

Title: Cabozantinib versus standard-of-care comparators in the treatment of advanced/metastatic renal cell carcinoma in treatment-naïve patients: A systematic review and network meta-analysis

Authors: Elvira Schmidt¹, Johanna Lister¹, Monika Neumann¹, Witold Wiecek¹, Shuai Fu¹, Anne-Lise Vataire², Jelena Sostar¹, Shengnan Huang¹, Florence Marteau²

Affiliations: 1. Analytica LA-SER Intl. Inc, Loerrach, Germany. 2. IPSEN Pharma SAS, Boulogne-Billancourt Cedex, France.

Supplementary Information

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1 Literature Review

1.1 Search strategy

1.1.1 Bibliographic data bases

Table A-1 Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline Daily)

Database		Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Platform:	Ovid	
Date of Search:	June 28, 2017 ,	
Date Range Searched:	[Last Database Update: Ovid MEDLINE(R): June Week 3 2017, Ovid MEDLINE(R) Epub Ahead of Print: Jun 27, 2017, In-Process & Other Non-Indexed Citations: Jun 27, 2017, Ovid MEDLINE(R) Daily: Jun 27, 2017] 1946-2017 For cabozantinib and tivozanib: restricted to 1980-2017 in the last step For other 1L treatments (Sunitinib, Pazopanib, Immunotherapy (Ifn-Alpha, Il-2), Bevacizumab, Temozolomide, Sorafenib): restricted to 2009-2017 in the last step	
Search Filters Used	RCT: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-and precision-maximizing version (2008 revision), slightly widened ¹ Systematic Reviews: SIGN Search Filter Systematic Reviews ²	
#	Search Terms	Hits
1	Carcinoma, Renal Cell/	28673
2	Kidney Neoplasms/	63488
3	(Renal adj3 (carcinoma\$1 or adenocarcinoma\$1 or cancer\$1 or neoplasm\$1 or tumo?r\$1 or malignanc\$3)).mp.	56267
4	(Kidney adj3 (carcinoma\$1 or adenocarcinoma\$1 or cancer\$1 or neoplasm\$1 or tumo?r\$1 or malignanc\$3)).mp.	69233
5	(hypernephroma\$1 or nephroid carcinoma\$1 or hypernephroid carcinoma\$1 or grawitz tumo?r\$1).mp.	1539
6	(rcc or mrcc or arcc).mp.	13549
7	or/1-6	86970
8	cabozantinib.nm.	191
9	(cabozantinib\$ or "bms 907351" or bms907351 or "xl 184" or xl184 or cabometyx\$ or cometriq\$).mp.	480
10	(1c39jw444g or dr7st46x58).rn.	191
11	(1140909-48-3 or 849217-68-1).rn.	0
12	or/8-11	480
13	Tivozanib.nm.	42
14	(tivozanib\$ or "AV-951" or AV951 or "KRN 951" or KRN951 or Kil8951 or "Kil-8951" or tivopath\$ or fotivda\$).mp.	103
15	475108-18-0.rn.	0
16	172030934T.rn.	42

¹ Source: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011, cited 25 June 2017]*. The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org.

² Source: Scottish Intermediate Guidelines Network (SIGN), Filter Systematic Reviews, URL: <http://sign.ac.uk/search-filters.html>, [Word document last modified 25 Apr 2017, cited 25 June 2017]

17	or/13-16	103
18	12 or 17	579
19	sunitinib.nm.	2992
20	(sunitinib\$ or "su 011248" or su011248 or "su 11248" or su11248 or su010398 or "su 010398" or su 10398 or su10398 or "pha-290940ad" or pha290940ad or sutent\$).mp.	5331
21	(lvx8n1ut73 or v99t50803m).rn.	2992
22	(341031-54-7 or 557795-19-4).rn.	0
23	pazopanib.nm.	588
24	(Pazopanib\$ or GW786034\$1 or (GW adj 786034\$1) or GW780604\$1 or (GW adj 780604\$1) or armala\$ or sb710468 or "sb 710468" or votrient\$).mp.	1264
25	(7RN5DR86CK or 33Y9ANM545).rn.	588
26	(444731-52-6 or 635702-64-6).rn.	0
27	Interferon-alpha/	27889
28	((interferon or ifn) adj1 (alpha\$ or alfa\$)).mp.	48316
29	(alfaferone or alferon or "alpha ferone" or cilferon or ginterferon or introma or kemron or leukiniferon or leukinferron or "leukocyte interferon" or "refecon a" or "referon a3" or sumiferon or sumipheron or veldona or "Intron A" or Alfatronol or Glucoferon or Urifron or Roferon or Laroferon or Roceron or ifnalpa or ifnalfa).mp.	3876
30	(74899-72-2 or 77907-69-8).rn.	0
31	47RRR83SK7.rn.	4619
32	Interleukin-2/	37742
33	("interleukin 2" or "interleukin II" or "il-2" or il2 or Ro-23-6019 or Ro236019 or Ro 236019 or RU 49637 or RU49637 or TCGF or T-Cell Growth Factor or T-Cell Stimulating Factor or bioleukin or proleukin or aldesleukin or tsf or Thymocyte Stimulating Factor).mp.	80562
34	(102524-44-7 or 110942-02-4).rn.	0
35	M89N0Q7EQR.rn.	98
36	Bevacizumab/	9656
37	(bevacizumab\$ or rhuMAB-VEGF or abp 215 or ro4876646 or nsc 704865 or nsc704865 or anti-vegf or avastin\$).mp.	18192
38	2S9ZZM9Q9V.rn.	9656
39	216974-75-3.rn.	0
40	Temsirolimus.nm.	807
41	(temsirolimus\$ or "cci 779" or "cell-cycle-inhibitor-779" or nsc683864 or "nsc 683864" or torisel\$).mp.	1506
42	162635-04-3.rn.	0
43	624KN6GM2T.rn.	807
44	Sorafenib.nm.	3840
45	(sorafenib\$ or "bay 43-9006" or "bay 439006" or "bay43 9006" or bay439006 or "bay 545-9085" or "bay 5459085" or "bay545-9085" or bay5459085 or "bay 54-9085" or "bay 549085" or "bay54-9085" or bay549085 or nexavar\$).mp.	6870
46	(284461-73-0 or 475207-59-1).rn.	0
47	(9ZOQ3TZI87 or 5T62Q3B36J).rn.	3840
48	or/19-47	155024
49	randomized controlled trial.pt.	467292
50	controlled clinical trial.pt.	94249
51	randomi?ed.ti,ab.	524123
52	placebo.ti,ab.	195947
53	clinical trials as topic.sh.	187000

