Supplementary Material

Substance	Mechanism	Status in other cancers	Status in GEP-NENs
Sunitinib/ Sunitinib malate	Inhibitor of several RTK	FDA approved for kidney cancer and for gastrointestinal stromal tumors; Multiple phase II, III and IV monotherapy trials and several combination under assessment	FDA approved for progressive well-differentiated pNENs in patients with unresectable, locally advanced, or metastatic disease; Phase IV to observe efficacy and safety in pNENs (NCT01525550), (NCT00444795); Phase II in poorly-differentiated advanced NENs (NCT01215578); Phase II + Lantreotide in NENs (NCT01731925); Phase III in patients with islet cell carcinoma (NCT00428597)
Ganitumab (AMG 479)	human mAb against IGF-1R	Phase III in pancreatic adenocarcinoma (NCT01231347): has been terminated; Several monotherapy Phase I/II studies in solid cancer entities (NCT01327612), (NCT00563680), (NCT00719212); several combination under assessment	Phase II in metastatic well-differentiated carcinoid or pNET (NCT01024387) Treatment with single-agent ganitumab failed to result in significant tumor responses [390]
NVP-AEW541	human mAb against IGF-1R	Preclinical [391-404]	Preclinical [14, 135, 405]
Cixutumumab (IMC-A12)	human mAb against IGF-1R	Monotherapy Phase II in recurrent solid cancer (NCT00831844), advanced sarcoma (NCT00668148), Advanced liver cancer (NCT00639509), metastatic melanoma of the eye (NCT01413191), 2nd line therapy in metastatic prostate cancer and mesothelioma (NCT00520481), (NCT01160458); several combination under assessment	Phase I + Everolimus in advanced NE carcinomas (NCT01204476) Phase II in metastatic NENs (NCT00781911)
MK-0646 (Dalotuzumab)	human mAb against IGF-1R	Phase I in solid tumors (NCT01431547),	Phase II in metastatic well-differentiated NENs

		(NCT00635778), (NCT00694356), CRC (NCT00925015), Breast cancer (NCT00759785) and multiple myeloma (NCT00701103); several combination under assessment	(NCT00610129), failed to result in significant tumor responses in monotherapy regimens [129]
Linsitinib (OSI-906)	inhibitor of IGF-1R and IR	Phase III in adrenocortical carcinoma (NCT00924989); Several phase I and II trials and several combination under assessment	N/A
NVP-ADW742	IGF-1R inhibitor	Preclinical [406-409]	N/A
BMS-536924 (HY-10262, CS-0117)	ATP-competitive IGF-1R and IR inhibitor	Preclinical [410-414]	N/A
BMS-754807	reversible inhibitor of IGF-1R/IR family kinases, inhibits IGF-1R, IR, Met, TrkA and TrkB	Phase I monotherapy in neoplasms (NCT00898716) and advanced solid cancer (NCT00569036); Phase I and II under assessment in several combinations	Preclinical [21, 415, 416]
Gefitinib (Iressa, ZD-1839)	EGFR inhibitor	FDA approved for NSCLC and several Phase IV in NSCLC; Various phase II and III trials	Preclinical [361, 417]
Afatinib (BIBW2992, Tovok)	irreversibly inhibits EGFR/HER2	Phase III monotherapy in head and neck neoplasms (NCT01427478), (NCT01345669); in NSCLC (NCT01853826), (NCT00656136); Several phase I and II trials and several combination under assessment	N/A
Erlotinib HCl(OSI-744, CP358774, NSC718781)	HER1/EGFR inhibitor	FDA approved for NSCLC, for first-line treatment and maintenance treatment of NSCLC; approved for pancreatic cancer; Several phase II and III trials and several combination under assessment	Preclincial [241]
Lapatinib (GW572016)	EGFR and ErbB2 inhibitor	FDA approved for hormone-positive and HER2-positive advanced breast cancer and for HER2-overexpressing breast cancer;	N/A

