Molekylær diagnostikk og presisjonsmedisin innen kreft – IMPRESS-Norway

Farmasidagene 2022

Åslaug Helland, Onkolog, OUS, Forskningsleder Kreftklinikken, Professor UiO, PI I IMPRESS-NOrway

Conflicts of interest

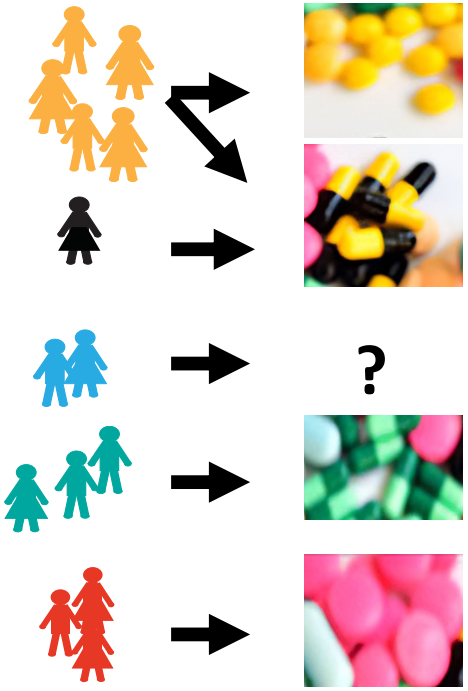
Have participated in advisory boards and meetings arranged by pharmaceutical companies. No personal honorarium, but to institution (ABBVIE, Roche, AstraZeneca, Bayer, Janssen, Pfizer, Takeda, BMS, Merch, Novartis, Sanofi, Eli Lilly)

Have received research funding (drug / funds): Roche, AstraZeneca, Novartis, Incyte, Eli Lilly, BMS, Ultimovacs

Kreftbehandling – store endringer siste tiden

One size fits all

Precision Medicine



Requirements:

Sufficient molecular diagnostics available

Knowledge on new drugs and mechanisms

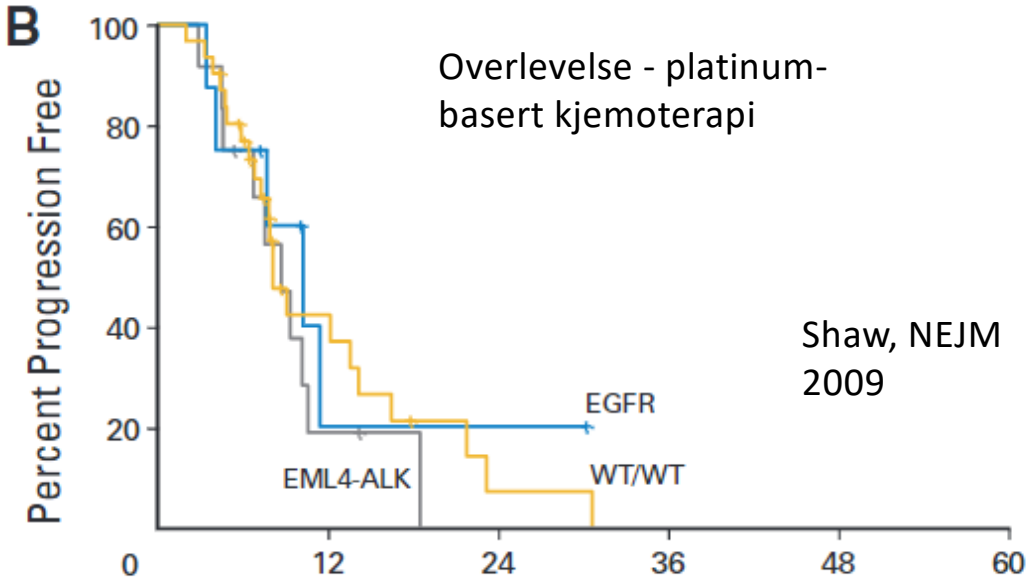
Available drugs

«The genes, not only the tissue, will steer the treatment»

Dr John Mendelsohn, Past President, MDACC, Texas

ALK-positiv sykdom

2-5% av pasientene med NSCLC



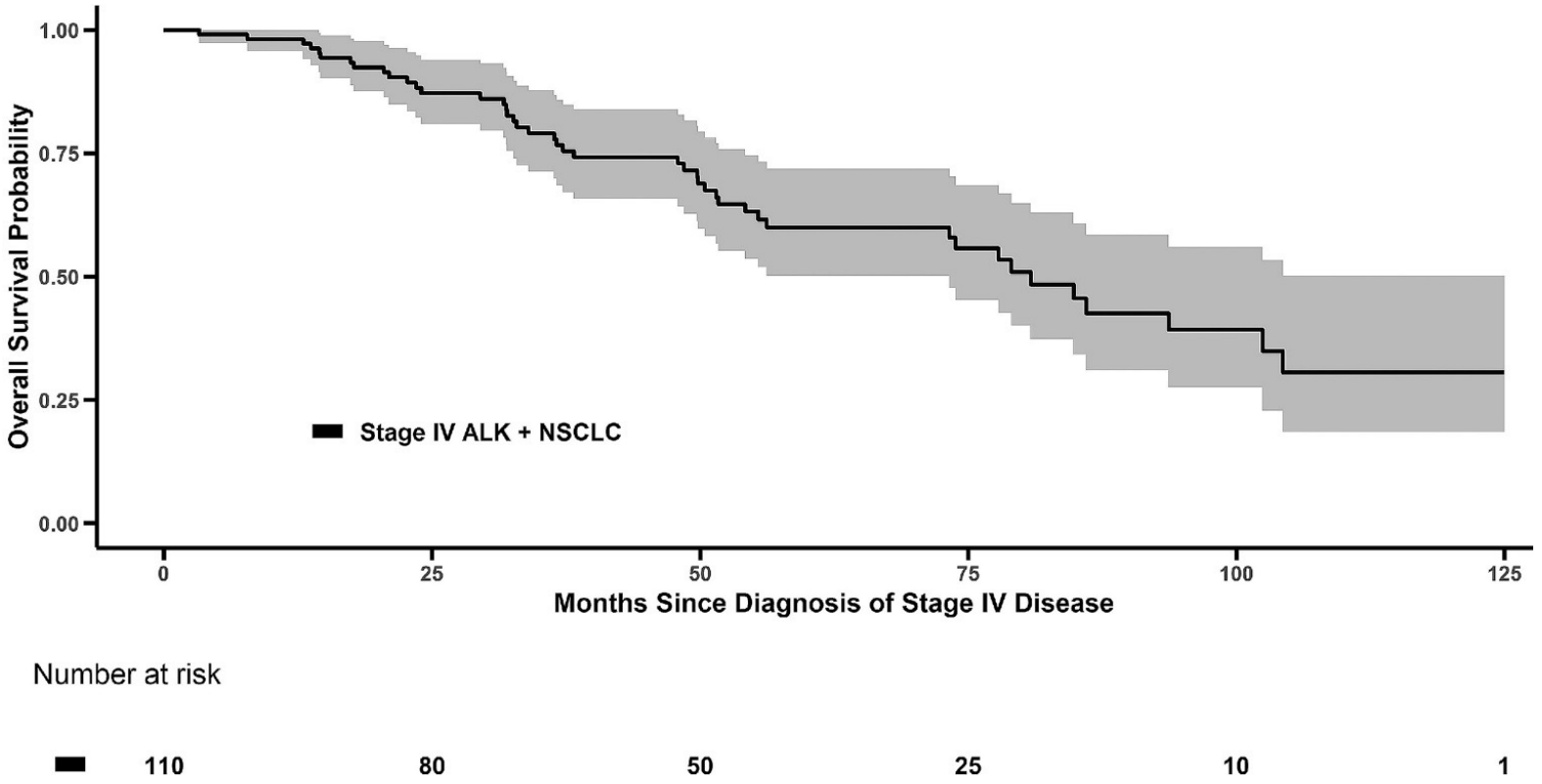
Overlevelse - platinum-basert kjemoterapi

Shaw, NEJM 2009

Cancer in Norway 2016

Table 8.1: Five-year relative survival by primary site, stage and period of diagnosis, 1977–2016, males

ICD-10	Site	Stage	Relative survival (%) 1977–81	1982–86	1987–91	1992–96	1997–01	2002–06	2007–11	2012–16*
C33–34	Lung, trachea	**Total**	**6.1**	**7.5**	**7.3**	**8.1**	**8.9**	**10.3**	**13.0**	**16.0**
		Localised	13.8	17.4	16.1	22.5	33.7	41.1	44.6	53.3
		Regional	5.9	8.0	9.4	8.4	9.3	11.8	15.4	19.4
		Distant	0.7	0.5	0.8	0.5	0.7	1.1	1.9	1.8