54	randomly.ti,ab.	284880
55	trial.ti,ab.	503546
56	or/49-55	1328541
57	56 not (exp animals/ not humans.sh.)	1221457
58	Meta-Analysis as Topic/	16142
59	(meta analy\$ or metaanaly\$).tw.	118521
60	Meta-Analysis/	82096
61	(systematic adj (review\$1 or overview\$1)).tw.	106897
62	exp Review Literature as Topic/	9583
63	cochrane.ab.	54991
64	embase.ab.	58053
65	(psychlit or psychlit).ab.	940
66	(psychinfo or psycinfo).ab.	18979
67	(cinahl or cinhal).ab.	18781
68	science citation index.ab.	2699
69	bids.ab.	447
70	cancerlit.ab.	659
71	reference list\$.ab.	14475
72	bibliograph\$.ab.	15305
73	hand-search\$.ab.	5632
74	relevant journals.ab.	1021
75	manual search\$.ab.	3538
76	selection criteria.ab. and review/	17484
77	data extraction.ab. and review/	10738
78	or/58-77	255226
79	78 not (comment/ or letter/ or editorial/)	244576
80	79 not (exp animals/ not humans.sh.)	241897
81	7 and 18	177
82	57 and 81	63
83	80 and 81	9
84	82 or 83	65
85	limit 84 to yr="1980 -Current"	65
86	7 and 48	7282
87	57 and 86	1937
88	80 and 86	161
89	87 or 88	1996
90	limit 89 to yr="2009 -Current"	1030
91	85 or 90	1058

Table A-2 Embase

Database		Embase
Search Platform:		Ovid SP
Date of Search:		Jun 28, 2017 [Last Database Update: Jun 26, 2017]
Date Range Searched:		1974-2017 For cabozantinib and tivozanib: restricted to 1980-2017 in the last step For other 1L treatments (Sunitinib, Pazopanib, Immunotherapy (Ifn-Alpha, Il-2), Bevacizumab, Temsirolimus, Sorafenib): restricted to 2009-2017 in the last step
Search Filters Used		<u>RCT</u> : SIGN Search Strategy Randomized Controlled Trials ³ <u>Systematic Reviews</u> : SIGN Search Filter Systematic Reviews ⁴
#	Search Terms	Hits
1	exp kidney carcinoma/	57692
2	exp kidney tumor/	116353
3	(Renal adj3 (carcinoma\$1 or adenocarcinoma\$1 or cancer\$1 or neoplasm\$1 or tumo?r\$1 or malignanc\$3)).mp.	73130
4	(Kidney adj3 (carcinoma\$1 or adenocarcinoma\$1 or cancer\$1 or neoplasm\$1 or tumo?r\$1 or malignanc\$3)).mp.	103877
5	(hypernephroma\$1 or nephroid carcinoma\$1 or hypernephroid carcinoma\$1 or grawitz tumo?r\$1).mp.	1628
6	(rcc or mrcc or arcc).mp.	21959
7	or/1-6	135513
8	Cabozantinib/	1790
9	(cabozantinib\$ or "bms 907351" or bms907351 or "xl 184" or xl184 or cabometryx\$ or cometriq\$).mp.	2085
10	(1c39jw444g or dr7st46x58).rn.	0
11	(1140909-48-3 or 849217-68-1).rn.	1544
12	or/8-11	2085
13	tivozanib/	414
14	(tivozanib\$ or "AV-951" or AV951 or "KRN 951" or KRN951 or Kil8951 or "Kil-8951" or tivopath\$ or fotivda\$).mp.	490
15	475108-18-0.rn.	346
16	172030934t.rn.	0
17	or/13-16	490
18	12 or 17	2498
19	Sunitinib/	18432
20	(sunitinib\$ or "su 011248" or su011248 or "su 11248" or su11248 or su010398 or "su 010398" or su 10398 or su10398 or "pha-290940ad" or pha290940ad or sutedent\$).mp.	18907
21	(lvx8n1ut73 or v99t50803m).rn.	0
22	(341031-54-7 or 557795-19-4).rn.	14922
23	Pazopanib/	5463

³ Source: Scottish Intermediate Guidelines Network (SIGN), Filter Randomized Controlled Trials
 URL: <http://sign.ac.uk/search-filters.html>, [Word document last modified 25 Apr 2017, cited 25 June 2017], Filter supplemented by an additional search term, mere animal studies excluded.

⁴ Source: Scottish Intermediate Guidelines Network (SIGN), Filter Systematic Reviews
 URL: <http://sign.ac.uk/search-filters.html>, [Word document last modified 25 Apr 2017, cited 25 June 2017]

24	(Pazopanib\$ or GW786034\$1 or (GW adj 786034\$1) or GW780604\$1 or (GW adj 780604\$1) or armala\$ or sb710468 or "sb 710468" or votrient\$).mp.	5595
25	(7rn5dr86ck or 33y9anm545).rn.	0
26	(444731-52-6 or 635702-64-6).rn.	4559
27	Alpha interferon/	50175
28	((interferon or ifn) adj1 (alpha\$ or alfa\$)).mp.	86323
29	(alfaferone or alferon or "alpha ferone" or cilferon or ginterferon or introma or kemron or leukiniferon or leukinferron or "leukocyte interferon" or "refecon a" or "referon a3" or sumiferon or sumipheron or veldona or "Intron A" or Alfatronol or Glucoferon or Urifron or Roferon or Laroferon or Roceron or ifnalpa or ifnalpa).mp.	10397
30	(74899-72-2 or 77907-69-8).rn.	0
31	47rrr83sk7.rn.	0
32	Interleukin-2/	84004
33	("interleukin 2" or "interleukin II" or "il-2" or il2 or Ro-23-6019 or Ro236019 or Ro 236019 or RU 49637 or RU49637 or TCGF or T-Cell Growth Factor or T-Cell Stimulating Factor or bioleukin or proleukin or aldesleukin or tsf or Thymocyte Stimulating Factor).mp.	127620
34	(102524-44-7 or 110942-02-4).rn.	6119
35	m89n0q7eqr.rn.	0
36	bevacizumab/	45802
37	(bevacizumab\$ or rhumab-vegf or abp 215 or ro4876646 or nsc 704865 or nsc704865 or anti-vegf or avastin\$).mp.	50782
38	2s9zrm9q9v.rn.	0
39	216974-75-3.rn.	38082
40	temsirolimus/	7072
41	(temsirolimus\$ or "cci 779" or "cell-cycle-inhibitor-779" or nsc683864 or "nsc 683864" or torisel\$).mp.	7263
42	624kn6gm2t.rn.	0
43	162635-04-3.rn.	6093
44	sorafenib/	22479
45	(sorafenib\$ or "bay 43-9006" or "bay 439006" or "bay43 9006" or bay439006 or "bay 545-9085" or "bay 5459085" or "bay545-9085" or bay5459085 or "bay 54-9085" or "bay 549085" or "bay54-9085" or bay549085 or nexavar\$).mp.	23129
46	(284461-73-0 or 475207-59-1).rn.	17721
47	(9zoq3tzi87 or 5t62q3b36j).rn.	0
48	or/19-47	280009
49	clinical trial/	932258
50	randomized controlled trial/	458556
51	controlled clinical trial/	437367
52	multicenter study/	158354
53	Phase 3 clinical trial/ or Phase 4 clinical trial/	30803
54	exp randomization/	74481
55	Single Blind Procedure/	27966
56	Double Blind Procedure/	140243
57	Crossover Procedure/	52092
58	Placebo/	308963
59	Randomized controlled trial\$.tw.	161718
60	rct.tw.	24705

