Come sono stati utilizzati i dati di Real World nel percorso di ricerca e sviluppo dei nuovi farmaci? Il punto di vista dei ricercatori

Dott.ssa Maria Carmela Piccirillo

SC Sperimentazioni Cliniche, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale - Napoli

Potenziali conflitti di interesse (2021-2023)

- Speaker activities
  - Astellas, Pfizer, Ipsen, Astrazeneca

- Financial support to Institutional research activities
  - Astra Zeneca, Bayer, Roche

Definiamo l'ambito

- RWD: dati sanitari raccolti al di fuori di RCT, tipicamente come parte della pratica clinica
- RWE: evidenza prodotta dai *Real World Data* (RWD) con applicazione di metodi di analisi epidemiologica e biostatistica
- Scopo: produrre conoscenza su benefici e rischi di un intervento terapeutico in un contesto di *real-life* (diverso da quello dei RCT)

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RWE vs RCT

- Diverso = Opposto?
- E quindi RWE come alternativa ai RCT?

- Diverso = Complementare?
- E quindi RWE come integrazione dei RCT?

- Io sono per l'inclusione

Da RCT a RWE

- I RCT sono considerati come il *gold standard* per stabilire la relazione causale tra un intervento e l'*outcome* di pazienti ad esso esposti
- Ma sono costosi e richiedono molto tempo
- E spesso sono ristretti ad una popolazione di pazienti selezionata
- Per le malattie rare, reclutare un numero sufficiente di pazienti in RCT potrebbe essere impossibile
- Per condizioni letali con nessun trattamento disponibile, l'assegnazione randomizzata di un trattamento molto promettente potrebbe non essere etica
- Per questi motivi, è nata l'esigenza di alternative ai RCT
- Già nel 2015 l'FDA nel *21st Century Cures Act* incoraggia l'uso di RWE, definita come dati "*derived from sources other than RCT*", per il processo decisionale regolatorio

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Real-world evidence framework to support EU regulatory decision-making

Report on the experience gained with regulator-led studies from September 2021 to February 2023

Secondo l'EMA "occorre compiere uno sforzo per anticipare la disponibilità di informazioni tratte dalla vita reale già dalla fase 1 alla fase 3" e metterle al servizio degli enti regolatori

Transformational journey to fully integrate RWE in EU regulatory decision making

By 2025 the use of real-world evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases to:

- support the planning and validity of studies performed/submitted by applicants;
- understand the clinical context;
- investigate associations and impact of regulatory decisions.

EMA's 3 main pathways for RWE generation

RWD can come from marketing authorisation applicants/holders, academia or national competent authorities. EMA can access RWD as follows:

EMA studies
Conducted by EMA's RWD analysts in collaboration with requester through direct access to 6 European primary healthcare data sources.

Framework contracts
Studies commissioned to research organisations and consortia with access to specialised data and expertise.

DARWIN EU®
Studies conducted via a federated network of data, expertise and comprehensive services with access to data partners and sets of analyses.

REVIEW

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 111 NUMBER 1 | January 2022

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Robert Flynn[1,2,†], Kelly Plueschke[1,†], Chantal Quinten[1], Valerie Strassmann[3], Ruben G. Duijnhoven[1,4], Maria Gordillo-Marañon[1,5], Marcia Rueckbeil[1,6], Catherine Cohet[1] and Xavier Kurz[1,*]

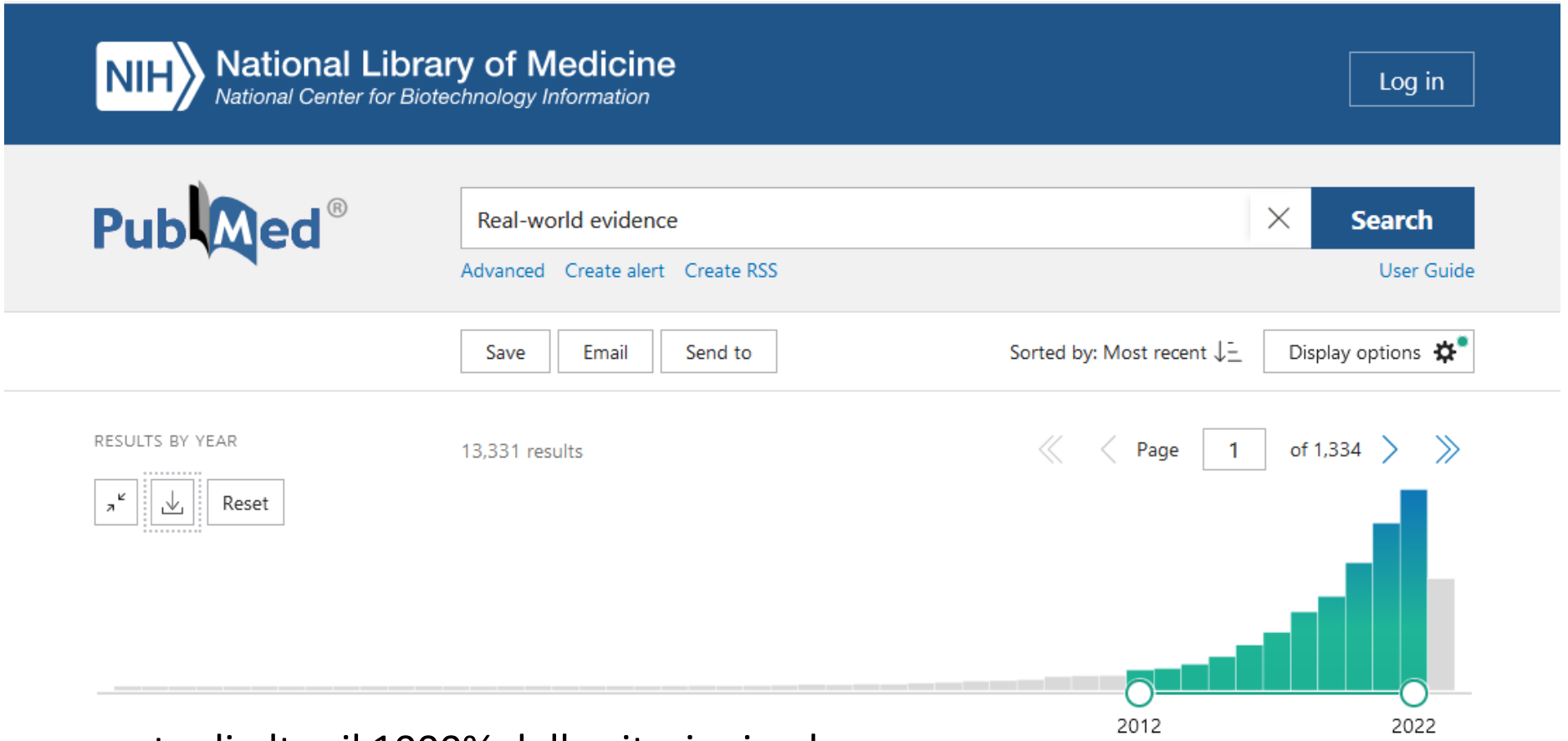
- For marketing authorization applications, 63 of 158 products (39.9%) contained RWE with a total of 117 studies
- RWE submitted was derived from data collected before the planned authorization for 31.7% of these products
- The most common data sources were registries (60.3%) followed by hospital data (31.7%)
- RWE was mainly included to support safety (87.3%) and efficacy (49.2%)
- Cohort study was the most frequently used study design (88.9%)

Insegnamenti post pandemia

- La pandemia di COVID-19 ha evidenziato la necessità di valutare tutti i tipi di evidenze per accelerare la comprensione epidemiologica della malattia e il valore degli interventi preventivi e terapeutici
- L'efficacia di diversi vaccini a mRNA contro il COVID-19 è stata stimata in tempo reale a livello di popolazione in contesti di *real-world,* analizzando le cartelle cliniche elettroniche e i dati sulle vaccinazioni

