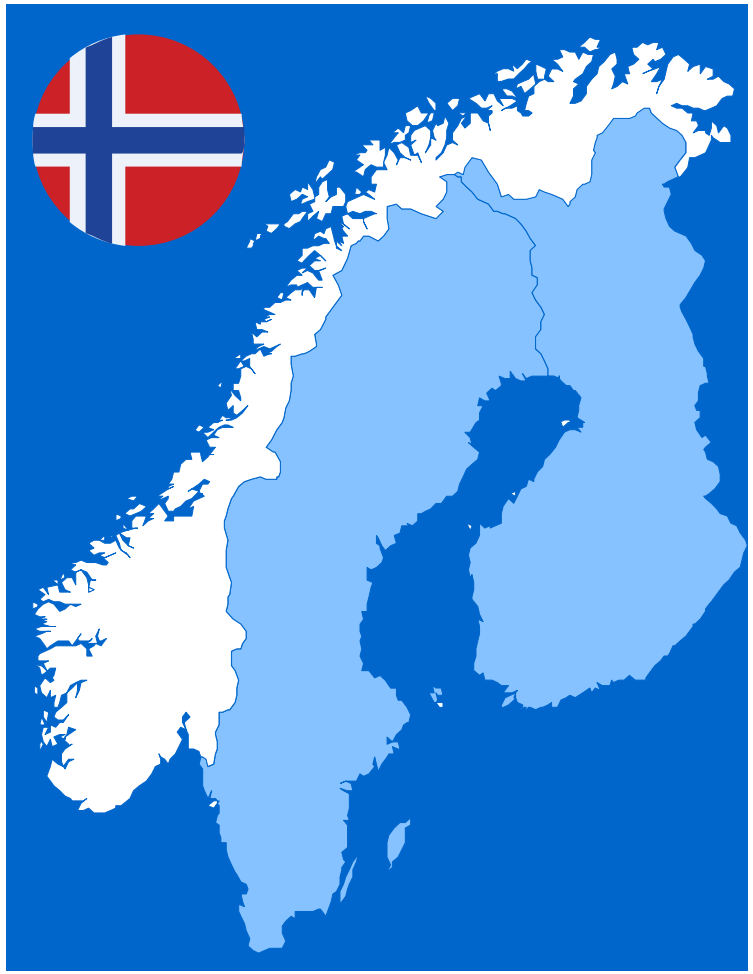
The Norwegian precision cancer medicine implementation initiative: Prototype learning ecosystem for precision oncology

Prof Kjetil Taskén

Implementing precision cancer medicine in Norway via interconnected initiatives:



InPreD Norway:
National infrastructure for precision diagnostics

IMPRESS-Norway:
Improving public cancer care by implementing **pre**ci**s**ion medicine in Norway

TRAIN:
Tumour **R**esponse Evaluation using **A**rtificial **I**ntelligence for **N**orway

INSIGHT / INCLUDE:
Regulatory framework for implementing precision medicine into the Norwegian health care system

CONNECT Public-private partnership:
Norwegian Precision Cancer Medicine Implementation Consortium

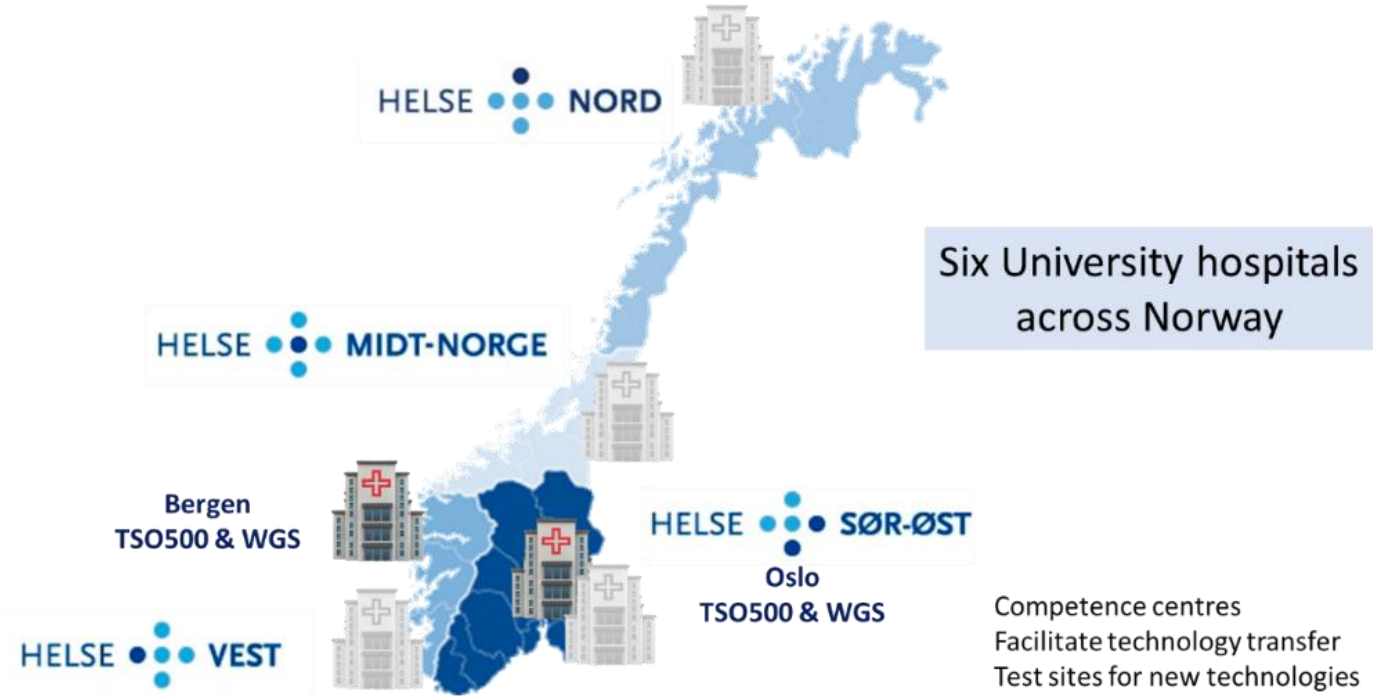
Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

IMPRESS-Norway: Strategic development towards a national trial as a public-private cooperation

DRUP, drug discovery protocol; HDIR, Directorate of Health; HTA, health technology assessment; NIPH, Norwegian Institute of Public Health; NoMa, Norwegian Medicines Agency; PCM, precision cancer medicine; PI, principal investigator; PPP, public-private partnerships; RWE, real-world evidence.

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

National infrastructure for precision diagnostics, InPreD Norway



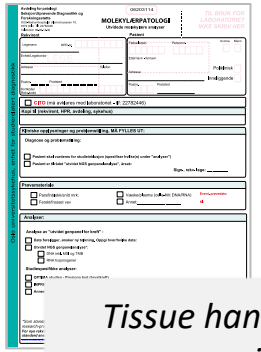
The six pathology departments at the university hospitals as core of InPreD-Norway

- Network for NGS accessible for all pathology departments being established
- Patient recruitment to clinical trials is available for all hospitals.

Aim: Equal access to expanded molecular testing – and experimental treatment for cancer patients

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

Institutional and national molecular tumour board*



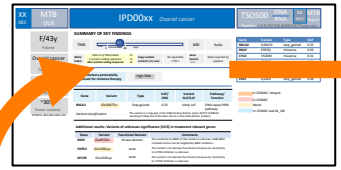
Ordering form

Tissue handling, processing, sequencing, data analysis, interpretation

Preliminary report

Molecular Multidisciplinary Team report

Final Molecular Multidisciplinary Team rapport



- Clinical note
- Pathology report: Molecular findings and the final Molecular Multidisciplinary Team rapport

Meeting:

Pre- Molecular Multidisciplinary Team meeting

Molecular Multidisciplinary Team meeting

Present:

- **Leader: Pathologist**
- **Co-leader: Oncologist**
- **5 Molecular Multidisciplinary Team key persons**
- IMPRESS study doctors
- InPreD staff involved lab/data
- Relevant researchers and clinicians/pathologists

- **Leader: Oncologist**
- **Co-leader: Pathologist**
- **5 Molecular Multidisciplinary Team key persons**
- IMPRESS study doctors
- **Referring clinician and pathologist**
- Other clinicians/pathologists
- **Virtual, national**

*Assignment from the Regional health authorities to OUS, InPreD.
Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

XX DEC | MTB OUS

IPD00xx *Ovarial cancer*

TSO500 DNA/RNA | XX NOV | MTB Report

Pipeline: 2.0.0.70/ 0.8.4/GRCh37/Tumor only

F/43y
Patient

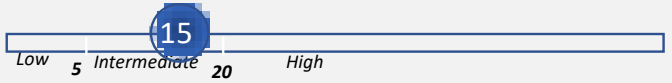
Ovarial cancer
Y of D: 20xx
Tumor type

Metastasis
FF
Sample type

~30%
Tumor content

IPD0011-D01/R03-M01-F03

SUMMARY OF KEY FINDINGS

TMB				MSI	Stable
SNVs/ indels	*Total nr of SNVs/indels* in protein coding sequence: **alter protein coding sequence**	20 14 **8**	**Copy number variants (>4, loss)**	No reportable CNVs	**Gene fusions** RNA: None reported by pipeline

Biomarkers potenatially relevant for immune therapy	High TMB

Gene	Variant	Type	VAF/ CNG	Variant GoF/LoF	Pathway/ function
BRCA2	Gln3047Ter	Stop gained	0.32	Likely LoF	DNA repair/HRR pathway

Variant classification: The variant is a stop gain in the DNA binding domain (exon 24/27) of BRCA2 resulting in likely loss of function due to a truncated protein product.