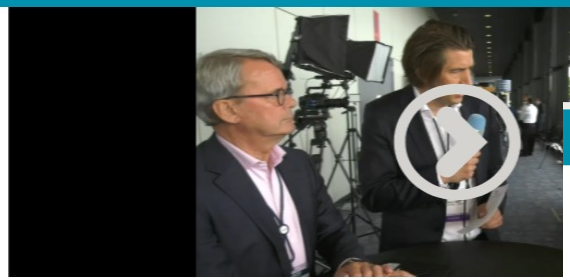
Overlevelse stadium IV ALK-positiv lungekreft: **Median Overlevelse (OS) 81 måneder (6.8 år)**

Hjernemetastaser på diagnosetidspunkt påvirket ikke overlevelsen signifikant

Pacheco et al, Journal of Thoracic Oncology 2019 14, 691-700DOI: (10.1016/j.jtho.2018.12.014)

Nasjonal enighet om behov for bedret molekylærdiagnostikk

DAGENS Medisin — Nyheter DMTV Debatt Pharma DM Arena Om oss



– Vi er nødt til å vurd pasientene med gensekvensering

Melanom, lungekreft og ASCO-oppsummering er temaer for denne se

Lasse Moe
lasse.moe@dagensmedisin.no
Publisert: 2019-06-03 — 23.34

DAGENS Medisin — Nyheter DMTV Debatt Pharma DM Arena Om oss

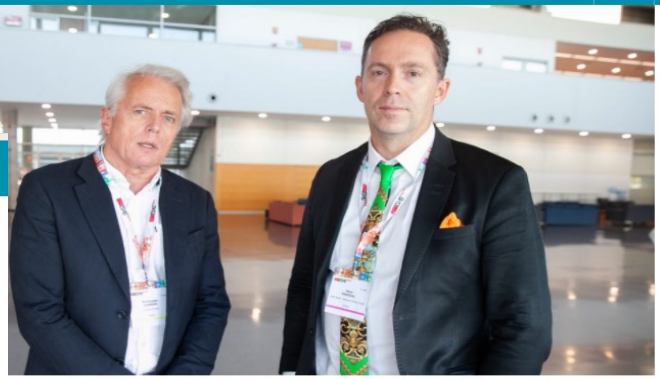
HASTER: – Det blir stadig nye tumor-agnostiske markører, som kan utnyttes i behandling. Vi trenger et raskt system for NGS (gensekvensering), sier overlege Christian Kersten ved Sørlandet Sykehus. Her avbildet under ESMO 2018, i München. **Foto:** Lasse Moe

Kritisk til treg innføring av gentesting

– I dag må jeg stadig oftere si til pasientene at jeg ikke kan tilby den beste utredningen, rett og slett fordi vi ikke tar de nødvendige testene, sier overlege Christian Kersten ved Sørlandet Sykehus.

Lasse Moe
lasse.moe@dagensmedisin.no

DAGENS Medisin — Nyheter DMTV Debatt Pharma DM Arena Om oss



ssorene og Haukeland-overlegene Per Eystein Lønning (t.v.) og Hans Petter Eikesdal mener norske myndigheter er ed persontilpasset medisin. **Foto:** Lasse Moe

ger mener Norge er for på diagnostikk

n innebærer at det finnes en kreftbehandling for alle pasienter – men da må timen.

sjonen@dagensmedisin.no

Strategisk arbeid mot en nasjonal klinisk studie

Bottom up:
- White paper for Norwegian concept, National PI (Åslaug Helland)
- Buy-in from oncology, haematology, pathology environments in all Norwegian health regions -> National approach

Top down:
- Dialogue with health authorities (regional health care systems, ministry)
- Engaging key national stakeholders: NoMa, NIPH, HDIR, Cancer Registry, Cancer Society

International: Joined DRUP network and building Nordic Task Force

Public-private: Dialogue with industry partners: trial participation and consortium formation for public-private partnership

Parallel development of diagnostic platforms (InPreD), PCM PPP (CONNECT) and research on RWE & controls, health economy & HTA, ethics, legal & org. of PCM (INSIGHT)

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.

Molekylærpatologi i Norge

De fleste patologiavdelinger utfører molekylære analyser (n=17)

- Enkeltmarkør analyser

10 av 17 avdelinger har tatt i bruk «neste generasjons sekvensering», NGS:

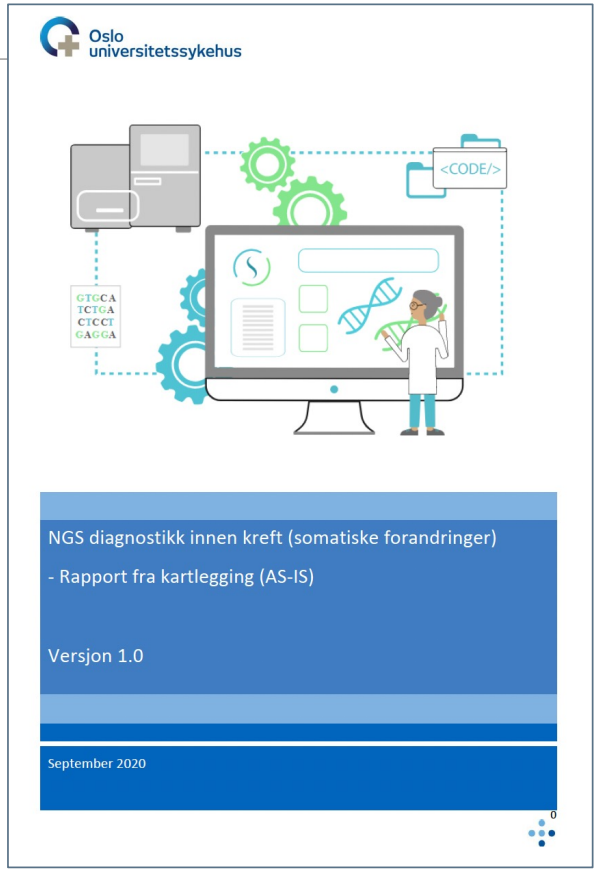
- Kan analysere mange gener samtidig for samme prøve
- Kan ha samme analyse på tvers av tumortyper

Teknologi: to ulike teknologier benyttes:

- Illumina (store sykehus) & Thermo Fisher (IonTorrent)

Genpaneler: ulike størrelser

- Små paneler (50-100 gener), mellomstore (100-400 gener), store (mer enn 400 gener)



Kartlegging utført av NGS undernettverkt i Nasjonalt kompetansenettverk for persontilpasset medisin – presisjonsmedisin 2020

NGS: store versus små genpaneler

Små genpanel:

- Kan ikke identifisere «profiler» , eks. Tumor mutasjons byrde (TMB) eller genomisk ustabilitet (GI)
- Egnet for gener som man undersøker ofte for og i mange krefttyper
- Raskere og mer automatisert (sekvenseringen)
- Krever mindre kompetanse da det er «kjente» forandringer man leter etter
- Mindre krav til tilpasset IT struktur

Store genpanel:

Trengs for å identifisere «profiler» , eks. Tumor mutasjons byrde (TMB) eller genomisk ustabilitet (GI)

Viktig for å finne lavfrekvente varianter

Kostbare og tar tid (sekvenseringen)

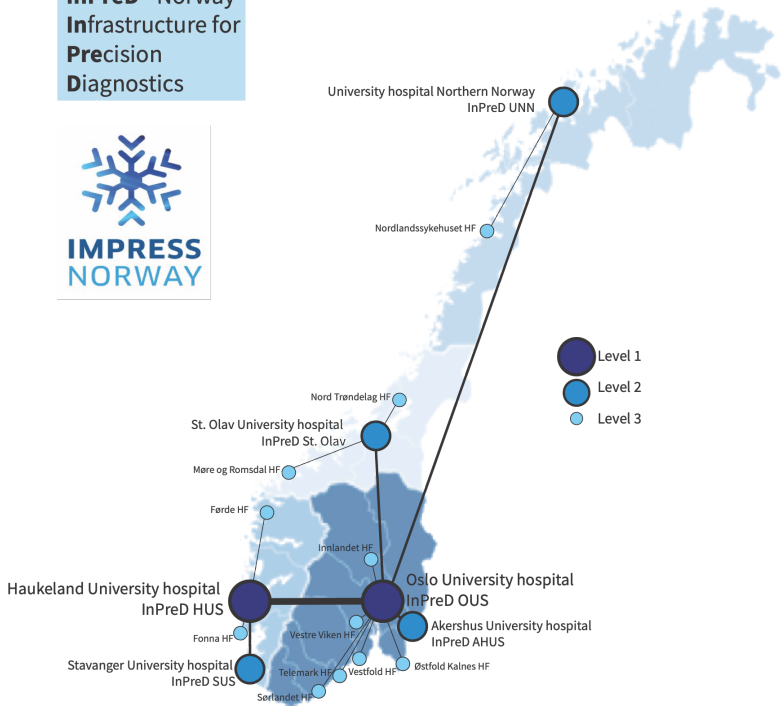
Krever kompetanse (bioinformatikk, molekylærbiologi, patologi og onkologi)

