
# Nonadherence to Oral Targeted Anticancer Drugs: What's the Problem and How to Address It ?

Prof. Marie Schneider, pharmacist, PhD

Pharmacie communautaire, Section des sciences pharmaceutiques,
Université de Genève, Université de Lausanne, Suisse

11th Swiss Pharma Day 2018, Bern, August 22nd, 2018

# Outline

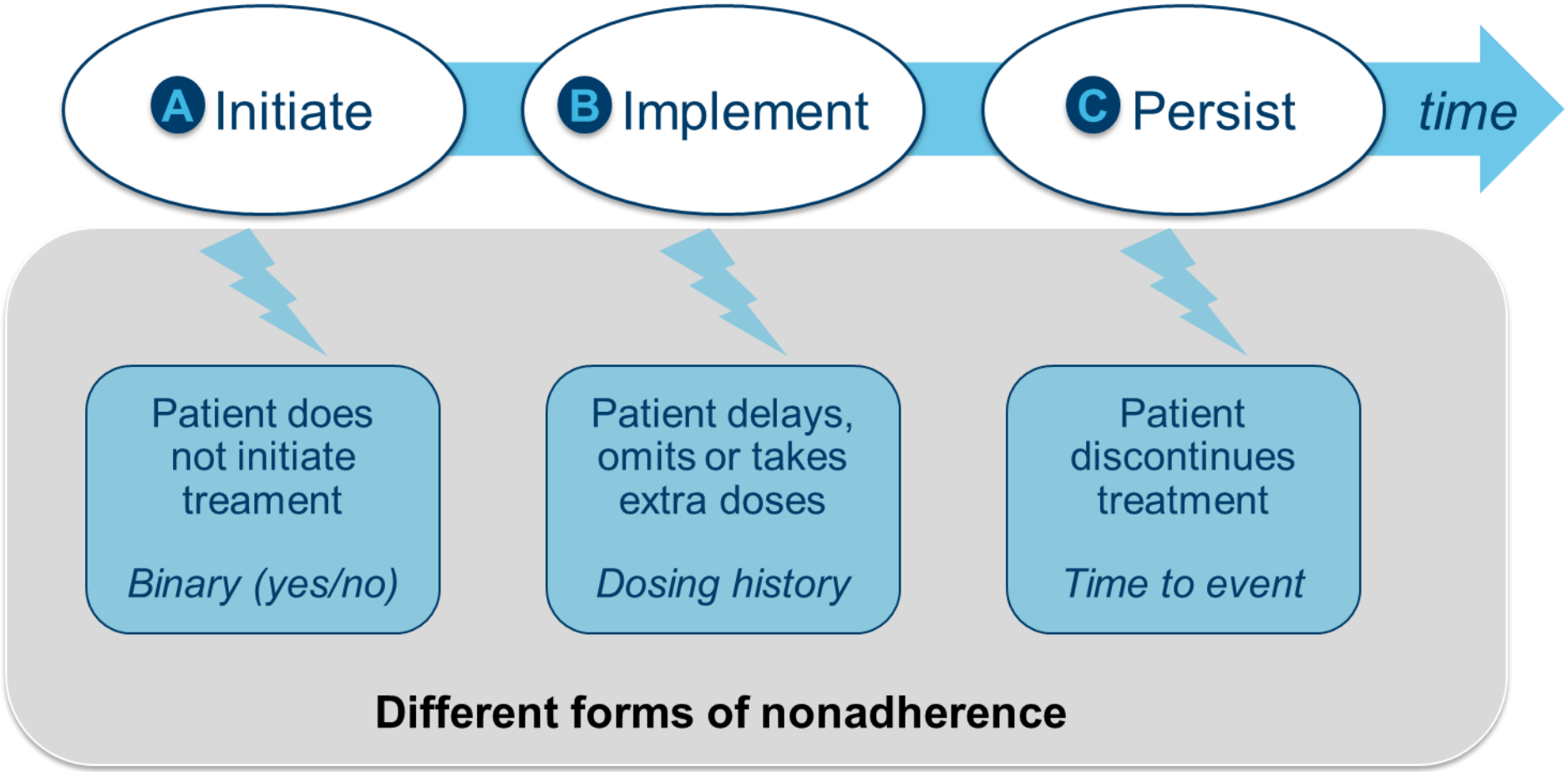
1. Introduction on medication adherence in oncology
2. Review of the literature: breast cancer; chronic myeloid leukemia (CML); gastrointestinal stromal tumor (GIST); non-small cell lung cancer
3. Patient education programs
4. Our on-going research project
5. Take-home messages

# Introduction

- Patients prefer oral to intravenous chemotherapy (Liu et al. 1997)
- Adherence: process by which patients take their medications as prescribed

- A behaviour which seems easy for the patient…
- A behaviour that seems easy to support for healthcare professionals …
- A behaviour that seems easy to investigate in research …
- … but which is extremely complex
- And healthcare providers and community pharmacists are at the interface

# Definition - Medication adherence




EU-sponsored research

Vrijens et al. *Br J Clin Pharmacol*. 2012;73:691-705

# Medication adherence as a corner stone to drug cost-effectiveness

↓ Hospitalisations

Heart failure

Riegel et al. Patient Preference and Adherence 2014;8:1-13

↓ Therapeutic failures

Chronic myeloid leukemia CCyR

Ibrahim et al. Blood 2011;117(14):3733-6.

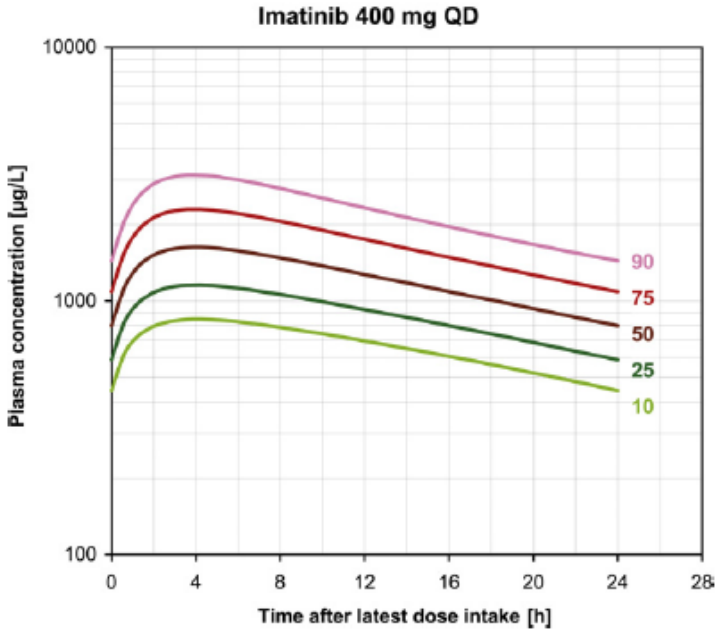
↓ Mortality

HIV

Glass et al. AIDS 2015; 29:2195–2200

# Cancers are becoming chronically manageable diseases

- Large scale use of oral targeted treatments in cancer
- Inter- and intra-individual variability in drug exposure
- Nonadherence is a public health issue




