UNIVERSITÀ DEGLI STUDI
DI MILANO

IEO
Istituto Europeo
di Oncologia

Sperimentazioni di Fase I: L'esperienza dell'Istituto Europeo di Oncologia di Milano

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Milano, Lombardia, Italy

Disclosures

Board Member : Ellipses

Consultant (honoraria) : Lilly, Novartis, Seattle Genetics

Research grants to my Institute : MSD, Astra Zeneca

Speakers bureau: Pfizer, Lilly, Novartis, Roche-Genentech, Samsung, Celltrion, Daichii Sankyo

Stock ownership: None

Organizzazione della struttura

Locali dedicati, spazi arredati ad hoc, pompe ad infusione dedicate, clinical pathway per pazienti in fase I.

Collaborazione con i servizi per avere slot dedicati di

. Radiologia
. ECG ed ecocardiogrammi
. Medicina Nucleare
. Radiologia interventistica

Organizzazione della struttura

Locali farmacia con frigoriferi a timer remotizzati

Locali dedicati alla conservazione della documentazione clinica relativa agli studi clinici di fase I

Telemetria

Disporre di accesso al pronto soccorso: IRCCS senza PS (reperibilità 24 ore)

Pathway differenziata per campioni biologici di fase I

Qualità

QUALITY ASSURANCE

SOP: Le procedure devono descrivere in modo dettagliato tutte attività svolte ed i singoli processi.

Le procedure devono essere comprensive di istruzioni operative di moduli/modelli finalizzati alla dimostrazione della avvenuta attività.

Personale

Staff dedicato alle fasi I: medici (7), infermieri di ricerca (3), data manager (3), study coordinator (2), farmacista (1), bioinformatic (1), biologa (1)

Quality Assurance esterno

Formazione

personale medico indicato in organigramma come in servizio resso l'Unità di Fase I deve ricevere formazione sul supporto mmediato delle funzioni vitali (Immediate Life Support – ILS) come chiesto dalla Determina AIFA.

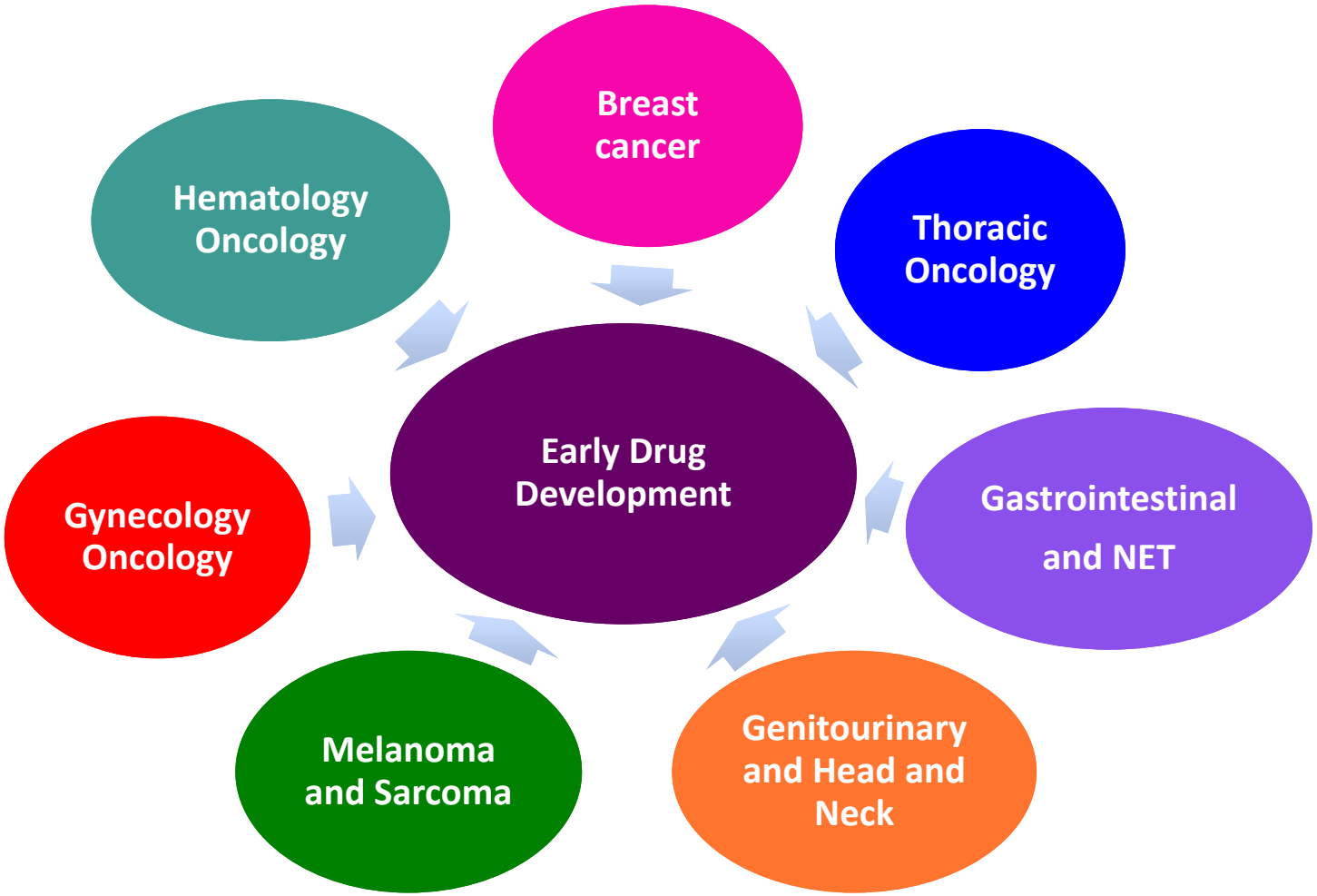
personale medico deve ricevere formazione sugli standard del upporto avanzato delle funzioni vitale (ALS) per effettuare perimentazioni con farmaci ad alto rischio che possono richiedere nterventi di emergenza avanzati.

