021 (Cohort B)	59.27	44.79–73.07	0.0413	0.2032	72.9%
Bodea 2022	59.62	44.93–73.59	0.0428	0.2068	73.4%
Dela Cruz 2025	62.59	48.17–76.09	0.0417	0.2043	73.3%
Yang 2024	61.50	46.11–75.94	0.0478	0.2186	74.2%
Palmerini 2024	61.70	47.29–75.26	0.0428	0.2068	74.2%
Chugh 2021	67.22	59.70–74.37	0.0017	0.0417	10.1%
Random-effects model (all studies)	61.13	47.29–74.22	0.0406	0.2014	72.2%

Proportions of the ORR and DCR leaving each study out are described in the "Proportion" column followed by the respective 95% confidence interval (CI).

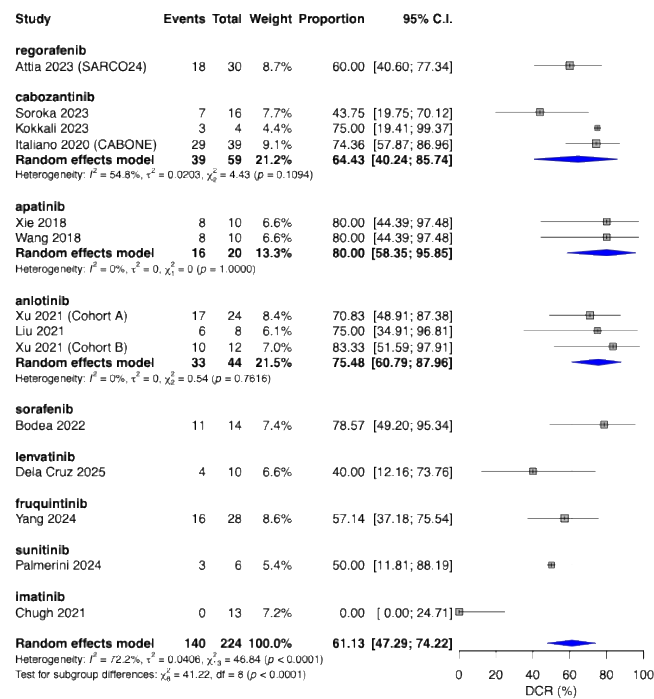
Figures

Figure S1: Response analyses according to the TKI used.

(A) Objective response rate (ORR)



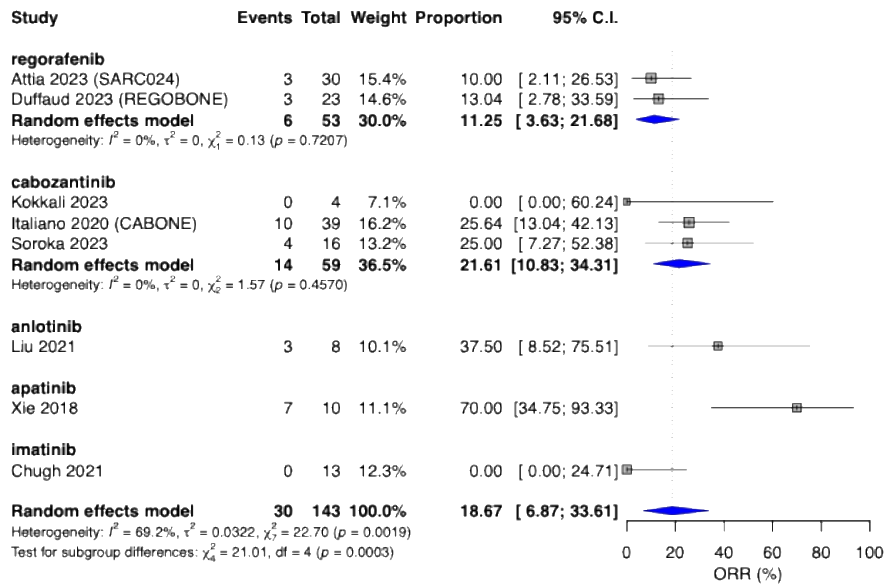
(B) Disease control rate (DCR)