Von Mehren and Widmer.
Cancer Treatment Reviews 37 (2011) 291–299

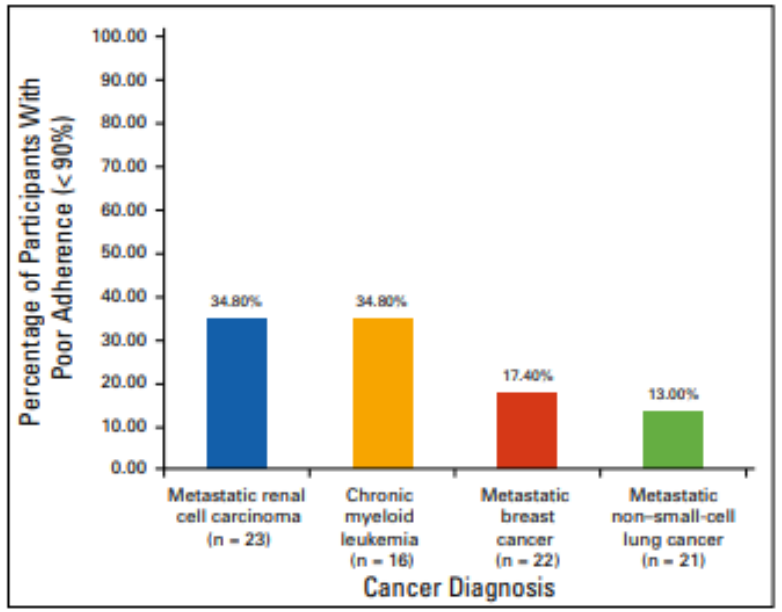
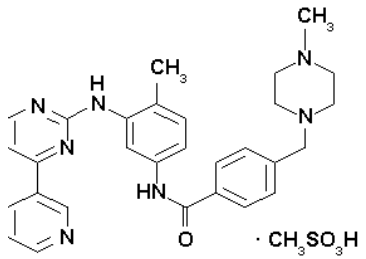



**Fig.** Proportion of patients with poor adherence by cancer type (poor adherence defined as < 90% adherent). NOTE. Percentages are out of total number of participants with available Medication Event Monitoring System data (n = 82).

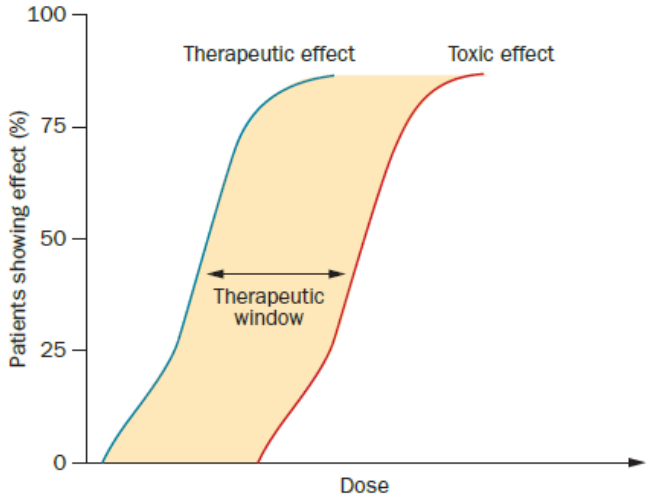
Jacobs et al. Journal of Oncology Practice 2017;13(5):e473-485

# Adherence to protein kinase inhibitors (PKI) and outcomes

- Despite large variability in pharmacokinetics, PKI are registered at a fixed oral dose.
- Proven exposure-response relation
- Challenge in research: dose optimization




[imatinib free drug]↑




Impact of patient adherence

Mathijssen et al. Nat Rev Clin Oncol 2014;11:272-281
Rowland et al. Expert Opinion on drug metabolism and toxicology 2017;13(1):31-49
Cardoso, Csajka, Schneider, Widmer. Clin Pharmacokinet 2018;57(1):1-6

# Unpredictable profile of adherence: >700 determinants

(Kardas et al. Frontiers Pharmacology 2013)