		Several phase II and III trials and several combination under assessment	
AG-1478 (Tyrphostin)	EGFR inhibitor	Preclinical [418-420]	Preclinical [32]
CI-1033 (Canertinib, PD183805)	inhibitor of EGFR and ErbB2	Phase II in lung and breast neoplasms (NCT00050830), (NCT00051051)	N/A
CUDC-101	multi-target inhibitor targeting HDAC, EGFR and HER2	Phase I monotherapy in several cancer entities (NCT01702285), (NCT01171924), (NCT00728793)	N/A
Pelitinib (EKB-569)	EGFR inhibitor	Phase II monotherapy in NSCLC (NCT00067548) and CRC (NCT00072748)	N/A
Icotinib (BPI-2009H)	epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor	Phase IV monotherapy in NSCLC (NCT01465243), (NCT01720901), (NCT01646450); Several phase II and III trials and several combination under assessment	N/A
Neratinib (HKI-272)	HER2 and EGFR inhibitor	Phase III monotherapy in breast cancer (NCT00878709); Several phase I and II trials and several combination under assessment	N/A
AZD4547	FGFR inhibitor targeting FGFR1, FGFR2, and FGFR3	Phase II in patients with Patients With FGFR1 or FGFR2 Amplified Tumors (NCT01795768); Some phase I and combined studies	N/A
Panitumumab	EGFR mAb	FDA approved for EGFR-expressing, metastatic colorectal cancer; Several phase II and III trials and several combination under assessment	Phase 2 in patients with metastatic carcinoid tumor and carcinoid syndrome (NCT01172717)

Suppl. 1: Selected inhibitors and antibodies targeting upstream receptors of the PI3K and MAPK pathway and that are currently under preclinical and clinical assessment in GEP-NENs and other cancer entities.

Substance	Mechanism	Status in other cancers	Status in GEP-NENs
Octreotide (SMS 201-995)	SSTR2 and 5 peptide agonist	Phase II and III in hepatocellular carcinoma (NCT00495846),	FDA approved for metastatic carcinoid tumors and VIPomas; Multiple phase I-IV monotherapy

		(NCT00386984), (NCT00241020); Phase II in liver cancer (NCT00257426); phase III in breast cancer (NCT00002967); Phase II I prostate cancer canceled due to lack of efficiency (NCT00510224); Phase II + fludarabine in non-hodgkin's lymphoma (NCT00002779); phase IV in pituitary adenoma (NCT01371643); Phase II in thyroid cancer (NCT01270321)	studies in neuroendocrine tumore (NCT00171873), (NCT01578239); and assessment in several combinations: e.g. + everolimus (NCT00412061), (NCT00113360), (NCT01567488); + interferon alfa (NCT00569127), (NCT00569127); Phase II + Bevacizumab (NCT00569127) & Pertuzumab (NCT01121939); Phase II + 5FU (NCT00953394); Phase II + Axitinib in WDNEC (NCT01744249)
Lanreotide (BIM23014)	SSTR2 and 5 peptide agonist	Phase II/III in hepatocellular carcinoma (NCT00495846)	Phase III in carcinoid syndrome (NCT00774930), endocrine tumors (NCT00353496); and in non-functioning entero-pancreatic endocrine tumor (NCT00842348), Phase IV in neuroendocrine tumors with carcinoid symptoms (NCT00681187), several phase II trials
Pasireotide (SOM 230)	SSTR1, 2, 3 and 5 peptide agonist	Phase II in thyroid cancer (NCT01270321); Phase II in hepatocellular carcinoma (NCT01639352), (NCT01488487); Phase II + everolimus in uveal melanoma (NCT01252251); Phase III in pancreatic cancer (NCT00994110); Phase II in prostate cancer (NCT01313559); Phase II in NE carcinoma of lung and thymus (NCT01563354); Phase II in non-functioning pituitary adenoma (NCT01283542), (NCT01620138); several phase I trials	Phase II and III in patients with metastatic carcinoid disease (NCT00690430), (NCT00088595); Phase I + everolimus in NENs (NCT00804336), (NCT01263353); Phase II + everolimus in islet cell carcinoma (NCT01374451)
Vapreotide (RC160)	SSTR2 and 5 peptide agonist	Phase III in pancreatic cancer canceled due to lack of response (NCT00014651)	Phase III in in neuroendocrine gastro-intestinal tumors [421]
Seglitide (MK-678)	SSTR2 and 5 peptide agonist	N/A	N/A