Gene	Variant	Type	VAF
BRCA2	Q3047X	stop_gained	0.32
BRAF	E695Q	missense	0.26
CYLD	V500M	missense	0.31
XPO1	S387C	missense	0.31
MTOR	E1336K	missense	0.27
STAT3	E272K	missense	0.25
ESR1	Q226X	stop_gained	0.38

In COSMIC- hotspot
In COSMIC
Novel
In COSMIC and GL_DB

Additional results: Variants of unknown significance (VUS) in treatment relevant genes

Gene	Variant	Functional Domain	Comments
BRAF	Glu695Gln	Kinase domain	The sensitivity to BRAFi of this variant is unknown. V600 BRAF mutated tumors can be targeted by BRAF inhibitors..
FGFR2	Glu1336Lys	none	The variant is of unknown functional consequence. Sensitivity to mTOR inhibitors is unknown.
MTOR	Glu1336Lys	none	The variant is of unknown functional consequence. Sensitivity to mTOR inhibitors is unknown.

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

IMPRESS-Norway: Improving public cancer care by implementing **pre**ci**s**ion medicine in Norway

Proposed national Drug Rediscovery Protocol (DRUP)-like study for Norway

IMPRESS NORWAY

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

DRUP in the Netherlands and similar studies in US, Canada, the Nordics and other European countries are ongoing or about to start

DRUP
the Drug Rediscovery Protocol

Expanded use of existing anticancer drugs

TAPUR
Targeted Agent and Profiling Utilization Registry Study
American Society of Clinical Oncology
ASCO

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

ProTarget

A Danish Nationwide Clinical Trial on Targeted Anti-Cancer Treatment based on Molecular Profiling

MEGALiT

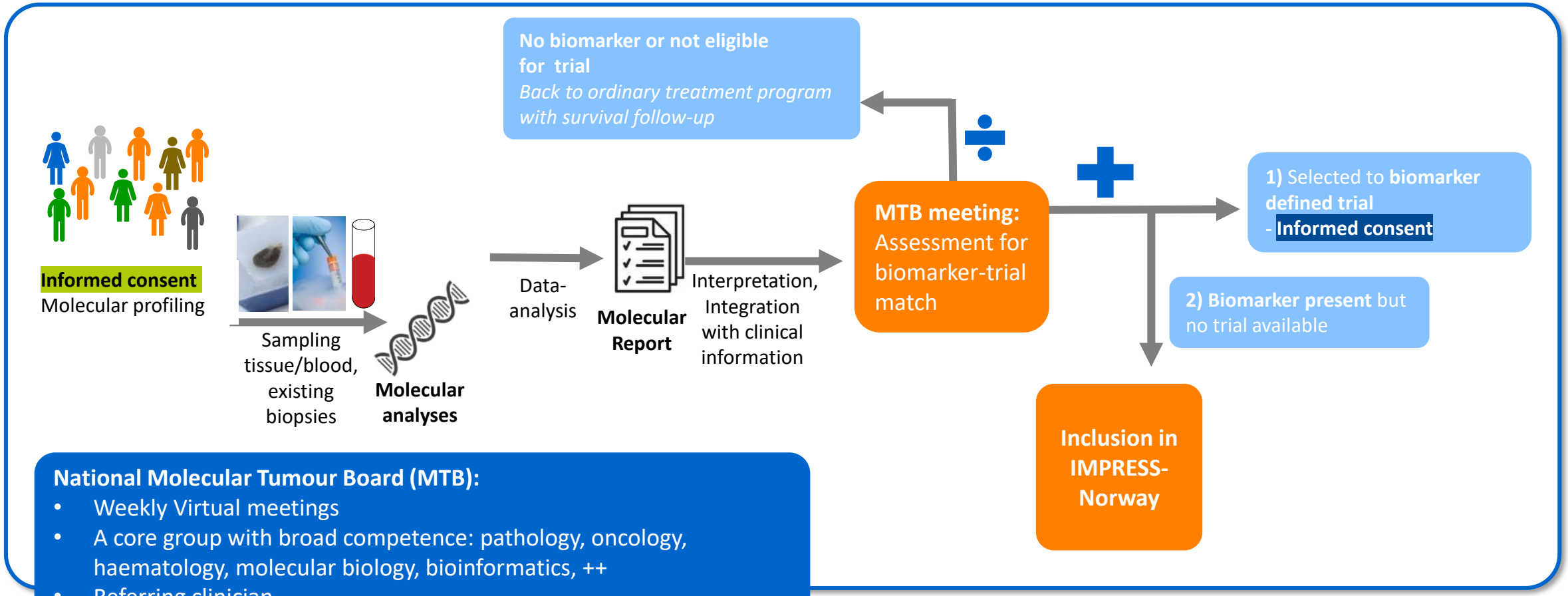
IMPRESS NORWAY

FINPROVE

DRUG REDISCOVERY PROGRAM IN FINLAND

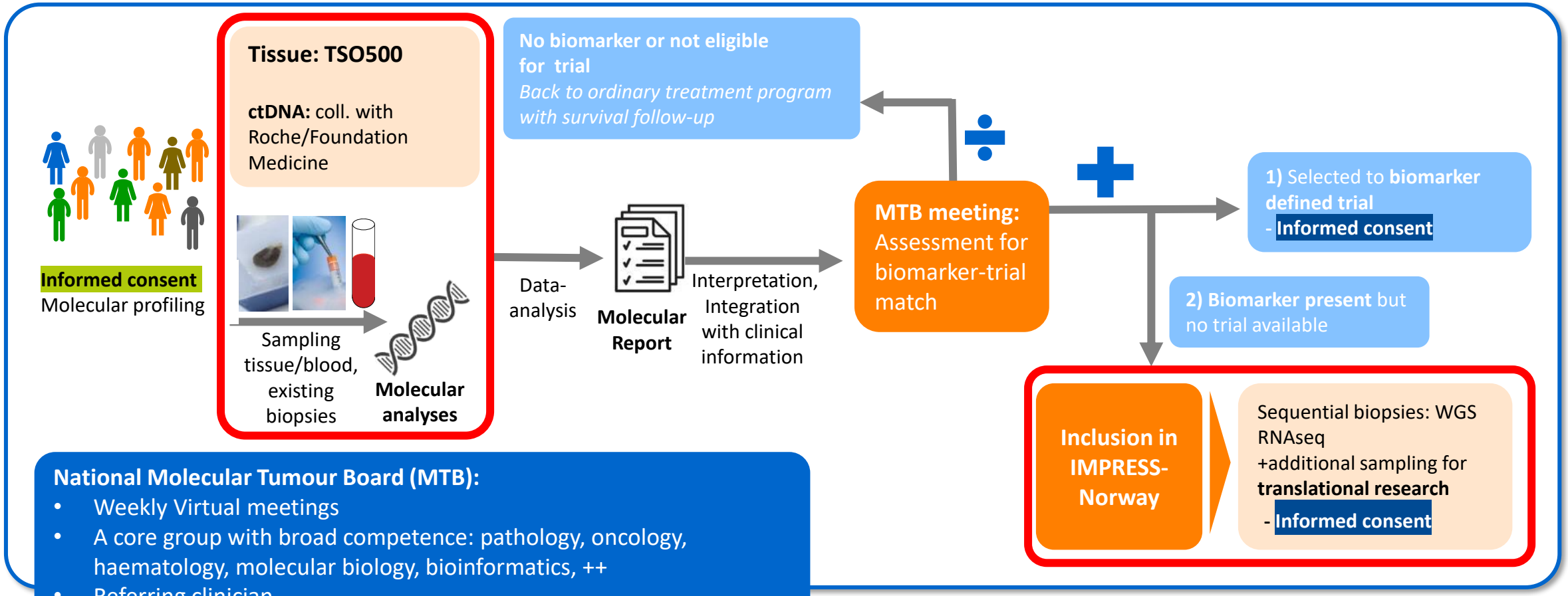
Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