Evidenza di valore

- RWD e RWE sono diventati componenti importanti dell'informazione scientifica a supporto della valutazione dei farmaci, del processo decisionale regolatorio, del *health technology assessment* e della salute pubblica in generale



Un incremento di oltre il 1000% delle citazioni nel periodo dal 2012 al 2022 (da circa 300 citazioni all'anno a oltre 3500 citazioni per anno)

Uso della RWE

- Classicamente per valutare *effectiveness*, *safety* e valore di un farmaco dopo l'autorizzazione all'immissione in commercio
- Più modernamente, in qualsiasi fase dello sviluppo di un farmaco, per valutare sottogruppi di interesse, trend geografici o temporali, o anche nuove ipotesi di ricerca

RWE post RCT

- Valutare come i risultati dei RCT si tradurranno nella popolazione di interesse in contesti di pratica clinica
  - A livello paziente: *outcome* clinici, biomarcatori, *PROs*, soddisfazione e *engagement* del paziente
  - A livello sistema: utilizzo delle risorse, percorsi e costi dell'assistenza assistenza sanitaria
- Integrare i risultati dei RCT rispondendo a domande sugli impatti di un intervento nei diversi contesti di routine (differenze nella popolazione eleggibile, nei percorsi di trattamento e nei contesti assistenziali)
  - Prevalenza d'uso e aderenza agli interventi
  - Risultati a lungo termine (efficacia e sicurezza)
  - Modello di relazione tra risultati surrogati e risultati finali (compresi i PROs)

VIEWPOINT

Overall Survival in Cancer Drug Trials as a New Surrogate End Point for Overall Survival in the Real World

Sham Mailankody, MB, BS
Myeloma Service, Division of Hematologic Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York.

Vinay Prasad, MD, MPH
Division of Hematology Oncology, Knight Cancer Institute, Portland, Oregon; and Department of Public Health and Preventive Medicine, Oregon Health & Science University, Portland.

trial survival as a surrogate end point should prompt 1 of 2 changes to current cancer drug regulation.

Option 1: Pragmatic Clinical Trials

The FDA has the authority to demand that data supporting the efficacy of novel cancer drugs come from pragmatic trials, where patients are in comparable proportions as patients in the United States for age, comorbidities, racial/ethnic minority status, and sex. We believe that the FDA can choose to exert this authority and require cancer drugs to be supported by efficacy data relevant to the US population, declining applications that do not meet this standard. The agency may use a sliding scale: as trials become more unrepresentative of the population, the FDA can demand larger magnitudes of benefit before approval to ensure that benefits will not be lost in the real world. In other words, the FDA may decline to approve drugs with very marginal effect, such as sorafenib in hepatocellular cancer or erlotinib hydrochloride in pancreatic cancer, while approving drugs with clear benefits, such as rituximab in large cell lymphoma.

Option 2: Survival as a Surrogate End Point

The FDA may, alternatively, use overall survival in idealized trials as a surrogate end point for drug approval. Thus, instead of providing traditional (full) approval to drugs such as sorafenib—a status that seldom entails further postmarketing efficacy studies—they may instead grant accelerated approval to these agents. Accelerated approval would empower the FDA to demand and enforce postmarketing studies that may confirm or refute the drugs' benefit on survival in real-world populations. This policy would benefit patients with cancer as well as physicians, as considerable data relevant for clinical practice would be generated, and ineffective drugs could later be removed from the market.

Conceptualizing survival in clinical trials as a surrogate end point may facilitate evidence-based medicine. Techniques to validate surrogate end points, which involve meta-analyses and linear regression, can be extended to trial survival.[1] We can formally answer the question: in what cancers is survival benefit in young, healthy patients associated with survival benefits among all Americans? Such work may draw on advances in big data and robust observational registries to probe and evaluate these correlations.

Conclusions

The benefit of most cancer drugs is marginal, and these benefits are seen in carefully selected, young, healthy populations—in part because such patients can be rapidly enrolled in clinical trials and comorbidities do not confound interpretations of the drug's activity. Whether such drugs retain their benefits when used in the real world is unknown but is clearly important for the purpose of drug regulation. Reconceptualizing trial survival in this way has the potential to improve the breadth and reliability of medical evidence for patients with cancer.

Una gerarchia di scenari per la RWE post RCT

1. Un RCT ha dimostrato l'efficacia di un intervento terapeutico e RWD vengono utilizzati per determinare se questa efficacia si traduca in *effectiveness* in pratica clinica

VOLUME 28 · NUMBER 21 · JULY 20 2010

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Adoption of Adjuvant Chemotherapy for Non–Small-Cell Lung Cancer: A Population-Based Outcomes Study

Christopher M. Booth, Frances A. Shepherd, Yingwei Peng, Gail E. Darling, Gavin Li, Weidong Kong, and William J. Mackillop

Purpose

Since 2004, several clinical trials have demonstrated that adjuvant chemotherapy (ACT) improves survival in patients with early-stage non–small-cell lung cancer (NSCLC). Here, we evaluate the uptake of ACT and its impact on outcomes in the general population of Ontario, Canada.

Methods

All patients diagnosed with NSCLC in Ontario from 2001 to 2006 who underwent surgical resection (n = 6,304) were identified using the Ontario Cancer Registry. We linked electronic records of treatment to the registry. We described uptake of ACT and compared survival of all patients with surgically resected NSCLC diagnosed from 2001 to 2003 with patients diagnosed from 2004 to 2006. As a proxy measure of ACT-related toxicity, we evaluated hospitalizations within 6 months of surgery.

Results

Demographic, disease, and treatment-related characteristics did not differ between the 2001 to 2003 and 2004 to 2006 study cohorts. Over the study period, the proportion of patients receiving ACT increased from 7% (192 of 2,950 patients) to 31% (1,032 of 3,354 patients; $P < .001$). The proportion of patients admitted to hospital within 6 months of surgery remained stable and (36% in the 2001 to 2003 cohort and 37% in the 2004 to 2006 cohort). However, within 2 years of surgery, there was a 33% reduction in the proportion of patients admitted to hospital with metastatic disease ($P < .001$). During the study period, there was a substantial improvement in 4-year survival among surgically resected patients, from 52.5% (2001 to 2003) to 56.1% (2004 to 2006; $P = .001$).

Conclusion

There has been a rapid uptake of ACT for NSCLC, which was not associated with an increased rate of hospitalization. The adoption of ACT was associated with a substantial improvement in overall survival, suggesting that the benefits seen in clinical trials are generalizable to the general population.

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Hepatobiliary

Sorafenib Effectiveness in Advanced Hepatocellular Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Carcinoma, hepatocellular • Liver neoplasms • Sorafenib • Drug costs • Medicare • Liver diseases • Aged

ABSTRACT

Background. Phase III trials show sorafenib improves survival in advanced hepatocellular carcinoma (HCC). Because of narrow trial eligibility, results may not be generalizable to a broader HCC population. We sought to evaluate the effectiveness of initial sorafenib versus no treatment among Medicare beneficiaries with advanced HCC.

Materials and Methods. Patients with advanced HCC diagnosed from 2008 to 2011 were identified from the Surveillance, Epidemiology, and End Results–Medicare database. Eligible patients received initial sorafenib or no therapy and were covered by Medicare parts A, B, and D. Sorafenib use and outcomes were described in this population. Using a propensity score (PS)-matched sample, we compared the effectiveness of sorafenib versus no treatment by Cox proportional hazards and binomial regression, using a landmark requiring all patients to survive ≥60 days after diagnosis.

