Monthly DRUP Study Newsletter #72, 09 March 2022

The Drug Rediscovery Protocol (DRUP Trial):

A Dutch National Study on Behalf of the CPCT to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to Determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile

Our colleague Maxime van Berge Hennegouwen is leaving the DRUP study team, to take on the next exciting challenge. For now, she will continue her career as a resident not in training at the department of clinical genetics of Erasmus Medical Centre, The Netherlands. We would like to thank Maxime for her great contribution to the DRUP study and wish her all the best with her new position.

Maxime (left) cheering on participants during Stelvio for Life, 2018

Highlights:

1) To date, a total of 1144 patients have been enrolled, of which 140 in stage 3

2) 3rd stage Nivolumab cohort data analysis is in full swing

3) Erdafitinib will be available within the coming week(s)

4) Niraparib availability is in the pipeline and will hopefully be a fact soon

Study Update

To date, a total of 2183 cases have been submitted to the study team and 1144 (52.4%) of these have started a treatment within the DRUP study. For the 3rd stage Nivolumab cohort, a number of 140 patients have been included and this cohort has been put on hold, because the maximum number has been reached. New submissions will be placed on a waiting list until further notice.

We are happy to report that erdafitinib will be available for the DRUP study within the coming week(s). Patients who have FGFR1-4 amplified tumors will be eligible for treatment with this drug, urothelial cell carcinoma patients excluded.

We are also eager to make niraparib available for potential patients in the DRUP study as soon as possible. The preparations to achieve this goal are proceeding well, and we expect the availability to be a fact soon. Niraparib is a PARP inhibitor, for which patients with an alteration in one of the HRD genes might be eligible.

Selpercatinib is expected to be available for the study in June/July 2022. Patients with RET mutations and RET fusions will be eligible for treatment with this compound

We have received good news from Norway that the Norwegian authority has approved our individualized reimbursement model for the third stage of the IMPRESS trial, which is a *DRUP-like trial*.

Information for Participating Sites

Erdafitinib is about to become available for the study within the coming weeks. We will notify you as soon as availability is a fact. This compound will be shipped to your site from our pharmacy.

We are making good progress with 3rd stage Nivolumab cohort data cleaning and validation, and statistical analysis is in full speed currently. We wish to thank you very much for your great effort in this matter.

Please find below some guidelines on stop/restart immunotherapy, and response evaluation time-points:

- For patients who have ongoing clinical benefit (CR, PR or disease control) after 1 year of treatment with nivolumab or atezolizumab + bevacizumab, an interruption of treatment can be considered.
- Pembrolizumab: Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.
- For patients who have ongoing clinical benefit (SD, PR or CR) and who have completed 35 treatments (approximately 2 years) of pembrolizumab interruption of treatment should be considered."

After treatment discontinuation, response evaluations need to be performed:

- First year after treatment interruption: every 3 months
- Second and third year after treatment interruption: every 4 months
- Fourth and fifth year after treatment interruption: every 6 months
- Thereafter: once a year

Warm regards,

Principal Investigators: Henk Verheul, Hans Gelderblom, Emile Voest
Study Coordinators: Maxime van Berge Henegouwen, Laurien Zeverijn, Gijs de Wit, Birgit Geurts, Ilse Spiekman
Clinical Project Manager: Hassan Mkadmi

Table 1: List of pharmaceutical companies & study drugs

Confidential, list might be subjected to change

Currently available

Amgen	Eisai	Bayer	Roche
Panitumumab	Lenvatinib	Regorafenib	Erlotinib
			Trastuzumab+
BMS	AstraZeneca	Clovis Oncology	Pertuzumab
Nivolumab	Olaparib	Rucaparib	Vemurafenib+
Ipilimumab	Durvalumab		Cobimetinib
		MSD	Vismodegib
Novartis	Pfizer	Pembrolizumab	Atezolizumab+
Dabrafenib	Axitinib		bevacizumab
Nilotinib	Crizotinib	Lilly	Alectinib
Trametinib	Sunitinib	Abemaciclib	Entrectinib
Ribociclib	Palbociclib		
Alpelisib	Talazoparib,	BI	Janssen
	dacomitinib	Afatinib	Erdafitinib
	Lorlatinib		