InPreD: Diagnosis and assessment for cancer patients where experimental treatment and clinical trial inclusion is an option



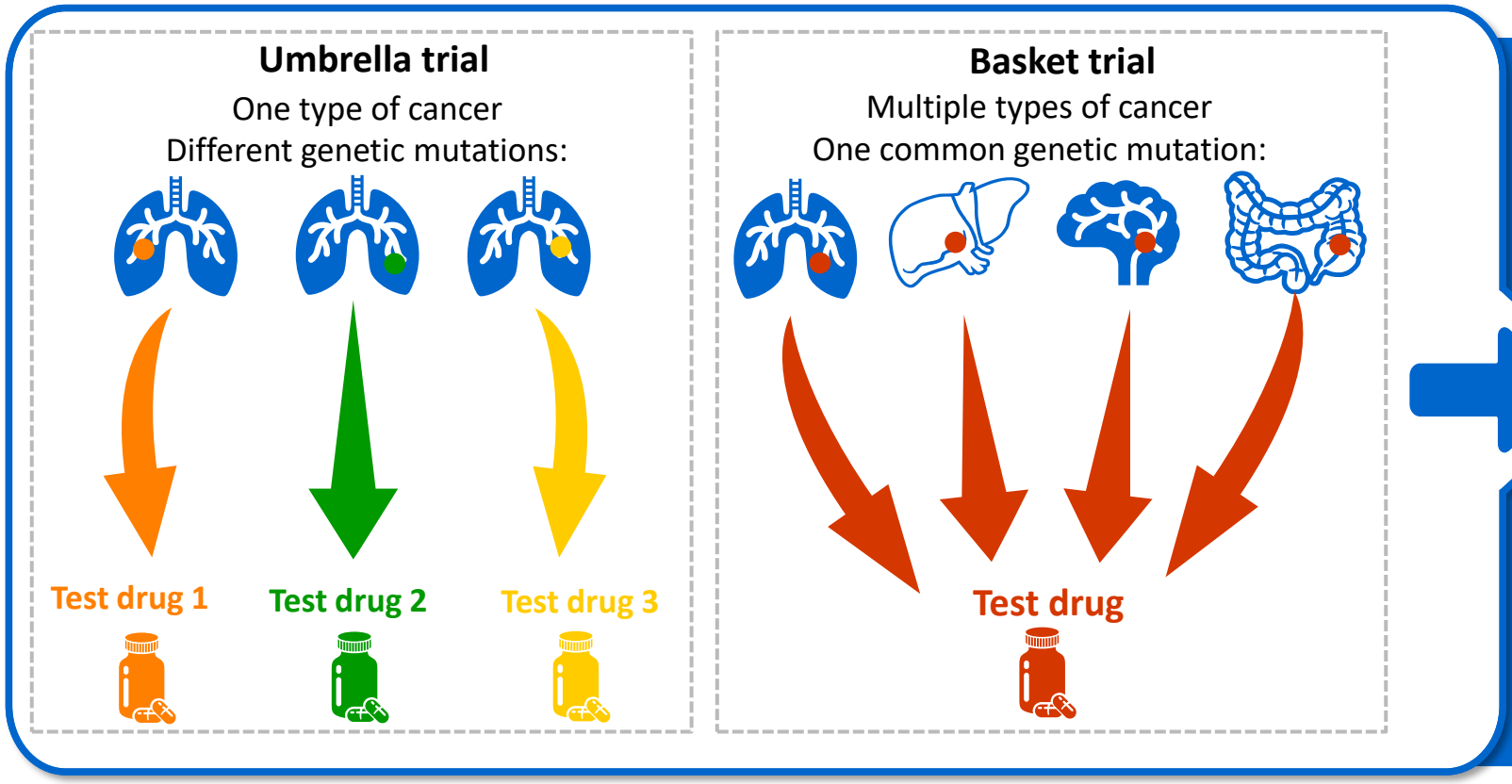
Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

InPreD: Diagnosis and assessment for cancer patients where experimental treatment and clinical trial inclusion is an option



Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

Study-design: combined umbrella-basket, Simon two-stage model

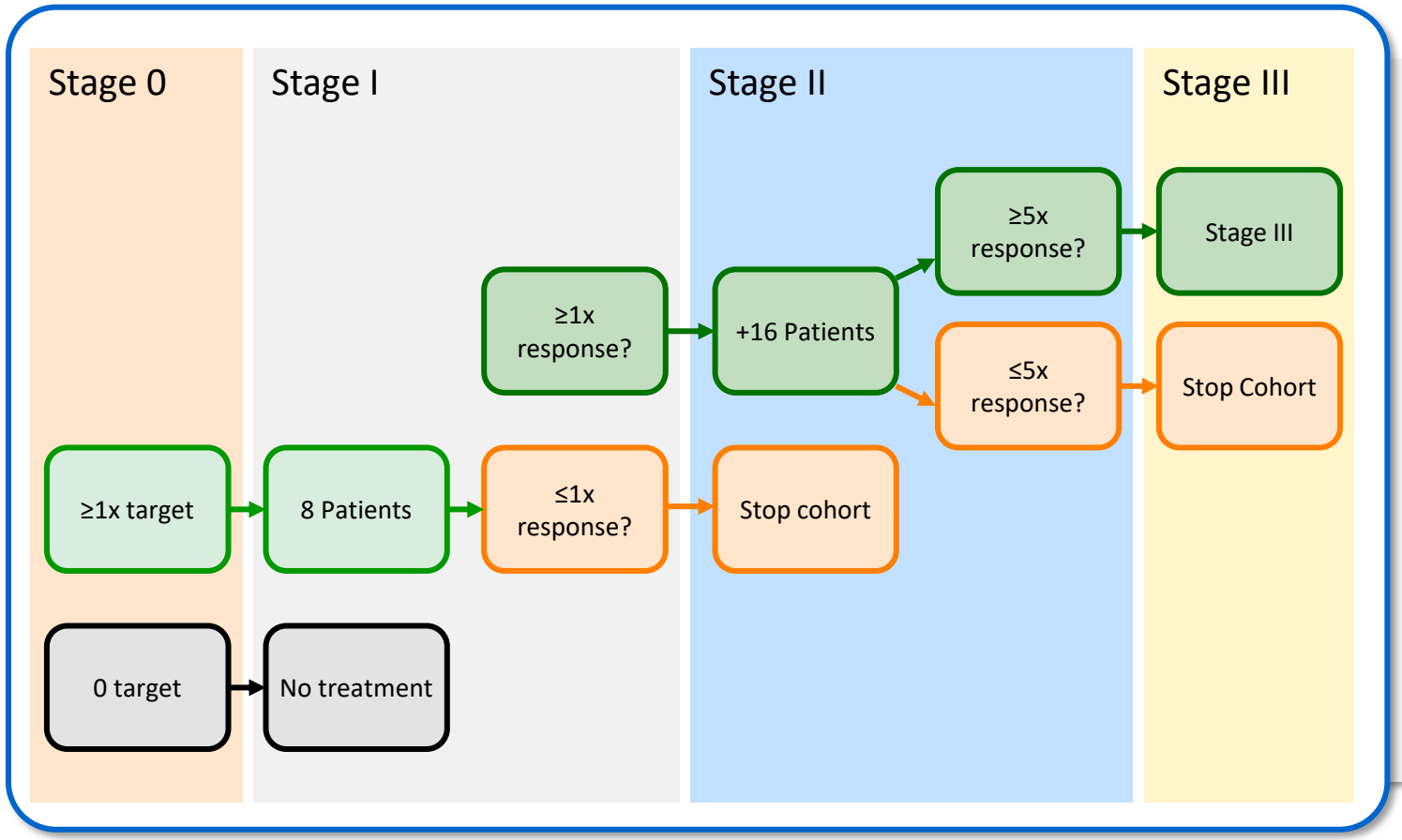


A combination:

- Different cancers
- Different genetic mutations or other disease-modifying changes
- Treatment to fit the individual patient disease and tumour profile
- A portfolio of registered drugs

Figure adapted from: West HJ. *JAMA Oncology* 2017; **3**:423.
Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

Study-design: combined umbrella-basket, Simon two-stage model



Eligible patients with identified actionable targets with matching drug from the study drug portfolio will be included in an IMPRESS-Norway cohort

A cohort will consist of patients with the same indication and same actionable target.