Formazione

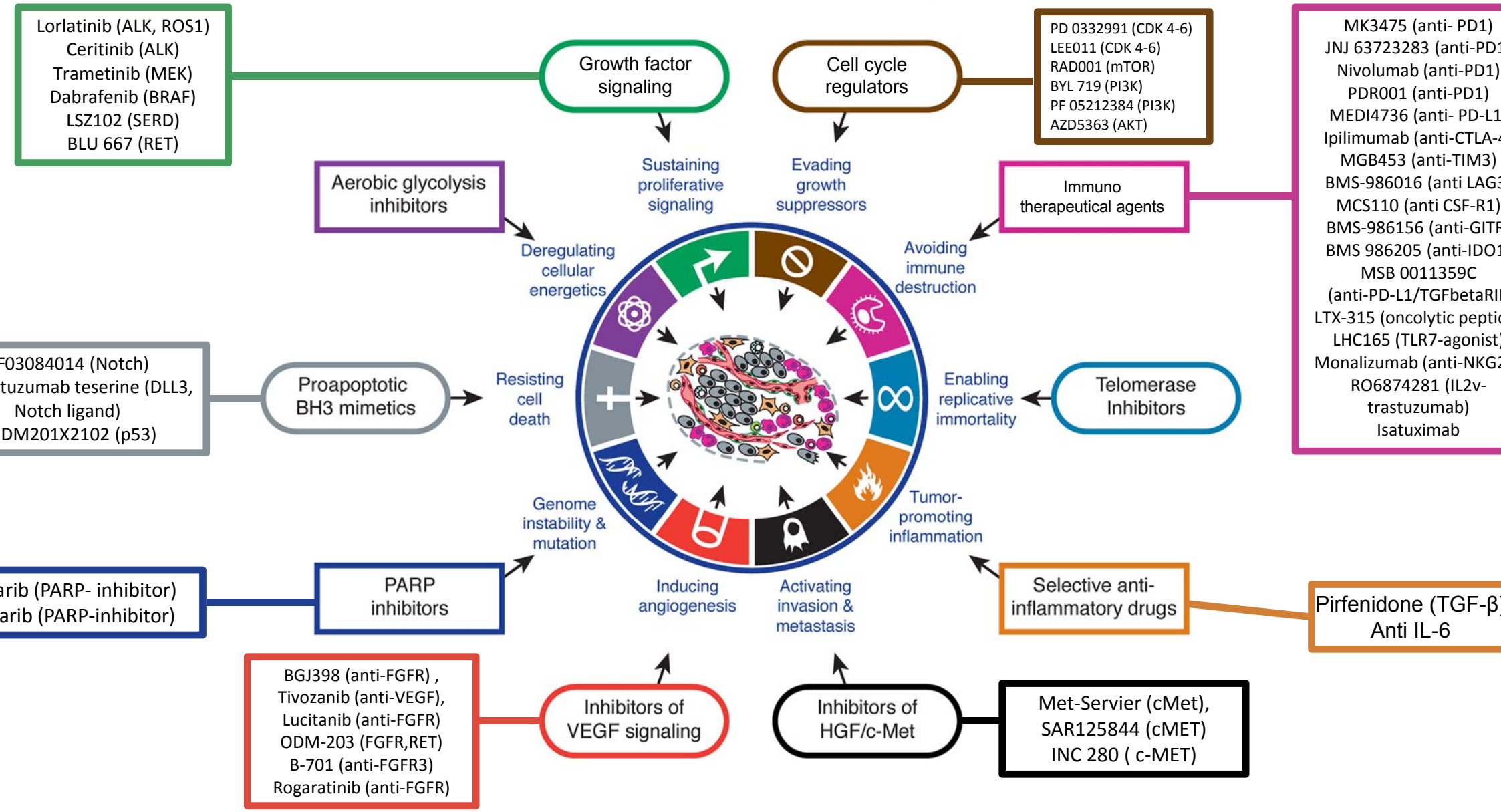
ocumentare la formazione, soprattutto quella sulle Norme di uona Pratica Clinica (GCP), e documentare di volta in volta ulterio orsi del personale