Krever tilpasset IT struktur

Utvikling innen molekylærpatologi – del av tjenesten

InPreD - Norway
Infrastructure for
Precision
Diagnostics

IMPRESS 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 biomarker driven clinical trials is available for all hospitals

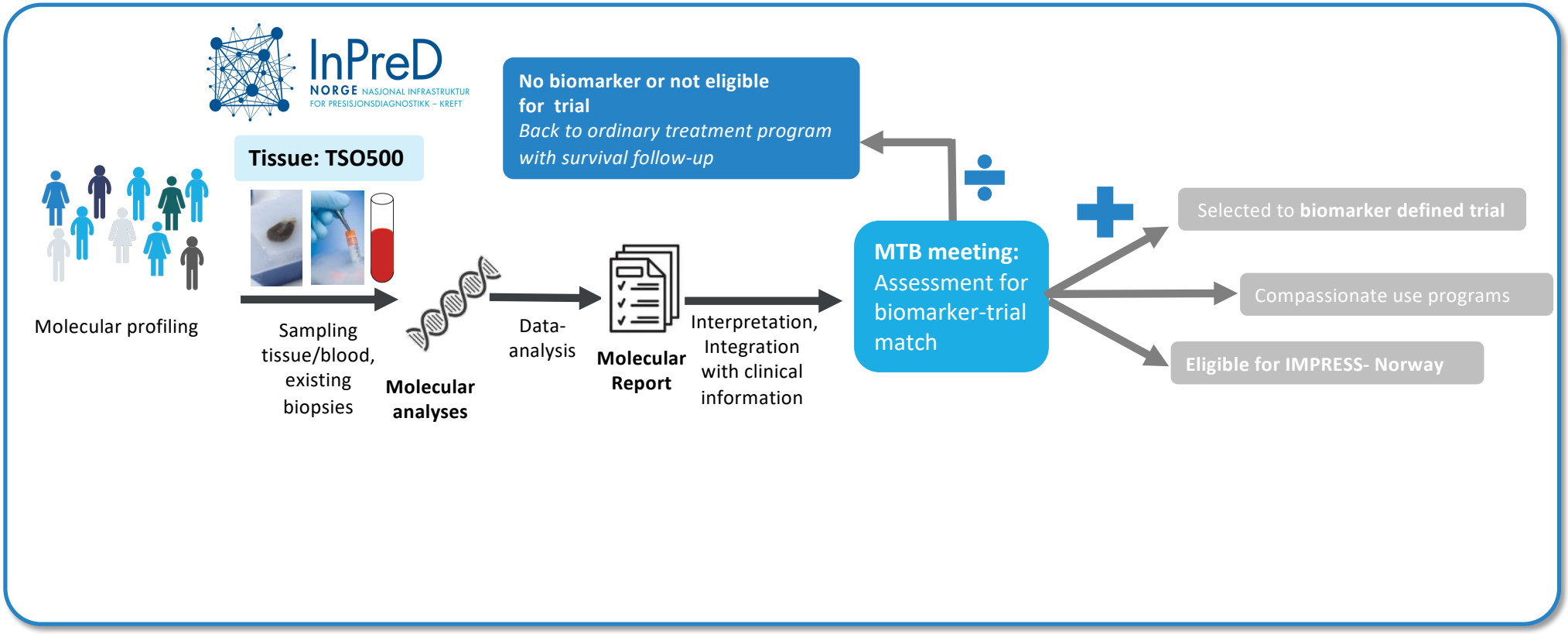
Funding:

- 100 MNOK + + from regional health autorities
- Large gene panel reimbursed

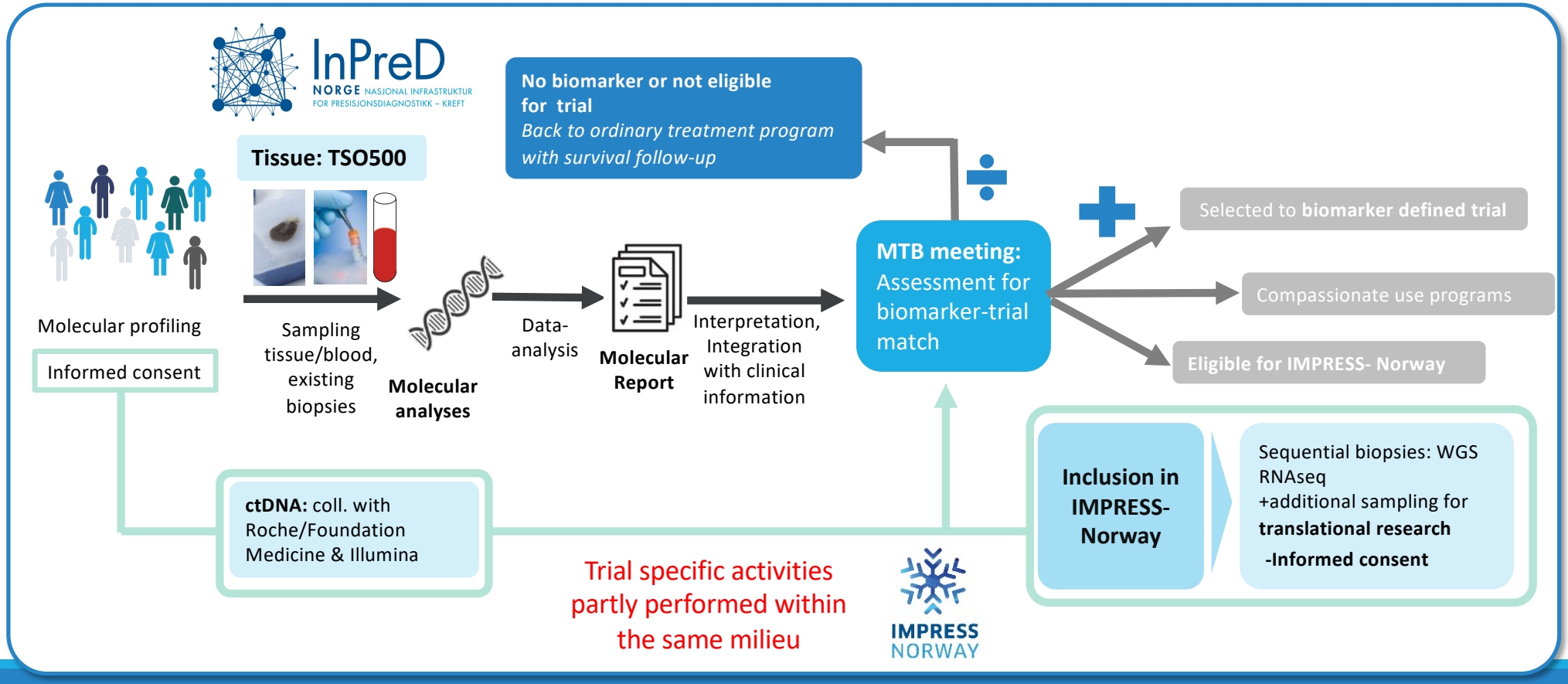
Aim: Equal access to expanded molecular testing – and experimental treatment for cancer patients

HELSE VEST | HELSE NORD | HELSE MIDT-NORGE | HELSE SØR-ØST

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



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



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	
	15 (Low 5 / Intermediate / 20 High)		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.

Små pasientgrupper – samarbeid nødvendig for å lære mest mulig

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

FINPROVE
DRUG REDISCOVERY PROGRAM IN FINLAND

MEGALiT

IMPRESS NORWAY

The Drup-trial

LETTER

https://doi.org/10.1038/s41586-019-1600-x

The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs

D. L. van der Velden[1,2,21], L. R. Hoes[1,2,3,21], H. van der Wijngaart[2,3,4,21], J. M. van Berge Henegouwen[2,3,5,21], E. van Werkhoven[6], P. Roepman[7], R. L. Schilsky[8], W. W. J. de Leng[9], A. D. R. Huitema[10,11], B. Nuijen[11], P. M. Nederlof[12], C. M. L. van Herpen[13], D. J. A. de Groot[14], L. A. Devriese[15], A. Hoeben[16], M. J. A. de Jonge[17], M. Chalabi[1,18], E. F. Smit[2,19], A. J. de Langen[19], N. Mehra[13], M. Labots[4], E. Kapiteijn[5], S. Sleijfer[2,17], E. Cuppen[3,7,20], H. M. W. Verheul[4,13], H. Gelderblom[5] & E. E. Voest[1,2,3]*