Patient-healthcare providers communication

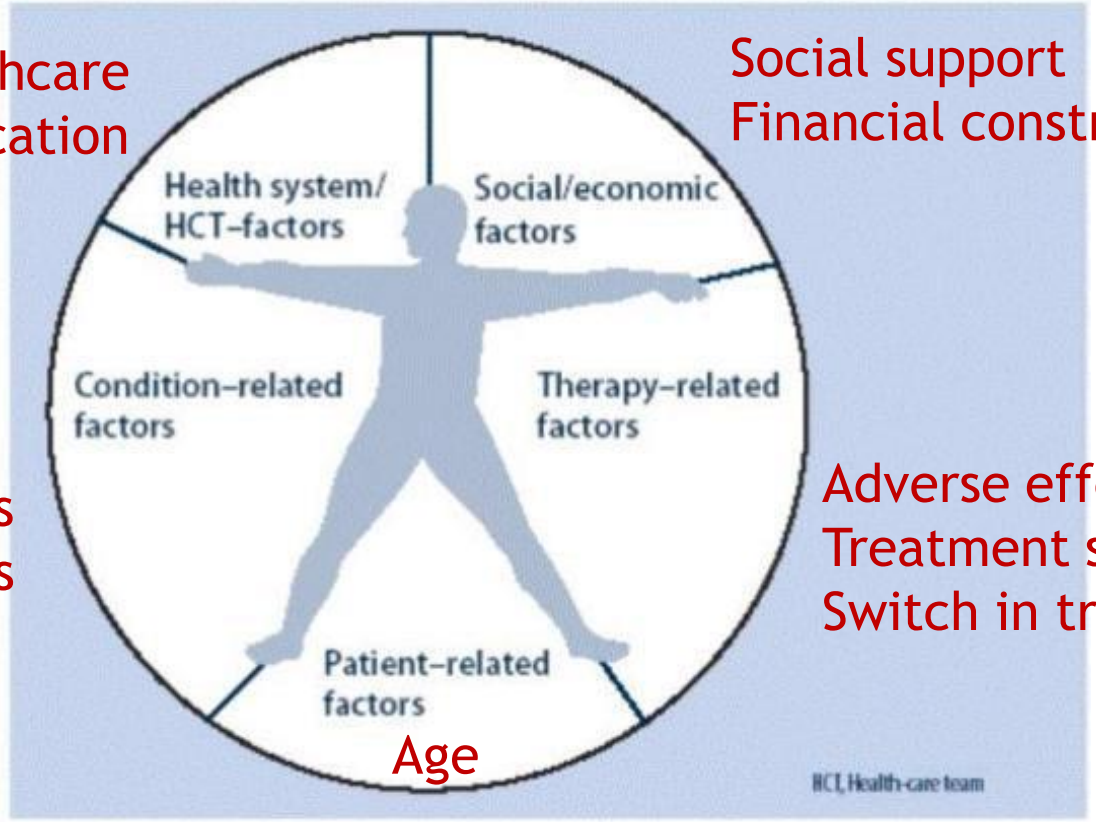
Social support
Financial constraints

Time since diagnosis
Comorbidities

Adverse effects
Treatment satisfaction
Switch in treatment

Age

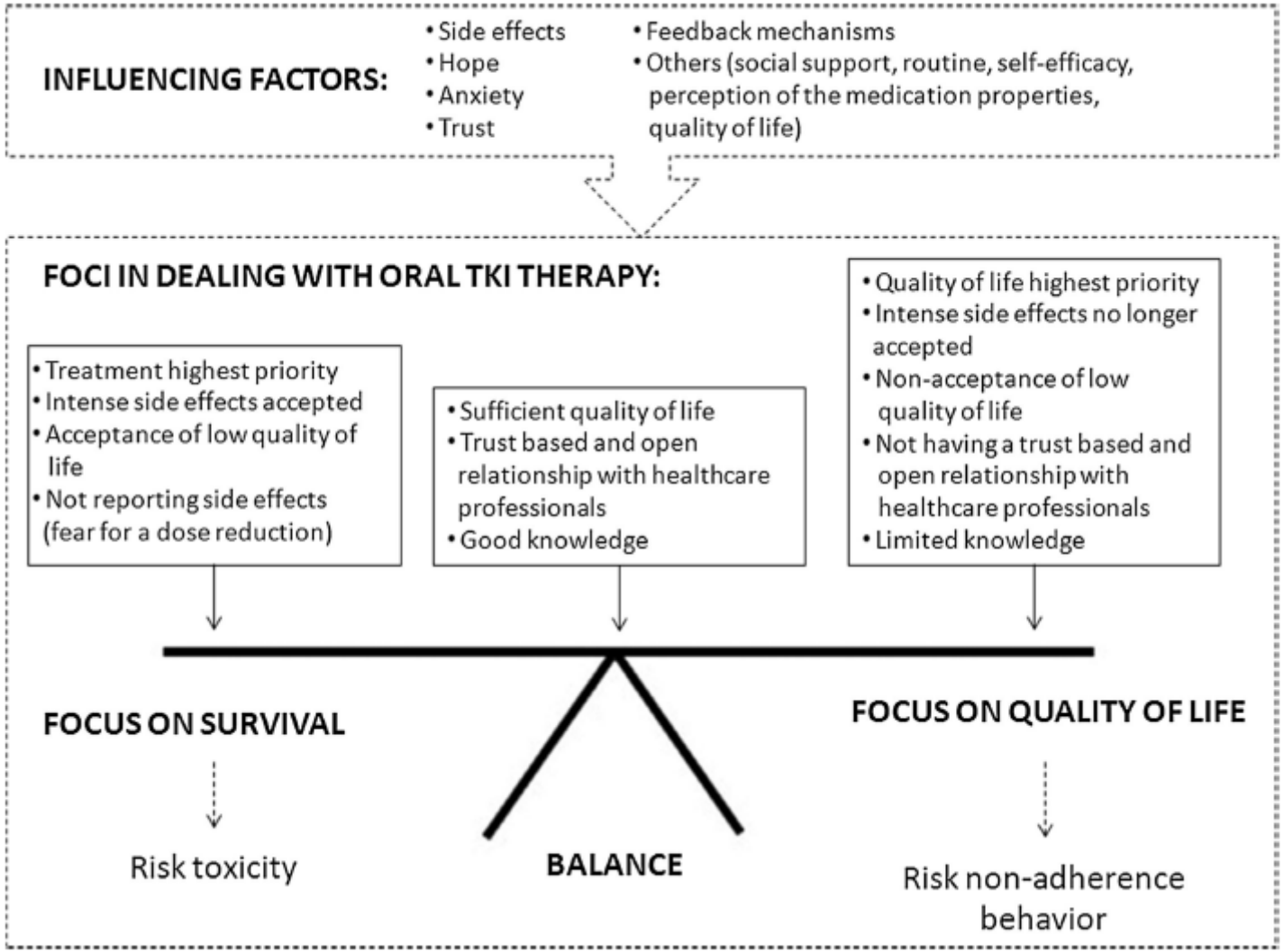
Figure 3 The five dimensions of adherence




www.who.org Adherence to long-term therapy. Evidence for action. 2003 (accessed 02.08.2018)

Marin 2010, Barthelemy 2015, Rychter 2017, Jacobs 2017; Breccia 2015, Murphy 2012, Cluze 2012, Myrick 2012, Gevnisman 2013

# Determinants of adherence to tyrosine kinase inhibitors




Verbrugghe et al. Cancer Nursing 2016;39(2):153-162

# Methods for measuring medication adherence

**Table 2. Measures of Adherence.**

| Measure | Pros | Cons |
|---|---|---|
| *Direct* | | |
| Direct observation | Most accurate | Not feasible in real-world practice |
| Serum drug levels | Objective measure of recent exposure to drug | Can be manipulated; acceptable ranges often unknown; assays not widely available |
| *Indirect* | | |
| Pill counts | Inexpensive | Difficult in real-world practice; easy to manipulate; may overestimate adherence; demeaning |
| MEMS (microelectronic event monitoring system) | Accurate data on when one opens the bottle; may be combined with reminder systems | Not easily feasible in real-world practice; expensive |
| Refill records | Objective higher level data; good for research purposes | Report fill rate and not actual intake; impractical for daily use |
| Biomarkers | May be important intermediaries to outcomes (e.g., hypertension with TKI use) | Few developed and validated |
| Outcomes | Most important variable | Difficult to discern nuances of adherence outside of clear extremes |
| *Indirect and Subjective* | | |
| Self-report | Quick; can use past validated instruments; does not require clinician time | Subject to significant bias such as the Hawthorne effect and overestimates adherence |
| Assessment by others | Inexpensive; allows for a dialogue | Hawthorne effect; time consuming |
| Diaries | Inexpensive; actively involves the patient | Subject to manipulation; demeaning; time consuming |

Geynisman Discov Med. 2013;15(83):231-41

# Outline

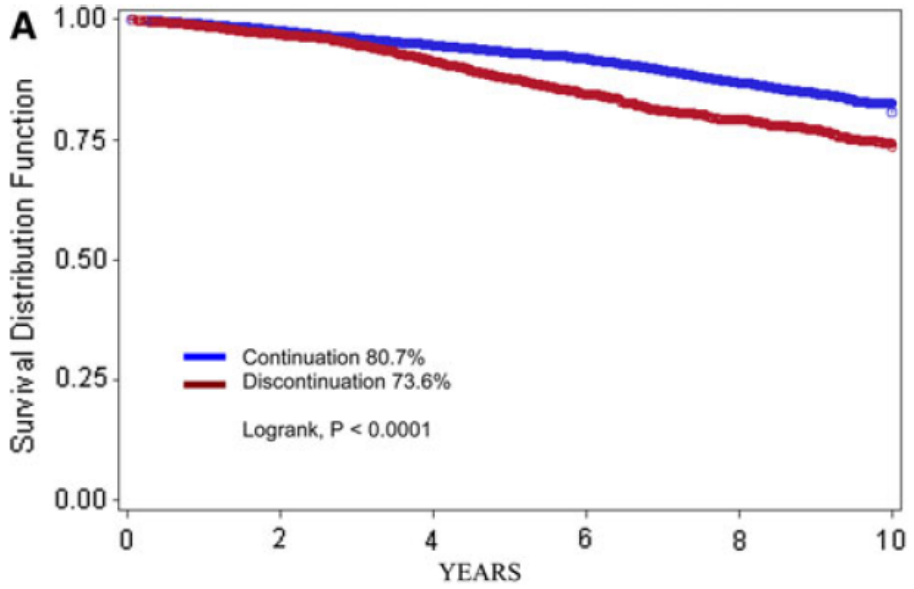
1. Introduction on medication adherence in oncology
2. Review of the literature: breast cancer; chronic myeloid leukemia (CML); gastrointestinal stromal tumor (GIST); non-small cell lung cancer
3. Patient education programs
4. Our on-going research project
5. Take-home messages