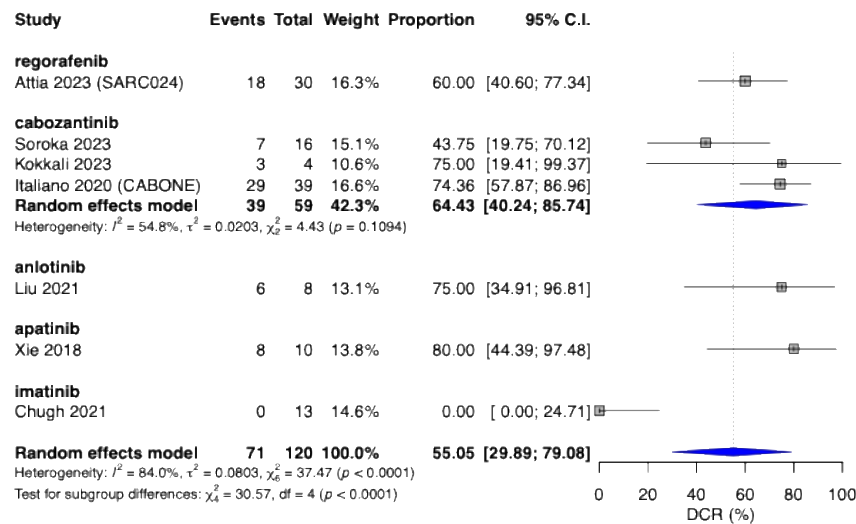
Squares represent proportions for each study, and the horizontal line crossing the squares indicates the 95% confidence interval. Diamonds represent the estimated overall effect of the meta-analysis based on a random-effects model. CI: confidence intervals; DCR: disease control rate; ORR: objective response rate; TKI: tyrosine kinase inhibitors.

Figure S2: Response analyses including only studies on single-agent TKI.

(A) Objective response rate (ORR)



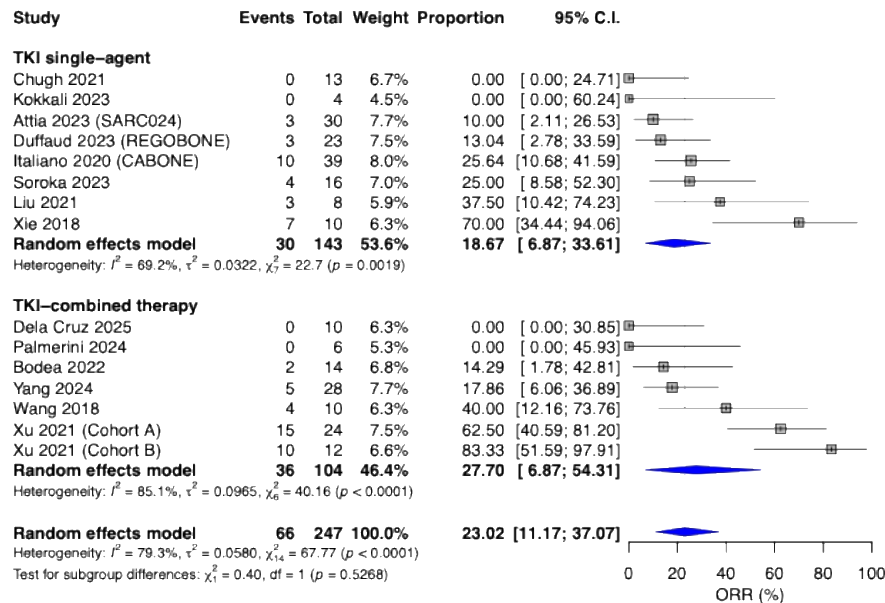
(B) Disease control rate (DCR)



