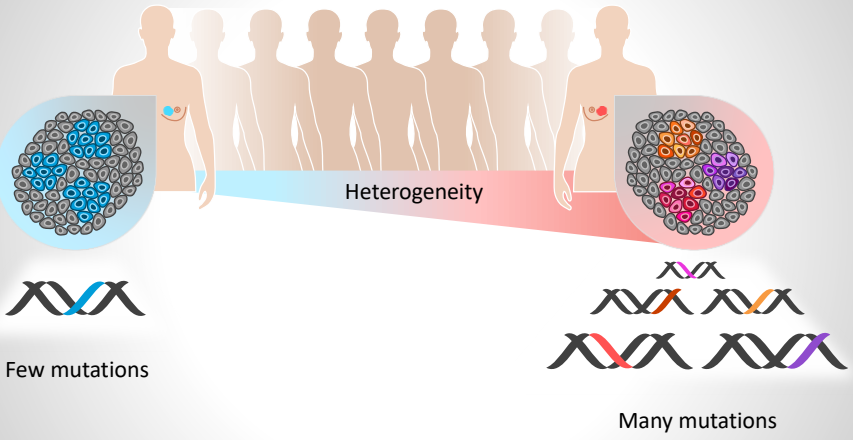
How to implement precision medicine in oncology?



Kjetil Taskén, Professor M.D., Ph.D.,
Head, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway

nature medicine
LETTERS
https://doi.org/10.1038/s41591-019-0424-4

Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial

Jordi Rodon[1,2,17], Jean-Charles Soria[3,17], Raanan Berger[4,17], Wilson H. Miller[5,17], Eitan Rubin[6], Aleksandra Kugel[6], Apostolia Tsimberidou[7], Pierre Saintigny[8], Aliza Ackerstein[4], Irene Braña[1], Yohann Loriot[3], Mohammad Afshar[8], Vincent Miller[9], Fanny Wunder[10], Catherine Bresson[10], Jean-François Martini[11], Jacques Raynaud[12], John Mendelsohn[10,13,18], Gerald Batist[5], Amir Onn[4], Josep Tabernero[1], Richard L. Schilsky[10,14], Vladimir Lazar[10,17], J. Jack Lee[15,17] and Razelle Kurzrock[10,16,17*]

Precision medicine focuses on DNA abnormalities, but not all tumors have tractable genomic alterations. The WINTHER trial (NCT01856296) navigated patients to therapy on the basis of fresh biopsy-derived DNA sequencing (arm A; 236 gene panel) or RNA expression (arm B; comparing tumor to normal). The clinical management committee (investigators from five countries) recommended therapies, prioritizing genomic matches; physicians determined the therapy given. Matching scores were calculated post-hoc for each patient, according to drugs received: for DNA, the number of alterations matched divided by the total alteration number; for RNA, expression-matched drug ranks. Overall, 303 patients consented; 107 (35%; 69 in arm A and 38 in arm B) were evaluable for therapy. The median number of previous therapies was three. The most common diagnoses were colon, head and neck, and lung cancers. Among the 107 patients, the rate of stable disease ≥6 months and partial or complete response was 26.2% (arm A: 23.2%; arm B: 31.6% ($P = 0.377$)). The patient proportion with WINTHER versus previous therapy progression-free survival ratio of >1.3 was 22.4%, which did not meet the pre-specified primary end point. Fewer previous therapies, better performance status and higher matching score correlated with longer progression-free survival (all $P < 0.05$, multivariate). Our study shows that genomic and transcriptomic profiling are both useful for improving therapy recommendations and patient outcome, and expands personalized cancer treatment.

been achieved with investigation of DNA structural abnormalities. Today, there are several models for choosing genome-targeted or immune-targeted therapies according to molecular abnormalities (for example, individual mutations or microsatellite instability/high mutational burden)[2]. Successes have been reported across diverse malignancies, with a few examples as follows: *EGFR* (encoding epidermal growth factor receptor) mutation with erlotinib, *KIT* mutation with imatinib, *BRAF* mutation with vemurafenib and *ALK* translocation with crizotinib[3–5].