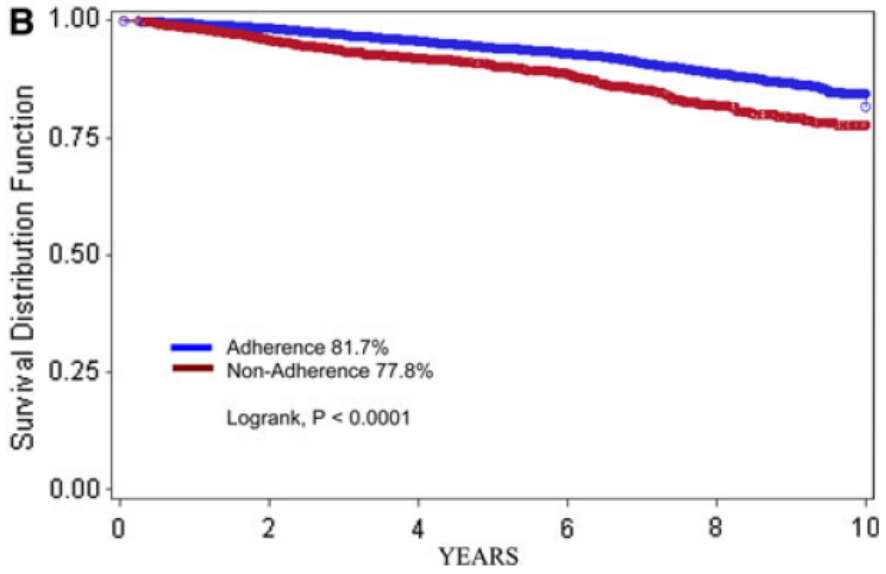
# Prevalence of nonadherence and mortality in breast cancer

- Prevalence of nonadherence: 28 to 59%
- 5-year nonpersistence: 31 to 73%

(Murphy et al. Breast Cancer Res Treat 2012;134:459–478)

- Noninitiation in patients age≥ 65 yrs: 14% (Sheppard et al. J Clin Oncol 2014;32:2318-2327)
- Low adherence and early nonpersistence are independant predictors of mortality.

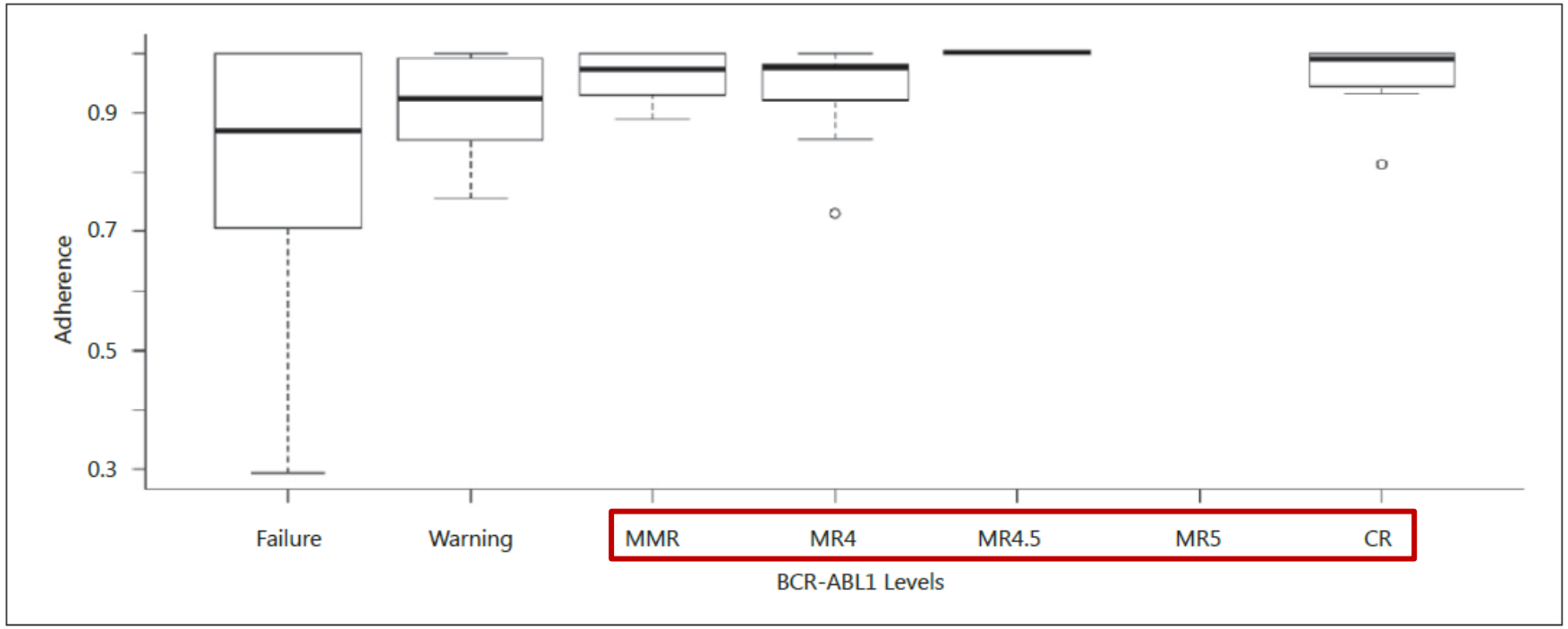



Hershman et al. Breast Cancer Res Treat (2011) 126:529–537

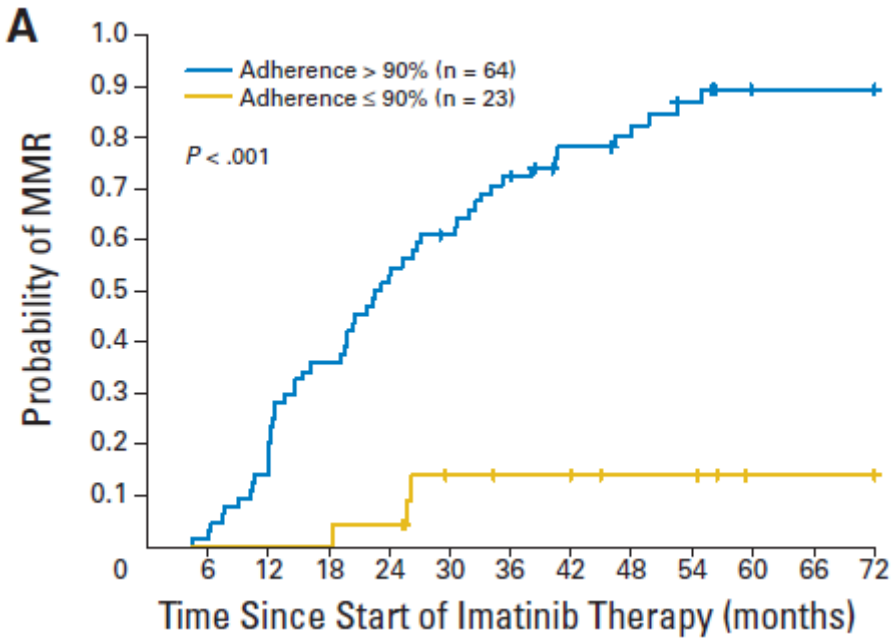
# Prevalence of non-adherence in Chronic Myeloid Leukemia (CML)