Results. Of 1,532 patients, 27% received initial sorafenib. Median duration of sorafenib use was 60 days (interquartile range [IQR], 30–107 days), and median survival from first prescription was 3 months (IQR, 1–8 months). In the PS-matched cohort, median survival was 3 months from the 60-day landmark in sorafenib-treated ($n = 223$) and 2 months in untreated ($n = 223$) patients (adjusted hazard ratio, 0.95 [95% confidence interval (CI), 0.78–1.16]). Sorafenib was associated with a nonsignificant reduction in mortality at 3 months (44% versus 51%; adjusted risk ratio, 0.88 [95% CI, 0.72–1.07]), but no reduction thereafter.

Conclusion. Survival after sorafenib initiation in newly diagnosed Medicare beneficiaries with HCC is exceptionally short, suggesting trial results are not generalizable to all HCC patients. The downsides of sorafenib use—high drug-related symptom burden and high drug cost—must be considered in light of this minimal benefit. ***The Oncologist*** 2016;21:1113–1120

Una gerarchia di scenari per la RWE post RCT

1. Un RCT ha dimostrato l'efficacia di un intervento terapeutico e RWD vengono utilizzati per determinare se questa efficacia si traduca in *effectiveness* in pratica clinica
2. Esistono alcune evidenza di efficacia (ma non di livello 1, cioè RCT di bassa potenza o studi a singolo braccio) e RWD vengono utilizzati per aggiungere informazioni utili alla base di conoscenza

VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer

Matthew D. Galsky, Kristian D. Stensland, Erin Moshier, John P. Sfakianos, Russell B. McBride, Che-Kai Tsao, Martin Casey, Paolo Boffetta, William K. Oh, Madhu Mazumdar, and Juan P. Wisnivesky

Purpose

Given that randomized trials exploring adjuvant chemotherapy for bladder cancer have been underpowered and/or terminated prematurely, yielding inconsistent results and creating an evidence gap, we sought to compare the effectiveness of cystectomy versus cystectomy plus adjuvant chemotherapy in real-world patients.

Patients and Methods

We conducted an observational study to compare the effectiveness of adjuvant chemotherapy versus observation postcystectomy in patients with pathologic T3-4 and/or pathologic node-positive bladder cancer using the National Cancer Data Base. We compared overall survival using propensity score (–adjusted, –stratified, –weighted, and –matched) analyses based on patient-, facility-, and tumor-level characteristics. A sensitivity analysis was performed to examine the impact of performance status.

Results

A total of 5,653 patients met study inclusion criteria; 23% received adjuvant chemotherapy post-cystectomy. Chemotherapy-treated patients were younger and more likely to have private insurance, live in areas with a higher median income and higher percentage of high school–educated residents, and have lymph node involvement and positive surgical margins ($P < .05$ for all comparisons). Stratified analyses adjusted for propensity score demonstrated an improvement in overall survival with adjuvant chemotherapy (hazard ratio, 0.70; 95% CI, 0.64 to 0.76), and similar results were achieved with propensity score matching and weighting. The association between adjuvant chemotherapy and improved survival was consistent in subset analyses and was robust to the effects of poor performance status.

Conclusion

In this observational study, adjuvant chemotherapy was associated with improved survival in patients with locally advanced bladder cancer. Although neoadjuvant chemotherapy remains the preferred approach based on level I evidence, these data lend further support for the use of adjuvant chemotherapy in patients with locally advanced bladder cancer postcystectomy who did not receive chemotherapy preoperatively.

Una gerarchia di scenari per la RWE post RCT

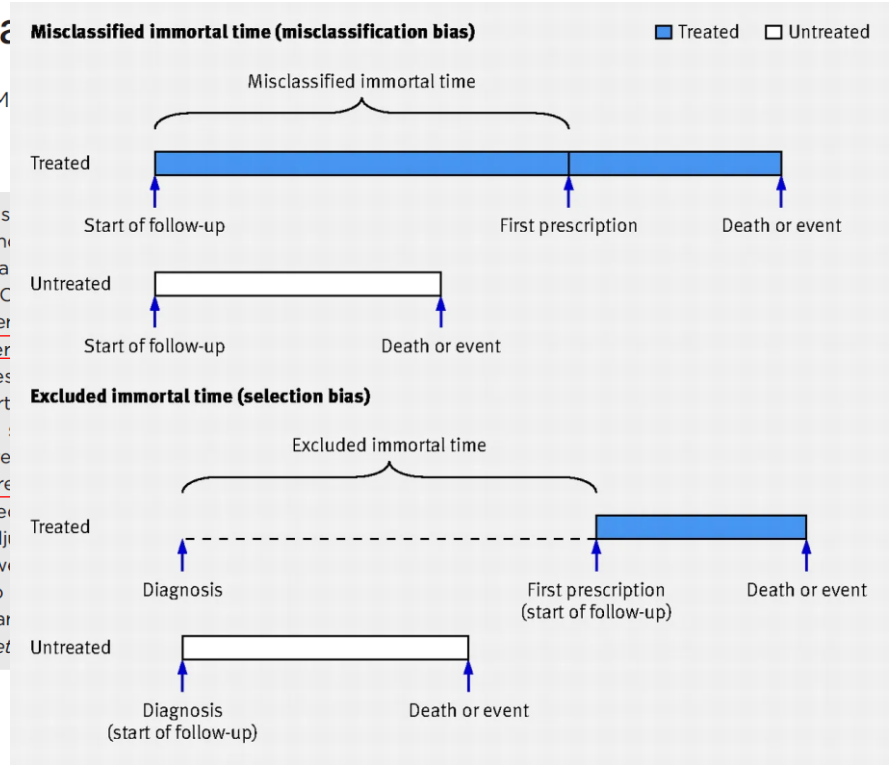
1. Un RCT ha dimostrato l'efficacia di un intervento terapeutico e RWD vengono utilizzati per determinare se questa efficacia si traduca in *effectiveness* in pratica clinica
2. Esistono alcune evidenza di efficacia (ma non di livello 1, cioè RCT di bassa potenza o studi a singolo braccio) e RWD vengono utilizzati per aggiungere informazioni utili alla base di conoscenza
3. Precedenti RCT hanno mostrato scarsa efficacia dell'intervento terapeutico e RWD vengono utilizzati per conferma dell'ipotesi non dimostrata… (è il contesto più problematico)

Original Article

Adjuvant Chemotherapy Is Associated With Improved Survival in Patients With Stage II Colon Ca

Leigh Casadaban, MD[1]; Garth Rauscher, PhD[2]; Mebea Aklilu, MD[3]; Dana Villenes, M
Ajay V. Maker, MD[1]

BACKGROUND: The role of adjuvant chemotherapy in patients with stage II colon cancer remains between patients and institutions. Currently, clinical guidelines suggest discussing adjuvant chem stage II disease in the absence of conclusive randomized controlled trial data. To further investiga the current study was to determine whether an association exists between overall survival (C patients stratified by age and pathological risk features. **METHODS:** Data from the National Cancer ographics, tumor characteristics, management, and survival of patients with stage II colon cancer 2006 with survival information through 2011. Pearson Chi-square tests and binary logistic regres and demographic data. Survival analysis was performed with the log-rank test and Cox proport Propensity score weighting was used to match cohorts. **RESULTS:** Among 153,110 patients with receiving chemotherapy included age <65 years, male sex, nonwhite race, use of a community tre ance, and diagnosis before 2004. Improved and clinically relevant OS was associated with the re all patient subgroups regardless of high-risk tumor pathologic features (poor or undifferentiate uated, positive resection margins, or T4 histology), age, or chemotherapy regimen, even after adj sity score weighting (hazard ratio, 0.76; *P*<.001). There was no difference in survival noted betw chemotherapy regimens. **CONCLUSIONS:** In what to the authors' knowledge is the largest group cer evaluated to date, improved OS was found to be associated with adjuvant chemotherapy regar age, or high-risk pathologic risk features. *Cancer* 2016;122:3277-87. © *2016 American Cancer Societ*



pazienti

Immortal-time bias

RWE in fase di progettazione

- L’uso della RWE nella fase iniziale del percorso di sviluppo di un farmaco, può ottimizzarne la strategia
  - Analisi di popolazione possono fornire stime su prevalenza e incidenza di patologie e individuare per esempio trend geografici e temporali o sottogruppi di interesse con maggiore *unmet need* terapeutico