L362,855	SSTR2, 3 and 5 peptide agonist	N/A	N/A
BIM 23268	SSTR5 peptide agonist	Preclinical [90, 120, 422-424]	N/A
BIM 23197	SSTR2 and 5 peptide agonist	Preclinical [120, 422, 423, 425]	N/A
BIM 23926	SSTR1 peptide agonist	Preclinical [426-429]	Preclinical [430]
BIM 23120	SSTR2 peptide agonist	Preclinical [425, 428-433]	Preclinical [430]
BIM 23206	SSTR5 peptide agonist	Preclinical [425, 427-433]	Preclinical [430]
BIM 23745	SSTR1 peptide agonist	Preclinical [426, 431, 432, 434]	N/A
NC8-12	SSTR2 and 3 peptide agonist	Preclinical [435]	N/A
BIM-23A779	SSTR1, 2, 3 and 5 peptide agonist	Preclinical [120, 424]	N/A
BIM23052	SSTR2, 3 and 5 peptide agonist	Preclinical [436]	N/A
KE108	SSTR1-5 peptide agonist	Preclinical [90, 437, 438]	N/A
L-054,264	SSTR2 non-peptide agonist	N/A	N/A
L-054,522	SSTR2 non-peptide agonist	Preclinical [54, 439, 440]	N/A
L-779,976	SSTR2 non-peptide agonist	Preclinical [441]	N/A
L-817,818	SSTR5 non-peptide agonist	Preclinical [90, 438, 441]	N/A
BIM-23A758	SSTR2/ D2R agonist	Preclinical: [121]	Preclinical: [122]
BIM-23A760	SSTR2/ D2R agonist	Preclincial: [120, 433, 442, 443]	Preclinical: [122] Phase II study in carcinoid syndrome has been terminated due to poor

			inhibition of GH and IGF-1 (NCT01018953)
BIM-23A387	SSTR2/ D2R agonist	Preclinical: [121, 428, 444-447]	N/A
BIM-23A761	SSTR2/ D2R agonist	Preclincial: [121, 433, 448]	N/A

Suppl. 2 Selected non-radiolabeled SSTR agonstist under current clinical and preclinical assessment in GEP-NENs and other cancer entities.

Substance	Mechanism	Status in other cancers	Status in GEP-NENs
NVP-BEZ235	ATP-competitive inhibitor of class I PI3Ks and mTORC1 and C2	Monotherapy: Phase I/II In PEComa and RCC (NCT01690871) (NCT01453595); Phase II/III in transitional cell carcinoma (NCT01856101); And in several combinations	Phase II in pNENs (NCT01628913, NCT01658436)
LY294002	Inhibitor of p110α, p110δ and p110β, and blocks autophagosome formation	Preclinical [449-457]	Preclinical [131, 132]
XL765/ SAR254409	dual inhibitor of mTOR/PI3k for mTOR, p110α, p110β, p110γ and p110δ	Phase I in solid cancer (NCT00485719) and recurrent glioblastoma (NCT01240460); Combined therapy (NCT00704080), (NCT00777699), (NCT01082068)	N/A
Wortmannin	PI3K, mTOR, DNA-PK, MAPK	Preclinical [458-463]	N/A
GDC-0980/ RG7422	inhibitor of PI3Kα, PI3Kβ, PI3Kδ and PI3Kγ and mTOR	Phase II in endometrial carcinoma (NCT01455493), and RCC (NCT01442090); Phase I in Non-Hodgkin's lymphoma, solid cancers (NCT00854126); combined therapy	N/A
PI-103	ATP-competitive PI3K inhibitor of DNA-PK, p110α, mTORC1, PI3KC2β,	Preclinical [464-469]	N/A

