L'importanza dei Gruppi di Lavoro Interdisciplinari nell'era dell'oncologia di precisione. Il Molecular Tumor Board: dalle indicazioni cliniche ai contesti regolatori.

Pierfranco Conte
DiSCOG, University of Padova
Istituto Oncologico Veneto IRCCS

PierFranco Conte

Disclosure of potential conflicts of interests

- Consultant:
  Novartis, EliLilly, Astra Zeneca, Tesaro
- Honoraria:
  BMS,Roche, EliLilly, Novartis, AstraZeneca
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  Novartis, Roche, EliLilly, BMS, Merck-Serono
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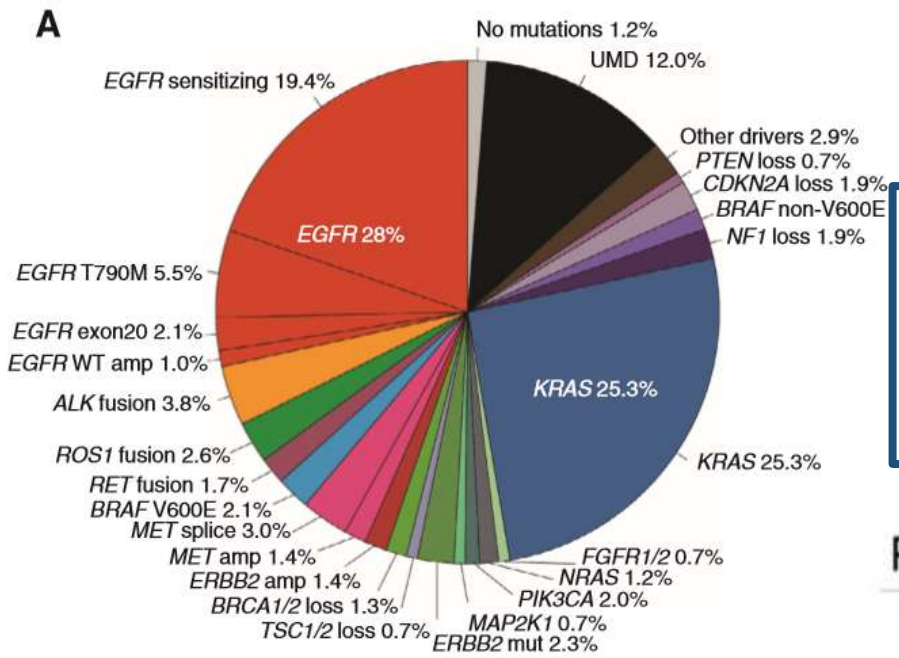
  National Research Council, Ministry of Education and Research, Italian Association for Cancer Research, Italian Drug Agency (AIFA), EmiliaRomagna Secretary of Health, Veneto Secretary of Health, University of Padova, Ministry of Health

Precision Oncology:

the dream, the awakening, the nightmare, the purpose

- **Molecular segmentation of common tumors**
- A patient history
- From knowledge to actionable information
- From actionable information to access to effective drugs
- Oncology Networks and Molecular Tumor Boards