Committed

Lilly	GSK
Selpercatinib	Niraparib

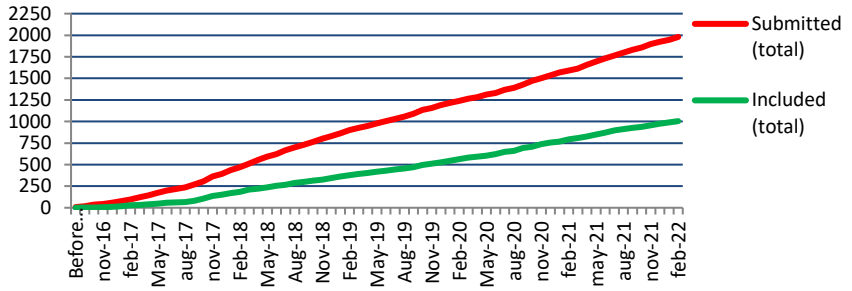
Calendar & publicity

April, 19th Pharma Meeting

Table 2: Submission and accrual overview

March 7th, 2022

Submitted	1980
Excluded	898 (45.4%)
Pending	78 (3.9%)
Enrolled	1004 (50.7%)



Submissions and accrual 3rd stage cohort Nivolumab for MSI tumors

March 7th, 2022

Submitted	203
Excluded	61 (30.0%)
Pending	2 (1.0%)
Enrolled	140 (69.0%)

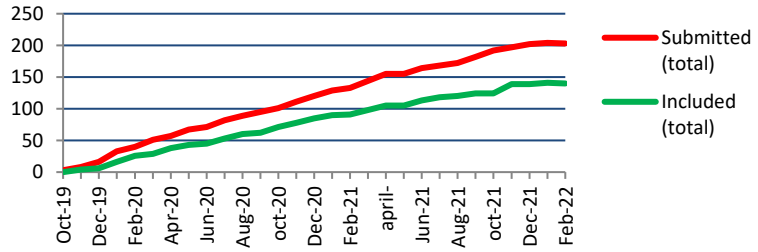


Table 3 : Participating sites

Currently open for inclusion (*n* = 35)

- AMC
- AVL
- Amphia
- Bravis
- Deventer Ziekenhuis
- Erasmus MC
- ETZ
- Franciscus
- Gelderse Vallei
- Gelre Ziekenhuizen
- Haaglanden MC
- Haga ziekenhuis
- Isala
- Martini
- Maxima MC
- MC Leeuwarden
- Meander
- Nij Smellinghe
- Treant Zorggroep
- NWZ
- Reinier de Graaf
- Rijnstate
- Spaarne Gasthuis
- St. Antonius
- UMC Groningen
- UMC Leiden
- Maastricht UMC
- Radboud UMC
- UMC Utrecht
- VieCuri
- ZG Twente
- Zuyderland
- Rivas Zorggroep
- OLVG
- VUMC