	p110δ, mTORC2, p110β, and p110γ		
GSK1059615	dual inhibitor of PI3Kα, PI3Kβ, PI3Kδ, PI3Kγ and mTOR, DNA-PK	Phase I in solid tumors and lymphoma (NCT00695448), Terminated due to lack of sufficient exposure	N/A
PKI-587/ PF-05212384	dual inhibitor of PI3Kα, PI3Kγ and mTOR	Phase I in neoplasms (NCT00940498) and Phase II in endometrial neoplasms (NCT01420081) and combined therapy (NCT01347866)	N/A
PF-04691502	ATP-competitive, selective inhibitor of PI3K(α/β/δ/γ), mTOR, and Akt phosphorylation on T308/S473	Phase I Monotherapy (NCT00927823) and II in combined approaches (NCT01658176), (NCT01430585)	N/A
(NVP)-BKM120	PI3K inhibitor of p110α, p110β, p110δ and p110γ	Multiple Phase II monotherapy studies, e.g. in locally advanced cervical cancer (NCT01613677), endometrial cancer (NCT01550380), thyroid cancer (NCT01830504), prostate cancer (NCT01385293), (NCT01695473), glioblastoma (NCT01339052), triple negative breast cancer (NCT01629615), CRC (NCT01591421); Several Phase I and multiple combined approaches	N/A
SF1126	pan-PI3K inhibitor	Phase I in solid tumors (NCT00907205)	N/A
PX-866	PI3K(α/δ/γ)	Phase I in advanced solid tumors (NCT00726583); Phase II in prostate cancer (NCT01331083) and glioblastoma (NCT01259869); Several combinations under phase I and II assessment	N/A
XL-147/ SAR245408	reversible class I PI3K inhibitor for wild type and mutant p110α	Phase II in endometrial cancer (NCT01013324), Phase I in glioblastoma (NCT01240460), solid tumors or lymphoma (NCT00486135); Several combinations under phase I and II assessment	N/A
ZSTK474	pan-class I PI3K inhibitor	Phase I/II in neoplasms (NCT01682473), (NCT01280487)	N/A
GSK615 /	dual inhibitor of	Phase I in solid tumors or lymphomas	N/A

GSK1059615	PI3Kα, PI3Kβ, PI3Kδ, PI3Kγ and mTOR	(NCT00695448)	
CH5132799	inhibitor of PI3Kα	Phase I in solid tumors (NCT01222546)	N/A
GDC-0941	inhibitor of PI3Kα, PI3Kβ, PI3Kδ and PI3Kγ, Flt3	Phase I as 2nd line therapy in solid tumors (NCT00876109) and Non-Hodgkin's lymphoma (NCT00876122); Several combinations under phase I and II assessment	N/A
BAY80-6946	reversible PI3K inhibitor for PI3Kα and PI3Kβ	Phase I in advanced cancer (NCT00962611) and lymphoma (NCT01660451); Some combinations under phase I assessment	N/A
CAL-101/ GS-1101 (Idelalisib)	PI3K class I inhibitor of p110δ	In Phase I,II and III assessment as monotherapy and combined regimen in multiple hematologic neoplasms (NCT01306643), (NCT01539291), (NCT01644799), (NCT01569295), (NCT01796470), (NCT01539512)	N/A
BYL719	Inhibitor of PI3K (p110α)	Phase I in Monotherapy of solid tumors (NCT01387321); Some combinations under phase I and II assessment	N/A
MLN1117/ INK1117	Inhibitor of PI3K (p110α)	Phase I in metastatic solid tumors (NCT01449370)	N/A
GSK2636771	Inhibitor of PI3K (p110β)	Phase I in PTEN-deficient solid tumors (NCT01458067)	N/A
TGX-221	Inhibitor of PI3K (p110β)	Preclinical [470]	N/A

Suppl. 3: PI3 kinase targeting biotherapy under current clinical and preclinical investigation

Substance	Mechanism	Status in other cancers	Status in GEP-NENs
Perifosine (KRX-0401)	Targets the PH domain of Akt1/2/3, MEK 1/2, ERK1/2, JNK	Phase III in multiple myeloma (NCT01002248), and + Capecitabine in CRC (NCT01097018); Several Phase I and II studies in solid and hematologic cancers; multiple combined approaches	Preclinical [196]
Triciribine and VD-0002 (Triciribine-phosphate, API-2, NSC-	Targets the PH domain of Akt1/2/3, DNA synthesis inhibitor	Phase I in leukemia (NCT00642031), metastatic cancer (NCT00363454); Phase I/II in combination with chemotherapy in breast cancer (NCT01697293) and ovarian cancer (NCT01690468)	Preclinical [169]

