Experiences, Insights and New Possibilities in Cancer Therapeutics Commercialization

Philip Jones
Vice President, Research Strategy, Transformation & Operations

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

MD Anderson | MERCK

How did I get here?

2009 Internal transfer
to Merck's Boston site

March 2011

Sept 2011

PhD Organic Chemistry

Life changing summer internship

1998 Merck's UK Neuroscience center

BSc Chemistry

Post-doc

2002 Internal transfer
to Merck's Italian site

MD Anderson | MERCK

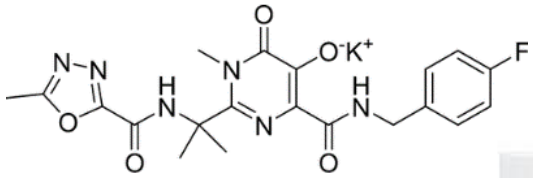
MENTORSHIP ENABLED ME TO DEVELOP AS A DRUG HUNTER

J. Med. Chem. **2008**, *51*, 5843–5855 5843

Discovery of Raltegravir, a Potent, Selective Orally Bioavailable HIV-Integrase Inhibitor for the Treatment of HIV-AIDS Infection

Vincenzo Summa,*,† Alessia Petrocchi,† Fabio Bonelli,† Benedetta Crescenzi,† Monica Donghi,† Marco Ferrara,† Fabrizio Fiore,† Cristina Gardelli,† Odalys Gonzalez Paz,† Daria J. Hazuda,‡ Philip Jones,† Olaf Kinzel,† Ralph Laufer,† Edith Monteagudo,† Ester Muraglia,† Emanuela Nizi,† Federica Orvieto,† Paola Pace,† Giovanna Pescatore,† Rita Scarpelli,† Kara Stillmock,‡ Marc V. Witmer,‡ and Michael Rowley†

Istituto Di Ricerche Di Biologia Molecolare, P. Angeletti SpA (Merck Research Laboratories, Rome), Via Pontina Km 30, 600, 00040 Pomezia, Italy, Department of Antiviral Research, Merck Research Laboratories, West Point, Pennsylvania



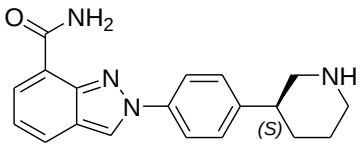
Raltegravir

7170 *J. Med. Chem.* **2009**, *52*, 7170–7185
DOI: 10.1021/jm901188v

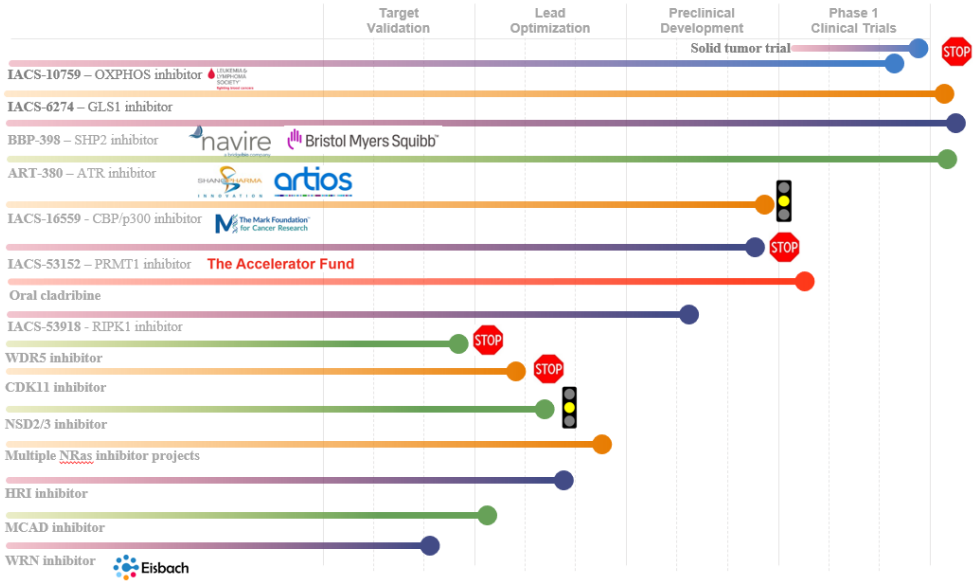
Journal of Medicinal Chemistry Article

Discovery of 2-{4-[(3*S*)-Piperidin-3-yl]phenyl}-2*H*-indazole-7-carboxamide (MK-4827): A Novel Oral Poly(ADP-ribose)polymerase (PARP) Inhibitor Efficacious in BRCA-1 and -2 Mutant Tumors