In preparation

- Maasstad

Table 4: DRUGS OPEN FOR INCLUSION			
Nilotinib	KIT_{mut} GIST	$PDGFRA_{mut}$ GIST	$PDGFRA_{mut}$ mesothelioma
	$PDGFRB_{ampl}$ CRC	KIT_{mut} melanoma	KIT_{mut} kiemcel tumor
Nivolumab + ipilimumab	HML tumors		
Olaparib	ATM_{mut} tumors	HRR deficient tumors (2x)	All other tumors with HRR alterations
Panitumumab	RAF/RAS_{wt} sarcoma	RAF/RAS_{wt} HNSCC	$EGFR_{mut}$ NSCLC
	RAF/RAS_{wt} thyroid ca	RAF/RAS_{wt} salivary duct ca	RAF/RAS_{wt} cervical ca
	RAF/RAS_{wt} endometrial ca	RAF/RAS_{wt} meningioma	RAF/RAS_{wt} eye melanoma
	BRAF-KRAS-NRASwt GBM	RAF/RAS_{wt} vulvar ca	RAF/RAS_{wt} ACUP
	RAF/RAS_{wt} anal ca		
Pembrolizumab	HML HNSCC	HML prostate ca	HML breast ca
	HML miscellaneous	HML > 290 (all type)	
Regorafenib	RET+ NSCLC	RET+ esthesioneuroblastoma	KIT_{mut} melanoma
	KIT_{mut} Thymuscarcinoma	$BRAF_{mut}$ ACC	$FLT1_{ampl}$ duodenal carcinoma
	RAF1mut NSCLC		
Dabraf + Tramet	$BRAF_{mut}$ GBM	$BRAF_{mut}$ low grade glioma	$BRAF_{mut}$ NEC colon
	$BRAF_{mut}$ cholangiocarcinoom	$BRAFV600E_{mut}$ breast cancer	$BRAFV600E_{mut}$ grade 3 glioma
Dabrafenib	$BRAF_{mut}$ GBM	$BRAF_{mut}$ UCC	
Trametinib	$NRAS_{mut}$ ovarian ca	$MAP2K1_{mut}$ NSCLC	$NRAS_{mut}$ NSCLC
	$MAP3K1_{mut}$ NEC	$MAP3K1_{mut}$ cervical ca	$MAP2K1_{mut}$ CRC
	$MAP2K4_{mut}$ CRC	$MAP3K1_{mut}$ ACUP	$MAP2K4_{mut}$ cholangioca
	$MAP2K4_{mut}$ ovarian ca	$MAP3K1_{mut}$ breast ca	$MAP2K4_{mut}$breast ca
	$NRAS_{mut}$ thyroid cancer	$MAP3K1_{mut}$ prostate	$NRAS_{mut}$ pleomorphic tumor
	$NRAS_{mut}$ prostate	$BRAF_{fusie}$ (pilocytair) astrocytoom	$NRAS_{mut}$ yolk sac tumor
	$GNA11_{mut}$ melanocytaire tumor	$NRAS_{mut}$ cholangio cancer	$BRAF_{exon\ 12\ deletion}$ NSCLC
	$BRAF_{fusie}$ NSCLC	$NRAS_{mut}$ salivary duct ca	$MAP2K4_{loss}$ pancreas cancer
	$NF1_{mut}$ low grade glioma	$BRAF_{fusie}$ pancreas cancer	$MAP2K1_{mut}$ pancreas cancer
	$MAP2K1_{mut}$ stomach cancer	BRAF-fusie Urotheelcelca	MAP2K1mut CUP
	KRASmut Erdheim Chester disease	BRAF fusie glioneurale tumor	NF1mut GBM
	MAP2K4mut/loss CRC		
Trastuz. + Pertuz.	$HER2_{ampl}$ CRC	$HER2_{ampl}$ cholangio ca	HER2mut Sinonasal carcinoom
	$HER2_{mut}$ ovarian ca	$HER2_{ampl}$ salivary duct ca	$HER2_{ampl}$ NSCLC
	$HER2_{mut}$ CRCglio	$HER2_{mut}$ cervical ca	$HER2_{ampl}$ vulvar ca
	$HER2_{ampl}$ cervical ca	$HER2_{ampl}$ hidradenoca	$HER2_{ampl}$ UCC
	$HER2_{ampl}$ ovarian ca	$HER2_{ampl}$ NEC	$HER2_{mut}$ UCC
	$HER2_{mut}$ ACC	$HER2_{ampl}$ duodenal cancer	HER2ampl melanoom
Vemur. + Cobimet.	$BRAF_{mut}$ salivary duct	$BRAF_{mut}$ ACUP	$BRAF_{mut}$ ovarian ca
	$BRAF_{mut}$ thyroid ca	$BRAF_{non\text{-}V600mut}$ NSCLC	$BRAF_{V600Emut}$ Erdheim Chester Disease
	BRAFV600 mut pap craniofaryngeoom	BRAFV600E mut NSCLC	
Vismodegib	PTCH1mut sarcoma (Ewing)	$PTCH1_{mut}$ medulloblastoma	
Erlotinib	$EGFR_{mut}$ GBM	CRC with EGFR mutations	EGFR fusions GBM