ianificare la formazione e documentare periodicamente tutte le ttività formative svolte

Piattaforma trasversale di Fase I

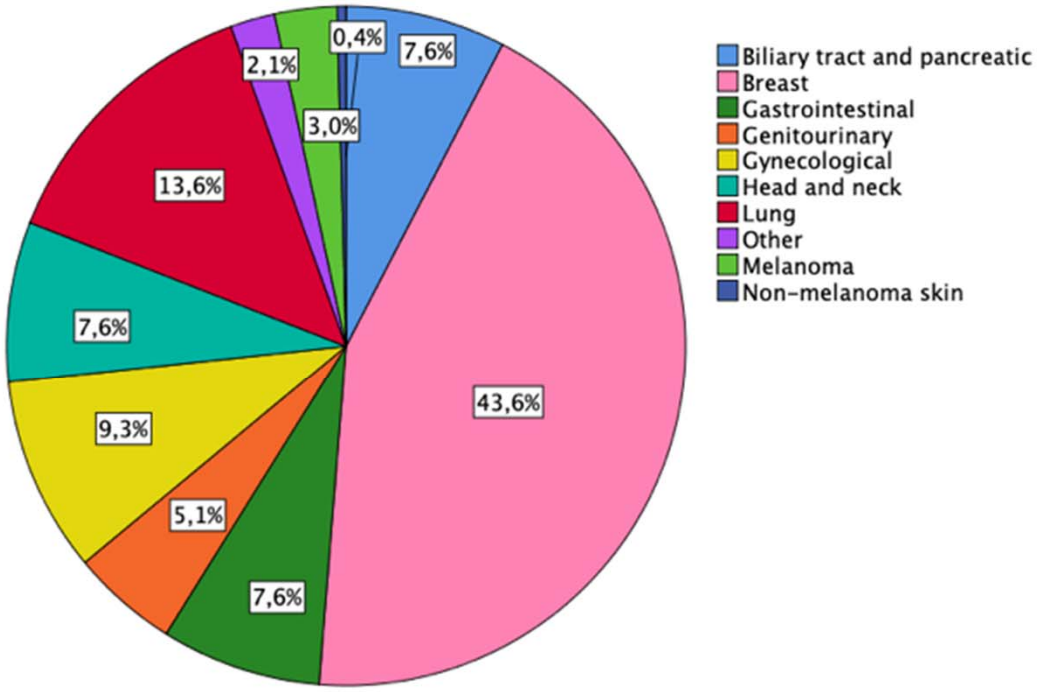


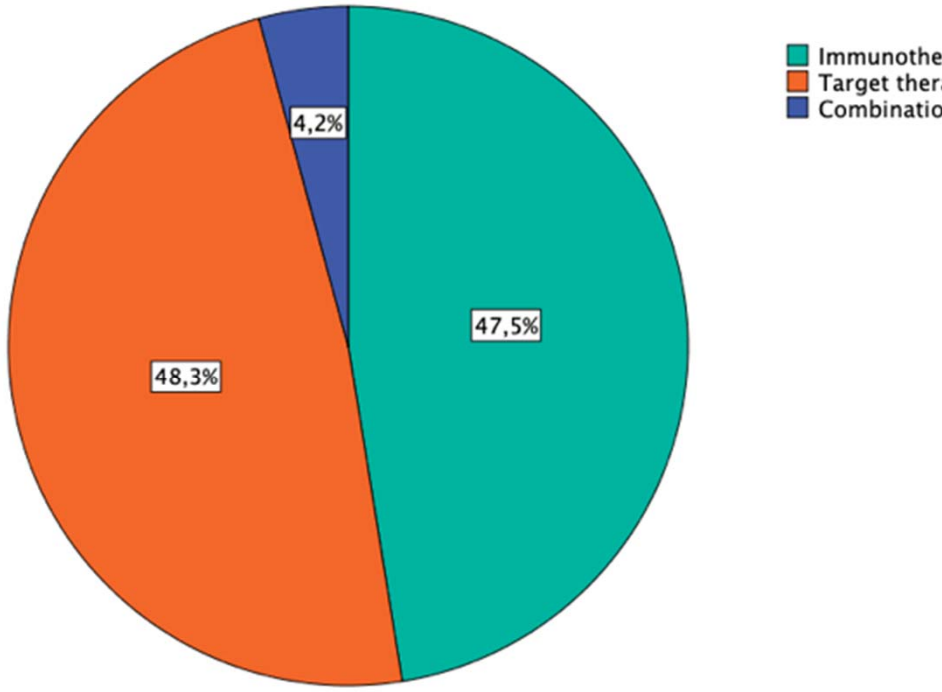
Drug Scouting



Our experience 2014-2018

66 patients screened for enrollment in Phase I trials

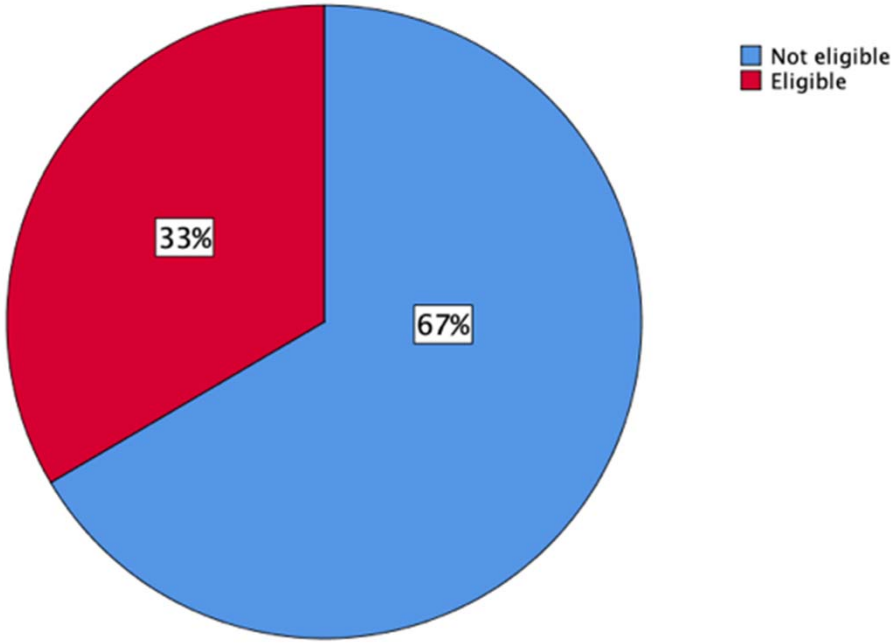




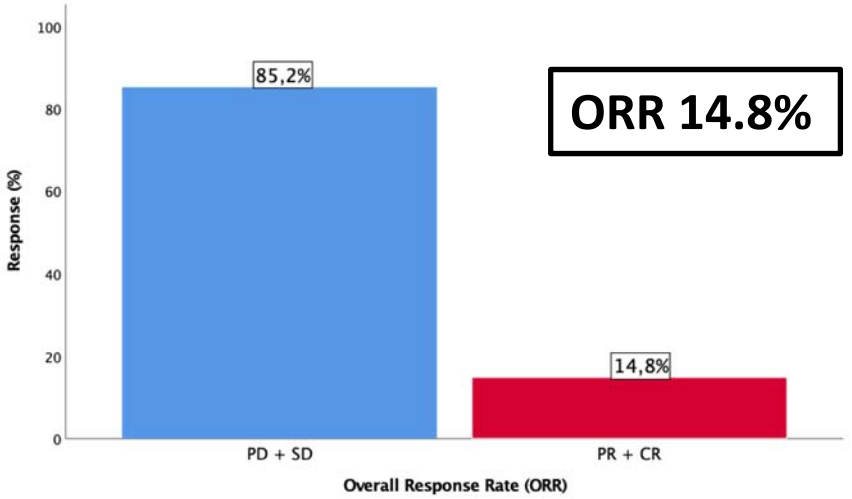
Marra A, Curigliano G et al. ESMO

Our experience 2014-2018

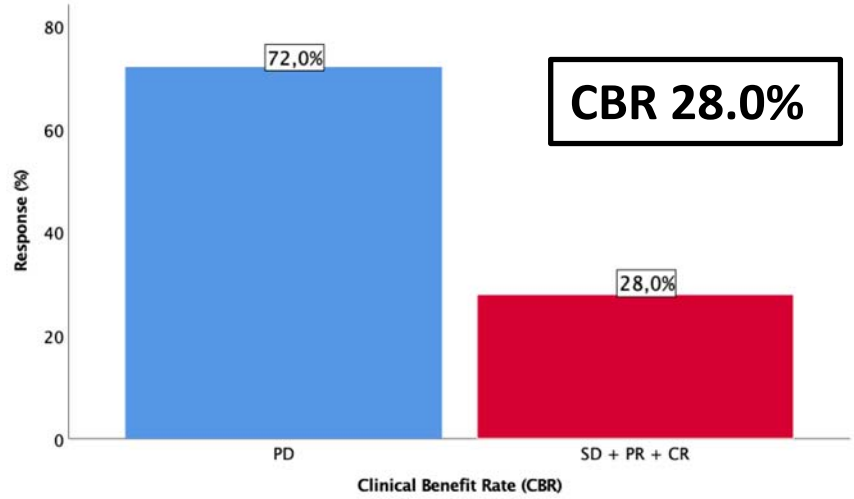
1366 patients screened



Reason for ineligibility	%
Absence of target alteration(s)	56.1
Abnormal lab results	12.7
Poor performance status	11.4
Other	19.8



ORR 14.8%



CBR 28.0%