The Tree of Knowledge

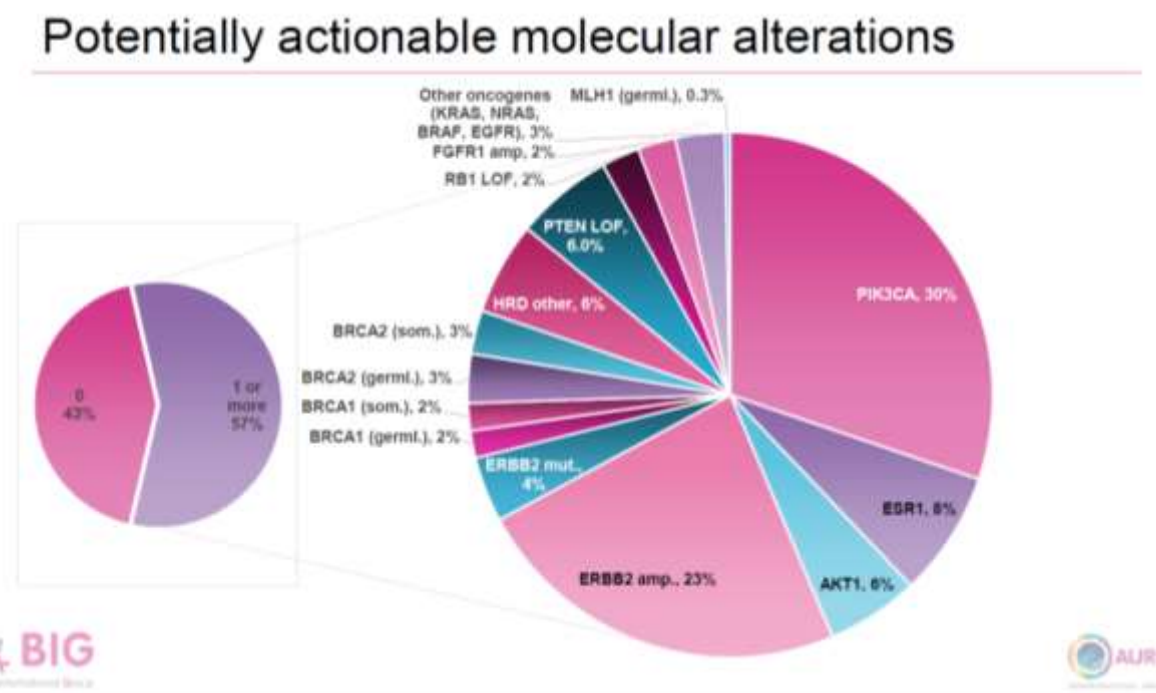


860 advanced lung adenocarcinoma
300 cancer-associated genes (MSK-IMPACT)

Jordan, CCR 2017; Planchard, Ann Oncol 2018

381 advanced breast cancers
411 genes Ion Torrent TGS for tissue
27 genes Ion Torrent TGS for ctDNA