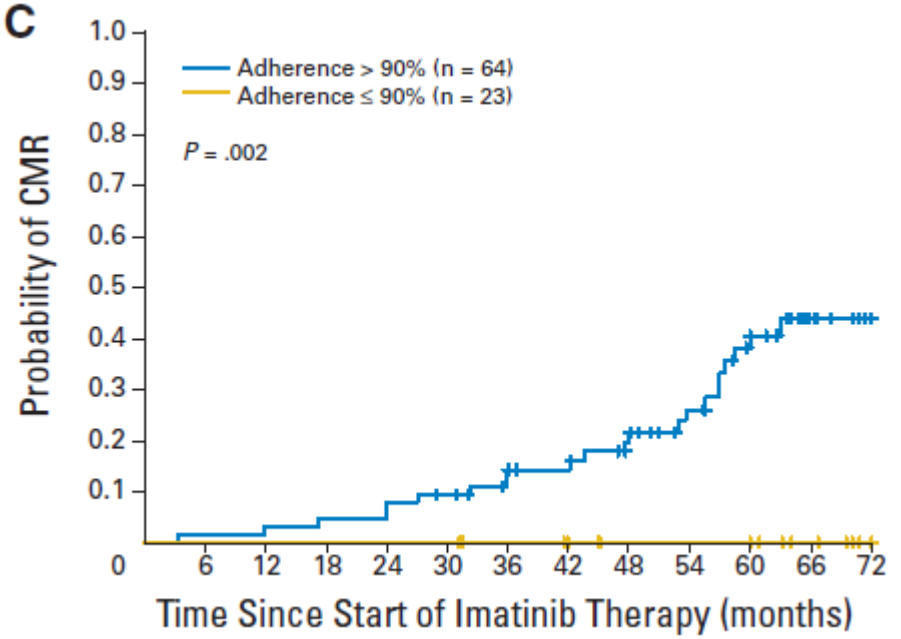
- 26.4% (Ibrahim et al. Blood. 2011; 117(14):3733-3736)
- 32.7% (ADAGIO study, Noens et al. Blood 2009; 113:5401-5411)
- 36.6% (Santoleri et al. Acta Haematol 2016;136:45–51)




90% adherence cutoff (Santoleri et al. Acta Haematol 2016;136:45–51)

# Probability of 6-year response in Chronic Myeloid Leukemia (CML)




MMR: major molecular response
13.9% if adherence ≤90% (23 pts) vs.
93.7% if adherence >90% (64 pts)

CMR: complete molecular response
43.8% vs 0%

Adherence is an independant predictor of MMR (RR 11.7, p=.001) and CMR.

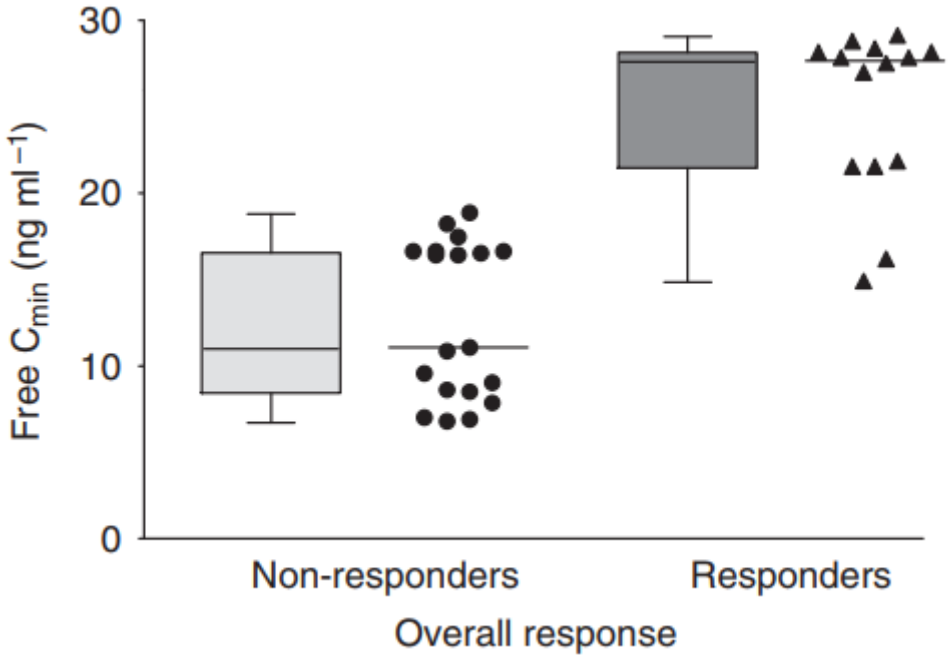
Marin et al. *J Clin Oncol 2010:28;2381-2388*

# Adherence to imatinib (>90%) is associated with lower health care utilization and costs

| | Good Adherence (MPR ≥ 90%) | Medium Adherence (MPR, 70%– < 90%) | Poor Adherence (MPR < 70%) | *P* Value (Good vs. Medium) | *P* Value (Good vs. Poor) |
|---|---|---|---|---|---|
| **Utilization and costs: entire follow-up period, mean (SD)** | | | | | |
| CML | *N* = 122 | *N* = 103 | *N* = 149 | | |
| Inpatient hospital stays | 0.5 (1.2) | 0.9 (2.8) | 1.9 (3.5) | 0.312 | < 0.001 |
| Inpatient length of stay, days | 3.8 (12.3) | 8.4 (27.6) | 21.0 (43.1) | 0.156 | < 0.001 |
| Total medical costs, $ | 30,212 (51,602) | 61,702 (149,568) | 133,072 (236,511) | 0.072 | < 0.001 |
| Total health care costs, $ | 120,762 (152,346) | 131,465 (152,346) | 172,050 (240,434) | 0.555 | 0.021 |

Halpern et al. JCOM 2009;*16 (5):215-223.*

# GIST patients:
# Imatinib plasma levels are correlated with clinical benefit

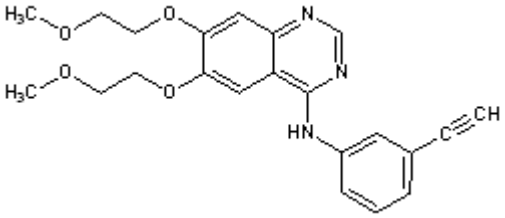



Non-persistence to imatinib is associated with rapid progression even in patients who had achieved complete remission.