280594)			
PHT-427	dual inhibitor of Akt and PDK1	Preclinical [471]	N/A
GDC-0068	Akt 1, 2, 3	Phase I in solid tumors (NCT01090960) and in Phase I/II in combined approaches	N/A
SR13668	Akt inhibitor	Phase 0/I chemoprevention study in healthy patients [472] (NCT00896207)	N/A
GSK690693	Inhibitor of Akt 1, 2, 3	Phase I in solid cancer (NCT00493818) and relapsed lymphoma (NCT00666081), both studies cancelled	N/A
KP372-1	Inhibitor of Akt, PDK-1, Flt3	Preclinical [473-475]	N/A
A-443654	Inhibitor of Akt	Preclinical [476-479]	N/A
XL-418	Inhibitor of Akt / p70S6K	Phase I in solid tumors (NCT00460278), suspended due to low drug exposure	N/A
MK-2206	Allosteric inhibitor of Akt 1, 2, 3	Phase II monotherapy in ovarian cancer (NCT01283035), in esophageal and gastric cancer (NCT01260701); DLBCL (NCT01466868), (NCT01481129); CRC (NCT01333475), (NCT01802320); AML (NCT01253447); endometrial cancer (NCT01307631), (NCT01312753); liver and biliary cancer (NCT01239355), (NCT01425879); head and neck cancer (NCT01349933), (NCT01370070); breast cancer (NCT01277757); kidney cancer (NCT01239342); various lymphomas (NCT01258998); Several combined approaches	preclinical [480], Phase II in metastatic NENs (NCT01169649)
UCN-01	Inhibitor of PDK-1, Chk1, PKC isoforms	Phase II monotherapy in T-cell lymphoma (NCT00082017), metastatic melanoma (NCT00072189), several phase I and combination studies	N/A
BX-320, BX-795, BX-912	Small molecule PDK-1 inhibitors	Preclinical [481]	N/A

Suppl. 4: Akt and PDK-1 inhibitors under clinical and preclinical assessment in GEP-NENs and other cancer entities.

Substance	Mechanism	Status in other cancers	Status in GEP-NENs
Everolimus (RAD001)	Allosteric inhibitor of mTORC1	FDA approved for subependymal giant cell astrocytoma (SEGA); for advanced hormone receptor-	Phase III—approved for pNENs (NCT00510068)

		positive, HER2-negative breast cancer in combination with Exemestane, for advanced RCC after failure of treatment with Sunitinib or Sorafenib; Several phase III and IV studies with and without combinations ongoing	[244]; Under clinical phase I and II assessment in several combinations (NCT00942682, NCT00576680, NCT01263353, NCT01204476, NCT00843531, NCT01229943); Preclinical assessment in PDNEC [242]
Temsirolimus (CCI-779)	Allosteric inhibitor of mTORC1	FDA approved for advanced RCC; Several phase III and IV studies with and without combinations ongoing	Phase II in advanced NE carcinomas (NCT00093782)[482]
CC-223	ATP-competitive inhibitor of mTORC1/ mTORC2	Phase I/II monotherapy for patients with advanced solid tumors, Non-Hodgkin lymphoma or multiple myeloma (NCT01177397)	N/A
NVP-BEZ235	ATP-competitive inhibitor of class I PI3Ks and both mTORC1 and C2 and DNA-PK	Monotherapy: Phase I/II In PEComa and RCC (NCT01690871), (NCT01453595); Phase II/III in transitional cell carcinoma (NCT01856101); And in several combinations	Phase II in pNENs (NCT01628913, NCT01658436)
LY2584702	Inhibitor of p70S6K	Phase I in solid tumors (NCT01241461)	N/A
AZD-8055	Inhibitor of mTORC1/ mTORC2	Phase I in solid tumors (NCT00731263), (NCT00973076); liver cancer (NCT00999882); and gliomas (NCT01316809)	N/A
OSI-027	Inhibitor of mTORC1/ mTORC2	Phase I in solid tumors and lymphoma (NCT00698243)	N/A
INK-128/ MLN0128	Inhibitor of mTORC1/ mTORC2	Phase I monotherapy in solid tumors (NCT01058707) and myelomas (NCT01118689)	N/A

Suppl. 5: mTOR und p70S6K inhibitors under clinical and preclinical investigation in GEP-NENs and other cancer entities.