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

Dynamic protocol

Patients with advanced disease
- Solid tumours and haematological indications

Entry by testing (level 1 lab / 500-gene panel test)

Approved (FDA/EMA) drugs (incl. approved combinations)
- Known safety-profile, off-label use
- Small molecule substances, monoclonal antibodies, immunotherapy

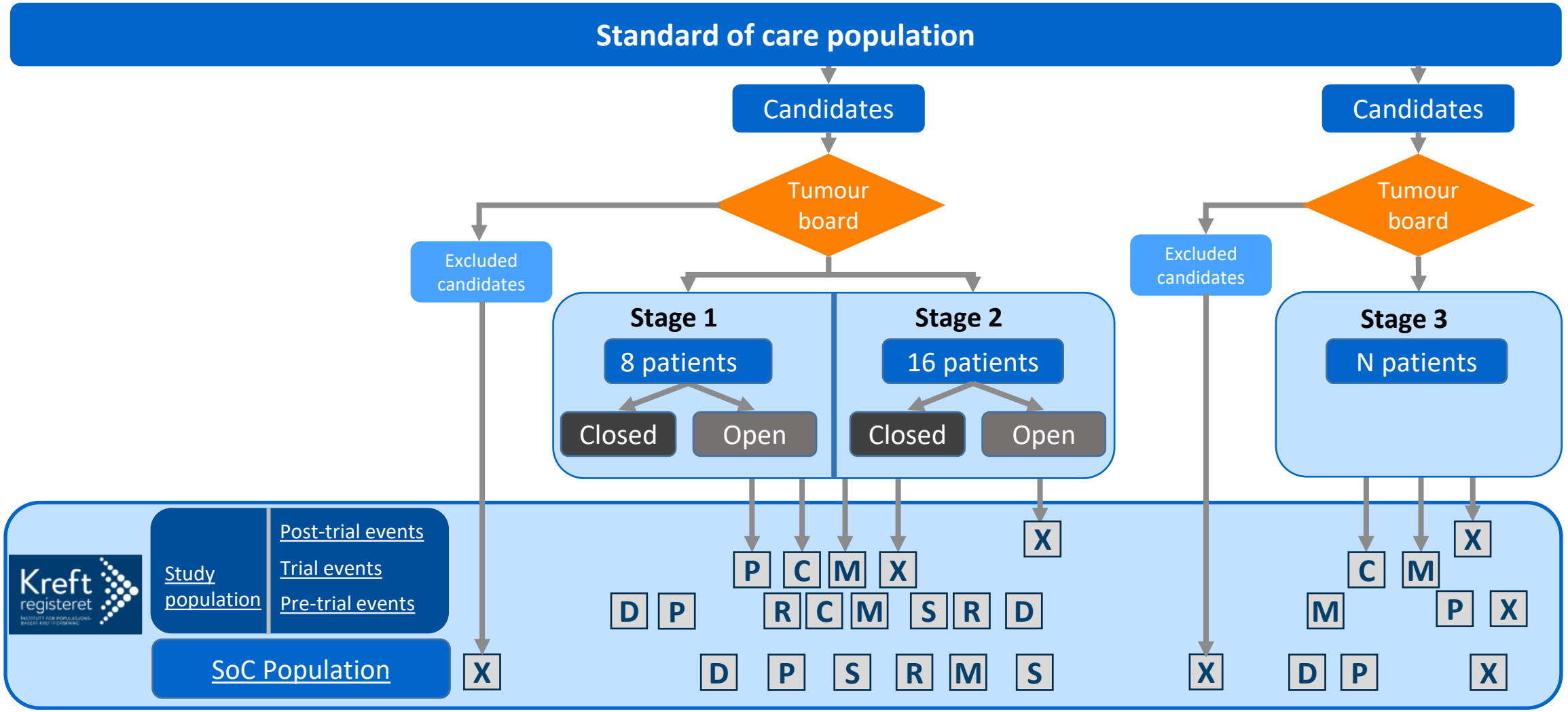
Close collaboration and coordination with DRUP-network trials in Europe and beyond:
- Negative cohorts from other countries not to open in Norway
- Data aggregation across studies for slowly accruing cohorts (details being defined)

Evaluation via national molecular tumour board
- Amalgamated algorithm defined by inclusion criteria for each drug

Integration into Cancer Registry of Norway
- Data in, can get data out for long-term follow up and for synthetic control cohorts

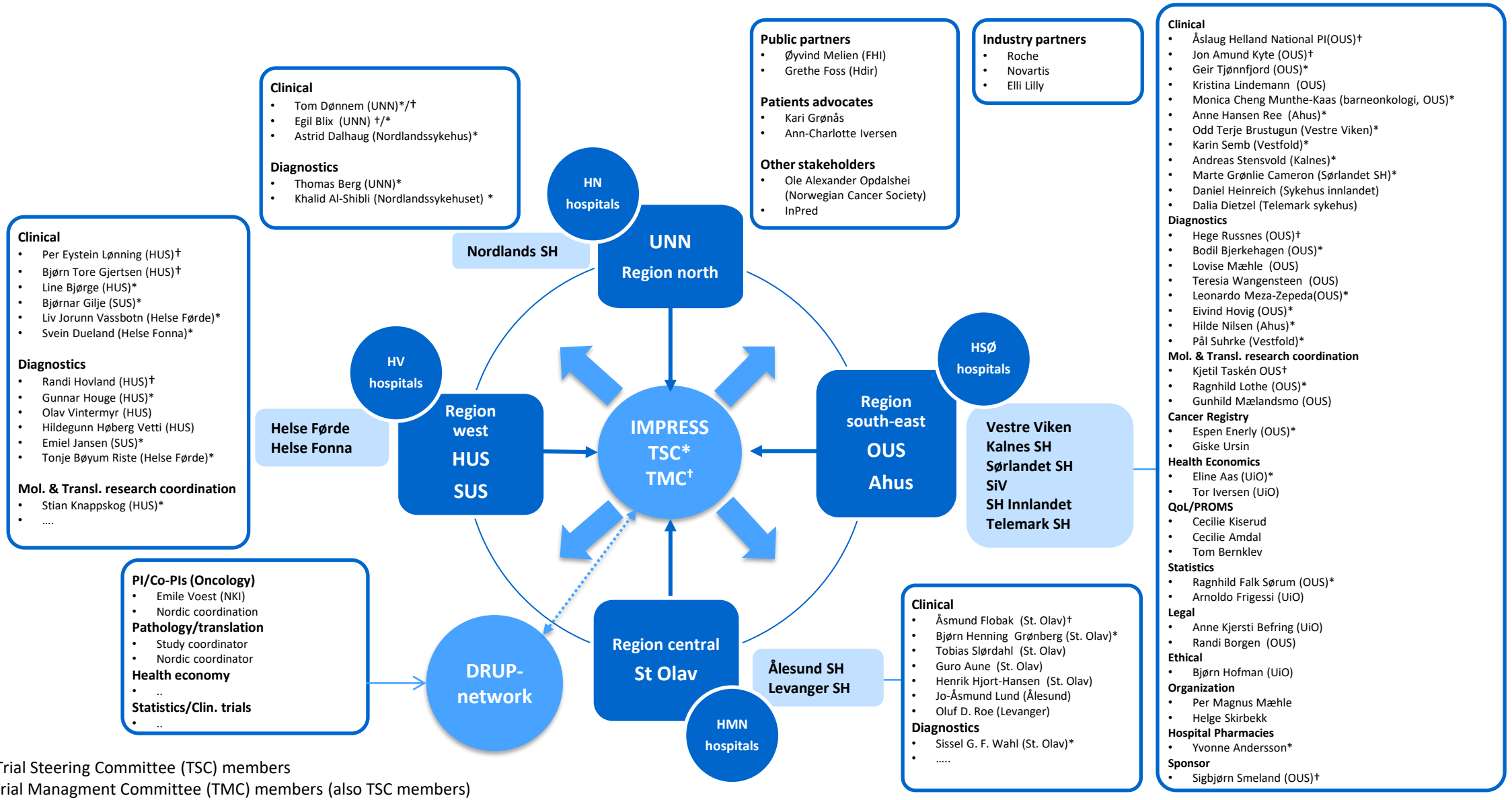
EMA, European Medicines Agency; FDA, Food and Drug Administration.
Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

Integration into Cancer Registry of Norway



SoC, standard of care.
Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

IMPRESS-Norway: Overview of organisation per May 2021



*Trial Steering Committee (TSC) members

†Trial Managment Committee (TMC) members (also TSC members)

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

IMPRESS-NORWAY:

1:1 Meetings with Pharma Companies from March 2020

AbbVie
Astra Zeneca
Bayer
BMS
Merck Serono
MSD
Novartis
Pfizer
Roche
Sanofi
Amgen
Astellas
GSK
Takeda
Karyopharm Blueprint medicines
Eli Lilly
Pierre Fabre
InCyte