Broder et al. BMC Pulmonary Medicine (2018) 18:135
https://doi.org/10.1186/s12890-018-0678-5

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Incidence and prevalence of neuroendocrine tumors of the lung: analysis of a US commercial insurance claims database

Michael S. Broder[1*], Beilei Cai[2], Eunice Chang[1] and Maureen P. Neary[2]

Methods: This descriptive epidemiological study used 2009–2014 data from 2 US claims databases: MarketScan and PharMetrics. Patients (18–64 years old) had ≥1 inpatient or ≥ 2 outpatient claims with NET of bronchus or lung, identified by International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes. Prevalence was number of lung NET patients divided by number of enrollees/year. Incidence was number of patients with a first observed NET diagnosis who were disease-free for 2 years prior, divided by number of enrollees. Age and gender adjustments performed.

Results: The annual number of patients with lung NET identified from 2009 to 2014 ranged from 435 to 796 (MarketScan) and 419–648 (PharMetrics). In MarketScan, there was a 7.4% (95%CI 2.1–13.0; $p = 0.027$) annual percent change (APC) in the age-adjusted incidence for males and 6.8% (− 0.2–14.3; 0.052) for females. In PharMetrics, APC was − 2.9% (− 13.8–9.4; 0.395) for males; 14.7% (− 12.9–51.2; 0.165) for females. In MarketScan, APC in age-adjusted prevalence for males was 9.9% (4.7–15.3; 0.006); 16.2% (11.4-21.1; <.001) for females. For PharMetrics, APCs were 9.5% (2.3–17.2; 0.021) for males; 16.3% (9.6–23.5; 0.002) for females.

Conclusions: From 2009 to 2014 there was a statistically significant increase in age-adjusted lung NET incidence for males in MarketScan, and a statistically significant increase in age-adjusted prevalence for both genders in PharMetrics. Incidence and prevalence changes, to the extent they exist, may be due to better diagnostic methods, increased awareness of NET among clinicians and pathologists, and/or an actual increase in US disease occurrence. Differences in rates across databases are difficult to explain. These results suggest the need for awareness of the clinically effective and safe treatment options available for lung NET patients among healthcare providers.

RWE in fase di progettazione

- L’uso della RWE nella fase iniziale del percorso di sviluppo di un farmaco, può ottimizzarne la strategia
  - Analisi di popolazione possono fornire stime su prevalenza e incidenza di patologie e individuare per esempio trend geografici e temporali o sottogruppi di interesse con maggiore *unmet need* terapeutico
  - Analisi di comorbidità nella popolazione di interesse possono individuare rischi di *drug-drug interaction* e quelli legati alla prevalenza di patologie epatiche e renali

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 110 NUMBER 1 | July 2021

Drugs in COVID-19 Clinical Trials: Predicting Transporter-Mediated Drug-Drug Interactions Using In Vitro Assays and Real-World Data

Sook Wah Yee[1,†], Bianca Vora[1,†], Tomiko Oskotsky[2], Ling Zou[1], Sebastian Jakobsen[1], Osatohanmwen J. Enogieru[1], Megan L. Koleske[1], Idit Kosti[2], Mattias Rödin[1], Marina Sirota[2] and Kathleen M. Giacomini[1,*]

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ As the coronavirus disease 2019 (COVID-19) pandemic continues to plague the world, approved drugs and new molecular entities are being evaluated at an unprecedented pace. Patients diagnosed with COVID-19 may be increasingly vulnerable to incur significant drug-drug interactions (DDIs), especially older patients who are more susceptible to COVID-19-related morbidities and in whom polypharmacy is most common. Although there have been a few studies of DDIs, caused by individual drugs in clinical trials for COVID-19, there has been no largescale study evaluating the potential of many drugs in clinical trials for COVID-19 to cause a clinical DDI.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ In this study, we conducted extensive *in vitro* experiments aimed at predicting the potential for 25 small molecule drugs in clinical trials for COVID-19 to cause transporter-mediated DDIs and used real-world data to provide preliminary support of our *in vitro* findings.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study resulted in three major findings. First, many of the drugs tested, which are in clinical trials for COVID-19, inhibited transporters in cellular assays, with certain transporters being sensitive to inhibition by multiple drugs. Second, the majority of the drugs are predicted to cause at least one clinical DDI; that is, the concentrations of these drugs that inhibited the transporters in cellular assays were equal to or greater than the drug levels known to result in clinical DDIs. Finally, real-world data from the electronic health records are consistent with our predictions of transporter-mediated DDIs.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study highlights that drugs used for COVID-19 have the potential to cause transporter-mediated DDIs. More recent drugs used for COVID-19 need to be assessed. Our study suggests that patients with COVID-19, who are often older and on various concomitant medications, should be carefully monitored for known adverse drug reactions.

RWE in fase precoce

- La valutazione del *burden* della malattia (es. costi dell'assistenza sanitaria, impatto sulla produttività, morbidità e mortalità) può fornire dati di *health economics and outcomes research* che possono sostenere il processo di accesso al mercato e definizione del prezzo, e consentire dei *value-based contracts*

Qualità e affidabilità della RWE

- Mancanza di dati spesso rilevanti
  - es. anamnesi fumo, comorbidità e tossicità, nelle cartelle cliniche elettroniche
- Granularità dei dati
  - es. in uno studio potrebbe essere necessario distinguere tra ictus emorragico e ischemico, ma la fonte dei dati potrebbe contenere dati su tutti gli ictus senza ulteriori dettagli
- Accuratezza dei dati
- Integrazione dei dati
  - interoperabilità dei sistemi elettronici
  - formato e qualità delle fonti

Information bias

Information bias

- Può derivare da dati mancanti o imprecisi su criteri di eleggibilità della popolazione, interventi, *outcomes* o covariate, ma anche da errata specificazione delle modalità o del periodo di follow-up
  - *Detection bias*: quando i processi assistenziali variano in base al tipo di intervento, in maniera tale che sia più probabile che un *outcome* di interesse venga identificato in un gruppo piuttosto che in un altro

- Il peso del bias aumenta se il problema dei dati è diverso tra i gruppi di intervento, se è sistematico, se riguarda una variabile primaria o una variabile prognostica rilevante

Selection bias

- Occorre quando la popolazione studiata non è rappresentativa della popolazione di interesse (ma «selezionata»)
- I fattori prognostici individuano sottogruppi di pazienti con probabilità di *outcome* (es. risposta o sopravvivenza) differenti
- L'entità di tali differenze può essere addirittura superiore al potenziale effetto del trattamento
- La prevalenza (anche involontaria) di fattori prognostici favorevoli o sfavorevoli può alterare (soverchiare e mascherare) il reale effetto del trattamento

