Monthly DRUP Study Newsletter #71, 07 February 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

May we please introduce to you our new colleague Ilse Spiekman

Hello everyone! My name is Ilse Spiekman and I am 27 years old. I'm a new study coordinator at the DRUP-trial, working form the Radboud University Medical Centre. After graduating as a medical doctor in 2018, I have been working as a resident, not in training, in the department of internal medicine in two different hospitals. I started my resident internal medicine last year. During this period, I've seen many patients diagnosed with cancer and how they were treated. This has sparked my interest in personalized cancer treatments and hopefully this will be the approach of the future! I'm happy to be part of this team and I am looking forward to discover new insights in this area.

Highlights:

1) To date, a total of 1130 patients have been enrolled, of which 141 in stage 3

2) Preparations for 3rd stage Nivolumab cohort analysis are in full swing

3) Selpercatinib, erdafitinib and niraparib compounds will be available soon

4) EU application was submitted to promote *DRUP-like* trials in Europe

Study Update

To date, a total of 2150 cases have been submitted to the study team and 1130 (52.6%) of these have started a treatment within the DRUP study. For the 3rd stage Nivolumab cohort, a number of 141 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.

Zorginstituut will hopefully grant approval to nivolumab in the near future. In the meantime, the pharmaceutical company and health insurers are searching for a solution to have the possibility to treat patients with a MSI-tumor with nivolumab until nivolumab is officially approved. We will inform you once we have received more information about this.

The compound selpercatinib is about to become available for the DRUP study. To get started, a kick-off meeting with our pharma partner Lilly has been planned for this week. We are making the same good progress for product erdafitinib, also this product will be introduced fairly soon. The same applies for niraparib, as the preparations are progression steadily for this compound.

Patients who have FGFR1-4 amplified tumors will be eligible for treatment with erdafitinib within DRUP, urothelial cell carcinoma patients excluded. Patients with RET mutations and RET fusions will be eligible for treatment with selpercatinib. Niraparib is a PARP inhibitor, for which patients with an alteration in one of the HRD genes might be eligible.

We are also working on a KWF application in which we describe the main challenges and our main future perspectives to receive a grant for the next few years. In the future we hope to preserve the DRUP infrastructure as it is now. Moreover, we aim to establish an international cooperation on data sharing, to collect more data for rare combinations of tumor types and 'actionable' molecular variants, and to validate and implement therapies more easily. One important step in the right direction has already been taken with the memorandum of understanding that has been signed between the Nordic DRUP-like trials and DRUP.

We are very happy to share with you that on 22nd of January, under the supervision of our co-principle investigator Hans Gelderblom, an EU application (PCM4EU) was submitted with the aim to promote initiation and conduct of *DRUP-like* trials within Europe in favour of Personalised Cancer Medicine. This application will allow more EU countries to benefit from the current successful DRUP trial design and infrastructure. On top of that, the following items were also part of this EU application: education, pooled data analysis of rare cohorts, set up of an MTB structure and uniform diagnostics. In addition to the Netherlands and Scandinavian countries, nine other EU countries are participating in this application.

Information for Participating Sites

3rd stage Nivolumab cohort data are currently being prepared (cleaned and validated) for analysis. You have been contacted by our data management, who requested you to complete data entry and to resolve any open queries for involved patients. We like to thank concerned sites for responding to our call and their great support in this matter! We need your help to achieve this milestone successfully!

We regulatory receive from you a so called *drug receipt conformation* for drugs which is delivered to you by our pharma partners Eisai or Roche. There is no need to provide us with it, so you can omit this. Please refer to table 1 for involved drugs.

Please be informed that if a site wants to transfer a patient to another site, this is only allowed in exceptional cases and it must always be discussed in advance with the study team.

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

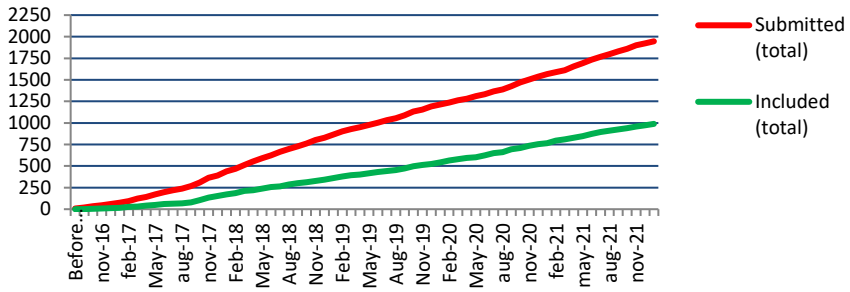
February, 10th : selpercatinib kick-off meeting (Lilly)

17-19 February: perspectivas em oncologia, Portugal

Table 2: Submission and accrual overview

February 7th, 2022

Submitted	1946
Excluded	823 (42.3%)
Pending	134 (6.9%)
Enrolled	989 (50.8%)



Submissions and accrual 3rd stage cohort Nivolumab for MSI tumors

February 7th, 2022

Submitted	204
Excluded	60 (29.4%)
Pending	3 (1.5%)
Enrolled	141 (69.1%)

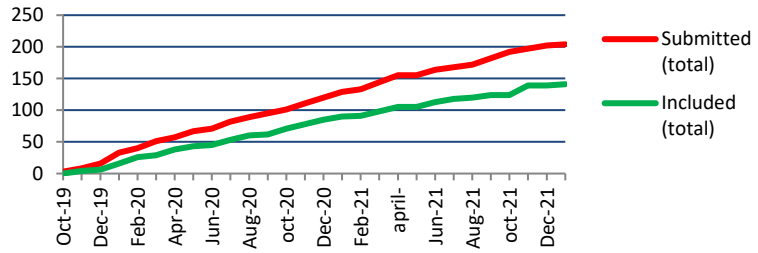


Table 3 : Participating sites

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
	RAF/RAS_{wt} 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
	$BRAF_{mut}$ 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	$PTCH1_{mut}$ sarcoma	$PTCH1_{mut}$ 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_{amp}l 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	
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
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		