Aftimos P, ESMO Breast 2019



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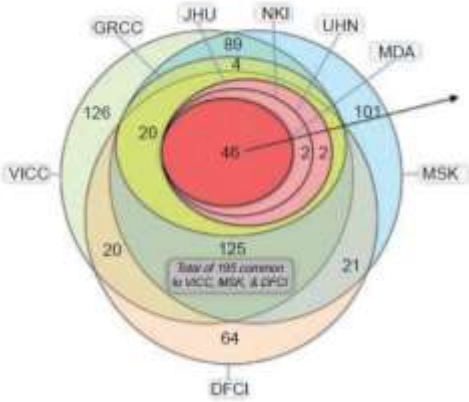
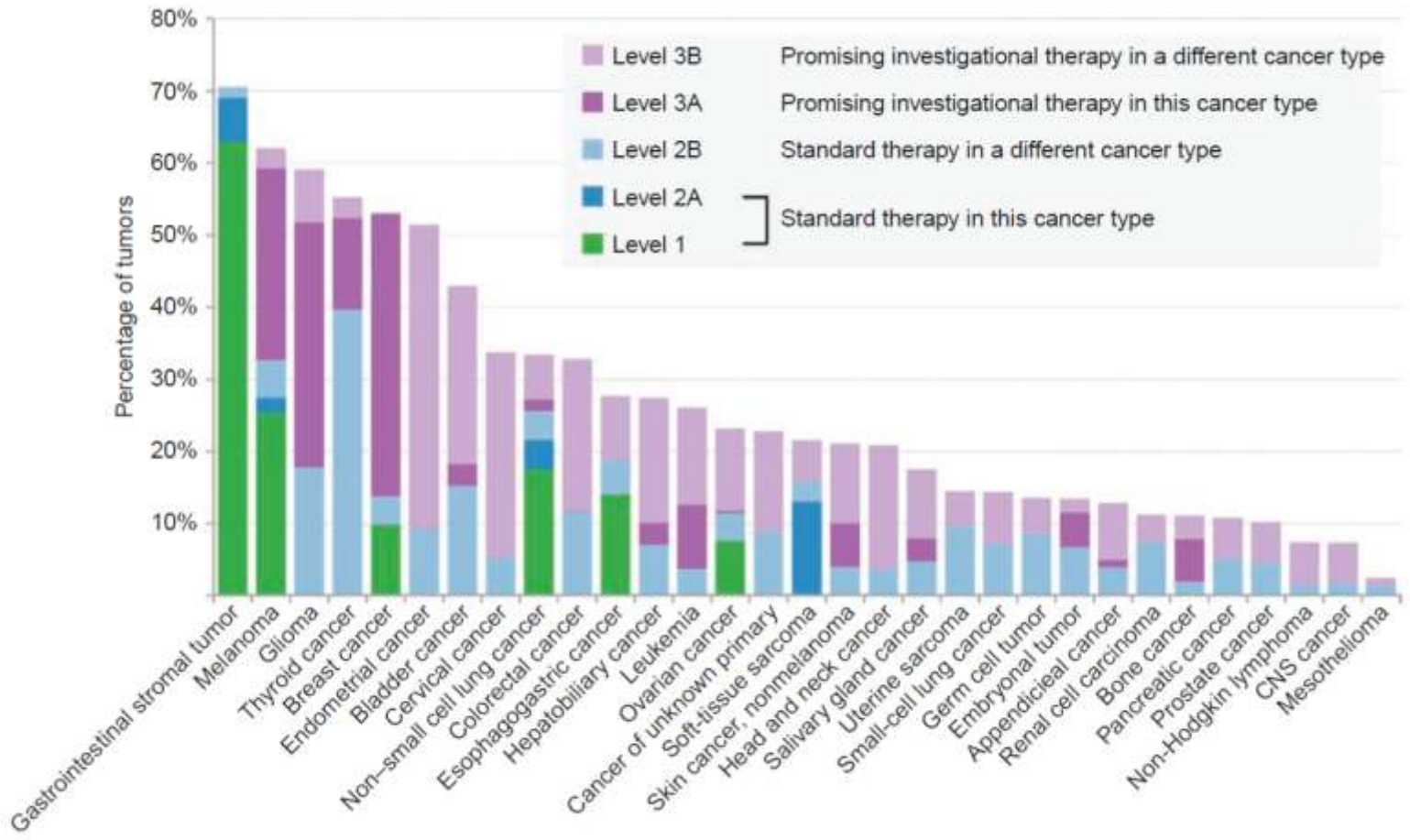
AACR Project GENIE: Powering Precision Medicine through an International Consortium





Multicentric data-sharing project to catalyze precision cancer medicine

Built to integrate clinical, genomic and outcome data

Data on first 19,000 pts

32% actionability rate:

- **7% level 1 or 2A**
- 7% level 2B
- 6% level 3A
- 11% level 3B

Actionable Information: NCI-MATCH trial

- The National Cancer Institute (NCI) recently announced that it has sequenced the tumors of **6,000 people** as part of its **Molecular Analysis for Therapy Choice**, or NCI-MATCH, trial.
- The study started enrolling patients in August 2015 with the goal of pairing anyone whose tumor has a particular molecular makeup with one of 21 drugs or drug combinations.
- So far, about **19%** of the people recruited have been **matched** with a drug or drug combination, and **more than half** of them have **rare cancers**.

Reliability of Whole-Exome Sequencing for Assessing Intratumor Genetic Heterogeneity

Weiwei Shi,[1,11] Charlotte K.Y. Ng,[2,3,4,11] Raymond S. Lim,[2,11] Tingting Jiang,[1] Sushant Kumar,[5,6] Xiaotong Li,[1,6] Vikram B. Wali,[1] Salvatore Piscuoglio,[2,3] Mark B. Gerstein,[5,6,7] Anees B. Chagpar,[8,9] Britta Weigelt,[2] Lajos Pusztai,[1,9] Jorge S. Reis-Filho,[2,10,*] and Christos Hatzis[1,9,12,*]