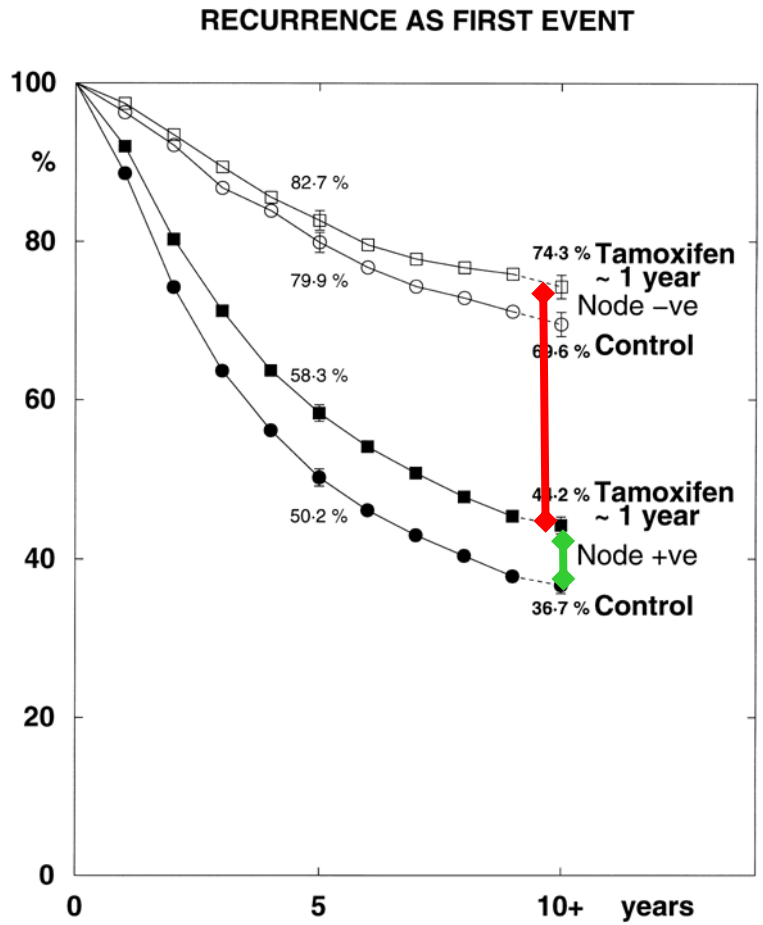
Un esempio storico

Meta-analisi degli studi sul trattamento adiuvante con tamoxifen del carcinoma mammario

Lancet 1998; **351:** 1451 - 1467

7.5% - size of treatment effect

30.1% - size of prognostic factor effect



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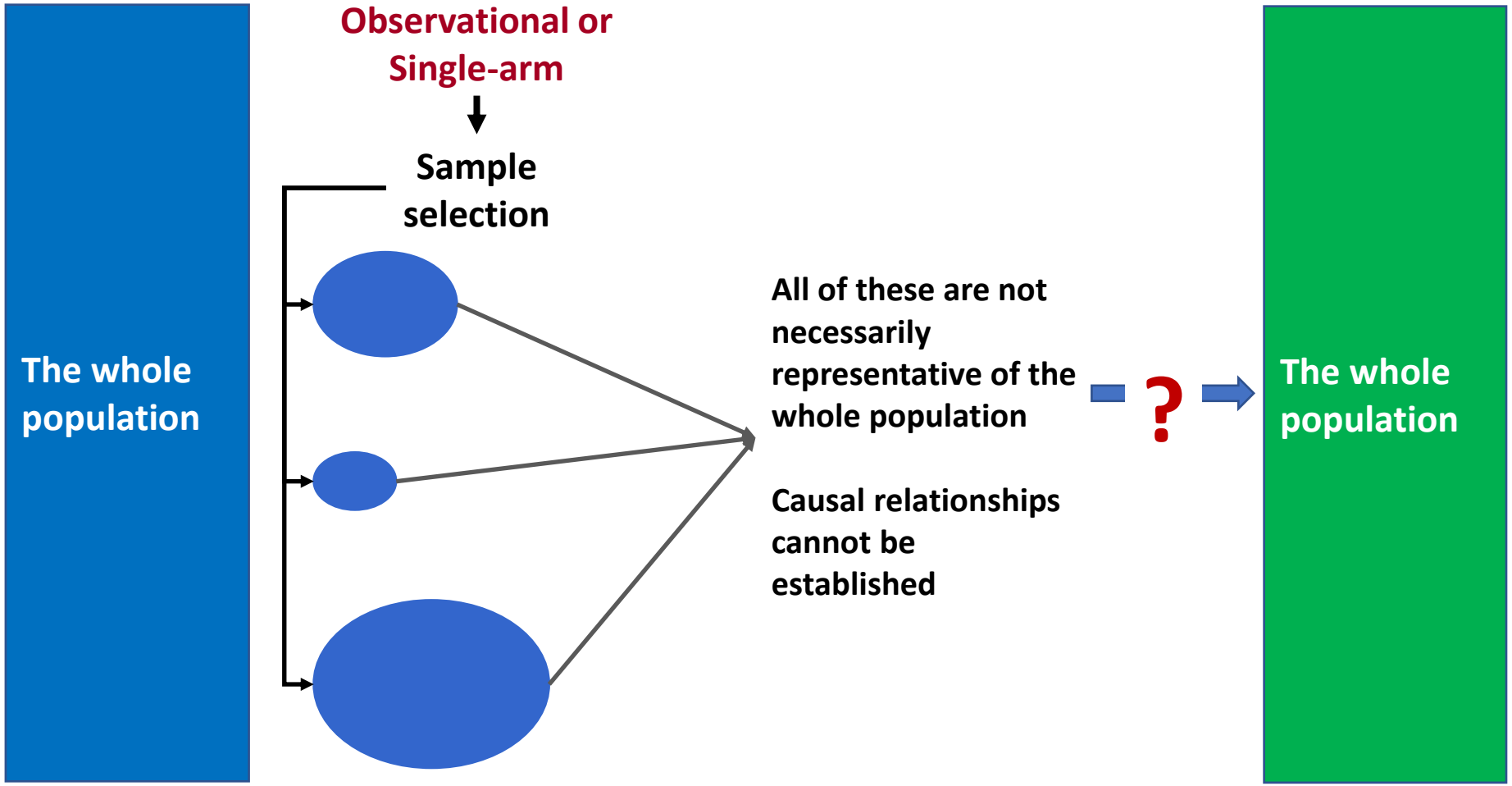
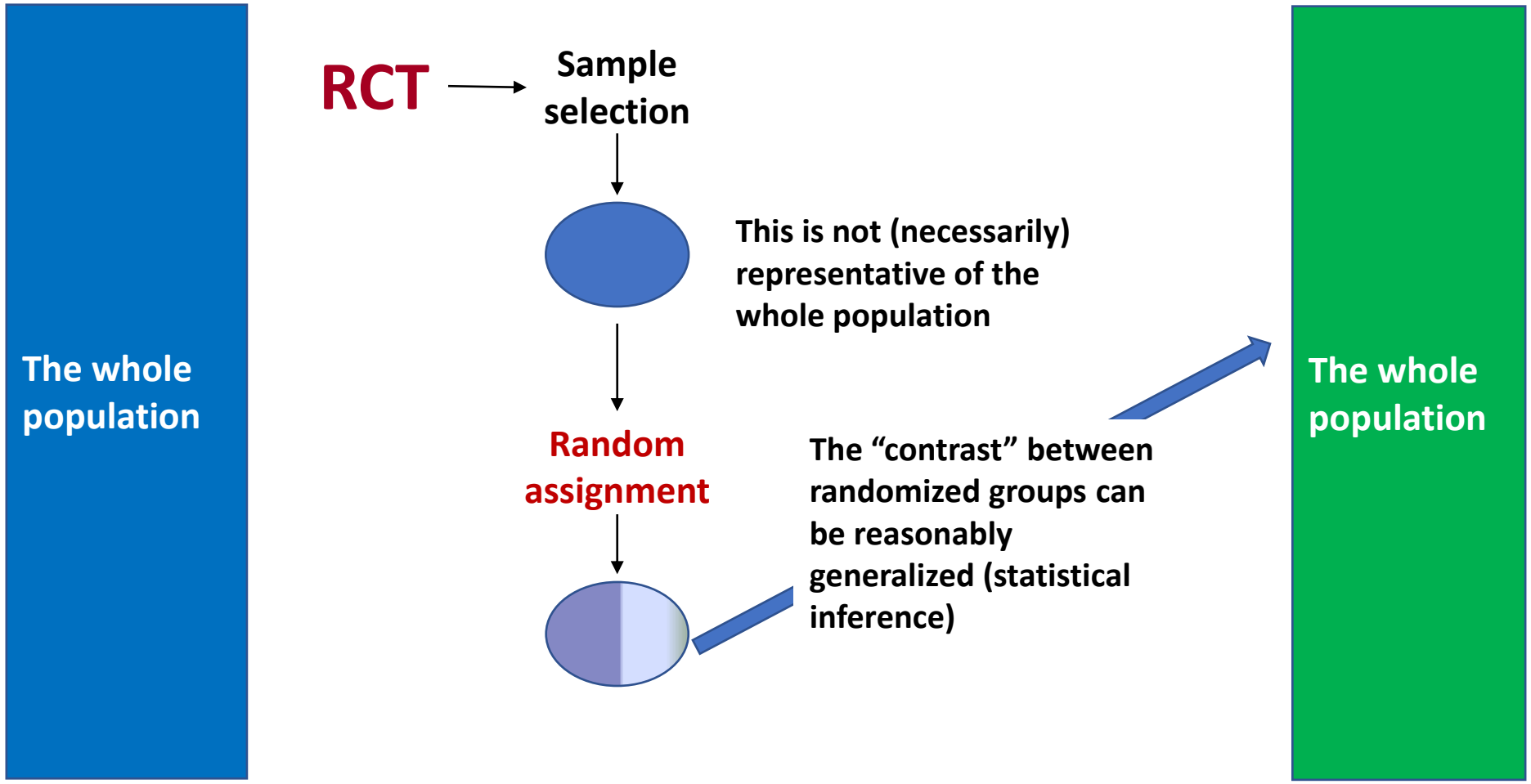
- La prevalenza (anche involontaria) di fattori prognostici favorevoli o sfavorevoli può alterare (soverchiare e mascherare) il reale effetto del trattamento
- Possibili cause:
  - Campionamento non casuale
    - *Indication bias*: la scelta del trattamento in pratica clinica è fortemente influenzata dalle caratteristiche basali del paziente
    - Inclusione di soggetti in grado di usare una tecnologia
  - Errata gestione dei casi *missing*
    - Gestione dei soggetti persi al follow-up
    - Esclusione dei soggetti con dati *missing*
    - Gestione dei soggetti con questionari *missing*