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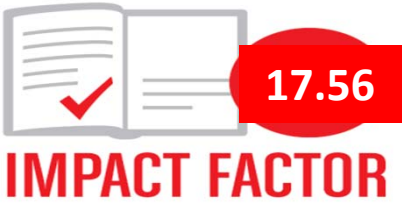
Our experience 2014-2018

January 2014 → Phase I unit accredited July 2016 **September 2019**

135 papers published (31 in the best 10% journals in the field).



3.5 million euros awarded to division members, including **grants** from the European Commission, National Institutes of Health, AIRC. **Almost 1.500.00 million euros** per year from pharma investigations fees

e division has been productive in terms of technology transfer, with **2 inventions** evaluated for patentability and ma
portunity, and **2 patent filings**.
-40 trials open to accrual. More than 100 patients included in phase I studies in 2019

National and International Network

work of 25 top Italian Research als, coordinated by the Italian Ministry alth: Member of the Clinical Trial g Group: implementation of a al program on Personalized Oncology

Member of the Steering Committee of TAT and of ESMO Precision Medicine Committee: A network of 17 Global Phase I unit to promote excellence in phase I research by: i) sharing of institutional practice & expertise; ii) accessing to multi-institutional teams; iii) contributing to global phase I trial design.

An alliance of 27 members across the (12 cancer centres and 17 univ hospitals) that pool their experti oncology and the development of cancer medicines.
Centers are selected according to qua data and number of trials ongoing