[1]Department of Medicine, Yale School of Medicine, Yale University, New Haven, CT, USA
[2]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[3]Institute of Pathology, University Hospital Basel, Basel, Switzerland
[4]Department of Biomedicine, University of Basel, Basel, Switzerland
[5]Molecular Biophysics and Biochemistry, Yale University, New Haven, CT, USA
[6]Program in Computational Biology and Bioinformatics, Yale University, New Haven, CT, USA
[7]Computer Science, Yale University, New Haven, CT, USA
[8]Department of Surgery, Yale School of Medicine, Yale University, New Haven, CT, USA
[9]Yale Cancer Center, New Haven, CT, USA
[10]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Highlights

- Genuine intratumor genetic heterogeneity is hard to distinguish from sequencing artifacts
- Cancer-only WES pipelines are unreliable (69% somatic mutations are false positive)
- 34%–80% of somatic variants contributing to genetic heterogeneity are technical noise
- Excluding mutations in low-mappability regions and higher coverage are needed

Cell Reports 25, 1446-1457, 2018

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Multigene Sequencing and treatment efficacy

SHIVA TRIAL

741 screened pts
Analysis limited to 3 pathways
293 pts with at least 1 molecular alteration matching available regimens
195 pts (20% BC) randomized between TPC and matched targeted therapy
Median PFS: 2.0 vs 2.3 months

Le Tourneau C, et al. Lancet Oncol 2015

MDACC

2601 enrolled pts
2000 pts genomic testing (655 BC)
789 pts with with actionable mutations
83 pts genomic matched trial

Meric Bernstam F, et al. J Clin Oncol 2015

MOSCATO 01 TRIAL

1035 enrolled pts
948 pts had biopsy
411 pts had actionable mutation
199 (~20% BC) received matched targeted therapy
N= **63** pts presented PFS2/PFS1 >1.3
N=**22** pts with an OR

Massard C, et al. Cancer Discovery 2017

Screen more to treat more?
73-gene NGS panel in clinical practice

LIQUID BIOPSY
129 NSCLC patients treated with ≥ Line

↓

115 (89%): tumor genetic alterations found

↓

34 (26%) potentially druggable alterations

↓

12 (9%) pts started treatment
1 pt died before starting

Screen more to treat more?
59-gene NGS panel in clinical practice

TISSUE
89 NSCLC patients treated with ≥ Line

↓

44 (49%): evaluable for analysis

↓

10 (23%) potentially druggable alterations

↓

7 (8%) pts started treatment

1 patient with adenocarcinoma (EGFR wt, ALK wt, ROS1 wt,PD-L1 <1%); PD after Cb/PEM: MET wt, KIF5B-RET rearrangement → starts cabozantinib (off label use) on may 2018, persistent disease control on may 2019

1 patient with adenocarcinoma (EGFR wt, ALK wt, ROS1 wt, PD-L1 10%); PD after Cb/PEM, PD on nivolumab: BRAFV600E mutation → starts dabrafenib+trametinib (off label use) on april 2018, persistent disease control on may 2019

L Bonanno et al, unpublished

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  In the biomedical literature there are 32 «exceptional responders» *(V Prasad, EJC 2018)*

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A patient's history

72 yrs old lady
M.D. , retired from an academic position
1998 diagnosis of pT1c, N0, HR+, HER2-ve tumor; 5 yrs adjuvant Tamoxifen
12/2018: chest pain; chest X-ray, TB-CT, Bone Scan, CT-PET: lytic bone lesions in two ribs;
CA 15.3 = 52 U
01/2019: treatment with Letrozole
03/2019: decline in CA 15.3 (now 41 U); improved pain
05/ 2019: further decline in CA 15.3 (now 38 U); no pain; negative CT-PET

Question from the patient

(also suggested by her daughter who is a biotechnologist working in a leading position in a US-based Pharma Company:

« May I have access to ctDNA test to monitor disease course and ask for a genomic analysis on ctDNA and tissue from primary tumor in order to identify genetic dysregulations which might be targeted in the future?»