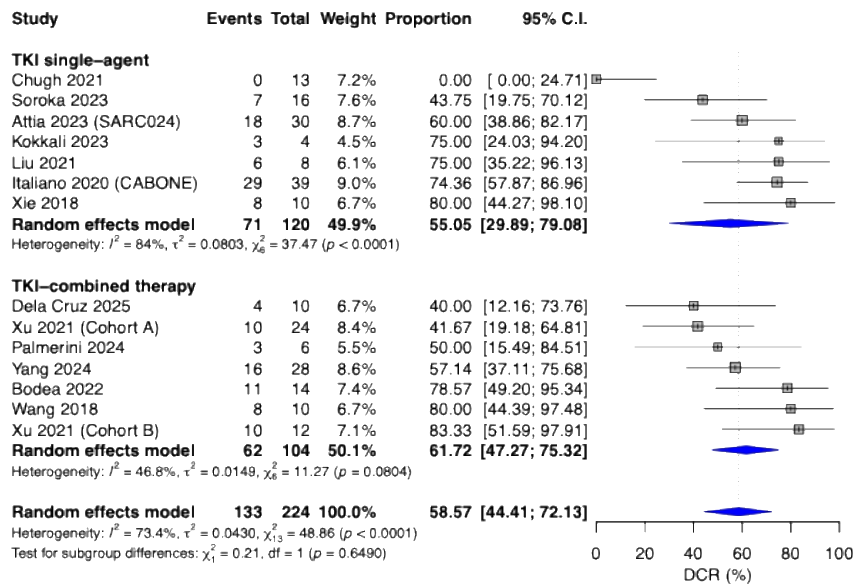
Squares represent proportions for each study, and the horizontal line crossing the squares indicates the 95% confidence interval. Diamonds represent the estimated overall effect of the meta-analysis based on a random-effects model. CI: confidence intervals; DCR: disease control rate; ORR: objective response rate; TKI: tyrosine kinase inhibitors.

Figure S3: Responses stratified per studies on single-agent TKI *versus* TKI-combined regimens.

(A) Objective response rate (ORR)

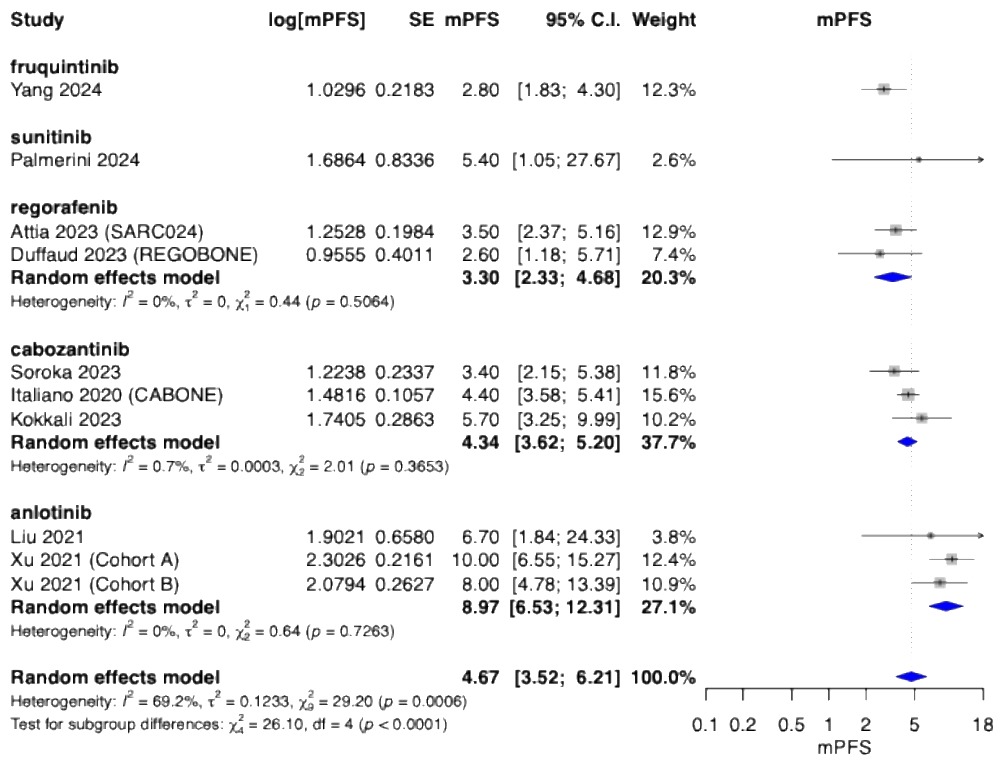


(B) Disease control rate (DCR)