L’analisi di uno studio di RWE

- È più complessa di quella di un RCT
- Dovrebbe prevedere lo stesso rigore metodologico dei RCT
- Esistono diversi metodi statistici per mitigare il bias di selezione (es. regressione multivariata, *propensity score*, *matching adjusted indirect comparison*), ma possono essere applicati solo a variabili note e misurabili
- Il confondimento residuo, quindi, rimane una limitazione importante delle analisi di RWE e può portare a significative sovrastime della dimensione dell'effetto


Observational or
Single-arm
Sample
selection
The whole
population
All of these are not
necessarily
representative of the
whole population
Causal relationships
cannot be
established
?
The whole
population


The whole population
RCT
Sample selection
This is not (necessarily) representative of the whole population
Random assignment
The "contrast" between randomized groups can be reasonably generalized (statistical inference)
The whole population

La randomizzazione contro l'errore sistematico

- Il confronto randomizzato, stratificato per i più rilevanti fattori prognostici noti, è il miglior modo per ridurre l'impatto del bias di selezione
- Assicura che i fattori prognostici (anche non noti) siano distribuiti a caso
- Senza randomizzazione "una differenza statisticamente significativa" potrebbe essere il risultato di differenze non casuali nella distribuzione dei fattori prognostici
- Con la randomizzazione l'effetto del trattamento osservato dipenderà solo dall'effetto vero e dalla variabilità casuale
- È quindi garanzia di validità dei test statistici

European Journal of Cancer 186 (2023) 52–61

Available online at www.sciencedirect.com

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Current Perspective

Defining the role of real-world data in cancer clinical research: The position of the European Organisation for Research and Treatment of Cancer

RWD versus RCT-derived data: a false dichotomy

- **RCT pragmatici** con criteri di inclusione «rilassati», procedure *RW-like* e *Patient-centered outcomes*
- Che usino dati da cartelle cliniche elettroniche, PRO, telemedicina
- Che misurino l'effetto dell'intervento terapeutico in condizioni di pratica clinica (***effectiveness***)
- Quindi, studi randomizzati che generino RWE → **R²WE**

Table 1
Overview of the optimal methodologies to address specific research questions.

Research question	Study sample	Temporal character of study	Delivery of study treatment	Study purpose	Optimal methodology
Is treatment A better than treatment B in terms of improving patient outcomes?	Subset	Study design predates data collection	Interventional	Hypothesis-testing/ confirmatory	Traditional RCT or R²WD study
Is treatment A given in a lower dose equally effective as treatment A given in a standard dose in terms of improving patient outcomes?	Subset	Study design predates data collection	Interventional	Hypothesis-testing/ confirmatory	Traditional RCT or R²WD study
Is treatment A given intermittently equally effective as treatment A given continuously in terms of improving patient outcomes?	Subset	Study design predates data collection	Interventional	Hypothesis-testing/ confirmatory	Traditional RCT or R²WD study
Is treatment A given for a limited duration of time equally effective as treatment A given lifelong in terms of improving patient outcomes?	Subset	Study design predates data collection	Interventional	Hypothesis-testing/ confirmatory	Traditional RCT or R²WD study
To what extent has treatment A been taken up by clinicians?	Population	Data collection predates study design	Observational	Hypothesis-generating/ exploratory	RWD study
What has been the impact of treatment A on patient outcomes in the general population?	Population	Data collection predates study design	Observational	Hypothesis-generating/ exploratory	RWD study
To what extent does treatment A improve patient outcomes in a specific subpopulation?	Subset	Study design predates data collection or data collection predates study design	Observational or interventional	Hypothesis-generating/ exploratory	RWD study or R²WD study

Received: 22 June 2020 | Revised: 25 August 2020 | Accepted: 27 August 2020
DOI: 10.1002/pds.5123

COMMENTARY

Pharmacoepidemiol Drug Saf. 2020;29:1514–1517.

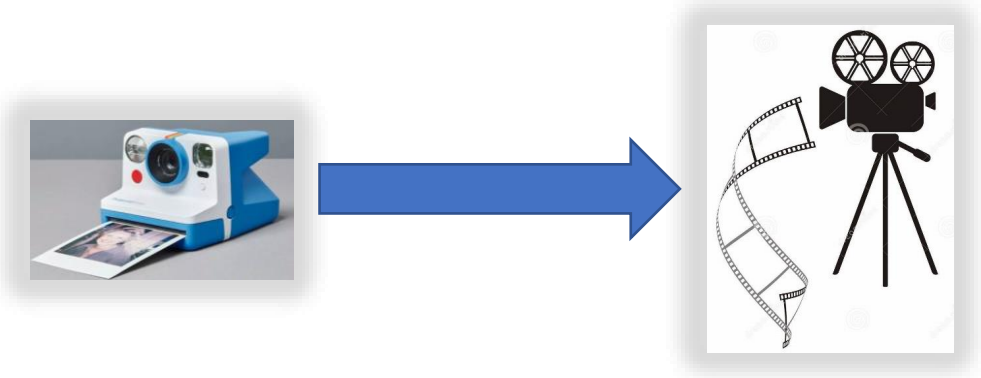
Randomized, observational, interventional, and real-world—What's in a name?