William Shakespeare, Stratford-upon-Avon, april 1564-april 1616

Precision Oncology:
go to bed with a dream, wake up with a purpose
(from a label inside my jeans)

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Precision Oncology:
a stepwise approach to bring dreams closer to reality

Oncology Networks and Molecular Tumor Boards

1) Standardization of available molecular tests
2) referral laboratories
3) eligibility criteria to NGS
4) registry of actionable dysregulations
5) access to drugs
6) registry of treated patients

Modified from N Martini, P Marchetti et al
N Normanno, studio Rational

Current Landscape anti-PD1/PD-L1

	Merck	BMS	Roche	AZ	Pfizer
	Pembrolizumab	**Nivolumab**	**Atezolizumab**	**Durvalumab**	**Avelumab**
Clone	22C3	28-8	SP142	SP263	73-10
Dx	Dako	Dako	Ventana	Ventana	Dako
Cutoffs	TC: ≥1, ≥50 CPS: ≥1, ≥10	TC: ≥1, ≥5, ≥10	TC: ≥1, ≥10, ≥50 IC: ≥1, ≥5, ≥10	TC: ≥25	TC: ≥1, ≥5, ≥25 IC: ≥10

- PD-L1 on tumor cells: % positive tumor cells (all antibodies)
- PD-L1 on immune (stromal) cells:
  - % positive cell area/total tumor area (SP142-Atezolizumab)
  - % positive cells (SP263-Durvalumab, 73-10-Avelumab)
- PD-L1 and «Combined Positive Score»
  - Positive tumor cells + positive immune (stromal) cells/total tumor cells x 100 (22C3-Pembrolizumab)

Modified from G Viale

ESCAT
The ESMO Scale for Clinical Actionability of molecular Targets

	ESCAT evidence tier		Required level of evidence	Clinical implication	Applied to breast cancer
Ready for routine use	Tier I	Alteration-drug match is associated with improved outcome in clinical trials (including other tumor types)	Prospective trials	Access to the treatment should be considered standard of care	ERBB2 ampl, gBRCA1/2mut, PIK3CA mut, MSI, NTRK transl
Investigational	Tier II	alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	Retrospective trials Prospective trials showing improved response but no survival data available	Treatment to be considered 'preferable' in the context of evidence collection (registry or clinical trial)	ESR1 mut, PTEN loss, AKT1 mut, ERBB2 mut
Hypothetical target	Tier III	alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration	Clinical benefit in pts with other tumor type(s); alteration with similar predicted functional impact already studied as tier I abnormality	Clinical trials to be discussed with patients	MDM2, somatic BRCA1/2, ERBB3mut
	Tier IV	Preclinical evidence of actionability	evidence in preclinical in vitro or in vivo models; actionability predicted in silico	Treatment should 'only be considered' in the context of early clinical trials. Lack of clinical data should be stressed to patients	ARID1A, ATR/ATM/PALB2, CDH1, IGF1R, INPP4B loss, MAP2K4/MAP3K1, MT4, MYC, NF1, PIK3R1, RUNX1/CBFB, SF3B1, TP53

Mateo J, Ann Oncol 2018; Condorelli R, Ann Oncol 2019

Requisito	Legge 94/98 (off label)	Legge 648/96	DM 7.9.2017 (compassionevole/ expanded access)	Cnn Legge 189/2012	Fondo 5% Legge 326/2003
Mancanza di valida alternativa terapeutica	Si (art.1, comma 796, titolo z, Legge Finanziaria 2007) (non e' applicabile agli usi diffusi e sistematici)	➢ Si ➢ quando vi e' alternativa terapeutica solo ai sensi dell'art.3 Legge 79/2014 (economicita' e appropriatezza)	Si	-	si
Consenso informato del paziente	Si	Si	Si	-	si
Documentazione scientifica minima a supporto	Pubblicazioni scientifiche accreditate in campo internazionale (almeno studi di fase II, art 2 comma 348, Legge 244/2007 – Finanziaria 2008)	Risultati studi di fase II	Studi di fase II §	-	Pubblicazioni scientifiche accreditate in campo internazionale
Assunzione di responsabilita' del medico	si	Si	si	-	si
Trasmissione dati di Spesa	-	AIFA e Regioni	Notifica AIFA	-	-
Registri di monitoraggio	-	Registri AIFA solo in alcuni registri presso le strutture prescrittrici (Provv . Luglio 2000)	-	-	-
Spesa sostenuta da	SSN (solo setting ospedaliero)	SSN	Azienda produttrice	✓ SSN (spesso a costo 1 euro) ✓ Campionatura	AIFA