Von Mehren, Widmer. Cancer Treatment Reviews 2011;37:291–299
Le Cesne et al. J Clin Oncology 2011;29(15 suppl):10015

# Erlotinib in non-small cell lung cancer

- Over one third of patients had an adherence <95%
- At 1-month, 21% patients did not always take the treatment under fasting conditions.
- AUCss was higher in patients with adverse effects (p = <0.05)
- 31% ( n = 19/62) reported adverse effects as a reason for non-persistence



[erlotinib]↑ → Adverse drug effects → Nonpersistence

Timmers et al. J Cancer Res Clin Oncol 2015; 141:1481-1491

# Adherence to targeted therapies decreases with time

| Duration of therapy | Number of patients reporting skipping TKI doses $n = 72$ | Number of patients, not reporting skipping TKI doses $n = 68$ | $P$ value | OR [95% PU] |
|---|---|---|---|---|
| Skipping doses within the entire duration of treatment | | | | |
| <1 year | 4 (5.6%) | 22 (32.4%) | <0.001 | |
| ≥1–<2 years | 8 (11.1%) | 14 (20.6%) | | 3.1 [0.8–12.4] |
| ≥2 years | 60 (83.3%) | 32 (47.0%) | | 10.3 [3.3–32.5] |

Rychter at al. Med Oncol (2017) 34:104
Santoleri et al. Acta Haematol 2016;136:45–51
Bathelelmy et al. Oncology 2015;88:1–8

# Outline

1. Introduction on medication adherence in oncology
2. Review of the literature: breast cancer; chronic myeloid leukemia (CML); gastrointestinal stromal tumor (GIST); non-small cell lung cancer
3. Patient education programs
4. Our on-going research project
5. Take-home messages

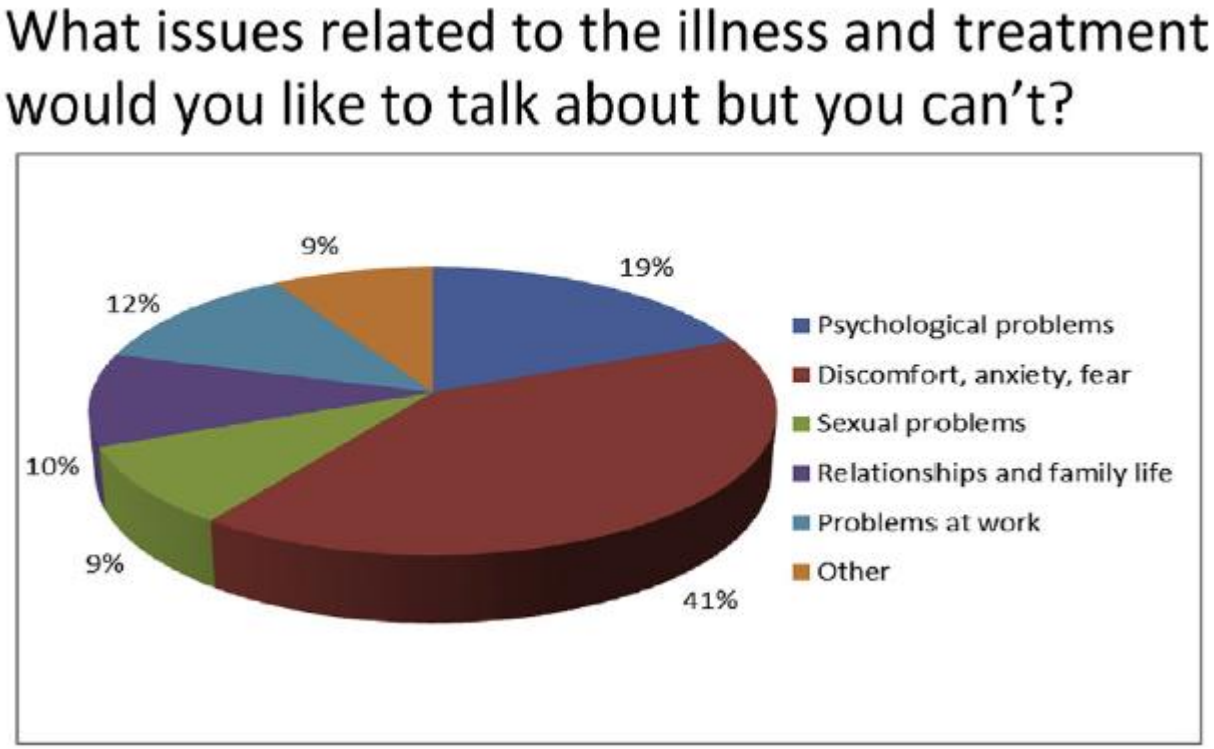
# Patient education in cancer care

- Lack of adherence intervention studies for oral anticancer agents (Mathes 2014 Cancer Treatment Reviews)
- Better patient education (Barthélémy Oncology 2015;88:1–8)
- Interprofessional care (Paolella et al. Pharmacy 2018, 6, 23; doi:10.3390)

| | Patients | Oncologists and Other Healthcare Professionals |
|---|---|---|
| Oral Therapies | Receive extensive amounts of information (e.g., administration, side effects) from oncology team in order to independently deliver, monitor, and safely handle oral anticancer medications. | Opportunity to educate and counsel patients at their respective health and digital literacy levels with the intention of better self-management |
| | Increased communication with outside providers and practitioners who might not be cancer care specialists | Non-verbal communication of patients unobservable during drug administration with the medication administered at home. Visual ques such as body fatigue, stress, and overall gestalt require patient to initiate conversation. |

# Patient care in cancer: CML

41% of CML patients reported that would like to discuss about discomfort, anxiety and fear of the future




Breccia et al. Leukemia Research 2015;39:1055–1059

# Patient care in breast cancer

“Improving persistence to adjuvant cancer therapy in premenopausal women is an important challenge for oncologists and other health care workers.
They must take more time to explain the role of therapy, to describe its side-effects, and to emphasize its importance.
Although the physician is likely to be the first person to explain the treatment, nurses and other health care professionals can deliver repeated information during follow-up.”