61	(random\$ adj2 allocat\$).tw.	34322
62	((single or double or treble or triple) adj blind\$).tw.	198362
63	Placebo\$.tw.	257316
64	Prospective Study/	386717
65	Randomi#ed.ti.	192913
66	or/49-65	1850244
67	66 not (Case study/ or case report.tw. or abstract report/ or note.pt.)	1799867
68	67 not (exp animal/ not exp human/)	1737657
69	exp Meta Analysis/	129377
70	((meta adj analy\$) or metaanalys\$).tw.	148423
71	(systematic adj (review\$1 or overview\$1)).tw.	127540
72	cancerlit.ab.	704
73	cochrane.ab.	67932
74	embase.ab.	70007
75	(psychlit or psyclit).ab.	972
76	(psychinfo or psycinfo).ab.	16532
77	(cinahl or cinhal).ab.	20653
78	science citation index.ab.	2970
79	bids.ab.	550
80	reference lists.ab.	14852
81	bibliograph\$.ab.	18642
82	hand-search\$.ab.	6457
83	manual search\$.ab.	4021
84	relevant journals.ab.	1152
85	selection criteria.ab. and review.pt.	12605
86	data extraction.ab. and review.pt.	9766
87	or/69-86	306284
88	87 not (letter or editorial).pt.	299011
89	88 not (exp animal/ not exp human/)	296252
90	7 and 18	782
91	68 and 90	330
92	89 and 90	36
93	91 or 92	338
94	limit 93 to yr="1980 -Current"	337
95	7 and 48	18314
96	68 and 95	5729
97	89 and 95	449
98	96 or 97	5887
99	limit 98 to yr="2009 -Current"	3367
100	94 or 99	3449

Table A-3 Cochrane Library

Databases		Cochrane Library (incl. Cochrane CENTRAL, Cochrane Reviews, DARE, NHSEED, HTA)
Search Platform:	Cochrane Library (Wiley), all databases included, see below	
Date of Search:	June 28, 2017 [Last Database Update: Cochrane Central Register of Controlled Trials: May 2017, Cochrane Reviews: June 2017, Other Reviews (DARE): April 2015, HTA Database: October 2016, NHSEED: April 2015),	
Date Range Searched:	For cabozantinib and tivozanib: restricted to 1980-2017 in the last step For other 1L treatments (Sunitinib, Pazopanib, Immunotherapy (Ifn-Alpha, Il-2), Bevacizumab, Temsirolimus, Sorafenib): restricted to 2009-2017 in the last step	
Search Filters Used	none	
#	Search Terms	Hits
#1	[mh ^"Carcinoma, Renal Cell"]	585
#2	[mh ^"kidney neoplasms"]	764
#3	(renal near/3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumor* or tumour*)):ab,ti,kw	1849
#4	(kidney near/3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumor* or tumour*)):ab,ti,kw	1746
#5	mrcc:ab,ti,kw or rcc:ab,ti,kw or arcc:ab,ti,kw or hypernephroma*:ab,ti,kw or (nephroid next/1 carcinoma*):ab,ti,kw or (hypernephroid next/1 carcinoma*):ab,ti,kw or (grawitz next/1 tumor*):ab,ti,kw or (grawitz next/1 tumour*):ab,ti,kw	797
#6	#1 or #2 or #3 or #4 or #5	2466
#7	cabozantinib*:ab,ti,kw	104
#8	("bms 907351" or bms907351 or "xl 184" or xl184 or cabometyx* or cometriq*):ab,ti,kw	28
#9	#7 or #8	105
#10	Tivozanib*:ab,ti,kw	31
#11	("AV-951" or AV951 or "KRN 951" or KRN951 or "Kil-8951" or tivopath* or fotivda*):ab,ti,kw	5
#12	#10 or #11	32
#13	#9 or #12	136
#14	Sunitinib*:ab,ti,kw	596
#15	(sutent* or "pha-290940ad" or pha290940ad or "su 011248" or su011248 or "su 11248" or su11248 or su010398 or "su 010398" or "su 10398" or su10398):ab,ti,kw	18
#16	Pazopanib*:ab,ti,kw	251
#17	(GW786034* or (GW next 786034*) or GW780604* or (GW next 780604*) or armala* or sb710468 or "sb 710468" or votrient*):ab,ti,kw	11
#18	[mh Interferon-alpha]	2878
#19	((interferon or ifn) near/1 (alpha* or alfa*)):ab,ti,kw	5969
#20	(alfaferone or alferon or "alpha ferone" or cilferon or ginterferon or introna or kemron or leukinferon or leukinferron or "leukocyte interferon" or "refecon a" or "referon a3" or sumiferon or sumipheron or veldona or "Intron A" or Alfatronol or Glucoferon or Urifron or Roferon or Laroferon or Roceron or ifnalpa or ifnalfa):ab,ti,kw	460
#21	[mh Interleukin-2]	868
#22	("interleukin 2" or "interleukin II" or "il-2" or il2 or Ro-23-6019 or Ro236019 or Ro 236019 or RU 49637 or RU49637 or TCGF or T-Cell Growth Factor or T-Cell Stimulating Factor or bioleukin or proleukin or aldesleukin or tsf or Thymocyte Stimulating Factor):ab,ti,kw	3606
#23	[mh bevacizumab]	710
#24	("rhuMAb-VEGF" or "abp 215" or ro4876646 or "nsc 704865" or nsc704865 or "anti-vegf" or avastin*):ab,ti,kw	548
#25	Temsirolimus*:ab,ti,kw	181
#26	("cci 779" or "cell-cycle-inhibitor-779" or nsc683864 or "nsc 683864" or torisel*):ti,ab,kw	24
#27	sorafenib:ab,ti,kw	808

#28	("bay 43-9006" or bay 439006 or "bay43 9006" or bay439006 or "bay 545-9085" or "bay 5459085" or "bay545-9085" or bay5459085 or "bay 54-9085" or "bay 549085" or "bay54-9085" or bay549085 or nexavar*):ab,ti,kw	34
#29	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28	11846
#30	#6 and #13	53
#31	#30 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations	53
#32	#31 Publication Year from 1980 to 2017	53
#33	#6 and #29	908
#34	#33 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials, Technology Assessments and Economic Evaluations	906
#35	#34 Publication Year from 2009 to 2017	561
#36	#32 or #35	587