The large-scale genetic profiling of tumours can identify potentially actionable molecular variants for which approved anticancer drugs are available[1–3]. However, when patients with such variants are treated with drugs outside of their approved label, successes and failures of targeted therapy are not systematically collected or shared. We therefore initiated the Drug Rediscovery protocol, an adaptive, precision-oncology trial that aims to identify signals of activity in cohorts of patients, with defined tumour types and molecular variants, who are being treated with anticancer drugs outside of their approved label. To be eligible for the trial, patients have to have exhausted or declined standard therapies, and have malignancies with potentially actionable variants for which no approved anticancer drugs are available. Here we show an overall rate of clinical benefit—defined as complete or partial response, or as stable disease beyond 16 weeks—of 34% in 215 treated patients, comprising 136 patients who received targeted therapies and 79 patients who received immunotherapy. The overall median duration of clinical benefit was 9 months (95% confidence interval of 8–11 months), including 26 patients who were experiencing ongoing clinical benefit at data cut-off. The potential of the Drug Rediscovery protocol is illustrated by the identification of a successful cohort of patients with microsatellite instable tumours who received nivolumab (clinical benefit rate of 63%), and a cohort of patients with colorectal cancer with relatively low mutational load who experienced only limited clinical benefit from immunotherapy. The Drug Rediscovery protocol facilitates the defined use of approved drugs beyond their labels in rare subgroups of cancer, identifies early signals of activity in these subgroups, accelerates the clinical translation of new insights into the use of anticancer drugs outside of their approved label, and creates a publicly available repository of knowledge for future decision-making.

is taken into consideration. However, with regards to drug sensitivity, the importance of a given genetic or molecular variant is usually tested in the subtype of cancer that most frequently contains this variant. The importance of the same variant in other cancers often remains unknown. Third, as drug development is challenging for rare subtypes of cancer, this can create inequality in care[12]. Finally, with growing pressure from society to increase the success rate of drug-development trials[13], there is hesitation amongst payers to reimburse large-scale sequencing efforts before they have proof that these efforts will make healthcare more sustainable. As a result, we are not using the full potential of rapidly expanding technological advances, knowledge of biomarkers and the spectrum of approved anticancer drugs for our patients.

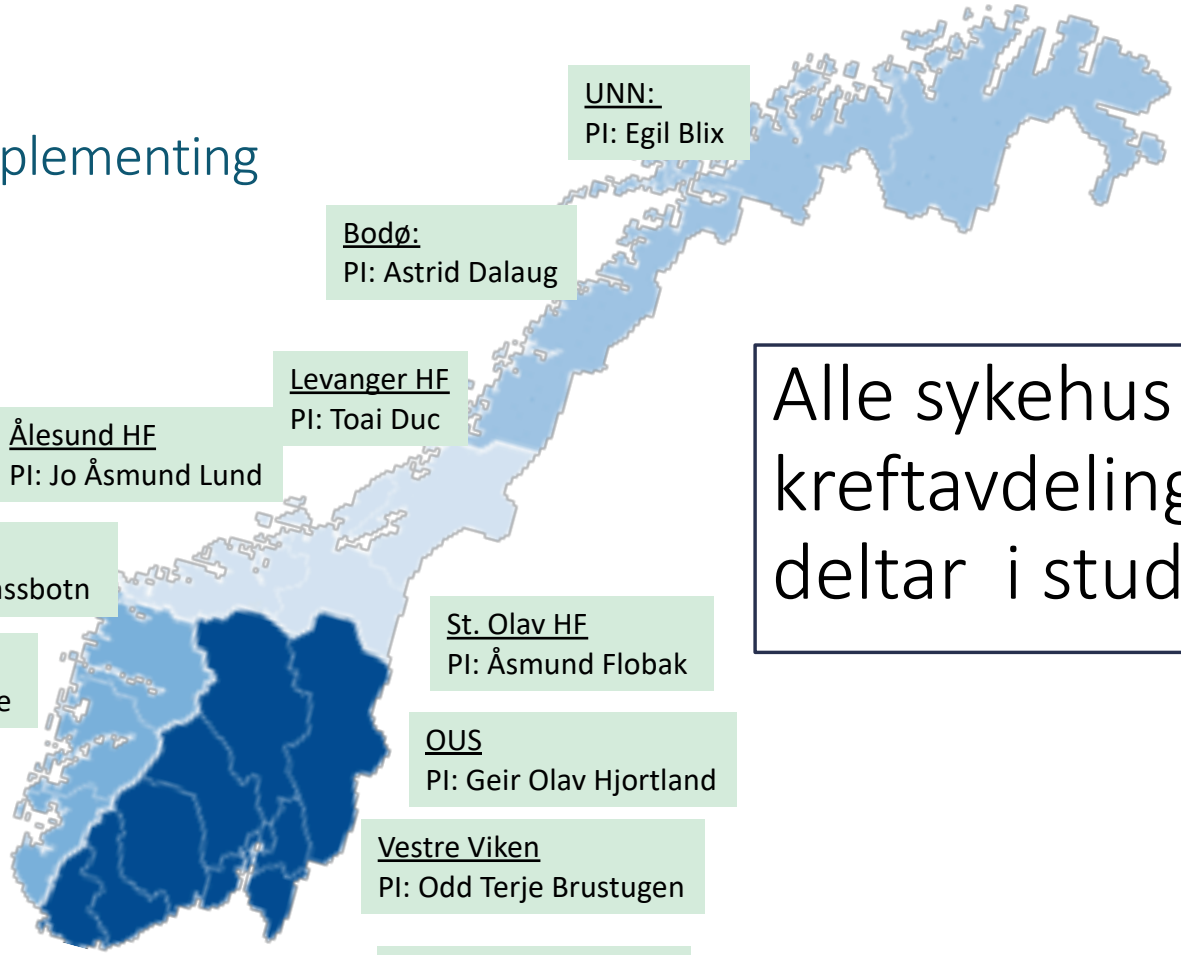
The Center for Personalized Cancer Treatment was founded in 2010[14] to address these issues. In this network (which now connects 45 hospitals in the Netherlands), patients with all types of metastatic cancer are offered the opportunity to undergo a fresh tumour biopsy for whole-genome sequencing (WGS) before starting systemic anticancer treatment. The WGS results are combined with treatment outcomes in a national, centralized database for research purposes, and returned to the physician who is treating the patient for future planning of treatment. This initiative has contributed to the identification of potentially actionable variants in cancers that are not routinely tested for these variants. To provide treatment opportunities for patients in whom such variants were identified (while simultaneously collecting clinical outcomes), we began the Drug Rediscovery protocol (DRUP), in which we seek to expand the use of targeted therapies that have been approved by the European Medicines Agency (EMA) and/or US Food and Drug Administration (FDA) beyond the approved indications of these therapies.

The DRUP is an ongoing, prospective multi-drug and pan-cancer

- High inclusion rate (46%)
- High level of clinical benefit (34%)

IMPRESS-Norway:
Improving public cancer care by implementing precision medicine in Norway