Cluze et al. Annals of Oncology 2012; 23: 882–890

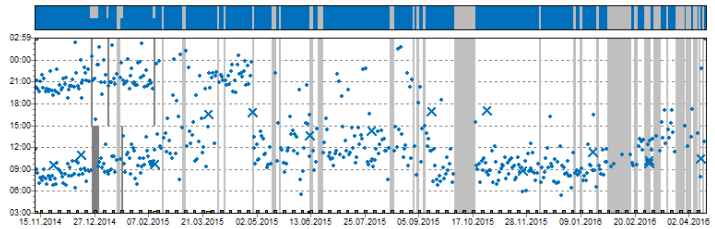
# Interprofessional Medication adherence program IMAP (Lausanne, Switzerland)

**Support** and **reinforce** medication adherence and patient's autonomy

**Motivational interviewing patient- pharmacist**

**Medication Event Monitoring System (MEMS®)**

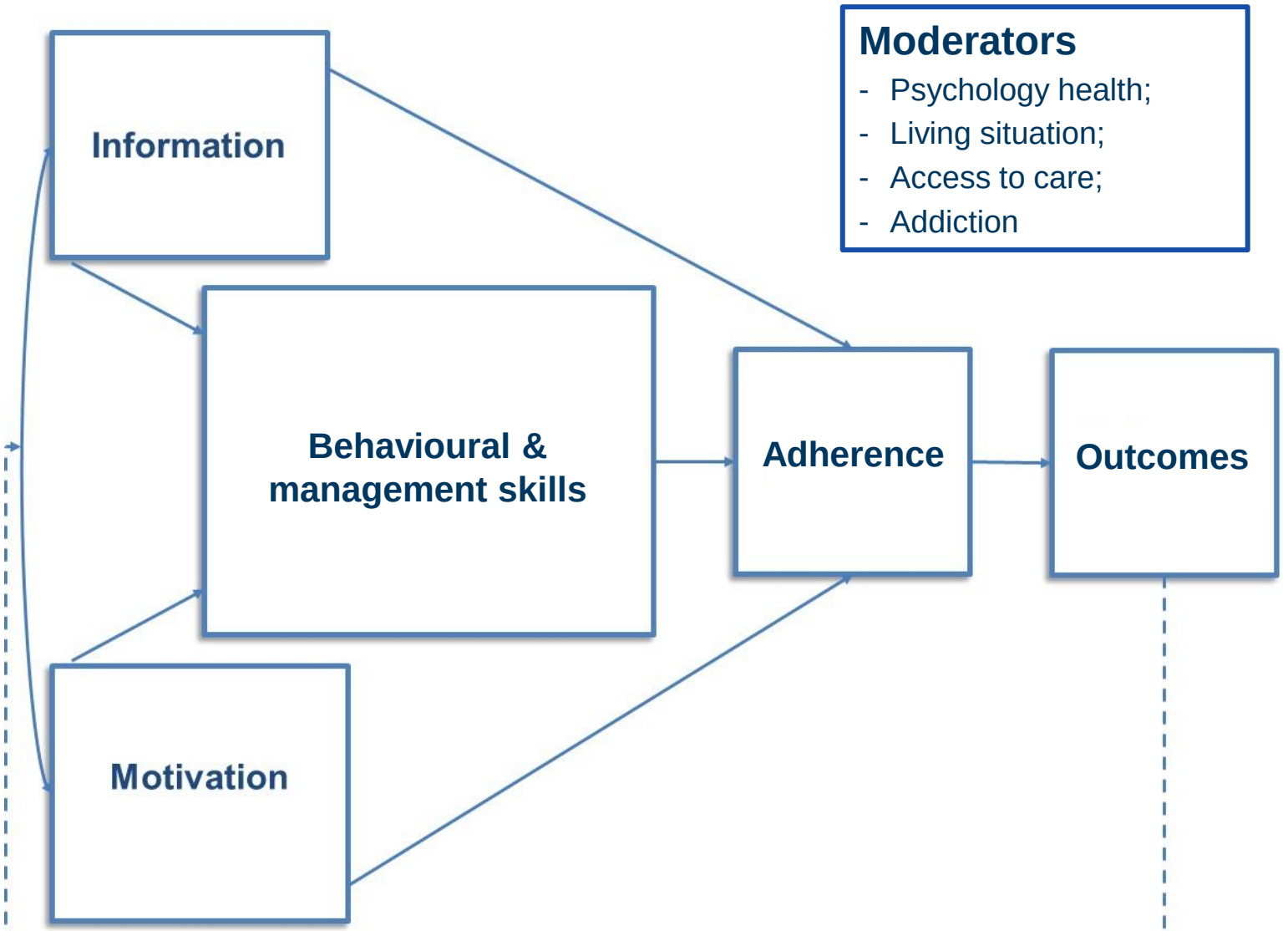
**Medication adherence report**



Lelubre M., Schneider M. et al. BioMed Research International 2015, Article ID 103546. DOI.org/10.1155/2015/103546
Schneider, Herzig, Hugentobler, Bugnon, RMS 2013;9:1032-6

# Theoretical model of the IMAP program IMB

Information
Motivation
Behaviour




Fisher et al. H*ealth Psychology 2006;* 25,4, 462–473

# Outline

1. Introduction on medication adherence in oncology
2. Review of the literature: breast cancer; chronic myeloid leukemia (CML); gastrointestinal stromal tumor (GIST); non-small cell lung cancer
3. Patient education programs
4. Our on-going research project
5. Take-home messages

# Optimization of Targeted Anticancer Therapies(OpTAT)

Health Services Research (2016) full application
Research v1.0

Cancer
Krebs
Cancro

Nationale Strategie gegen Krebs
Stratégie nationale contre le cancer
2014–2017


krebsforschung schweiz
recherche suisse contre le cancer
ricerca svizzera contro il cancro
swiss cancer research

ACCENTUS

**HSR-4077-11-2016**
**Optimizing targeted anti-cancer therapies: from better medication adherence to individualized treatments**

PI and co-PI:

- Prof. Marie Schneider, Medication adherence program, Pharmacy, Outpatient Medical Clinic, PMU, Lausanne
- Prof. Chantal Csajka, Clinical Pharmacology, CHUV, Lausanne
- Dre Dorothea Wagner, Medical Oncology, CHUV, Lausanne

PhD student: Evelina Cardoso

SCIENCES PHARMACEUTIQUES
Ecole de Pharmacie EPGL Genève - Lausanne

UNIL | Université de Lausanne

Ecole de Pharmacie EPGL Genève – Lausanne

UNIVERSITÉ DE GENÈVE
FACULTÉ DES SCIENCES
Section des sciences pharmaceutiques

# Objectives of the OpTAT study

1. Evaluation of the effect of the medication adherence program on patient self-management and treatment effectiveness compared to usual care.

2. Determination of the relation between dose-plasma drug concentrations and efficacy / toxicity endpoints to define or confirm thresholds maximizing treatment success and minimizing toxicity.