Substance	Mechanism	Status in other cancers	Status in GEP-NENs
Vemurafenib (PLX4032, RG7204, RO5185426)	inhibitor of mutant B-RafV600E	FDA and EMA approved for unresectable or metastatic melanoma with the BRAFV600E mutation (NCT01006980) (NCT01667419),	N/A

		Several Phase I, II and III, several combined approaches	
PLX-4720	inhibitor of mutant B-RafV600E and C-Raf-1Y340D/ Y341D	Preclinical [325, 483-488]	N/A
Dabrafenib (GSK2118436)	ATP-competitive inhibitor of B-Raf, mutant B-RafV600E and C-Raf	FDA approved for unresectable or metastatic melanoma with BRAF V600E mutation (NCT01584648), Several Phase I and II, Several combined approaches [489-491]	N/A
MLN2480	pan-Raf inhibitor	Phase I in solid tumors (NCT01425008)	N/A
PF-04880594	inhibitor for B-Raf and C-Raf	Preclinical [492, 493]	N/A
Regorafenib (BAY73-4506, Fluoro-Sorafenib)	multi-target inhibitor for VEGFR1, VEGFR2, VEGFR3, PDGFRβ, Kit, RET and C-Raf	FDA approved for 2^{nd} line therapy in Metastatic CRC (NCT01103323) and 2^{nd} and 3^{rd} line therapy of GIST (NCT01646593), Several Phase I and II, Several combined approaches	N/A
AZ628	wild-type C-Raf and mutant BRAFV600E	Preclinical [494, 495]	
PD98059	non-ATP competitive MEK inhibitor	Preclinical [496-501]	Preclinical [132, 312]
U-0126 (U0126-EtOH)	inhibitor of MEK1 and MEK2	Preclinical [502-515]	Preclinical [274, 312, 385, 516, 517]
BAY43-9006 (Sorafenib)	multikinase inhibitor of C-Raf, B-Raf and VEGFR-2	FDA Approved for advanced renal cell carcinoma and hepatocellular carcinoma	Phase II in Progressive Metastatic Neuroendocrine Tumors (NCT00131911); and in NEN + Cyclo-phosphamide (NCT00605566); Preclinical [309]
Raf265	B-Raf and VEGFR2	Phase II in metastatic carcinoma (NCT00304525),	Preclinical [135, 310, 311]

	inhibitor	Phase I + MEK162 in solid tumors with BRAFV600E Mutations (NCT01352273)	
Teriflunomide (TFN)	Tyrosine kinase inhibitor	Preclinical [518, 519]	Preclinical [318]
Leflunomide (LFN)	Tyrosine kinase inhibitor,	Phase II In brain and central Nervous System Tumors (NCT00003775), Phase II and III in combination in Stage IV Prostate Cancer (NCT00004071)	Preclinical [318]
Tautomycin (TTY)	serine/ threonine phosphatase inhibitor	Preclinical [520-522]	Preclinical [319]
ZM336372	C-Raf inhibitor	Preclinical [523]	Preclinical [321, 517]
AZD6244 (Selumetinib, ARRY 142886)	MEK1 inhibitor	Phase II as monotherapy and in several combined approaches in BRAF mutated solid tumors (NCT00888134),NSCLC (NCT01229150),(NCT01750281), (NCT00890825),(NCT00372788); in differentiated thyroid cancer (NCT01843062); Pancreatic cancer (NCT00372944),CRC (NCT01333475), (NCT00514761); Futher phase II studies in liver cancer, multiple myeloma, melanoma, breast cancer	N/A
PD0325901	ATP-competitive MEK inhibitor	Phase I + PI3K pathway inhibitors in advanced cancer (NCT01347866); Both, Phase II in NSCLC (NCT00174369) and Phase I/II in breast cancer, colon cancer and melanoma (NCT00147550) have been prematurely terminated due to safety concerns	N/A
GSK1120212 (Trametinib, GSK212, JTP-74057)	MEK1 and MEK2 inhibitor	Phase III in BRAF V600E/K Mutation-positive Melanoma (NCT01245062), (NCT01597908), (NCT01584648), (NCT01682083)	N/A
CI-1040 (PD184352)	ATP non-competitive MEK1/2 inhibitor	Phase II in NSCLC, Breast, Colon and Pancreatic Cancer (NCT00034827), (NCT00033384)	N/A
BIX 02189	MEK5 inhibitor	Preclinical [524]	N/A
AS703026 (Pimasertib,	non-competitive inhibitor of	Phase II in N-Ras mutated melanoma (NCT01693068);	N/A