John Concato[1] | Peter Stein[2] | Gerald J. Dal Pan[3] | Robert Ball[3] | Jacqueline Corrigan-Curay[1]

In the current era of RWE, the FDA is evaluating whether and how observational studies intended to evaluate efficacy can contribute persuasive results from scientific and regulatory perspectives. In this context, a "randomized trial versus observational study" dichotomy is overly simplistic as short hand for strength of study design to support causal inference. Clarity is needed regarding interventional or noninterventional design, primary collection or secondary use of data, and characteristics of comparison group(s), as well as an assessment of prognostic determinism for the corresponding cause-effect association.

	Interventional	Non-Interventional
Primary data collection for research	• traditional RCTs • decentralized RCTs	• registry-based analyses*
Secondary use of clinical data	• pragmatic RCTs • cluster RCTs	• health records- or claims-based analyses*

*Non-interventional research designs include observational cohort and case-control studies; RCT = randomized, controlled trial.



Patient-journey studies

Open access Communication

BMJ Open

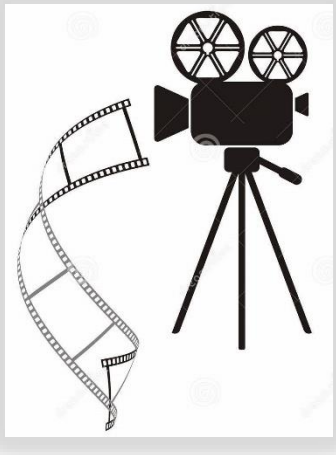
The opportunity of patient-journey studies for academic clinical research in oncology

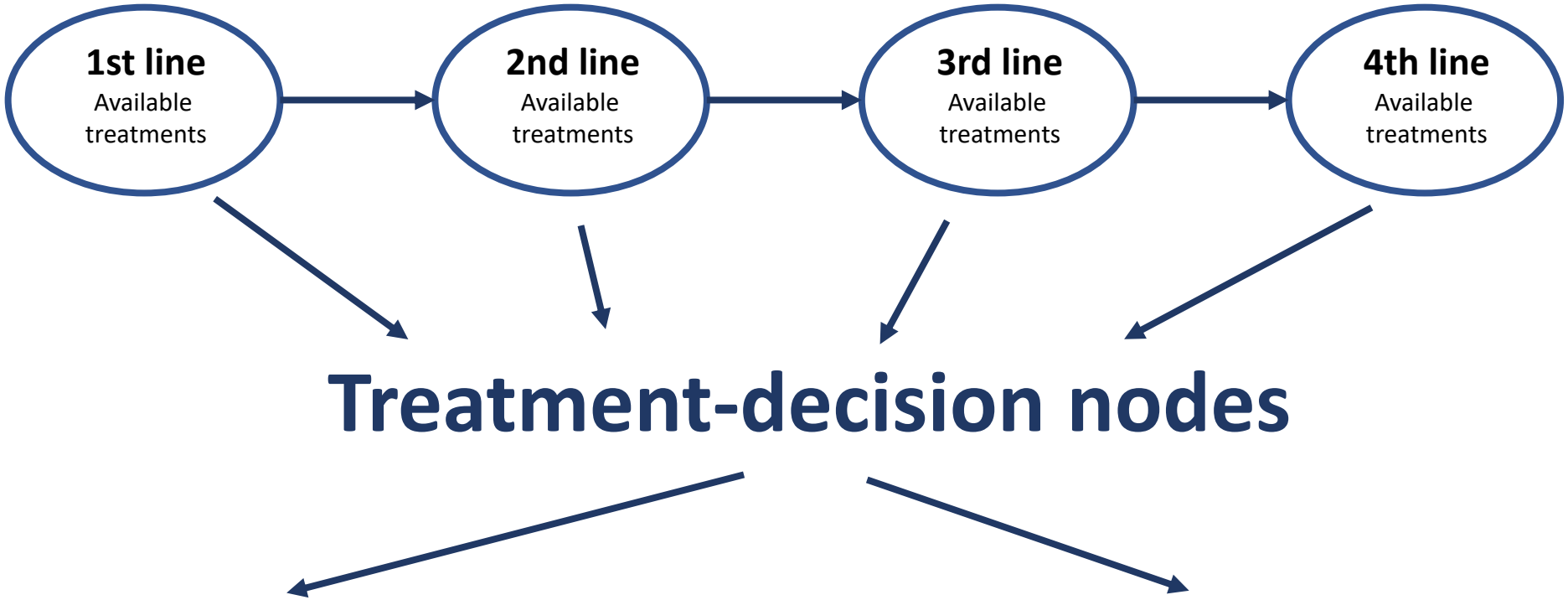
Francesco Perrone ,[1] Raimondo Di Liello ,[1] Piera Gargiulo,[1] Laura Arenare,[1] Lorenzo Guizzaro,[2,3] Paolo Chiodini ,[2] Ciro Gallo ,[2] Maria Carmela Piccirillo[1]

Moving from the snapshot to the movie

We propose that academy, in collaboration with patient organisations, should react implementing a research strategy focused on the therapeutic pathways of patients (patient-journey study (PJS)) rather than on the efficacy of single treatments. A PJS might enrol patients at diagnosis and follow them across subsequent lines of treatment. At each treatment-decision node, within a desirable framework of shared decision-making,[7] to the patient would be offered the option to choose according to guidelines, randomise where uncertainty exists (according to a formal protocol with its own study design) or access to other trials (regardless of phase and sponsor) when available and reasonable. Therefore, the master protocol of a PJS will prospectively integrate trials and real-world evidence, overcoming the existing dualism and favouring the quality of both.[8] It will empower shared