April 2020 – May 2020: Internal evaluation ongoing

June 2020 – applications and moving to decisions

- Company-specific processes
- Involvement of and decision making on Nordic, European, Global level within Pharma
- Individual follow-up by OUH team in close collaboration with OCC

January 2021 – Roche enters IMPRESS with 8 drugs, number of treatment slots and project with Roche Dagnostics / Foundation Medicine on Ct-DNA

June 2021 – Novartis enters IMPRESS with 2 drugs, number of treatment slots and plans for including more drugs H2021

September 2021- Eli Lilly enters IMPRESS with 1 drug, number of treatment slots and plans for inluding more drugs H2021

Ct-DNA, circulating tumour DNA

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

IMPRESS-NORWAY

OSLO CANCER CLUSTER

ABOUT US

Ingvild Hagen, Area Owner of Personalized Healthcare at Roche Norway, hopes this will motivate other companies to join the effort of bringing precision medicine to cancer patients. Photo: Roche

First pharma company joins IMPRESS-Norway

Friday, January 29, 2021 / by Sofia Lindén

- ALK-inhibitor (Alecensa/alectinib)
- Hedgehog signaing inhibitor (Erivedge/vismodegib)
- ROS-1 inhibitor (Rozlytrek/entrectinib)
- Immune checkpoint inhibitor (Tecentriq/atezolizumab)
- VEGF-inhibitor (Avastin/bevacizumab) combined with immune checkpoint inhibitor (Tecentriq/atezolizumab)
- BRAF inhibitor (Zelboraf/vemurafenib) combined with MEK inhibitor (Cotellic/cobinemtinib)
- HER-2 inhibitor (PHESGO/pertuzumab-trastuzumab)

https://oslocancercluster.no/2021/01/29/first-pharma-company-joins-impress-norway/

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

Drug Specific Amendments – tailored to each drug

Drug specific amendment – Name of Drug

IMPRESS NORWAY

Protocol Title:
Improving public cancer care by implementing Precision medicine in Norway

Version number: 1.2
Sponsor Name: Sigbjørn Smeland, Oslo University Hospital
EudraCT no: 2020-004414-35

2 DRUG-SPECIFIC SCHEDULE OF ACTIVITIES

The table only includes drug-specific activities. All activities described in the protocol should be followed.

Study procedures	Screening	Treatment phase						EOT	Survival FU
	(1-21 days)	D1	W8	W16	W26	W39	QW13		Q6M for2 years
TSH / fT4*	x			x	x	x	x		x

* Addition of more endocrine markers ACTH/cortisol/FSH/LH/IGF1/prolactin if clinical indicated

3 DRUG-SPECIFIC SELECTION CRITERIA

The general inclusion / exclusion criteria in the main protocol section 5.1 and 5.2 are valid unless otherwise is specified in this drug specific manual.

Inclusion criteria:

- Performance status ECOG 0-1.
- Biomarkers indicating response to immunotherpy, like high tumour mutation burden (10 mut/MB, - or otherwise agreed with Roche representatives), mutation in the POLE -gene, MSI-high are characteristics that will be analysed and used in cohort definitions.
- 18 years or older

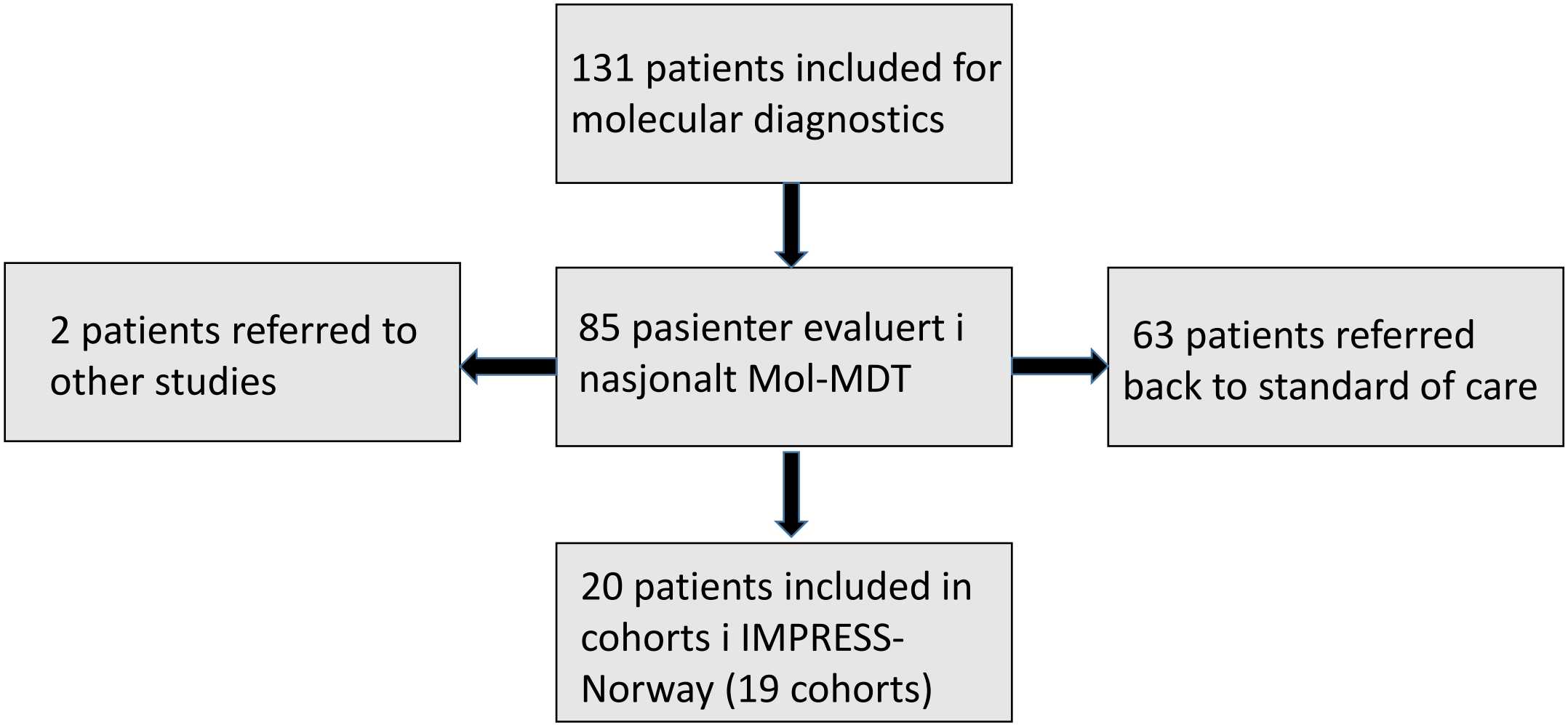
Exclusion criteria:

- Diagnosis of immunodeficiency or medical condition requiring high doses (>30 mg prednisolone daily) of systemic steroids or other forms of immunosuppressive therapy
- Presence of resistance mutations in XX or XX