MSC1936369B)	MEK1/2	Phase I in solid tumors (NCT01668017), (NCT00982865), (NCT01390818); Hematological malignancies (NCT00957580); Some combined therapy studies	
TAK-733	non ATP-competitive MEK inhibitor	Phase I in advanced non-hematologic malignancies (NCT00948467)	N/A
BIX 02188	MEK5 inhibitor	Preclinical [524-526]	N/A
GDC-0973/ XL518	MEK inhibitor	Phase 3 + vemurafenib in patients with malignant melanoma (NCT01689519); Several phase I combinatory studies in solid cancers (NCT00467779), (NCT01562275), (NCT00996892), (NCT01506973)	N/A
MEK162	MEK ihibitor	Phase II in metastatic carcinoma (NCT00304525), Phase I + Raf265 in solid tumors with BRAFV600E Mutations (NCT01352273)	N/A
Pazopanib	VEGFR/PDGR/ Raf Inhibitor	FDA approved for advanced soft tissue sarcoma and advanced renal cell carcinoma; Several phase III and IV studies	N/A
BMS-908662/ XL281	RAF Inhibitor	Phase I + Ipilimumab in patients with melanoma (NCT01245556); Phase I/II in CRC (NCT01086267)	N/A
Refametinib, (RDEA119, BAY 86-9766)	MEK inhibitor, MAPK inhibitor	Phase I monotherapy in neoplasms (NCT01179295) and in patients with advanced cancer [527] Phase I and II in several combinations	

Suppl. 6: Inhibitors and activators of Raf and MEK under preclinical and clinical assessment in GEP-NENs and other cancer entities.

Substance	Mechanism	Status in other cancers	Status in GEP-NENs
SCH772984	inhibitor of ERK1/2	Preclinical [528]	N/A
SB 203580	p38 MAPK inhibitor and inhibitor of Akt phosphorylation	Preclinical [529, 530]	Preclinical [132]
BIRB 796 (Doramapimod)	selective p38α MAPK inhibitor	Preclinical [531, 532]	N/A
SB 202190	p38 MAPK inhibitor targeting p38α and p38β	Preclinical [533, 534]	N/A
LY2228820	inhibitor of p38 MAPK	Phase I in advanced cancer (NCT01393990);	N/A

		Phase I/II in ovarian cancer (NCT01663857)	
VX-745	inhibitor of p38α MAPK and p38β MAPK	Preclinical [535]	N/A
SP600125 (EI-305)	inhibitor for JNK1, JNK2 and JNK3	Preclinical [536-544]	N/A
JNK-IN-8	irreversible JNK inhibitor for JNK1, JNK2, JNK3 and JNK4	Preclinical [545]	N/A
LY3007113	inhibitor of p38 MAPK	Phase I in advanced cancer (NCT01463631),	N/A
BVD-523	ERK1/2 inhibitor	Phase I/II in solid tumors (NCT01781429)	N/A
SCH772984	inhibitor of ERK1/2	Preclinical [528]	N/A
SB 203580	p38 MAPK inhibitor and inhibitor of Akt phosphorylation	Preclinical [529, 530]	Preclinical [132]
BIRB 796 (Doramapimod)	selective p38α MAPK inhibitor	Preclinical [531, 532]	N/A
SB 202190	p38 MAPK inhibitor targeting p38α and p38β	Preclinical [533, 534]	N/A
LY2228820	inhibitor of p38 MAPK	Phase I in advanced cancer (NCT01393990); Phase I/II in ovarian cancer (NCT01663857)	N/A
VX-745	inhibitor of p38α MAPK and p38β MAPK	Preclinical [535]	N/A
SP600125 (EI-305)	inhibitor for JNK1, JNK2 and JNK3	Preclinical [536-544]	N/A
JNK-IN-8	irreversible JNK inhibitor for JNK1, JNK2, JNK3 and JNK4	Preclinical [545]	N/A
LY3007113	inhibitor of p38 MAPK	Phase I in advanced cancer (NCT01463631),	N/A
BVD-523	ERK1/2 inhibitor	Phase I/II in solid tumors (NCT01781429)	N/A

Suppl. 7: Selected MAPK inhibitors under clinical and preclinical investigation in GEP-NENs and other cancer entities.