§ In caso di malattie rare o tumori rari, devono essere disponibili studi clinici sperimentali almeno di fase I, gia' conclusi e che abbiano documentato l'attivita' e la sicurezza del medicinale, ad una determinata dose e schedula di somministrazione, in indicazioni anche diverse da quella per la quale si richiede l'uso compassionevole. In tal caso la possibilita' di ottenere un beneficio clinico dal medicinale deve essere ragionevolmente fondata in base al meccanismo d'azione ed agli effetti farmacodinamici del medicinale.

Personalised reimbursement: a risk-sharing model for biomarker-driven treatment of rare subgroups of cancer patients

Experimental: drug paid by MAH

Confirmatory: partly reimbursed on pay for performance model

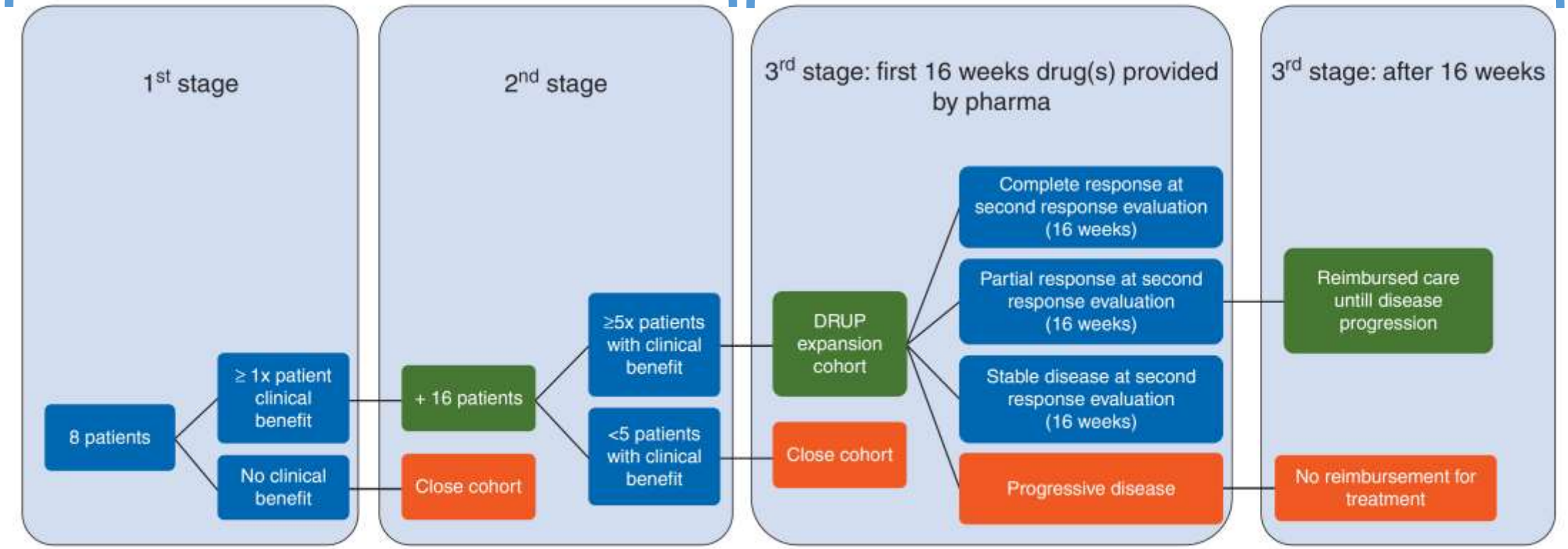

Figure 1. A performance-based, personalised reimbursement scheme after 16 weeks of clinical benefit at stage III, when the effectiveness is proven for an individual patient, commercial medication will be reimbursed by payers.

van Waalwjik van Doorn-Koshrovani SB et al. Ann Oncol 2019

Rete Oncologica Veneta
Ricerca, innovazione, assistenza