Lenvatinib	$FGFR1_{ampl}$ CRC	$FGFR2_{ampl}$ CRC	$FGFR2_{ampl}$ breast ca
	$FGFR1_{ampl}$ osteosarcoma	$FGFR1_{ampl}$ NSCLC	$FGFR3_{mut}$ anal ca
	$FGFR2_{ampl}$ esophageal ca	$FGFR2_{mut}$ endometrial ca	$FGFR3_{ampl}$ SGT
	$FGFR2_{fusie}$ ACUP	$FGFR2_{fusie}$ cholangioca	$FGFR1_{ampl}$ breast ca
	$FGFR2_{ampl}$ urachal ca	$FGFR3_{mut}$ UCC	$FGFR2_{mut}$ ACC
	$FGFR3_{amp}$ NEC nasal cavity	$FGFR1_{mut}$ glioneural tumor	$FGFR3_{mut}$ HNSCC
	$FGFR3_{fusie}$ GBM	$FGFR2_{mut}$ digital papillary cancer	$FGFR2_{fusion}$ pancreas cancer
	$FGFR2_{amp}$ NSCLC	$FGFR3_{fusie}$ cholangioca	$FGFR2_{mut}$ cholangioca/biliary tract
	$FGFR1_{amp}$ pancreas cancer	$FGFR2_{mut}$ salivary duct cancer	FGFR3 mut cholangiocarcinoma
	FGFR3 mut anaplastisch schildklierca	FGFR3 fusie NSCLC	FGFR1mut glioma
Sunitinib	KIT_{mut} thymus ca	$PDGFRA_{mut}$ prostate ca	$FGFR1_{ampl}$ UCC
	$PDGFRB_{ampl}$ breast ca	$PDGFRB_{mut}$ osteosarcoma	$PDGFRA_{ampl}$ ACC
	$FGFR1_{ampl}$ ovarian cancer	$PDGFRA_{ampl}$ tyroid cancer	$FLT3_{ampl}$ CRC
	$CSF1R_{mut}$ CRC	KIT_{ampl} NSCLC	$FGFR2_{ampl}$ ovarian cancer
	RET fusion pancreatic cancer	FLT3mut CRC	FLT3 mut PMP
Crizotinib	ALK_{fus} IMT	MET_{ampl} CRC	ALK_{mut} CRC
	MET_{mut} NSCLC	MET_{ampl} esophageal ca	MET_{ampl} NSCLC
	ALK_{mut} thyroid	ALK+ sarcoom	ALK_{fusion} CUP
	MET_{fusion} anaplastic tyroid cancer	MET_{ampl} HCC	MET_{ampl} GEJ-tumor
	MET_{amp} ovarium cancer	MET_{mut} (papillair) kidney cell cancer	ALK+ Anaplastisch grootcellig T-cellymfoom
Axitinib	$FLT1_{ampl}$ CRC		
Rucaparib	HRR_{alt} ovarian cancer	HRR_{alt} prostate cancer	HRR_{alt} pancreatic cancer
	HRR_{alt} Breast cancer	All other tumor types	
Alectinib	ALK fusion (all tumor types)	ALK mutations/amplification (all tumor types)	
Abemaciclib	$CCND1_{ampl}$ UCC	$CCND1_{ampl}$ NSCLC	$CCND1_{ampl}$ prostate cancer
	$CCND1_{ampl}$ melanoma	$CCND3_{ampl}$ small intestine	CDK4ampl (lipo)sarcomen
	CCND1ampl urachusca	CDK4 amp GBM	CDK4 amp duodenumcarcinoom
	CCND1ampl plaveiselcelca blaas	CCND3ampl oesofagusca	CCND1ampl ovariumcarcinoom
Alpelisib	Miscellaneous tumors with $PIK3CA_{mut}$	$PIK3CA_{mut}$SCC gynecologic tumors	PIK3CAmut gynecologic tumors
	PIK3CAmut upper-GI tumors (esophagus, stomach)	PIK3CAmut HNSCC	$PTEN_{loss}$ prostate cancer
	Double hit cohort (histology-agnostic)	PIK3CAmut prostaatcarcinoom	PTENloss RCC
	PTENloss gyn tumors (ovarian/endometrial)	PIK3R1mut gyn tumors (cervix/endometrial)	PTENloss salivary gland carcinoma
Talazoparib	ATM/ATRmut tumors	FANCA/FANCC/FANCD2/FANCF/FANCMmut tumors	RAD51/RAD51B/RAD54L/NBN/MRE11mut tumors
	mutations in other HRR genes (BARD1/BRIP1/CHECK1/2/PALB2/PRA1)	Tumors with HRD signature (with or without BRCA VUS)	Tumors with double-hit in HRR pathway
lorlatinib	ROS-1 fusion NSCLC		
Legend	Cohort closed	Cohort on hold	Slots available