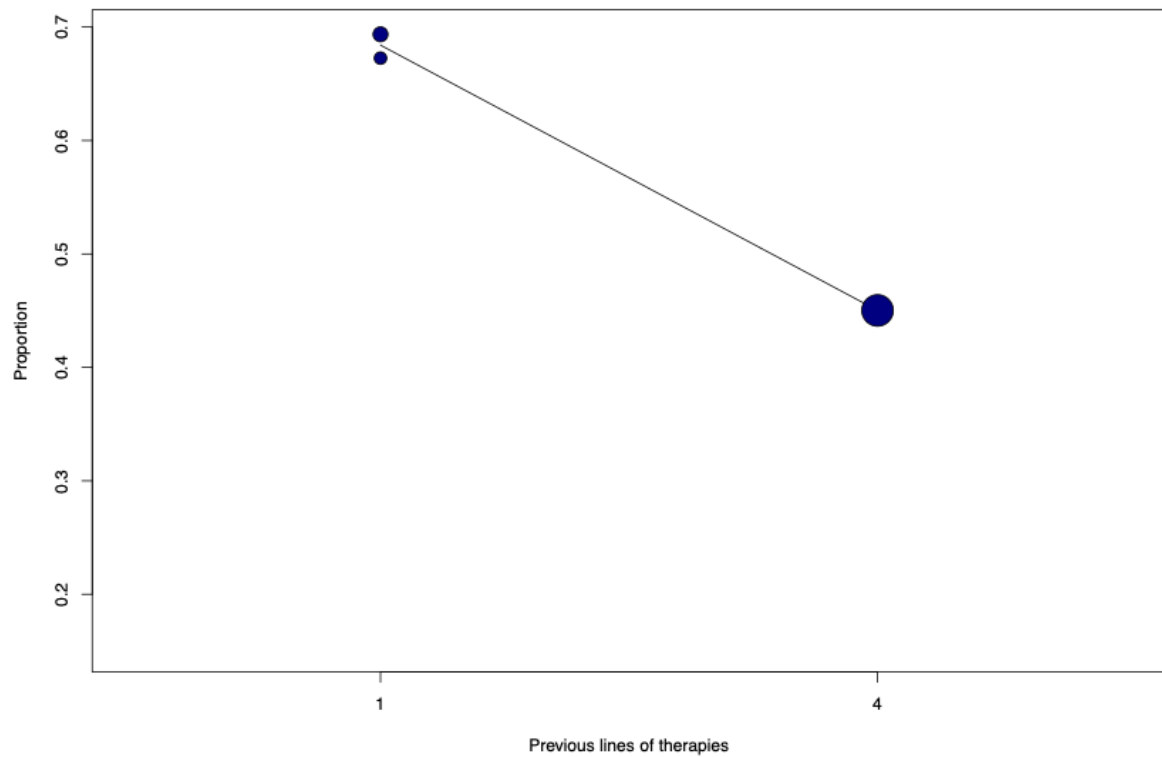
Squares represent proportions for each study, and the horizontal line crossing the squares indicates the 95% confidence interval. Diamonds represent the estimated overall effect of the meta-analysis based on a random-effects model. CI: confidence intervals; DCR: disease control rate; ORR: objective response rate; TKI: tyrosine kinase inhibitors.

Figure S4: Median progression-free survival (mPFS) per TKI agent used.



Squares represent mPFS for each study, and the horizontal line crossing the squares indicates the 95% confidence interval. Diamonds represent the estimated overall effect of the meta-analysis based on a random-effects model. CI: confidence intervals; mPFS: median progression-free survival; TKI: tyrosine kinase inhibitors.

Figure S5: Meta-regression on the impact of the median number of prior lines of therapy on the ORR.



The dots represent individual studies, the median number of previous therapies is shown on the x-axis, and the response rate on the y-axis. The line indicates the tendency of responses according to the number of previous therapies. ORR: objective response rate

	Effect estimate	p value	I ²	R ²	p value for residual heterogeneity
Intercept	0.68	<0.0001			
1.5 vs 1 line	-0.19	0.36			
2 lines vs 1 line	-0.28	0.04	19.9%	13.8%	0.27
3 lines vs 1 line	-0.31	0.03			
4 lines vs 1 line	-0.23	0.16			