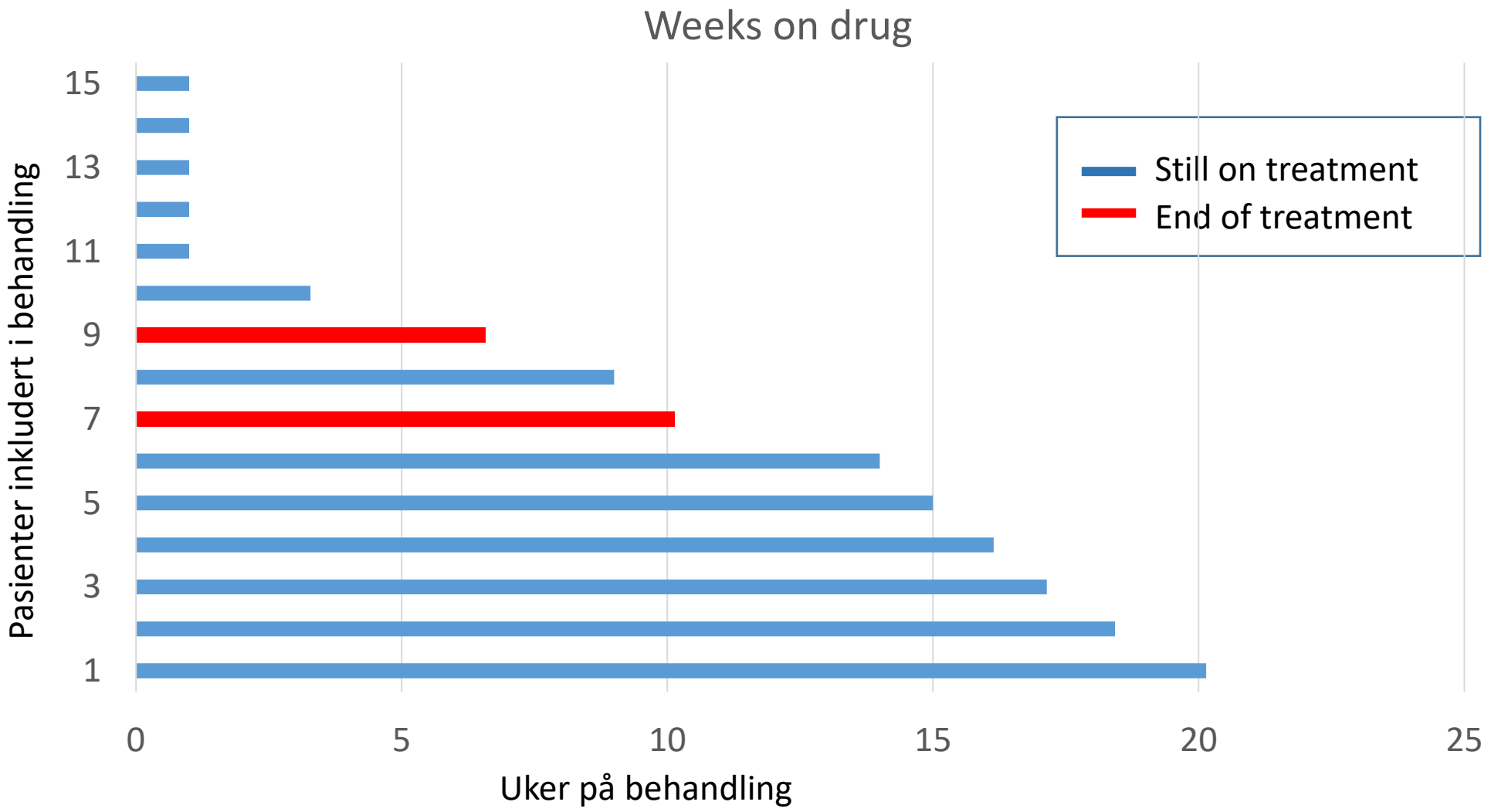
Drugs in IMPRESS-Norway - Status per 19.10.2021

1	Alecensa (Alectinib hydrochloride)	Roche	ALK-inhibitor	Included
2	Phesgo (Pertuzumab and Trastuzumab)	Roche	Anti-Her2	Included
3	Tecentriq (Atezolizumab)	Roche	Anti-PDL1	Included
4	Avastin (Bevacizumab)	Roche	Anti-VEGF	Included
5	Cotellic (Cobimetinib)	Roche	BRAF-V600-inhibitor	Included
6	Zelboraf (Vemurafenib)	Roche	MEK-inhibitor	Included
7	Erivegde (Vismodegib)	Roche	Hedgehog (SMO)-inhibitor	Included
8	Rozlytrek (Entrektinib)	Roche	TRK-, ROS1- and ALK-inhibitor	Included
9				
10	Tafinlar (dabrafenib)	Novartis	BRAF-inhibitor	Exp. Okt 2021
11	Mekinist (trametinib)	Novartis	MEK-inhibitor	Exp. Okt 2021
12				
13				
14				
15				
16				
17				
18	Retevmo (selpercatinib)	Eli Lilly	RET-hemmer	Exp. Feb 2022
19				
20	Melfalan (lav-dose), AML subpopulation	Generic	Alkylerende cytostatika	Exp. Nov 2021
21	Gleevec (imatinib) for pas. W. suitable mut.profil	Generic	BCR-Abl/c-kit/PDGF-R TKI	Exp. Jan 2022
22				
23				