1.1.2 Study registry

Table A-4 US National Institute of Health's (NIH) clinical trial registry (ClinicalTrials.gov)

Study registry	clinicaltrials.gov
URL	https://clinicaltrials.gov/ct2/search/advanced https://clinicaltrials.gov/ct2/results/refine?show_xprt=Y
Date of Search	Aug 17, 2017
Advanced Search	
Search strategy (Expert Search), With restriction to Studies with Results	(random OR randomized OR randomised OR RCT OR randomization OR randomisation) AND NOT NOTEXT [FIRST-RECEIVED-RESULTS-DATE] AND (Carcinoma, Renal Cell OR RCC OR mRCC OR aRCC OR (renal OR kidney OR nephroid OR hypernephroid OR grawitz) AND (cancer OR cancers OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR neoplasm OR neoplasms OR tumor OR tumors)) [DISEASE] AND (cabozantinib OR "bms 907351" OR bms907351 OR "xl 184" OR xl184 OR Tivozanib OR "AV-951" AND or AV951 or AND "KRN 951" AND or KRN951 or Kil8951 or AND "kil-8951" OR sunitinib OR "su 011248" OR su011248 OR "su 11248" OR su11248 OR su010398 OR "su 010398" OR "su 10398" OR su10398 OR "pha-290940ad" OR pha290940ad OR Pazopanib OR GW786034 OR "GW 786034" OR GW780604 OR "GW 780604" OR sb710468 OR "sb 710468" OR immunotherapy OR "interferon alpha" OR "interferon alpha" OR "IFN alpha" OR "ifn alfa" OR alfaferone OR alferon OR "alpha ferone" OR cilferon OR ginterferon OR introma OR kemron OR leukinferon OR leukinferron OR "leukocyte interferon" OR "refecon a" OR "referon a3" OR sumiferon OR sumipheron OR veldona OR "Intron A" OR Alfatronol OR Glucoferon OR Urifron OR Roferon OR Laroferon OR Roceron OR ifnalpha OR ifnalfa OR "interleukin 2" OR "interleukin II" OR "il-2" OR il2 OR "Ro-23-6019" OR Ro236019 OR "Ro 236019" OR "RU 49637" OR RU49637 OR TCGF OR "T-Cell Growth Factor" OR "T-Cell Stimulating Factor" OR bioleukin OR proleukin OR aldesleukin OR tsf OR "Thymocyte Stimulating Factor" OR bevacizumab OR "rhuMAB-VEGF" AND or AND "abp 215" AND or ro4876646 or AND "nsc 704865" AND or AND "nsc704865" AND or AND "anti-vegf" OR temsirolimus OR "cci 779" OR "cell-cycle-inhibitor-779" OR nsc683864 OR "nsc 68386" OR sorafenib OR "bay 43-9006" OR "bay 439006" OR "bay43 9006" OR bay439006 OR "bay 545-9085" OR "bay 5459085" OR "bay545-9085" OR bay5459085 OR "bay 54-9085" OR "bay 549085" OR "bay54-9085" OR bay549085) [TREATMENT]
Condition / Disease:	Carcinoma, Renal Cell OR RCC OR mRCC OR aRCC OR (renal OR kidney OR nephroid OR hypernephroid OR grawitz) AND (cancer OR cancers OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR neoplasm OR neoplasms OR tumor OR tumors)
Intervention / Treatment:	cabozantinib OR "bms 907351" OR bms907351 OR "xl 184" OR xl184 OR Tivozanib OR "AV-951" AND or AV951 or AND "KRN 951" AND or KRN951 or Kil8951 or AND "kil-8951" OR sunitinib OR "su 011248" OR su011248 OR "su 11248" OR su11248 OR su010398 OR "su 010398" OR "su 10398" OR su10398 OR "pha-290940ad" OR pha290940ad OR Pazopanib OR GW786034 OR "GW 786034" OR GW780604 OR "GW 780604" OR sb710468 OR "sb 710468" OR immunotherapy OR "interferon alpha" OR "interferon alpha" OR "IFN alpha" OR "ifn alfa" OR alfaferone OR alferon OR "alpha ferone" OR cilferon OR ginterferon OR introma OR kemron OR leukinferon OR leukinferron OR "leukocyte interferon" OR "refecon a" OR "referon a3" OR sumiferon OR sumipheron OR veldona OR "Intron A" OR Alfatronol OR Glucoferon OR Urifron OR Roferon OR Laroferon OR Roceron OR ifnalpha OR ifnalfa OR "interleukin 2" OR "interleukin II" OR "il-2" OR il2 OR "Ro-23-6019" OR Ro236019 OR "Ro 236019" OR "RU 49637" OR RU49637 OR TCGF OR "T-Cell Growth Factor" OR "T-Cell Stimulating Factor" OR bioleukin OR proleukin OR aldesleukin OR tsf OR "Thymocyte Stimulating Factor" OR bevacizumab OR "rhuMAB-VEGF" AND or AND "abp 215" AND or ro4876646 or AND "nsc 704865" AND or AND "nsc704865" AND or AND "anti-vegf" OR temsirolimus OR "cci 779" OR "cell-cycle-inhibitor-779" OR nsc683864 OR "nsc 68386" OR sorafenib OR "bay 43-9006" OR "bay 439006" OR "bay43 9006" OR bay439006 OR "bay 545-9085" OR "bay 5459085" OR "bay545-9085" OR bay5459085 OR "bay 54-9085" OR "bay 549085" OR "bay54-9085" OR bay549085
Other Terms	(random OR randomized OR randomised OR RCT OR randomization OR randomisation)
Study Results	Studies with Results
URL	https://clinicaltrials.gov/ct2/results?show_xprt=Y&xprt=%28+random+OR+randomized+OR+randomise+d+OR+RCT+OR+randomization+OR+randomisation+%29+AND+NOT+NOTEXT+%5BFIRST-RECEIVED-RESULTS-DATE%5D+AND+%28+Carcinoma%2C+Renal+Cell+OR+RCC+OR+mRCC+OR+aRCC+OR+%28+renal+OR+ki dney+OR+nephroid+OR+hypernephroid+OR+grawitz+%29+AND+%28+cancer+OR+cancers+OR+carcino ma+OR+carcinomas+OR+adenocarcinoma+OR+adenocarcinomas+OR+neoplasm+OR+neoplasms+OR+t umor+OR+tumors+%29+%29+%5BDISEASE%5D+AND+%28+cabozantinib+OR+%22bms+907351%22+O R+bms907351+OR+%22xl+184%22+OR+xl184+OR+Tivozanib+OR+%22AV-951%22+AND+or+AV951+or+AND+%22KRN+951%22+AND+or+KRN951+or+Kil8951+or+AND+%22kil-8951%22+OR+sunitinib+OR+%22su+011248%22+OR+su011248+OR+%22su+11248%22+OR+su11248+ OR+su010398+OR+%22su+010398%22+OR+%22su+10398%22+OR+su10398+OR+%22pha-290940ad%22+OR+pha290940ad+OR+Pazopanib+OR+GW786034+OR+%22GW+786034%22+OR+GW780604+OR+%22GW+780604%22+OR+sb710468+OR+%22sb+710468%22+OR+immunotherapy+OR+%22interferon+alpha%22+OR+%22interferon+alpha%22+OR+%22IFN+alpha%22+OR+%22ifn+alfa%22+OR+alfaferone+OR+alferon+OR+%22alpha+ferone%22+OR+cilferon+OR+ginterferon+OR+introma+OR+kemron+OR+leukinferon+OR+leukinferron+OR+%22leukocyte+interferon%22+OR+%22refecon+a%22+OR+%22referon+a3%22+OR+sumiferon+OR+sumipheron+OR+veldona+OR+%22Intron+A%22+OR+Alfatronol+OR+Glucoferon+OR+Urifron+OR+Roferon+OR+Laroferon+OR+Roceron+OR+ifnalpha+OR+ifnalfa+OR+%22interleukin+2%22+OR+%22interleukin+II%22+OR+%22il-2%22+OR+il2+OR+%22Ro-23-6019%22+OR+Ro236019+OR+%22Ro+236019%22+OR+%22RU+49637%22+OR+RU49637+OR+TCGF+OR+%22T-Cell+Growth+Factor%22+OR+%22T-Cell+Stimulating+Factor%22+OR+bioleukin+OR+proleukin+OR+aldesleukin+OR+tsf+OR+%22Thymocyte+Stimulating+Factor%22+OR+bevacizumab+OR+%22rhuMAB-VEGF%22+AND+or+AND+%22abp+215%22+AND+or+ro4876646+or+AND+%22nsc+704865%22+AND+or+AND+%22nsc704865%22+AND+or+AND+%22anti-veg f%22+OR+temsirolimus+OR+%22cci+779%22+OR+%22cell-cycle-inhibitor-779%22+OR+nsc683864+OR+%22nsc+68386%22+OR+sorafenib+OR+%22bay+43-9006%22+OR+%22bay+439006%22+OR+%22bay43+9006%22+OR+bay439006+OR+%22bay+545-9085%22+OR+%22bay+5459085%22+OR+%22bay545-9085%22+OR+bay5459085+OR+%22bay+54-9085%22+OR+%22bay+549085%22+OR+bay549085