AACR 2019 Plenary Session

AACR American Association for Cancer Research ANNUAL MEETING 2019 ATLANTA

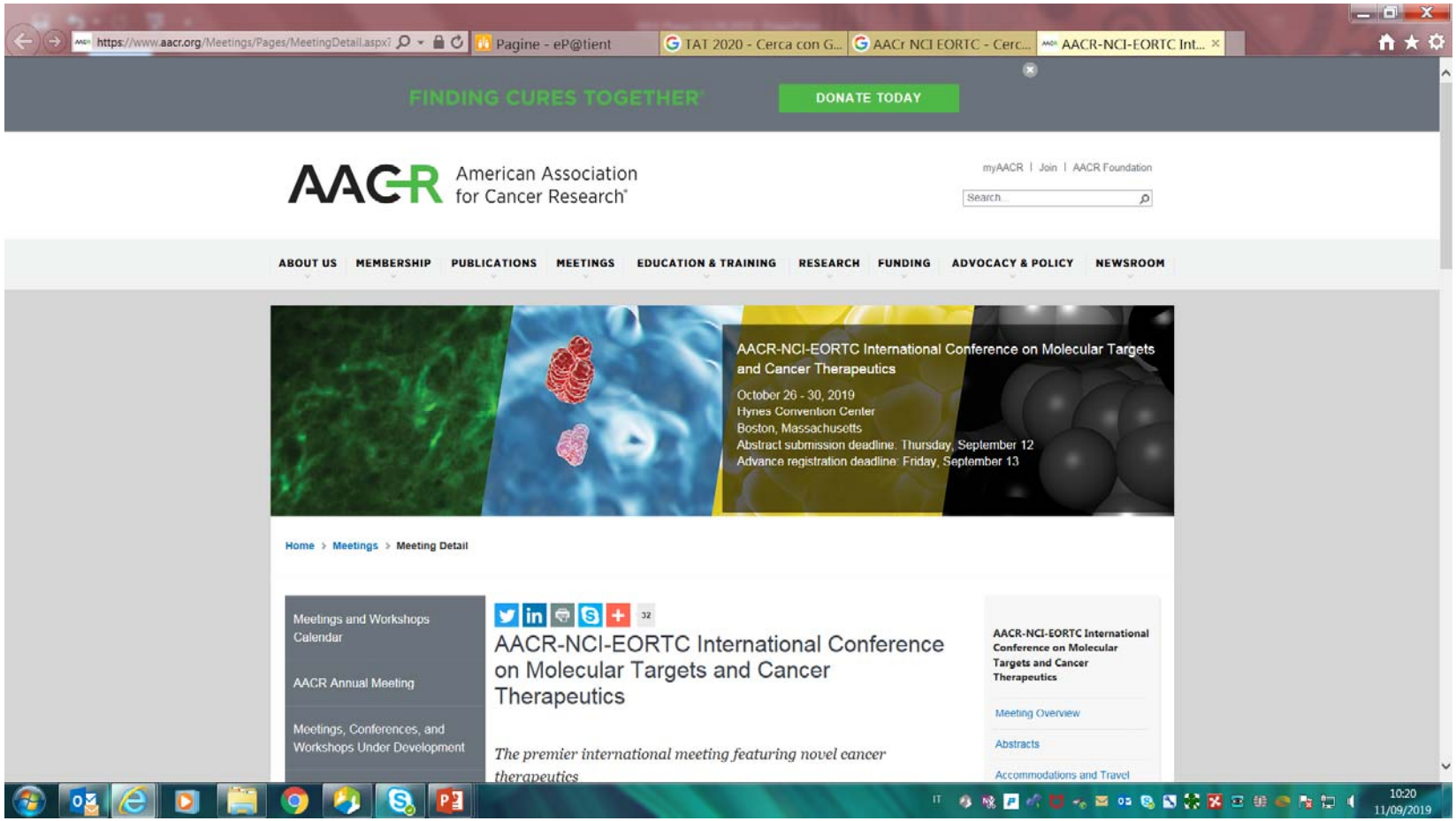
CT183

Phase I/II study of MBG453 ± spartalizumab (PDR001) in patients with advanced malignancies

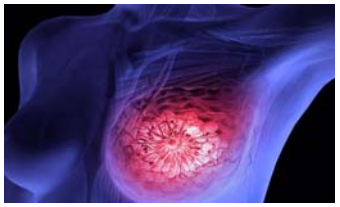
Giuseppe Curigliano,[1] Hans Gelderblom,[2] Nicolas Mach,[3] Toshihiko Doi,[4] Wai Meng David Tai,[5] Patrick Forde,[6] John Sarantopoulos,[7] Philippe L. Bedard,[8] Chia-Chi Lin,[9] Stephen Hodi,[10] Sofie Wilgenhof,[11] Armando Santoro,[12] Catherine Sabatos-Peyton,[13] Tyler Longmire,[13] Kitty Wan,[14] Panagiotis Nikolopoulos,[14] Luigi Manenti,[15] Aung Naing[16]

[1]University of Milan, Istituto Europeo di Oncologia, IRCCS, Milan, Italy; [2]Leiden University Medical Center, Leiden, The Netherlands; [3]Geneva University Hospitals, Geneva, Switzerland; [4]National Cancer Center Hospital East, Kashiwa, Japan; [5]National Cancer Centre Singapore, Singapore; [6]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; [7]Institute for Drug Development, Mays Cancer Center at University of Texas Health San Antonio MD Anderson Cancer Center, San Antonio, TX; [8]Princess Margaret Cancer Centre, Toronto, ON, Canada; [9]National Taiwan University Hospital, Taipei, Taiwan; [10]Dana-Farber Cancer Institute, Boston, MA; [11]Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [12]IRCCS Humanitas Cancer Center, Milan, Italy; [13]Novartis Institutes for BioMedical Research, Cambridge, MA; [14]Novartis Pharma AG, Basel, Switzerland; [15]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [16]MD Anderson Cancer Center, Houston, TX