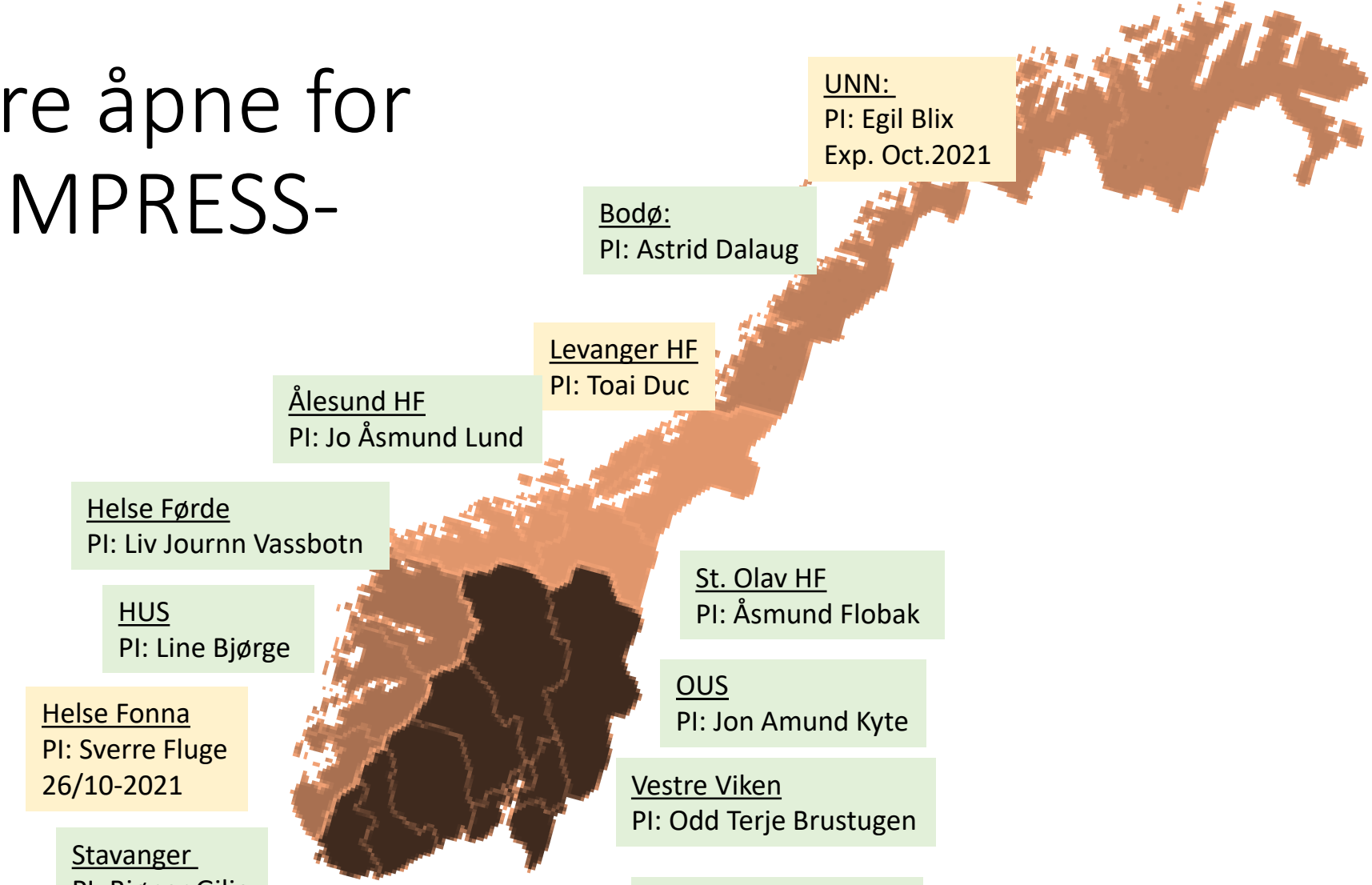
IMPRESS-Norway – Status per 31.10.2021



IMPRESS-Norway – Status per 19.10.2021

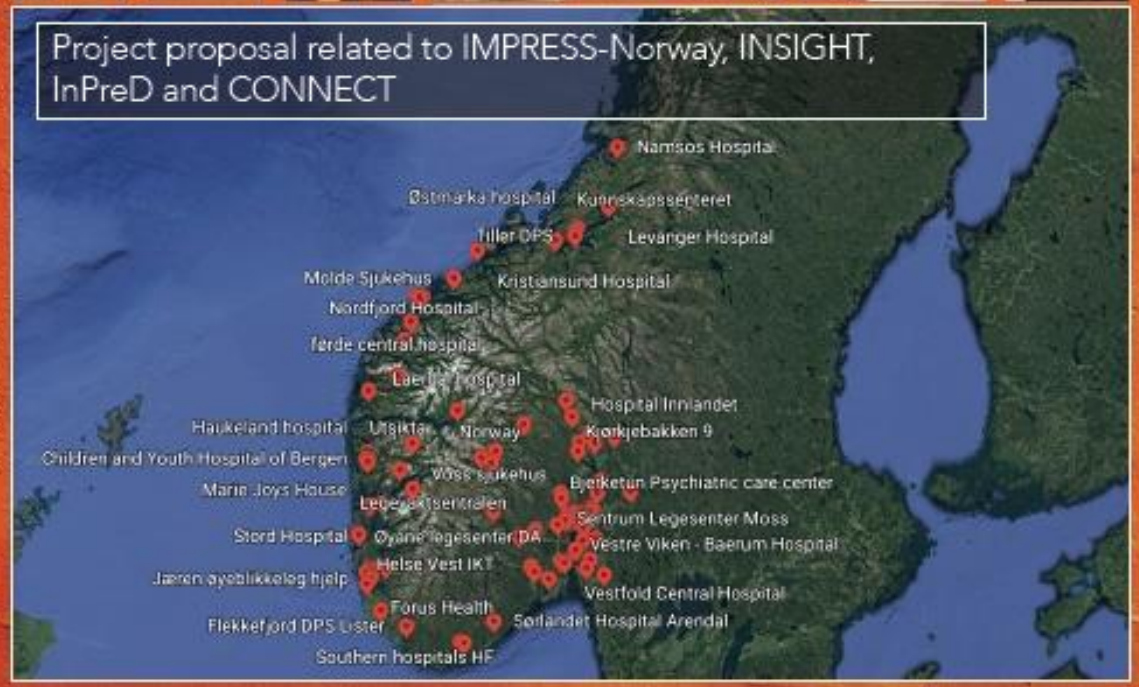


Status sentre åpne for inklusjon i IMPRESS-Norway



Tumour Response Evaluation using Artificial Intelligence for Norway

TRAIN



Application number: ES673500 - IPOFFENTLIG20

Innovation Project for the Public Sector

Project phase: *Under assessment*

Helse Bergen HF - Dept. of Radiology + MMIV

Workflow integration of the technical solution

Oslo University Hospital

Sponsor for IMPRESS-Norway trial

Goal: Simplify the radiology-anchord tumour response evaluation using RECIST criteria. Allow for the exchance of RECIST-based assessments.

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

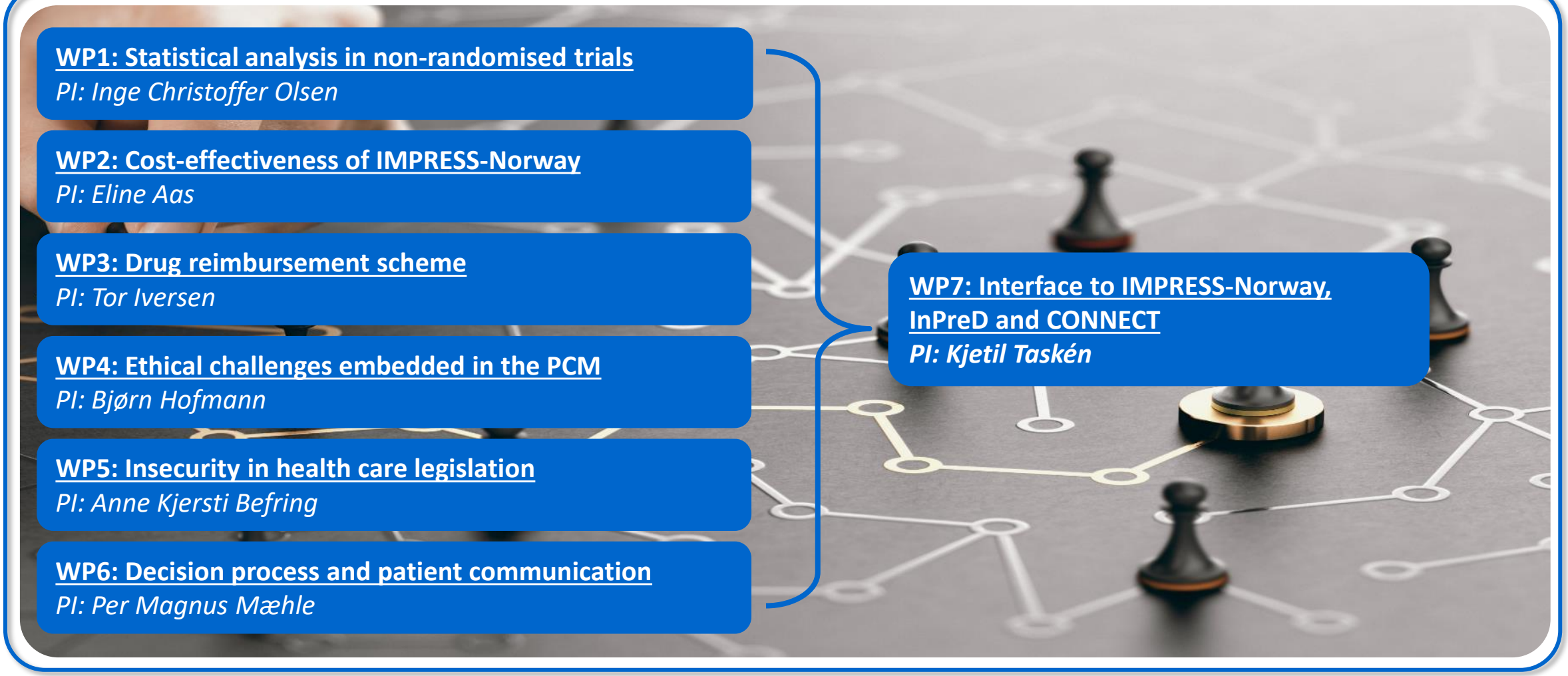
INSIGHT/INCLUDE: Regulatory framework for implementing precision medicine into the Norwegian health care system

PI: Eline Aas

Application to NFR Behandling

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

INSIGHT/INCLUDE – Work Packages



WP1: Statistical analysis in non-randomised trials
PI: Inge Christoffer Olsen

WP2: Cost-effectiveness of IMPRESS-Norway
PI: Eline Aas

WP3: Drug reimbursement scheme
PI: Tor Iversen

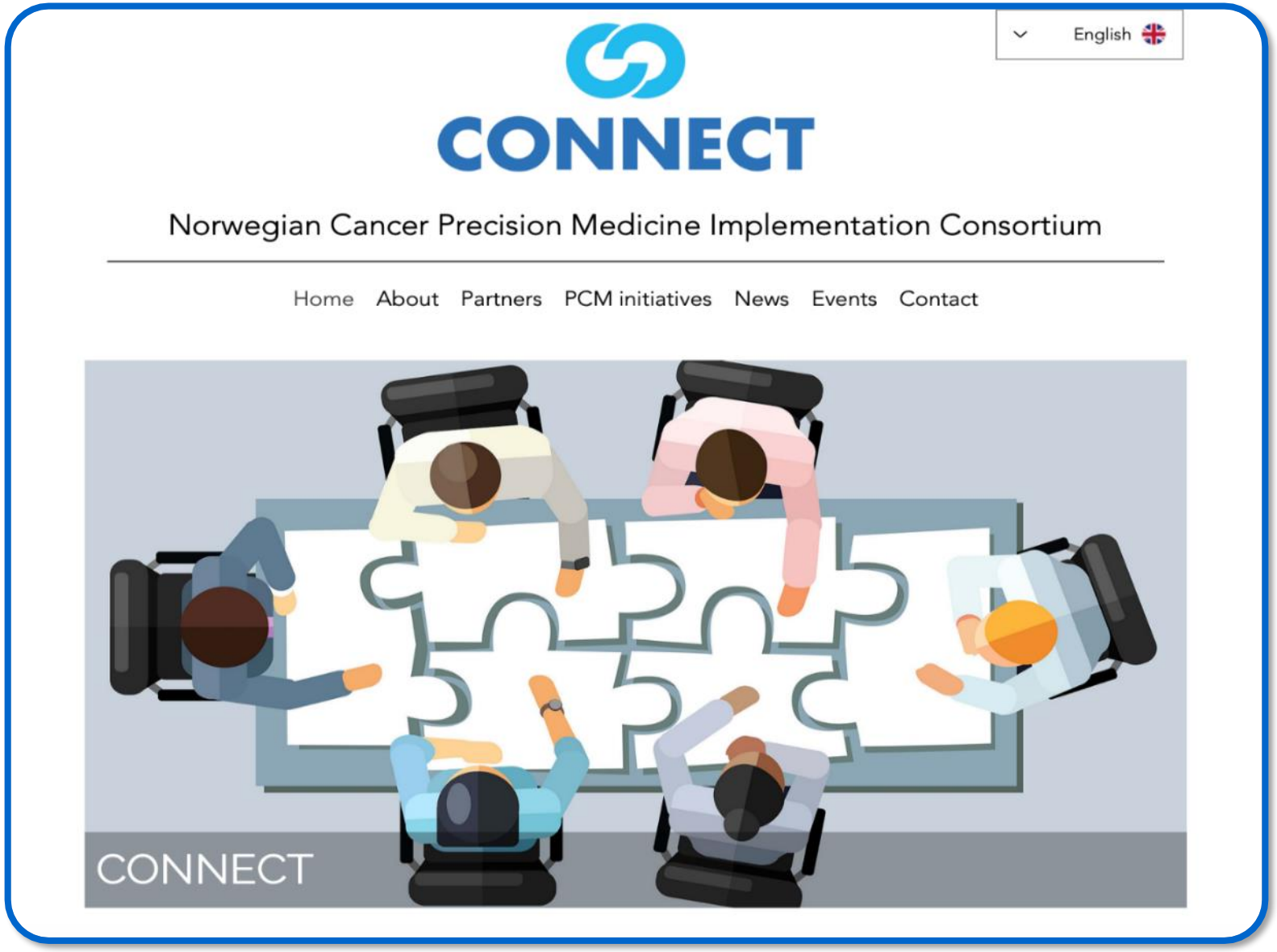
WP4: Ethical challenges embedded in the PCM
PI: Bjørn Hofmann