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Note: The original search string in clinicaltrials.gov included an error. When Boolean operators “or” were used in lowercase, clinicaltrials.gov added some AND-Operators. The search was reproduced with a corrected search string and yielded 42 instead of the initial 41 hits. 41 hits were identical to the initial search. The additionally identified trial was excluded after review.

1.2 Search Results

1.2.1 Overview of the results of the literature search

Table A-5 Overview of the results-Bibliographic search

Database	Search Filter for RCT	Search Filter for Systematic Reviews	Intervention	Restrictions	No. of findings
Medline	Cochrane Highly Sensitive Search Strategy for RCT: sensitivity-and precision-maximizing version	SIGN Search Strategy Systematic Reviews	Cabozantinib, Tivozanib	1980 - 2017	65
Medline	Cochrane Highly Sensitive Search Strategy for RCT: sensitivity-and precision-maximizing version	SIGN Search Strategy Systematic Reviews	Sunitinib, Pazopanib, Immunotherapy (Ifn-Alpha, Il-2), Bevacizumab, Temsirolimus, Sorafenib	2009 - 2017	1030
Total Medline					1058
Embase	SIGN Search Strategy Randomized Controlled Trials	SIGN Search Strategy Systematic Reviews	Cabozantinib, Tivozanib	1980 - 2017	337
Embase	SIGN Search Strategy Randomized Controlled Trials	SIGN Search Strategy Systematic Reviews	Sunitinib, Pazopanib, Immunotherapy (Ifn-Alpha, Il-2), Bevacizumab, Temsirolimus, Sorafenib	2009 - 2017	3367
Total Embase					3449
Cochrane Library (Cochrane CENTRAL, Cochrane Reviews, HTA, DARE, NHSEED)	None (restriction to Cochrane Central Register of Controlled Trials)	None (restriction to Cochrane Database of Systematic Reviews, DARE, NHSEED, HTA)	Cabozantinib, Tivozanib	1980 - 2017	53
Cochrane Library (Cochrane CENTRAL, Cochrane Reviews, HTA, DARE, NHSEED)	None (restriction to Cochrane Central Register of Controlled Trials)	None (restriction to Cochrane Database of Systematic Reviews, DARE, NHSEED, HTA)	Sunitinib, Pazopanib, Immunotherapy (Ifn-Alpha, Il-2), Bevacizumab, Temsirolimus, Sorafenib	2009 - 2017	561
Total Cochrane Library					587
Total					5094
Findings without 1086 duplicates					4008

Table A-6 Overview of the results-Study registries

Database	Intervention	Restrictions	No. of findings
ClinicalTrials.gov	Cabozantinib, Tivozanib, Sunitinib, Pazopanib, Immunotherapy (Ifn-Alpha, Il-2), Bevacizumab, Temsirolimus, Sorafenib	Studies with Results	41

1.3 Inclusion and Exclusion Criteria

Table A-7 Summary of the review inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	Adult patients with advanced or metastatic renal cell carcinoma, previously untreated	> Patients <18 years of age > Healthy subjects > Animal studies
Intervention	The following interventions in the first-line setting: > Cabozantinib (Cabometyx™) [monotherapy] > Sunitinib (Sutent®) [monotherapy] > Pazopanib (Votrient®) [monotherapy] > Interferon alfa [monotherapy] > Interleukin-2 [monotherapy] > Sorafenib (Nexavar®) [monotherapy] > Bevacizumab (Avastin®) + Interferon alfa > Temsirolimus (Torisel®) [monotherapy] > Tivozanib (Fotivda) [monotherapy]	Combination therapies of listed interventions
Comparator	> Any from the included list > Placebo > Best supportive care (BSC)	
Outcome	> Overall Survival (OS) > Progression-free survival (PFS) > Treatment discontinuation > Adverse events (AE) (incidence of AE, SAE, grade 3/4)	
Study design	> RCT > Letters reporting a RCT > Systematic reviews, meta-analyses, HTA [for screening of bibliographies only, thereafter excluded]	
Language	English, French, German, Italian, Spanish	
Country	No restrictions	
Search time	1980 onwards	