Table 5: DRUGS CLOSED FOR INCLUSION			
Palbociclib	$CDKN2A_{loss}$ GBM	$CDKN2A_{loss}$ CRC	$CDKN2A_{loss}$ PEComa
	$SMARCA4_{mut}$ ovarian ca	$CDKN2A_{mut}$ cholangio ca	$CDKN2A_{mut}$ melanoma
	$CDKN2A_{loss}$ duodenal ca	$CCND1_{ampl}$ NSCLC	$CDKN2A_{loss}$ RCC
	$CDKN2A_{loss}$ HNSCC	$CDKN2A_{del}$ esophageal ca	$CCND1_{ampl}$ melanoma
	$CDKN2A_{mut}$ uveal melanoma	$CDK4_{ampl}$ Sarcoma	$CCND1_{ampl}$ NET
	$CDKN2A_{loss}$ pancreatic ca	$CDKN2A_{loss}$ vulvar ca	$CDK4_{ampl}$ astrocytoma
	$CDKN2A_{del}$ NSCLC	$CDK4_{ampl}$ prostate cancer	$CDK4_{ampl}$ esophageal cancer
	$CDKN2A_{loss}$ pNET	$CDKN2A_{loss}$ ovarian cancer	$CCND2_{ampl}$ CRC
	$CDK6_{ampl}$ prostate cancer	$SMARCA4_{mut}$ CRC	
Durvalumab	MSI tumors		
Cabozantinib	MET_{ampl} melanoma	RET_{fusion} NSCLC	MET_{ampl} teratoma
	$NTRK2_{mut}$ GIST	MET_{mut} oesofagus cancer	
Ribociclib	$CDKN2A_{loss}$ prostate cancer	$CDKN2A_{loss}$ ependymoma	$CDK4_{ampl}$ melanoma
	$CDKN2A_{del}$ anaplastic meningioma	$CDKN2A_{loss}$ thymus carcinoma	$CDKN2A_{loss}$ Ewing Sarcoma
	$CDKN21_{del/mut}$ bladder cancer	$CDK6_{amp}$ mucoepidermoid cancer	$CDKN2A_{del}$ mesothelioma
	$CDKN2A_{loss}$ ceruminous cancer	$CDKN2A_{del}$ salivary gland cancer	
Afatinib	$NRG1_{fusie}$ NSCLC	$NRG1_{fusie}$ breast ca	$NRG1_{fusie}$ GI tumors
	$NRG1_{fusie}$ miscellaneous (all tumors)	$HER4_{mut}$ NSCLC	
Nivolumab	MSI tumors	HML tumors	
Olaparib	$BRCA_{mut}$ tumors		
Pembrolizumab	HML CRC	HML eso/card/stomach	
Dabraf + Tramet	$BRAF_{mut}$ NSCLC		
Trastuz. + Pertuz.	HER2 (exon 20) mut NSCLC		
Nivolumab	3rd stage MSI tumors		