3. Analysis of the relation between adherence and plasma drug concentrations.

# Randomized clinical design (OpTAT)

Randomisation

**Medication adherence program**

- Electronic monitoring
- Monthly motivational interviewing
- Interprofessional collaboration

**Standard care**

- Blinded electronic monitoring

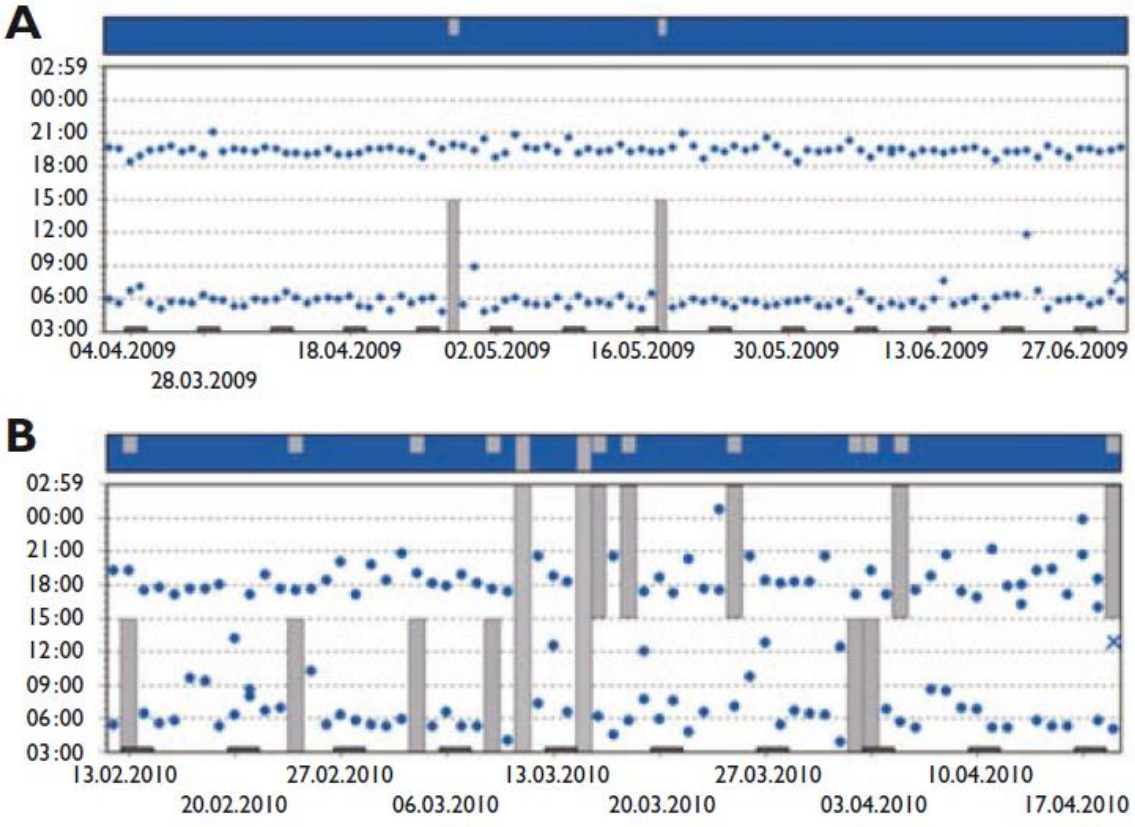
Sample size: 204 patients in 5 years

Study duration: 12 months

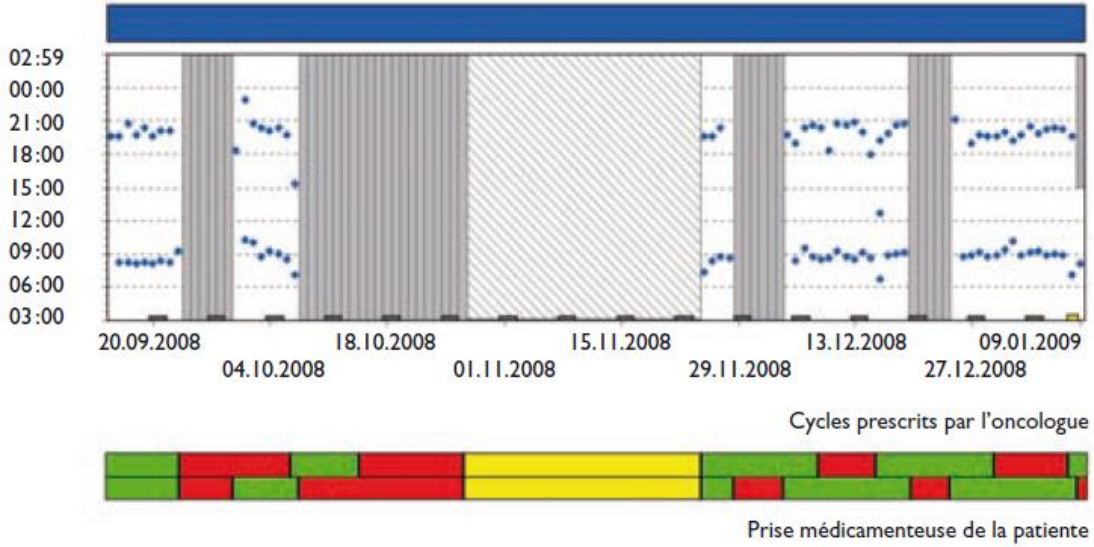
# Protein kinase inhibitors under investigation (OpTAT)

| Indication | PKIs approved by FDA |
|---|---|
| Leukemia | Imatinib, Dasatinib, Nilotinib, Bosutinib, Ponatinib |
| Gastrointestinal stromal tumors (GIST) | Imatinib, Sunitinib, Regorafenib |
| Non-small cell lung cancer (NSCLC) | Gefitinib, Erlotinib, Crizotinib, Afatinib |
| Pancreatic cancer | Erlotinib, Sunitinib |
| Hepato-cellular carcinoma (HCC) | Sorafenib |
| Renal cell carcinoma (RCC) | Sorafenib, Sunitinib, Pazopanib, Axitinib |
| Thyroid cancer | Sorafenib, Vandetanib, Cabozantinib |
| Breast cancer | Lapatinib palbociclib |
| Colorectal cancer (CRC) | Regorafenib |
| Melanoma | Vemurafenib, Dabrafenib, Trametinib, *Cobimetinib* |

# Clinical cases




70 years old, GIST, imatinib 400mg 1-0-1




74 years old
Metastatic colorectal cancer,
Capecitabine, 2-0-2, 2 weeks q21 days
Green: periods ON
Red: periods OFF

Achtari, Schneider, Bugnon, Lüthi. Rev Med Suisse 2011;7:1154-60

# Take-home messages

The NEW ENGLAND JOURNAL of MEDICINE

April 2010

Perspective

Thinking Outside the Pillbox — Medication Adherence as a Priority for Health Care Reform

David M. Cutler, Ph.D., and Wendy Everett, Sc.D.

N Engl J Med 2010; 362:1553-1555 | April 29, 2010 | DOI: 10.1056/NEJMp1002305

- Medication adherence is a public health priority in cancer
- Medication adherence has to be monitored in cancer clinical trials but also in real-life routine care, in other malignancies than breast cancer, CML or GIST, and with other targeted treatments than imatinib.
- Responsibility has to be shared between patients and healthcare professionals
- Interprofessional role of pharmacists has to be investigated and defined in order to optimize treatment effectiveness and increase patient safety
- Research in medication adherence will help rethink our outpatient healthcare system

# Thank you!


Prof. Chantal Csajka
Dr Ana Dorothea Wagner
Evelina Cardoso
Kim Ellefsen-Lavoie
Saskia Wherli
Dr Nicolas Widmer
All the pharmacists and technicians, Pharmacy, PMU
All the patients participating in the OpTAT study
Prof. Olivier Bugnon

marie.schneider@unige.ch