2 Network plots

2.1 Network of intermediate risk PFS

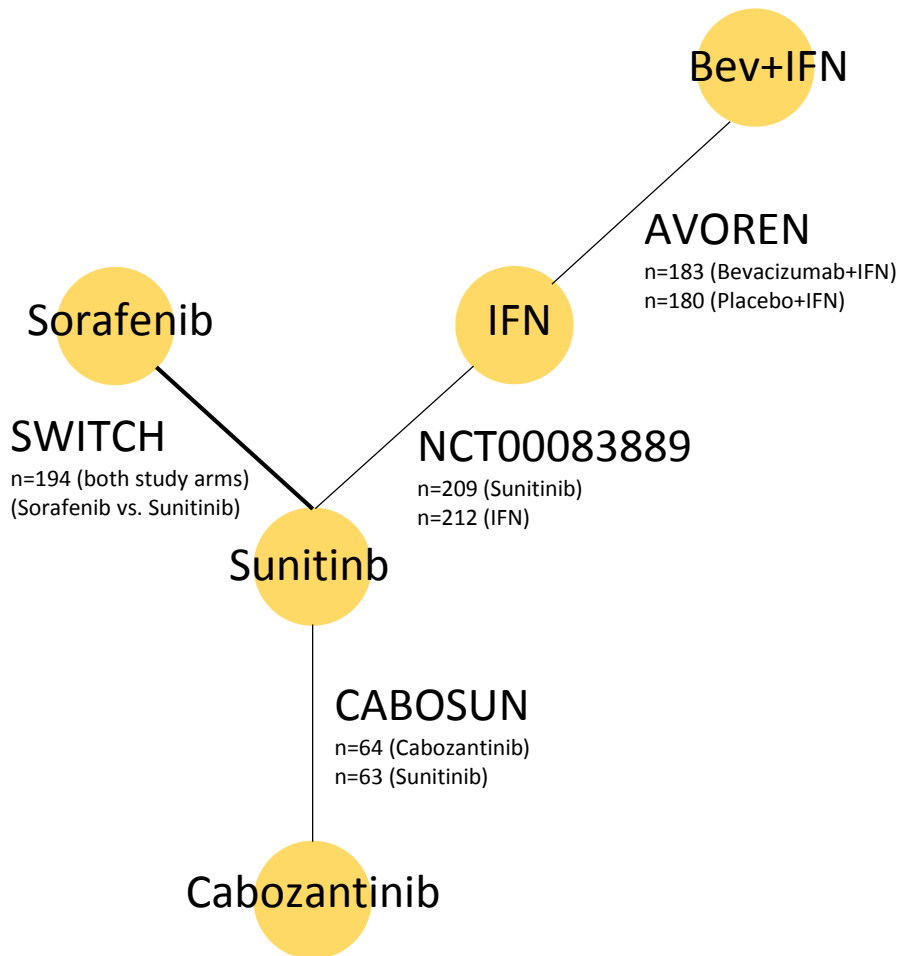


Fig A-1 Network of intermediate risk PFS

Bev: bevacizumab; IFN: Interferon

2.2 Network of poor risk PFS

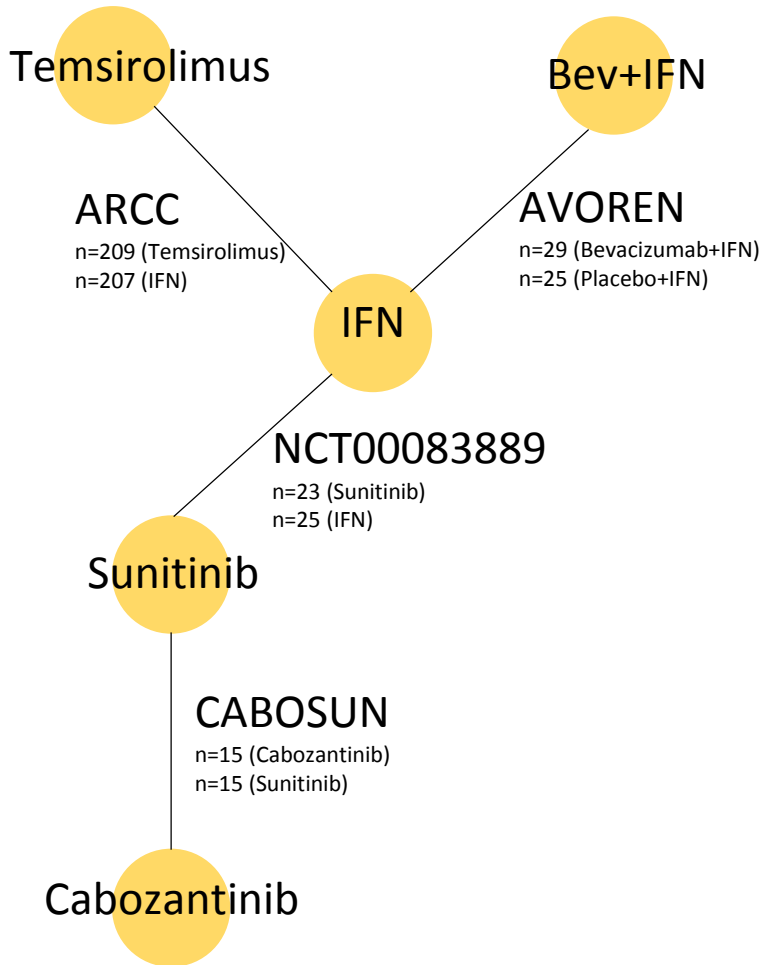


Fig A-2 Network of poor risk PFS

Bev: bevacizumab; IFN: Interferon