Unfortunately, not all patients' tumors have pharmacologically tractable DNA alterations. Thus, extending the application of precision medicine requires a deeper understanding of cancer biology. There is a need to explore oncogenic mechanisms beyond the identification of genomic driver aberrations and to incorporate new methodologies, such as those interrogating gene expression. Hence, we initiated an international trial—WINTHER—that prospectively navigated patients to therapy according to either DNA-guided next-generation sequencing (NGS) or transcriptional analysis that specifically compared tumor to matched normal tissue[6]. Grounded in the precision medicine knowledge at the trial start, the protocol prioritized genomic (DNA) matches, and RNA-guided therapy was exploratory. The design and primary end point centered on the Von Hoff model that uses the patient as their own control—comparing progression-free survival (PFS) on the trial (PFS2) to the PFS recorded on the therapy administered immediately prior to enrollment (PFS1)[10]. As integration of transcriptomic investiga-

LETTER

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

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

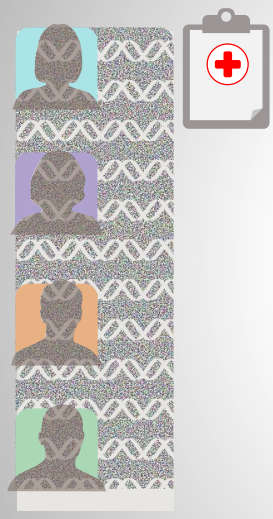
D. L. van der Velden[1,2,21], L. R. Hoes[1,2,3,21], H. van der Wijngaart[2,3,4,21], J. M. van Berge Henegouwen[2,3,5,21], E. van Werkhoven[6], P. Roepman[7], R. L. Schilsky[8], W. W. J. de Leng[9], A. D. R. Huitema[10,11], B. Nuijen[11], P. M. Nederlof[12], C. M. L. van Herpen[13], D. J. A. de Groot[14], 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.

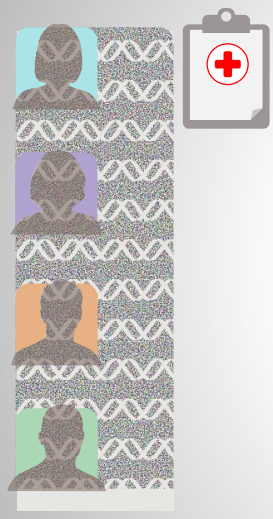
The Center for Personalized Cancer Treatment was founded in 2010[14] to address these issues. In this network (which now connects 45 hospitals in the Netherlands), patients with all types of metastatic cancer are offered the opportunity to undergo a fresh tumour biopsy for whole-genome sequencing (WGS) 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



Precision Medicine Challenge

- Each patient his or her disease
- One disease in each patient
- Observations are n=1
- Challenges disease classification and diagnosis systems



Challenges with individualised therapy

- "Crashes" with how we traditionally documents efficacy of medical treatment
- Challenges current decision- making systems for implementing new treatments
- Calls for other study designs
- Demands well-functioning molecular diagnostics
- Should not squeeze out established treatments with well documented effect (and low cost)

Objectives – Oslo University Hospital PM strategy for cancer (draft plan)

- *Patients who are referred to OUH with cancer and where advanced molecular cancer diagnostics will be instrumental for selection of treatment should be offered such diagnostics at the right time during the course of the disease.*
- *Cancer patients should have opportunity to receive individualised treatment where this is shown to impact on clinical outcome or where it is probable that it would give patient benefit.*
- *OUH will learn and build competence in advanced molecular cancer diagnostics and individualised treatment and contribute to development and production and dissemination of knew knowledge in this area.*

What is necessary for implementation?

Three main areas:

I. Establishment of an platform that can provide advanced (experimental) molecular cancer diagnostics. Develop such service also in the standard process to examine and diagnose patients.

II. Increase the volume of clinical trials and number of patients in trials in the precision medicine area (industry studies, researcher-initiated trials). Phase IV studies

III. Offer individualised cancer treatment in the ordinary standard of care in OUH according to national and international guidelines.

Questions

- ***Q**: Why is genomics important – the dream aspiration* – **A**: In cancer, can understand the molecular mechanisms of disease and use this as a basis for guiding clinical decisions in individualized treatment
- ***Q**: How do we measure outcomes and cost effectiveness for Genomics today and what should we be measuring tomorrow?* **A**: Most recent outcomes such as DRUP study (Nature Sept 30 from then Netherlands) included 46% into clinical trials after NGS and report early patient benefit in some cancers for up to 26%. Health economy analyses yet to be fully developed, BUT potential health cost savings by only treating patients with effect. Will require changes in current models for reimbursement.
- ***Q**: How can we move forward – what is the first thing to change and/or the biggest change needed?* **A**: Need a diagnostic motor in molecular pathology to be able to screen patients and stratify for PM. Need funding for this, studies do not pay.
- ***Q**: Who needs to be part of the changing ecosystem going forward?* **A**: Health care system / hospital multidisciplinary teams, payers, regulators, industry. PPPs needed.