IMPRESS NORWAY



UNN:
PI: Egil Blix

Bodø:
PI: Astrid Dalaug

Levanger HF
PI: Toai Duc

Ålesund HF
PI: Jo Åsmund Lund

Helse Førde
PI: Liv Journn Vassbotn

HUS
PI: Line Bjørge

St. Olav HF
PI: Åsmund Flobak

Helse Fonna
PI: Sverre Fluge

OUS
PI: Geir Olav Hjortland

Stavanger
PI: Bjønar Gilje

Vestre Viken
PI: Odd Terje Brustugen

Sørlandet sykehus
PI: Marte Cameron

Vestfold Sykhus
PI: Karin Semb

AHUS
PI: Anne Hansen Ree

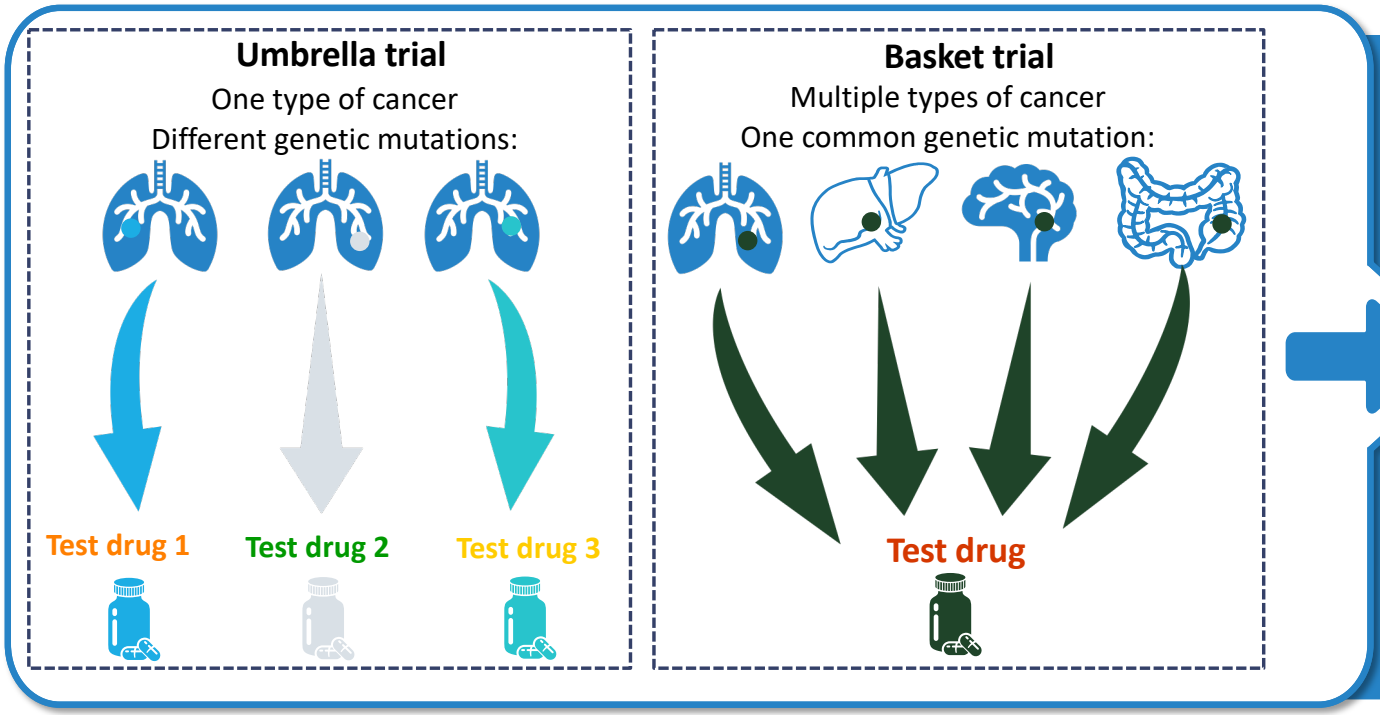
Telermark Sykehus
PI: Dalia Dietzel

Kalnes Sykehus
PI: Andreas Stensvold

Innlandet sykehus
PI: Daniel Heinrich

Alle sykehus med kreftavdeling deltar i studien

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

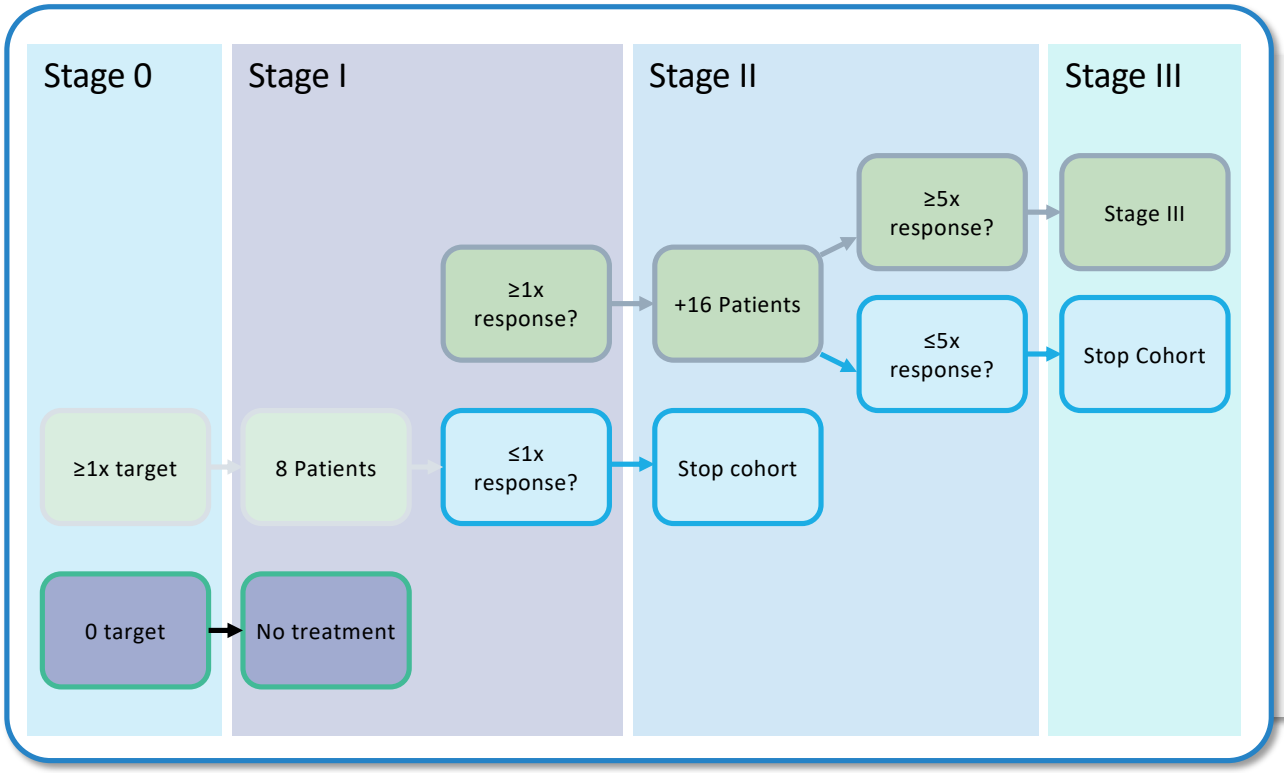


A combination:

- 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.
.

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.

Stage 3 - ekspansjonskohort

- Aktuelt når ≥5 av 24 pasienter i en kohort har nytte av behandlingen etter 16 ukerts behandling
- Da har man data på effekt, median/gjennomsnittlig varighet av behandlingen
- Legemiddelet har en kjent pris / er allerede godkjent
- Legemiddelet har kjent bivirkningsprofil
- Frekvensen / forventet antall pasienter er kjent

- Firma betaler behandling i 16 uker (+50000 per pasient til sykehuset som behandler),
- Det offentlige overtar finansieringen av legemiddelet etter 16 uker
  - Nylig vedtak på Olaparib / biallelisk inaktivert BRCA1/2

Unntak på gruppenivå for olaparib som monoterapi til behandling av pasienter med biallelisk BRCA1/2-mutasjoner (inaktivering) for pasienter som er deltakere i IMPRESS-Norway

Fagdirektørene i de regionale helseforetakene besluttet 14. februar 2022 å gi unntak på gruppenivå for olaparib som monoterapi til behandling av pasienter med metastatisk kreft og biallelisk BRCA1/2-mutasjoner (inaktivering) som har progrediert på standard behandling, og som er deltakere i IMPRESS-Norway.

Behandlingen er aktuell ved alle kreftformer med unntak for pasientgrupper der olaparib allerede har markedsføringstillatelse.

Pasientene skal følges opp i en særskilt behandlingskohort i den nasjonale studien IMPRESS-Norway, for å fremskaffe dokumentasjon om effektene av slik behandling.

IMPRESS-Norway

- Aktuelt for pasienter med avansert kreftsykdom etter standard behandling
- Aktuelle pasienter screenes med utvidet genpanel – pt TSO500 + ctDNA analyser
- En hovedprotokoll og medikamentspesifikke manualer
- Resultater diskuteres i nasjonalt molekylært MDT-møte
- Hvis funn indikerer inklusjon i annen klinisk studie eller IMPRESS-Norway kohort -> henvisning til studieinklusjon
- Farmaseutisk / diagnostisk industri deltar med legemiddel / diagnostikk
- Alle medikamenter er godkjent av EMA / FDA – brukes utenfor indikasjon
- Biobanking (WGS, RNAseq), livskvalitetsmålinger
- Standard responsevaluering(RECIST osv) og monitorering – GCP
- Kopling til helseregister - helseøkonomianalyser

InPreD NORGE NASJONAL INFRASTRUKTUR FOR PRESISJONSDIAGNOSTIKK – KREFT

Infrastructure for precision diagnostics

01.04.2021 – 12.10.2022

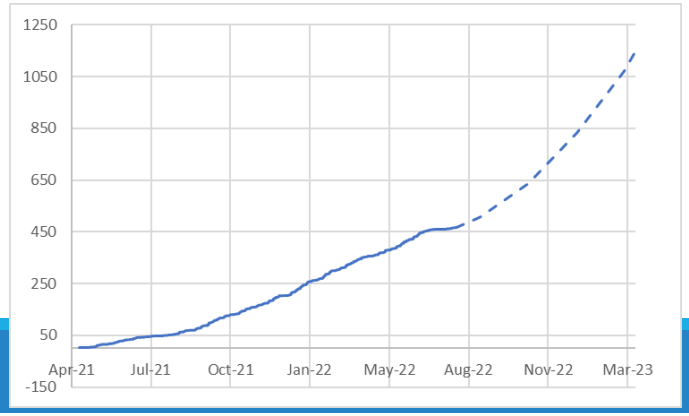
573 included for molecular profiling#

522 discussed in National Mol-MDT

- IMPRESS-Norway (24%)*
- Clinical studies (2%)**
- Early access programs (approx. 10%)**
- Pallative care (approx 64%)**