2.3 Network of overall PFS

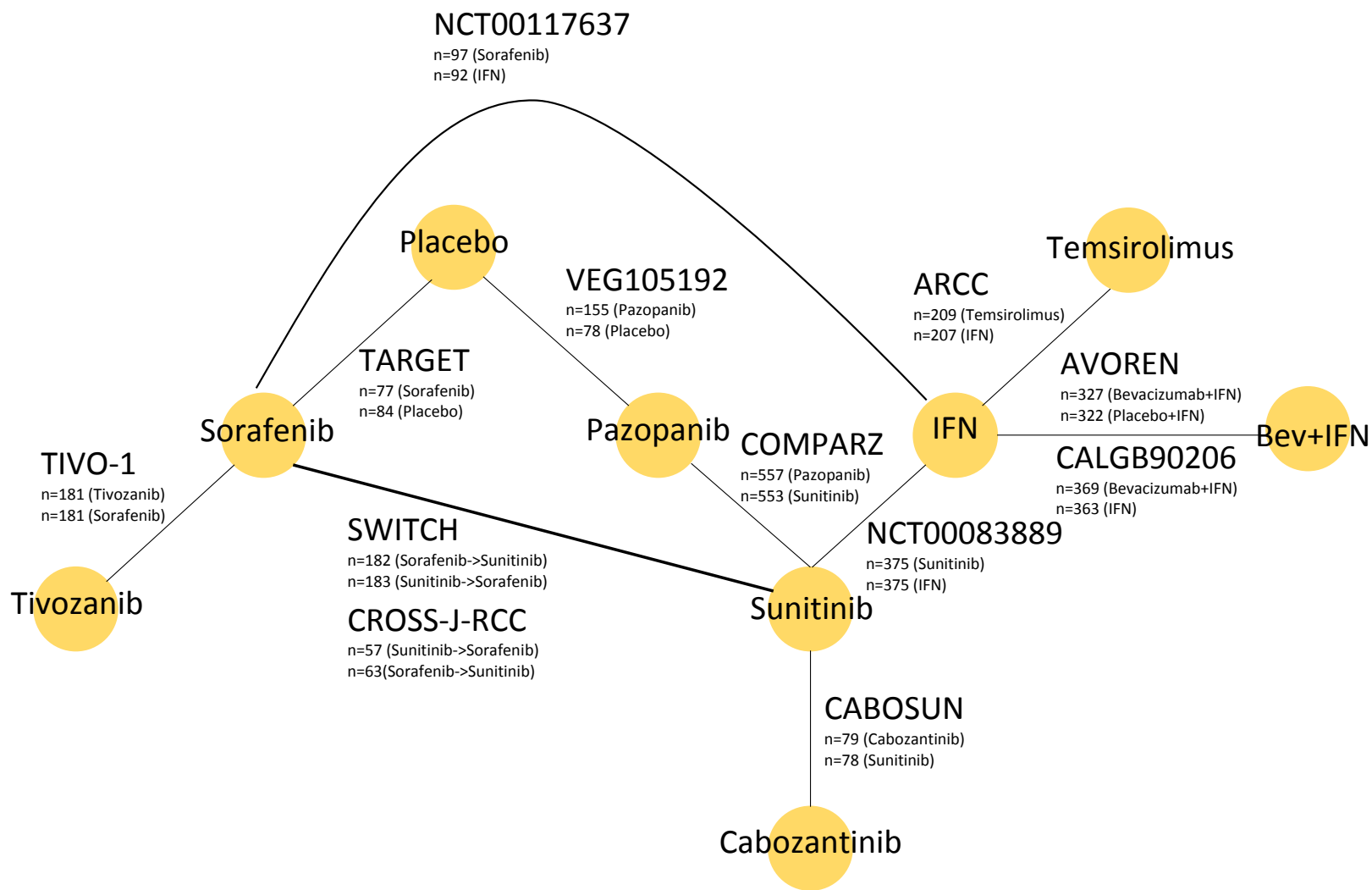


Fig A-3 Network of overall PFS

Bev: bevacizumab; IFN: Interferon

2.4 Network of intermediate risk OS

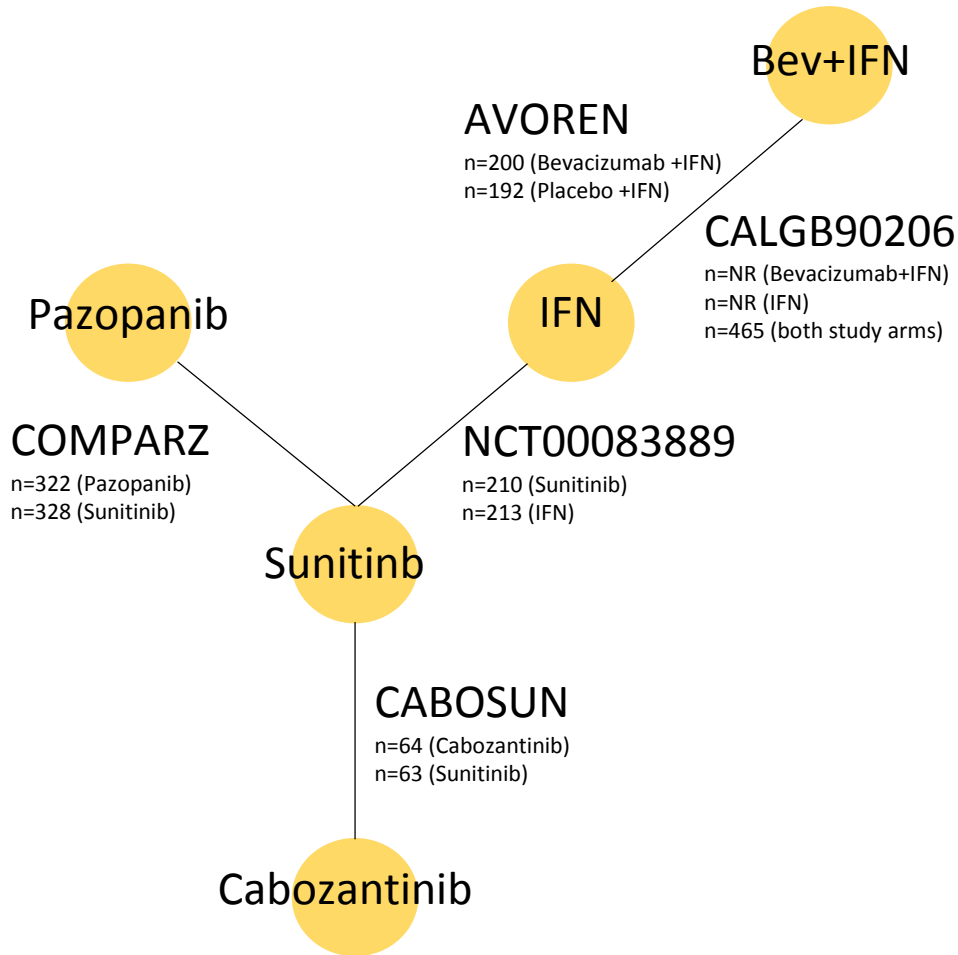


Fig A-4 Network of intermediate risk OS

Bev: bevacizumab; IFN: Interferon; NR=Not reported