National and International Network

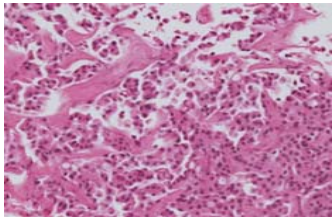


Beyond Phase I



Screening

- Tumor Biopsy



Central Lab evaluation

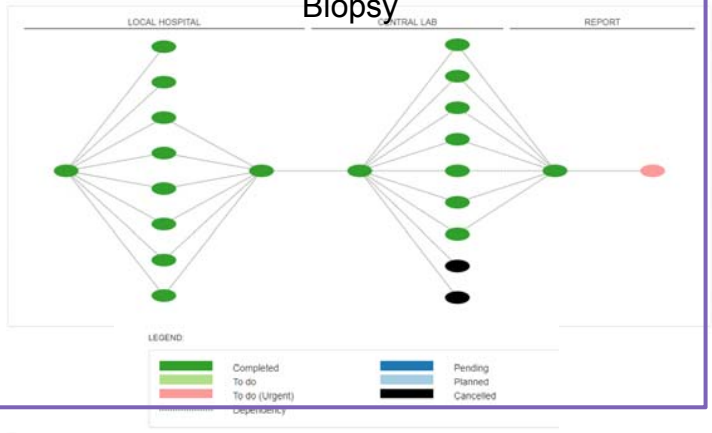
- Cellularity
- Histopathology

Molecular Tumor Board
annotation of patient reports

MTB Output:
Patient reports
Variants to be annotated
Outcome

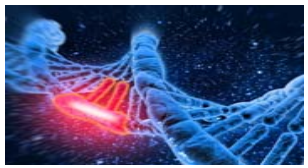
Informed consent, Registration and Samples collection

Biopsy



Molecular analysis

- Ion Torrent TGS (411 genes for tissue)
- Ion Torrent TGS (27 genes for ctDNA)
- Illumina, TrueSeq RNA seq
- OncoScan, FFPE, SNP/CNV



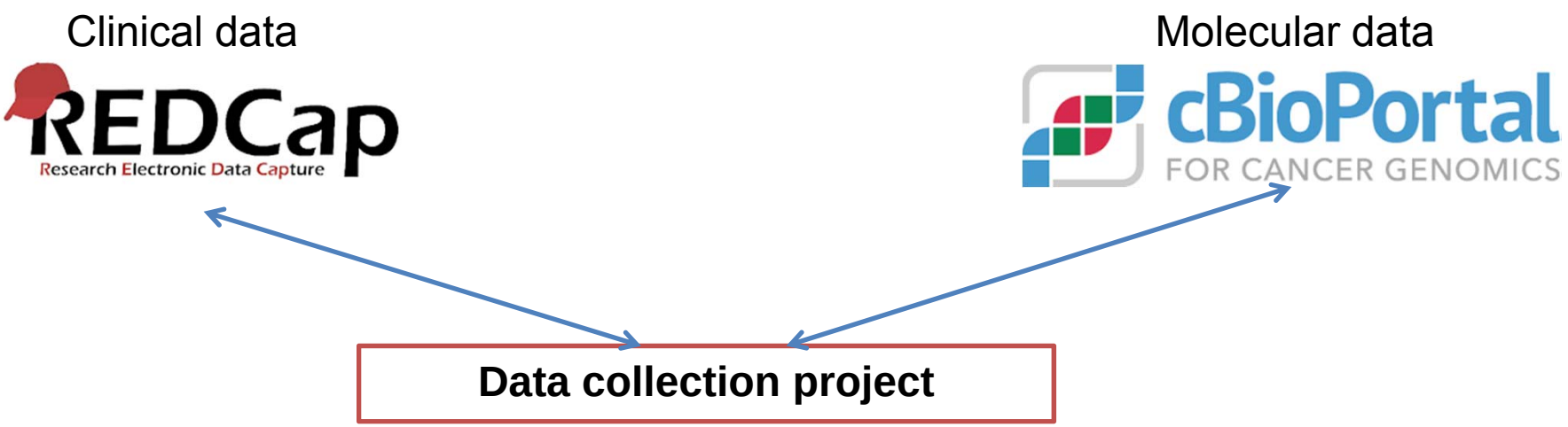
Feedback to clinician

- Consolidated MTB report
- « Advice » to clinicians

Detected gene deletions (copy-number ≤ 1)