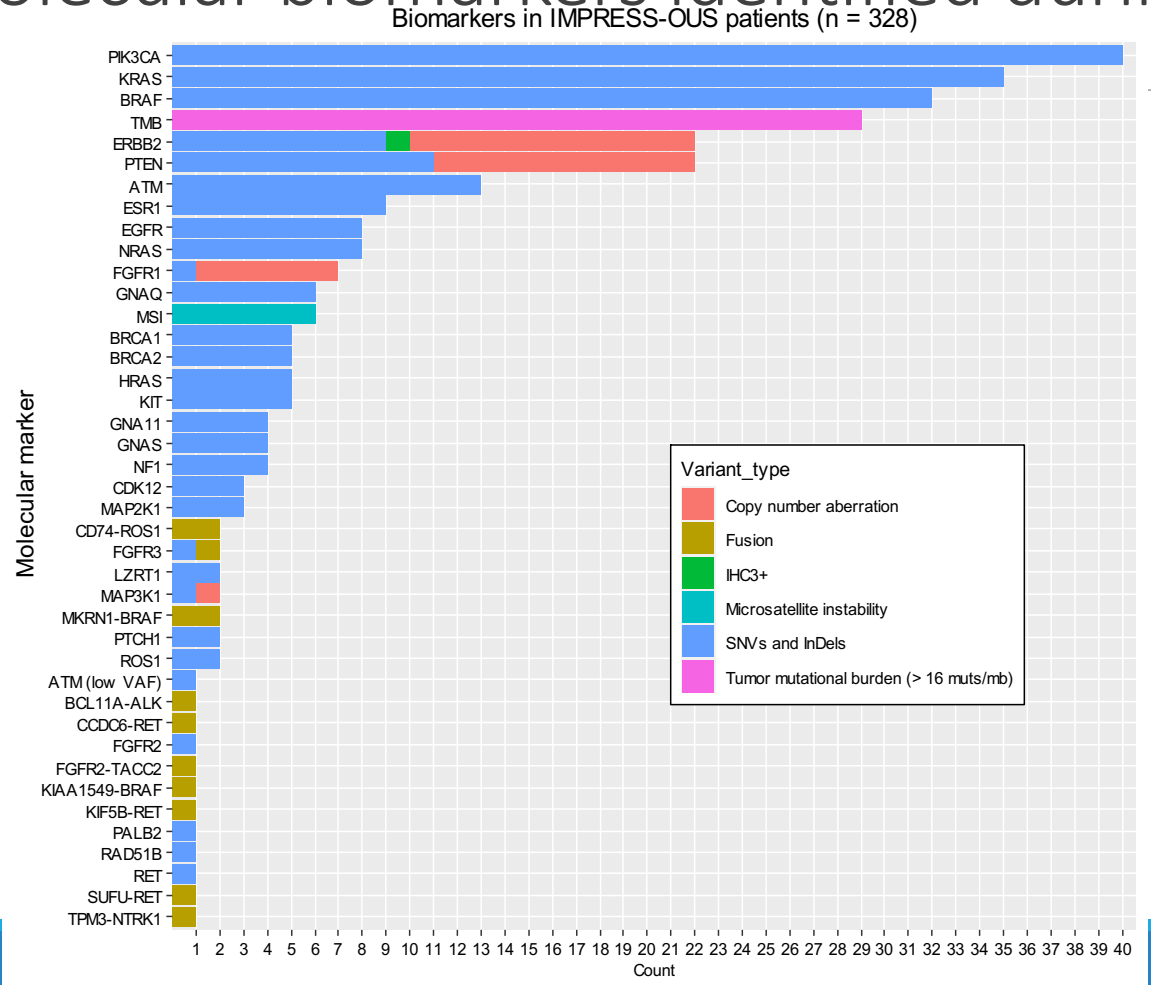
* 127 patients included in a cohort of 522 discussed in National Mol-MDT

** lag time for screening before inclusion into clinical trials and early access program giving uncertain no. of acctual included.



Graph: No. Of patients included for molecular profiling as function of time. Solid line are patients included to date and stippled lined is expected no. of patient included. Capasity increase mainly due to opening of new site (HUS) and planned automization.

Molecular biomarkers identified during screening phase



Alterations in PI3K/AKT/ mTOR and RAS/MAPK pathways, changes in ERBB2, FGFR, HRR genes and high tumor mutational burden (TMB) are the most commonly detected biomarkers.

IMPRESS-Norway - oppdatering

01.04.2021 – 12.10.2022

127 patients included in cohorts

- 5 Deaths
- 1 Did not meet the inclusion/ecxlusion criteras
- 43 Delayed treatment start

78 patients started treatment*

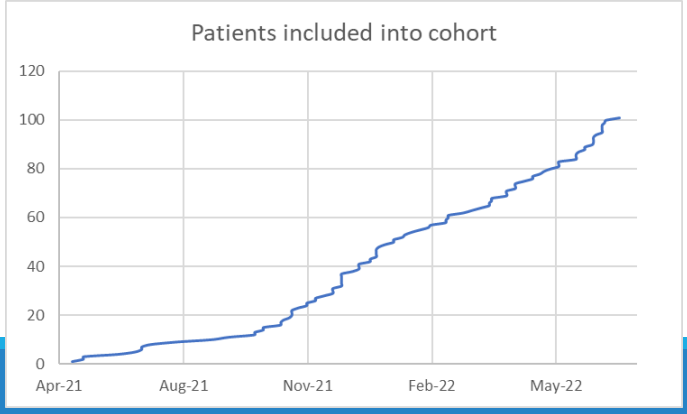
- 12 less than 16 weeks on treatment (treatment ongoing)

47 % effect W16 (SD/PR/CR)**

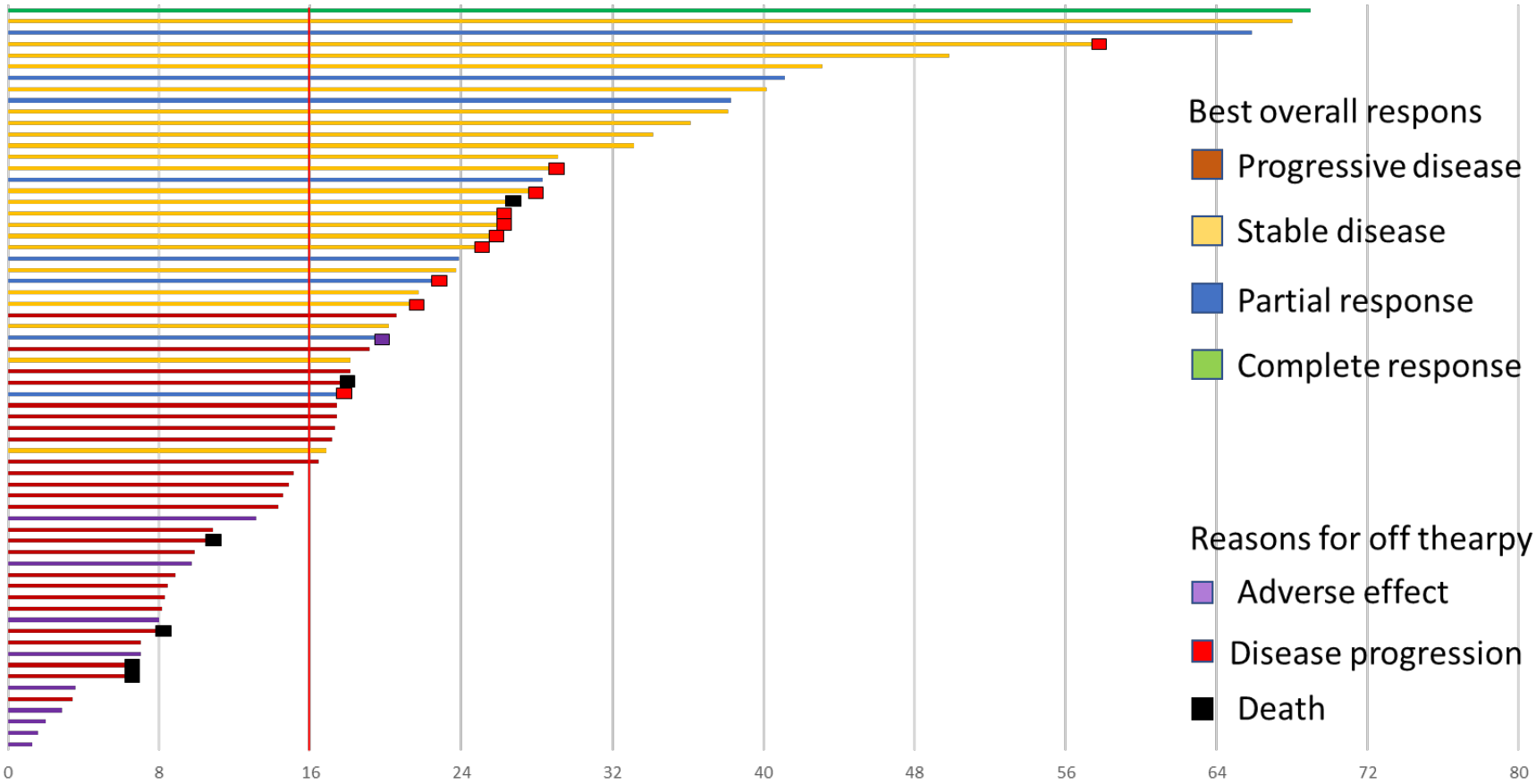
- 21 patients had PD as best over all response
- 9 patients stopped treatment before W16 due to Tox
- 5 patients died before W16

* Lag time between included into cohort and start treatment mainly due to still effect of last line of treatment.