2.5 Network of poor risk OS

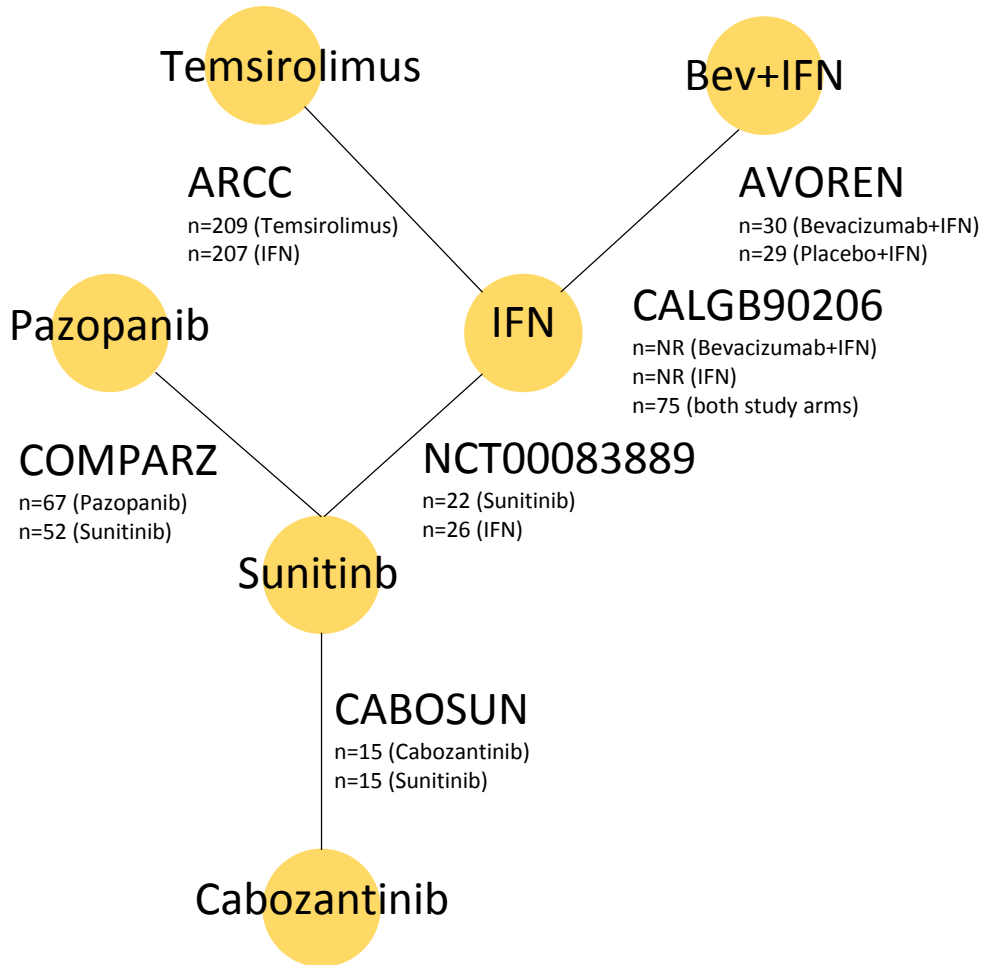


Fig A-5 Network of poor risk OS

Bev: bevacizumab; IFN: Interferon; NR=Not reported

2.6 Network of overall OS

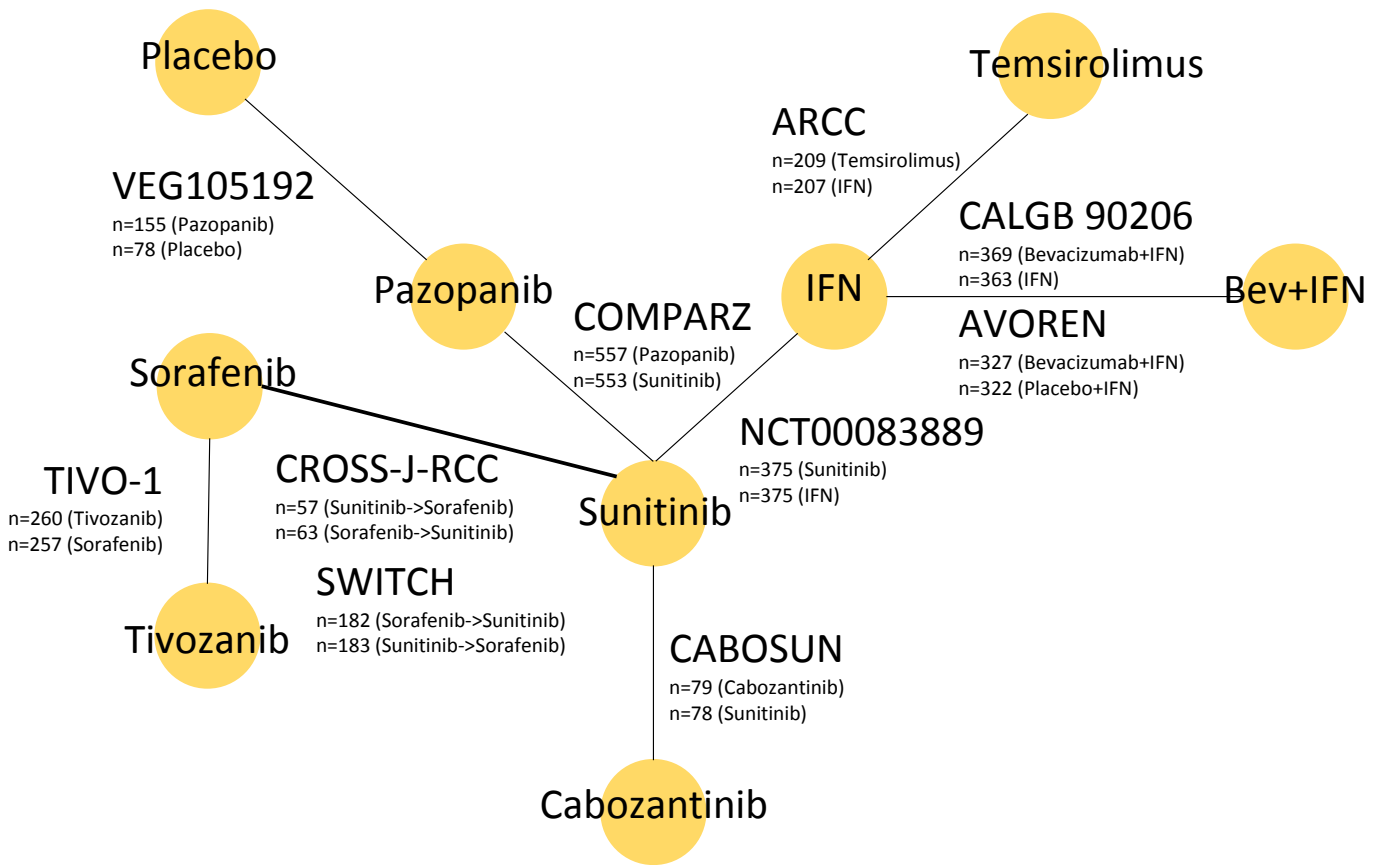


Fig A-6 Network of overall OS

Bev: bevacizumab; IFN: Interferon