CRKL	chr22:21272220-21304221	Primary: 1.0	Meta: 1.5
PIK3CD	chr1:9770468-9787161	Primary: 1.5	Meta: 1.0
MAF	chr16:79628302-79633837	Primary: 1.0	Meta: 1.0
ING4	chr12:6760342-6772272	Primary: 1.0	Meta: 2.5
TNK2	chr3:195590930-195622288	Primary: 1.5	Meta: 1.0
RPS6KA2	chr6:166826214-167275671	Primary: 1.0	Meta: 1.5
CBL	chr11:119077066-119170497	Primary: 1.0	Meta: 1.5
SMO	chr7:128829224-128852373	Primary: 1.0	Meta: 2.5
IGF2R	chr6:160412137-160526168	Primary: 1.0	Meta: 1.5
CDH1	chr16:68771243-68867431	Primary: 1.0	Meta: 1.0
CDH5	chr16:66413223-66437149	Primary: 1.5	Meta: 1.0
CYP2D6	chr22:42522525-42526792	Primary: 1.0	Meta: 1.0
IGF2	chr11:2154213-2161533	Primary: 1.5	Meta: 1.0
IRF4	chr6:393089-407569	Primary: 1.0	Meta: 1.5
FLT3	chr13:28578144-28644781	Primary: 1.0	Meta: 1.0
FLT1	chr13:28877210-29069106	Primary: 1.0	Meta: 1.0
MYH9	chr22:36678627-36745288	Primary: 1.0	Meta: 1.0
FANCA	chr16:89804902-89882998	Primary: 1.0	Meta: 1.0
RALGDS	chr9:135973939-136024364	Primary: 1.5	Meta: 1.0

Molecular Tumor Board

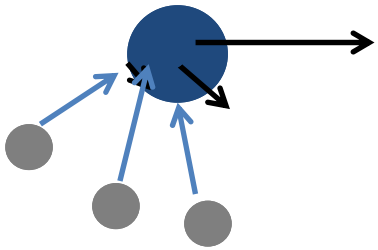


moleculartumorboard@ieo.it

Molecular Tumor Board

Public, Small

Public, Big



Private, Small

Private, Big

Harmony DFCI Profile

Data Held Privately or Among Partners Only

1M
100K
10K
1K

No Support of Linkage
Willing to Consider Linkage
No border Does or Will Link Data

Large, Integrated data assets are starting to emerge and advance real world data research – but platform trials and registries continue to have highly tuned data for particular diseases.

X-Axis: Dataset Quality refers to the integration of (a) molecular, (b) disease-specific, structured clinical, (C) longitudinal data
Y-Axis: Higher up organizations are sharing openly and for free. Mid-axis organizations have commercial offerings and closed, private data are inaccessible to anyone

Genomic Data Commons contains data from FoundationCORE, Broad's CCLE program, NCI's CCGI, TARGET and TCGA programs.

HARVARD BUSINESS S
Kraft Precision Accelerator

Criticità culturale

enerare una cultura delle fasi I in Italia

reare staff altamente professionali sulla gestione de
perimentazione clinica precoce.

a fase I è una opportunità, non “ruba” studi ai referenti di patolog

mplementare il sistema regolatorio, accelerare i tempi
pprovazione, ridurre i costi

Criticità culturale

- enerare una partnership tra mondo delle pharma e sperimentat
  “CRO” leadership nella selezione dei centri)
- enerare una cultura dell’innovazione come opportunità per il pae
- oncentrare gli studi in centri di volume per generare poli
  ccellenza distribuiti sul territorio nazionale
- reare un network nazionale dei centri di studi di fase precoce

Criticità

- L’unica fase di trial in aumento è quella tradizionalmente ricondotta sotto la definizione di fase I, che però è rappresentata prevalentemente da trial complessi di fase I-II o I-III piuttosto che da trial tradizionali di fase I

p://www.aifa.gov.it/sites/default/files/Rapporto-OsSC_17-2018.pdf

Challenges

- Tempistiche autorizzative poco competitive o scelte strategiche della pharma
- Conseguente difficoltà allocazione slots in escalation phase
- Costo poco competitivo (incentivi fiscali per l'innovazione in ricerca biomedica)
- Mancanza network nazionale pre-screening mutazionale

Thank You

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