** 31/66 patients clinical effect at W16



Graph: No. Of patients included into cohort as function of time. The inclusion rate is mainly effected by capacity for molecular profiling and access to drugs. Increase end 2021 due to inclusion of Novartis drugs.

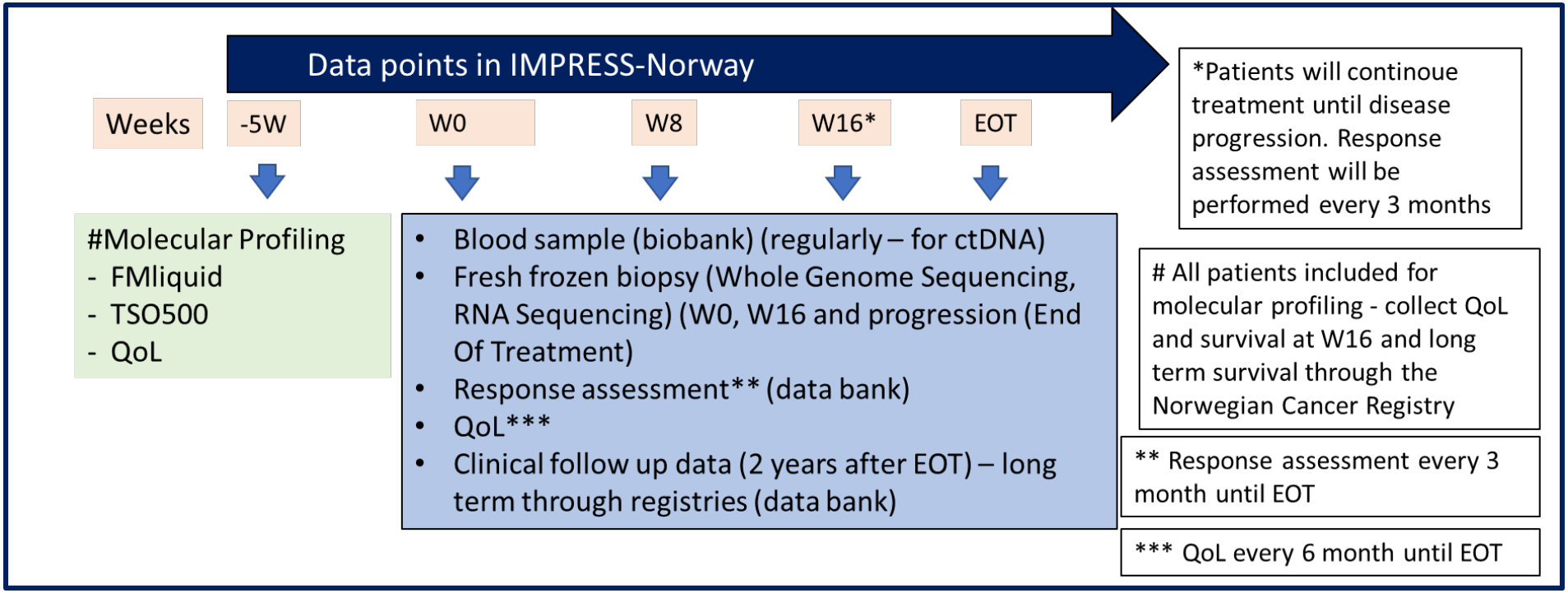


66 patients evaluated at W16. 5 patients died before W16, 9 patients stopped treatment before W16 due to toxicity and 21 patients had progressive disease as best overall response. 31/66 patients had effect according to protocol at W16. 1 patients had complete response at W16, 8 patients had partial response at W16 and 22 patients had stable disease at W16.

Medikamenter

	Drug	Company	Status
1	Alecensa	Roche	Included
2	Phesgo (Pertuzumab and Trastuzumab)	Roche	Included
3	Tecentriq (Atezolizumab)	Roche	Included
4	Avastin (Bevacizumab)	Roche	Included
5	Cotellic (Cobimetinib)	Roche	Included
6	Zelboraf (Vemurafenib)	Roche	Included
7	Erivegde (Vismodegib)	Roche	Included
8	Rozlytrek (Entrektinib)	Roche	Included
9			
10	Tafinlar (dabrafenib)	Novartis	Included
11	Mekinist (trametinib)	Novartis	Included
12	Piqray (alpelisib)	Novartis	Included
13	Tabrecta (capmatinib)	Novartis	Exp. 1 November 2022
14			
15			
16	Lynparza (olaparib)	Astra Zeneca	Included
17			
18	Retsevmo (selpercatinib)	Eli Lilly	Exp. 1. January 2023
19	Pemazyre (Pemigatinib)	Incyte	Exp. 1. Nov 2022
20	Melfalan	Generisk	Included
21	Imatinib	Generisk	Included
22	Bortezomib (KLL)	Generisk	
23	Actinomycin D og hydroxyurea (AML)	Generisk	

Extensive collection of data



A national precision cancer medicine implementation initiative for Norway

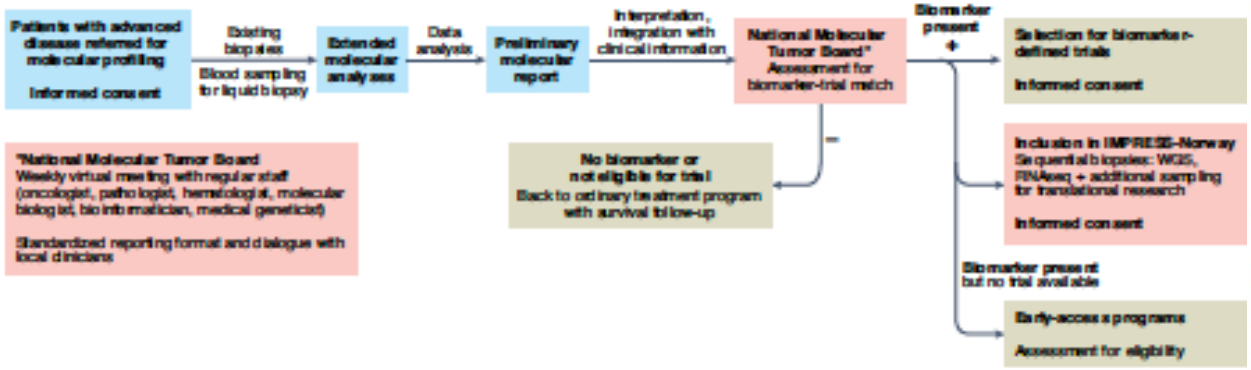


Table 1 | CONNECT: a public–private partnership of stakeholders in precision cancer medicine

CONNECT working-groups interfacing			
InPreD (WG1)	**IMPRESS (WG2)**	**Innovative implementation methods (WG3)**	**Data governance, storage and sharing for secondary use and analysis (WG4)**
InPreD national testing infrastructure	IMPRESS-Norway national PCM trial	INSIGHT-INCLUDE: impact of precision cancer medicine health economics and regulatory framework for implementation	INSIGHT-INCLUDE legal framework; InPreD ICT solution: IMPRESS aggregation of data in Europe

CONNECT is operationalized via working groups (WG1–WG4) that engage experts from the public and private sector. p ICT, information and communications technology; PCM, precision cancer medicine.