WP5: Insecurity in health care legislation
PI: Anne Kjersti Befring

WP6: Decision process and patient communication
PI: Per Magnus Mæhle

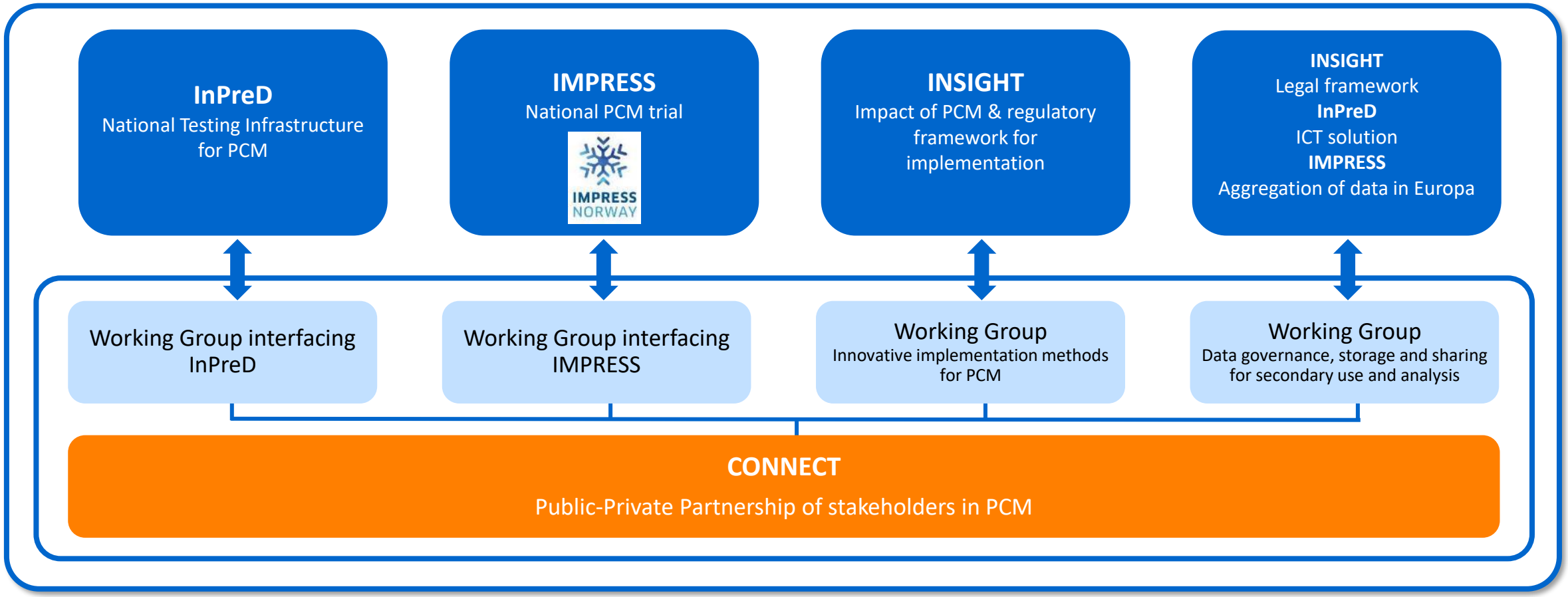
WP7: Interface to IMPRESS-Norway, InPreD and CONNECT
PI: Kjetil Taskén

WP, work package.
Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.



Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

CONNECT is operationalised via working groups engaging experts from the public and private sector



Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

CONNECT process

Public and Private Partners invited to team up for CONNECT

- Consortium Contract, project details and budget developed
- Project Management via Oslo Cancer Cluster
- 22 partners and observers committed to founding CONNECT and signed December 2020
- Project started in January 2021
- Two more public partners as observers (HDIR, NOMA)
- Three more pharma joined (MSD, Eli Lilly, Janssen (J&J)

- Akershus universitetssykehus HF
- Helse Bergen HF
- Helse Stavanger HF
- St. Olavs hospital HF
- Universitetssykehus Nord-Norge HF
- Oslo Universitetssykehus med Kreftregistret
- Folkehelseinstituttet
- Oslo Cancer Cluster SA
- Kreftforeningen
- Legemiddelindustrien
- Roche Norge AS
- Bristol-Myers Squibb Norway Ltd NUF
- Novartis Norge AS
- Merck AB NUF
- Takeda AS
- Amgen AB Norge NUF
- AstraZeneca AS
- AbbVie AS
- Bayer AS
- PubGene AS
- Pfizer Norge AS
- NEC Corporation

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

InPreD-IMPRESS-TRAIN-INSIGHT-CONNECT *National impact*

By establishing the national diagnostics platforms (InPreD), the IMPRESS trial, CONNECT and INSIGHT/INCLUDE :

- Harmonised molecular testing, equal standard of care and increased access to clinical trials for cancer patients across Norway
- Mechanism for referral of patients with progressive cancer disease to advanced molecular cancer diagnostics
- A national molecular tumour board for implementation of precision medicine in cancer trials
- A considerable number of cancer patients will have access to one or more lines of treatment with experimental drugs beyond what is available now.
- Strengthen translational research and innovation by extensive biobanking and data generation
- Provide structures for “benchmarking” new diagnostic procedures
- Considerable competence building nationally
- Complement National Registries with drug efficacy and health economy data for STA/HTA assessments

Transformation of clinical practice and standard of cancer care in Norway

STA, single technology appraisal.

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

InPreD-IMPRESS-TRAIN-INSIGHT-CONNECT

Driving the implementation of cancer precision medicine in Norway

- High level political support for implementation of precision cancer medicine in Norway
- Aligned with national PCM strategy and responding to instructions in the Commission Documents from the Minister of Health and Social Services to the national health care system and other public institutions in the health sector
- Close cooperation with the national public health care system
- Public funding so far in excess of 175 million Norwegian krone
- IMPRESS embedded in public-private partnership with parallel work packages on Exit- / Reimbursement strategies and Data sharing
    - Collection of drug efficacy and health economy data for STA/HTA assessments
    - Regulators and payors involved in public-private partnership as partners or via regular meetings

Changing decision making processes and access to novel cancer treatments

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

Outlook

- More companies (and drugs into IMPRESS) – will make the aggregated algorithm work. Looking at each company's needs
- IMPRESS trial can live much longer than the individual drugs in the trial (rotate in/out drugs)
- IMPRESS 2.0 & IMPRESS 3.0 with next types of diagnostics - protein biomarkers (IHC, Hyperion, flow cytometry), drug screening and pharmacogenomics -> Functional precision medicine
- Integration of artificial intelligence-based approaches to prediction drug synergies and optimal combinations to be tested for each patient
- Moving forward in the lines of treatments
- PCM trial network and trial infrastructure suitable for other trials, building capacity
- Rapidly moving field – also wrt evidence, control-cohorts, HTA, reimbursement strategies also ongoing

IHC, immunohistochemistry

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.

Key learnings from setting up a national precision cancer medicine implementation initiative

Oslo University Hospital taking national lead – how to handle

Structuring the field of precision cancer medicine in Norway

Importance of clinician/ diagnostician/researcher interaction in PCM implementation

Public-private partnerships, two-way street of understanding needs and positions

Health economy and road to reimbursement a necessary aspect

Policy and politics at multiple levels – difficult to navigate

High expectations created and must be met

International position and unique aspects of nation-wide initiative

Content courtesy of, and based on personal experience and observations of, Prof Kjetil Taskén.