In most cancers, we have >1 treatment option and >1 potential therapeutic line

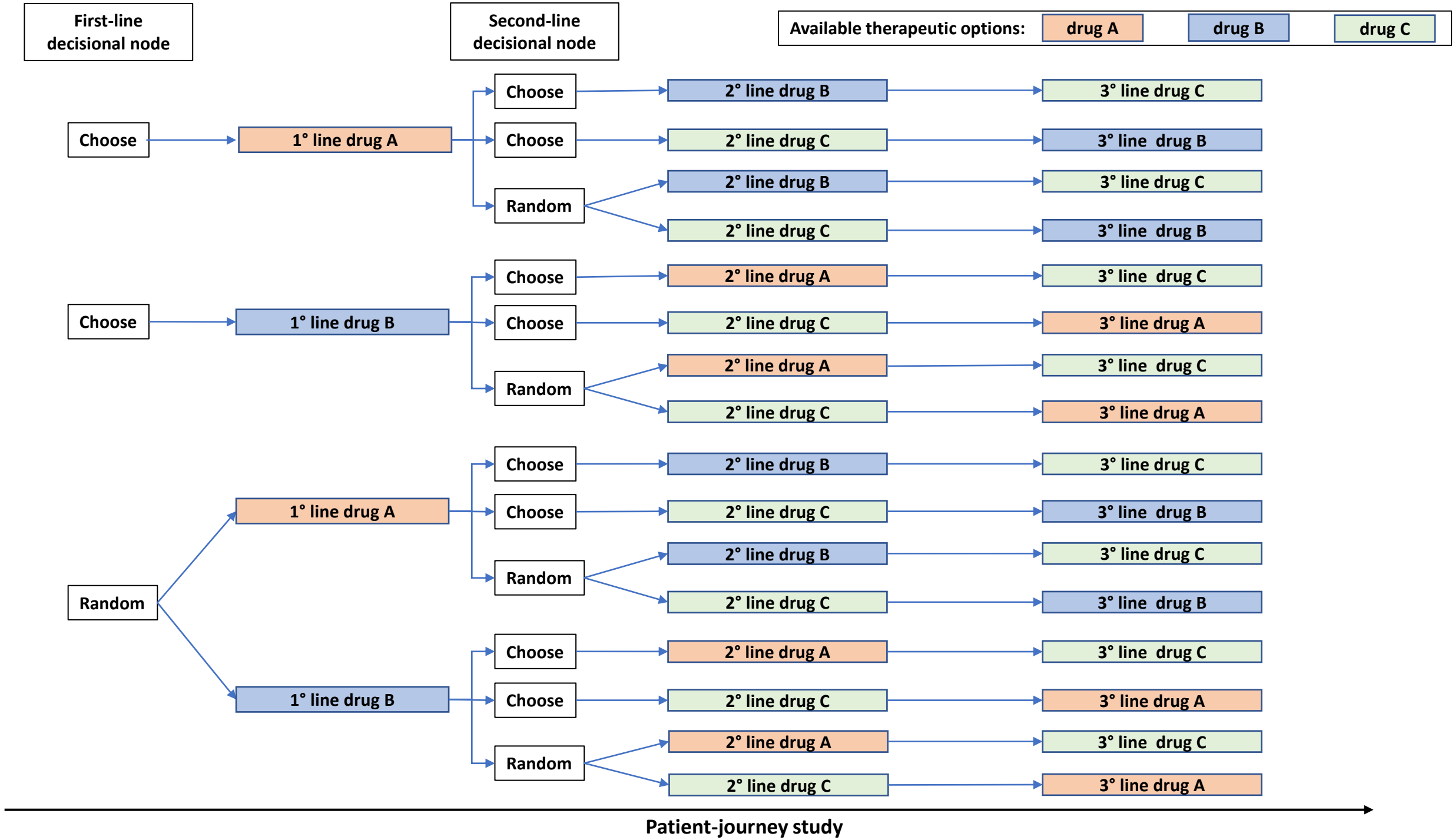




Clinical practice
Share, discuss and
choose

Patient-journey study (PJS)
Share, discuss and
choose or randomize if uncertain

Courtesy of F. Perrone


First-line decisional node
Second-line decisional node
Available therapeutic options:
drug A
drug B
drug C
Choose
1° line drug A
1° line drug B
Random
Choose
Choose
Random
2° line drug B
2° line drug C
2° line drug B
2° line drug C
2° line drug A
2° line drug C
2° line drug A
2° line drug C
3° line drug C
3° line drug B
3° line drug C
3° line drug B
3° line drug C
3° line drug A
3° line drug C
3° line drug A
Patient-journey study

AGENZIA ITALIANA DEL FARMACO

BANDO AIFA RICERCA INDIPENDENTE 2023

SEQUENZIAMENTO TERAPEUTICO IN ONCOLOGIA

Assegnazione di finanziamento per la Ricerca Indipendente sui farmaci

L'Agenzia Italiana del Farmaco, d'ora in poi denominata AIFA, nell'ambito della promozione della ricerca indipendente sui farmaci, finanziata ai sensi dell'articolo 48, comma 5, lettera g), e comma 19, lettera b), numero 3, del decreto-legge 30 settembre 2003, n. 269, convertito, con modificazioni, dalla legge 24 novembre 2003, n. 326, intende promuovere ricerche volte a generare nuove evidenze, con potenziali ricadute sul Servizio Sanitario Nazionale (di seguito SSN).

Scopo principale del presente Bando è quello di incentivare la ricerca su tematiche coerenti con finalità ed obiettivi del SSN, mediante il finanziamento di studi di rilevante interesse per la salute dei cittadini, in considerazione anche delle potenziali ricadute sull'attività regolatoria dell'AIFA.

Attualmente la valutazione delle strategie di sequenziamento terapeutico con i nuovi farmaci si bas su una evidenza scientifica limitata, costituita in prevalenza su dati di *real world*, in assenza di stu di confronto diretto *head-to-head*.

Tutto ciò è ampiamente evidenziato nelle raccomandazioni dell'Associazione Italiana di Oncologi Medica (AIOM) ed della *European Society for Medical Oncology* (*ESMO*) che, nonostante la mancanza di dati provenienti da *trial ad hoc*, orientano i clinici verso l'utilizzo dei farmaci disponibili attribuendo spesso un basso livello alla forza delle evidenze a supporto delle sequenze terapeutiche.

Nello scenario attuale, la ricerca indipendente dovrebbe focalizzarsi sul trattamento complessivo dei pazienti piuttosto che sul singolo farmaco, superando il dualismo tra la *real word evidence* e i *trial* clinici prospettici randomizzati, migliorando la qualità della prima e la generalizzabilità dei secondi.

La finalità di questo Bando è quella di finanziare studi clinici volti a definire il sequenziamento ottimale di trattamenti sistemici dei seguenti tumori in stadio avanzato: epatocarcinoma, carcinoma del polmone non a piccole cellule (*NSCLC*, *Non Small Cell Lung Cancer*), carcinoma renale.

AREE DI INDAGINE

Le proposte di studio presentate nell'ambito del presente Bando dovranno riguardare espressamente studi clinici in oncologia ed essere riferite in maniera esclusiva a una delle seguenti tre aree:

1) Epatocarcinoma
2) Carcinoma del polmone non a piccole cellule (*NSCLC*, *Non Small Cell Lung Cancer*)
3) Carcinoma renale

AGENZIA ITALIANA DEL FARMACO

AIFA Call 2023 for Independent Research

THERAPEUTIC SEQUENCING IN ONCOLOGY

Principal Investigator (PI)

Maria Carmela Piccirillo

Principal Investigator PEC

Please indicate the certified email (PEC) address of Scientific Responsible. If not available, please report the PEC address of the PI Centre.

usc@pec.istitutotumori.na.it

Date of birth (dd/mm/yy)

Grant in AIFA Call past editions

Please indicate if PI received AIFA grant in the past editions.

YES ○
NO ◉
If yes, please indicate the year(s) :

Proposal title

The NSCLC patient-journey study: a prospective, adaptive, master protocol, to assess the value of the available sequences of treatment for patients with advanced non-small-cell lung cancer.
The Journey of Lung Cancer Patient - J-Lu

J-LU is an adaptive prospective master protocol that includes several RCT within a prospective cohort real-world-like framework, aimed to describe and analyse the NSCLC patient-journey produced by the sequencing of the therapeutic choices among the available therapeutic options

J-LU: R^2WE within prospective RWE

- Gli effetti delle sequenze di trattamento nella popolazione complessiva saranno descritti in termini di *patient-centered endpoint* (sopravvivenza globale, qualità della vita, *safety* e tossicità finanziaria) e del punto di vista del servizio sanitario nazionale (costi e *cost-effectiveness*)
- All'interno della popolazione complessiva, verrà eseguita un'analisi approfondita riguardo ai determinanti del processo decisionale clinico a ciascun nodo decisionale
- La randomizzazione sarà proposta nei nodi decisionali in cui sia prevedibile una possibile incertezza (con un disegno di studio *hypothesis-based*)

Conclusioni

- La RWE può trovare spazio per in tutte le tappe di sviluppo di un farmaco
- Una «*good*» RWE dipende da fonte e qualità dei dati e dalla validità del disegno di studio
- La R^2WE potrebbe ottimizzare l'impiego di tempo e risorse, umane ed economiche, di produttore, pagatore, ricercatore e paziente
- L'uso ottimale dei RWD può creare un *learning healthcare environment* dove le transizioni tra ricerca e pratica clinica sono più fluide e dove la comprensione dell'esperienza del paziente è più olistica

Non esistono grandi scoperte né reale ***progresso*** *finché sulla Terra esiste un bambino infelice.*

(Albert Einstein)

Grazie per l'attenzione!