Kjetil Taskén[1,2✉], Hege E. G. Russnes[2,3,4], Eline Aas[5,6], Line Bjørge[7,8,9], Egil S. Blix[10,11], CONNECT Public-Private Partnership Consortium*, Espen Enerly[12], Gro L. Fagereng[13], Åsmund Flobak[14,15], Bjørnar Gilje[16], Bjørn T. Gjertsen[8,9,17], Tormod K. Guren[18], Jutta Helx[19], Eivind Hovig[20,21], Randi Hovland[22], InPreD-Norway and National Molecular Tumor Board Consortium*, IMPRESS-Norway Consortium*, Per E. Lønning[8,23], Leonardo A. Meza-Zepeda[20,24], Per M. Mæhle[25], Hilde L. Nilsen[7,26], Steinar Ø. Thoresen[27], Ketil Widerberg[28], Sigbjørn Smeland[2,29] and Aslaug Helland[2,4,18]

CONNECT Public-Private Partnership Consortium

Steinar Ø. Thoresen[27,37], Sigbjørn Smeland[2,29], Eline Aas[5,6], Terje C. Ahlquist[38], Nyosha Alikhani[39], Ali Areffard[40], Ell Bergli[41], Hege Edvardsen[42], Gry Festervoll[43], Åsmund Flobak[14,15], Grethe S. Foss[44], Petter Foss[45], Bjørn T. Gjertsen[8,9,17], Ingvild Hagen[39], Kåre B. Hagen[5], Håvard H. Hauge[34], Bjørn V. Herikstad[46], Kristian Hveem[36,37,38], Elisabeth Jarnaess[39], Kristin Kittelsen[42], Kristin Krogsrud[39], Monica Larsen[42], Mariam Lotfander[47], Birgitta Lygren[39], Aslaug Muggerud[42], Cathrine S. Notland[42], Ole A. Oppdalshol[34], Hege E. G. Russnes[2,3,4], Ravinder Singh[48], Svein Skole[49], Fredrik Sund[50], Lars P. Strand[49], Kjetil Taskén[1,2], Lidziya Ulvenes[42], Gisko Ursin[51], Sverrir Valgardsson[49], Katil Widerberg[39], Pål Wilk[49], Naoko Yamagata[52] and Jutta Helx[19]

[39]*Roche Norge AS, Oslo, Norway.* [40]*Bayer AS, Oslo, Norway.* [41]*Bristol-Myers Squibb Norway Ltd NUF, Oslo, Norway.* [42]*Novartis Norge AS, Oslo, Norway.* [43]*Association of the Pharmaceutical Industry in Norway, Oslo, Norway.* [44]*Norwegian Directorate of Health, Oslo, Norway.* [45]*Pubgene AS, Oslo, Norway.* [46]*AstraZeneca AS, Oslo, Norway.* [47]*Department of Oncology, Nord-Trøndelag Hospital Trust, Levanger, Norway.* [48]*K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.* [49]*HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger, Norway.* [50]*AbbVie AS, Oslo, Norway.* [51]*MSD Norge AS, Oslo, Norway.* [52]*Amgen AB Norway NUF, Oslo, Norway.* [53]*GlaxoSmithKline AS, Oslo, Norway.* [54]*Pfizer Norge AS, Oslo, Norway.* [55]*Norwegian Cancer Society, Oslo, Norway.* [56]*Eli Lilly Norge AS, Oslo, Norway.* [57]*Department of Research, Stavanger University Hospital, Stavanger, Norway.* [58]*Takeda AS, Oslo, Norway.* [59]*Janssen-Cilag AS, Oslo, Norway.* [60]*Unit for Medicine and Health Sciences, Akershus University Hospital, Lørenskog, Norway.* [61]*NEC Corporation, Tokyo, Japan.*

InPreD-Norway and National Molecular Tumor Board Consortium

Hege E. G. Russnes[2,3,4], Thomas Berg[62], Egil S. Blix[10,11], Diana L. Bordin[39], Hans-Rickard Brattbakk[63], Richard Doughty[62], Karl Ersland[42], Åsmund Flobak[14,15], Rakel Forthun[42], Bjørnar Gilje[16], Einar Gudlaugsson[64], Hanne Hamre[34], Hans Kristian Haugland[20,21], Eivind Hovig[20,21], Randi Hovland[22], Emiel Janssen[65,66], Mari Jobsen[67], Tonje Lien[3,4], Susanna Lorenz[24], Torben Lüders[68], Leonardo A. Meza-Zepeda[20,24], Per M. Mæhle[25], Pitt Niehusmann[3], Hilde L. Nilsen[7,26], John C. Noone[39], Vigdis Nygaard[3], Ulla Randen[2,69], Anne Renolen[2], Anne J. Skjulsvik[67], Sigmund V. Sperstad[63], Olav K. Vintermyr[20,70], Daniel Vodak[24], Teresia Wangensteen[34], Ragnhild M. Wold[39], Kristin Åberg[39] and Tormod K. Guren[18]

[62]*Department of Clinical Pathology, University Hospital of North Norway, Tromsø, Norway.* [63]*Department of Pathology, Akershus University Hospital, Lørenskog, Norway.* [64]*Department of Pathology, Stavanger University Hospital, Stavanger, Norway.* [65]*Department of Oncology, Akershus University Hospital, Lørenskog, Norway.* [66]*Department of Pathology, Haukeland University Hospital, Bergen, Norway.* [67]*Department of Chemistry, Bioscience and Environmental Engineering, University of Stavanger, Stavanger, Norway.* [68]*Department of Pathology, St. Olav University Hospital, Trondheim, Norway.* [69]*Department of Medical Genetics, Oslo University Hospital, Oslo, Norway.*

IMPRESS-Norway Consortium

Åslaug Helland[2,4,18], Hege E. G. Russnes[2,3,4], Gro Live Fagereng[13], Eline Aas[5,6], Khalid Al-Shibli[49], Yvonne Andersson[60], Thomas Berg[62], Line Bjørge[7,8,9], Egil Blix[10,11], Bodil Bjørkehagen[2], Sigmund Brabrand[39,71], Odd Terje Brustugun[60], Marte G. Cameron[42], Astrid Dalhaug[69], Dalia Dietzel[64], Tom Dønnem[51,72], Espen Enerly[12], Ragnhild S. Falk[60], Åsmund Flobak[14,15], Sverre Fluge[66], Bjørnar Gilje[16], Bjørn T. Gjertsen[8,9,17], Bjørn H. Grønberg[14,73], Karl Grønås[67], Tormod K. Guren[18], Hanne Hamre[34], Åse Haug[69], Daniel Heinrich[69], Geir Olav Hjortland[74], Eivind Hovig[20,21], Gunnar Hoge[2,69], Randi Hovland[22], Ann-Charlotte Iversen[9,75], Emiel Janssen[65,66], Stian Knappskog[8,23], Jon Amund Kyte[76], Hadda von der Lippe Gythfeldt[68], Kristina Lindemann[77], Ragnhild A. Lothe[2,72], Jo-Åsmund Lund[78], Per Eystein Lønning[8,23], Leonardo Meza-Zepeda[20,24], Monica C. Munthe-Kaas[24], Olav T. D. Nguyen[36], Pitt Niehusmann[3,25], Hilde L. Nilsen[7,26], Katarina Puco[25], Ulla Randen[2,69], Anne H. Rise[2,34], Tonje B. Riste[79], Karin Semb[36], Elí Sihn S. Steinskog[80], Andreas Stensvold[81], Pål Suhrke[82], Øyvind Tennøe[27], Geir E. Tjønnfjord[2,29], Liv I. Vassbotn[60], Sissel F. Wahl[67], Kjetil Taskén[1,2] and Sigbjørn Smeland[2,29]

[70]*Department of Pathology, Nordland Hospital Trust, Bodø, Norway.* [71]*Southern and Eastern Norway Pharmaceutical Trust, Oslo, Norway.* [72]*Department of Oncology, Vestre Viken Hospital Trust, Drammen, Norway.* [73]*Department of Oncology, Hospital of Southern Norway, Kristiansand, Norway.* [74]*Department of Oncology, Nordland Hospital Trust, Bodø, Norway.* [75]*Department of Oncology, Telemark Hospital Trust, Skien, Norway.* [76]*Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway.* [77]*Department of Oncology, Finnmarkssykehuset Hospital Trust, Hammerfest, Norway.* [78]*IMPRESS-Norway Patient representative, Oslo, Norway.* [79]*Department of Oncology, Innlandet Hospital Trust, Brumunddal, Norway.* [80]*Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway.* [81]*IMPRESS-Norway Patient representative, Trondheim, Norway.* [82]*Department of Gynecological Oncology, Oslo University Hospital, Oslo, Norway.* [83]*Department of Molecular Oncology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway.* [84]*Department of Oncology, Møre og Romsdal Hospital Trust, Ålesund, Norway.* [85]*Department of Pediatric Medicine, Oslo University Hospital, Oslo, Norway.* [86]*Department of Pathology, Førde Hospital Trust, Førde, Norway.* [87]*Department of Oncology, Vestfold Hospital Trust, Tønsberg, Norway.* [88]*Department of Oncology, Østfold Hospital Trust, Kalnes, Norway.* [89]*Department of Pathology, Vestfold Hospital Trust, Tønsberg, Norway.* [90]*Department of Haematology, Oslo University Hospital, Oslo, Norway.* [91]*Department of Oncology, Førde Hospital Trust, Førde, Norway.*

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Author contributions

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Competing interests

Participation in the CONNECT Public–Private Partnership is regulated by a consortium agreement that handles conflicts of interest and regulates interaction with the publicly funded infrastructure InPreD-Norway and the investigator-initiated and publicly funded trial IMPRESS-Norway. IMPRESS-Norway (principal investigator Å.H.) has company contributions from Roche, Novartis, Incyte and Eli Lilly and collaboration projects with Roche Foundation Medicine and Illumina, regulated by separate agreements with Oslo University Hospital as the coordinating institution. The authors declare no competing interests.

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