Philip Jones,* Sergio Altamura, Julia Boueres, Federica Ferrigno, Massimiliano Fonsi, Claudia Giomini, Stefania Lamartina, Edith Monteagudo, Jesus M. Ontoria, Maria Vittoria Orsale, Maria Cecilia Palumbi, Silvia Pesci, Giuseppe Roscilli, Rita Scarpelli, Carsten Schultz-Fademrecht, Carlo Toniatti, and Michael Rowley



Niraparib



navire a bridgebio company

artios

Magnolia NeuroSciences

IMMUNOGENESIS

What does it take to be a successful drug hunter?

Drug hunting is a rewarding career. Not for the faint hearted

Its going to take, lots of:

- Talent
- Sweat and tears
- Perseverance
- Team work
- Willingness to learn
- Time
- Money

- Focus on what you are trying to achieve
- Be prepared to get stuck in to get stuff done
- Surround yourself with people who are smarter than you
- Have willingness to learn along the way
- Keep you eyes wide open
- Be stringent
- Be honest. Would your treat a loved one?
- Expect road bumps and be prepared to pivot

WE'VE COME A LONG WAY

THE NEW YORK TIMES, SUNDAY, OCTOBER 6, 1946.

WAR GASES TRIED IN CANCER THERAPY

Army Branch Joins Research Groups in Study of Using Nitrogen Blister Chemicals

EDGEWOOD ARSENAL, Md., Oct. 5—The possibility that deadly blister gases prepared for wartime use may aid victims of cancer will be investigated by the Army Chemical Corps' Medical Division, it was announced here today.

The gases will be part of a large variety of chemicals to be used in a search for new compounds for cancer treatment. The work will be conducted in close collaboration with leading cancer research groups.

After the fall of France in 1940, information about new blister gases known to the French and Germans reached this country. These gases were classified as "nitrogen mustards" because they blistered the skin like mustard gas but contained nitrogen instead of sulphur.

Study by the Chemical Corps and agencies of the Office of Scientific Research and Development disclosed that the gases were poisonous to nearly all parts of the body but particularly destructive to bone marrow and lymph glands.

Most white and red blood cells are formed in the bone marrow. Other white blood cells and lymphocytes originate in the lymph glands.

Use of the nitrogen mustards was suggested to treat diseases in which there is a great overproduction of white blood cells—the leukemias, or a great overgrowth of lymph glands, Hodgkin's disease and lymphosarcoma, fatal forms of cancer.

Because the nitrogen mustards were extremely toxic, they had to be tested carefully before being administered to human patients. The first trials, made at New Haven, Conn., by Dr. Louis Goodman and Dr. Alfred Z. Gilman, led to further experiments.

Results of the use of the gases in the first sixty-seven cases treated, recently published in The Journal of the American Medical Association, showed that while the nitrogen mustards do not cure any form of cancer, they do prolong life in many instances and bring about remarkable remissions in a few cases.

The chemicals were most effective in treating Hodgkin's disease, where results equaled those obtained with the best x-ray treatment. They gave temporary relief to some cases which no longer responded to X-ray.

Reports are awaited on other cases similarly treated at Memorial Hospital in New York, Walter Reed General Hospital in Washington and Chicago hospitals.

Only three types of nitrogen mustards have been used in cancer treatment. More than sixty others have been made in the chemical laboratory and it is among them that the medical division will search for better cancer drugs.

MORE PARKERS WARNED

185 Autoists Are Told by Police They Must Obey Ban

Few of the cars that normally crowd the streets of the midtown section appeared yesterday in the area restricted against parking, but the police continued their drive on curb-parking in the section.

Patrolmen assigned to traffic details and foot patrols issued 185 warnings to parking regulation violators during the day, forty-six of them before 2 P. M. In the five days of the drive 2,388 warnings have been issued.

Parking is permitted in most restricted streets today, for the signs banning parking there say "Except Sunday." In some stretches, however, no exception is made for Sunday, and motorists were warned by police officials to look at the parking signs today when they were ready to park to make sure that parking is allowed at the curb on Sunday.

15,000 See Air Show

Special to THE NEW YORK TIMES.

TETERBORO, N. J., Oct. 5—Fifteen thousand persons witnessed air stunts, simulated air rescues, parachute landing of emergency food stuffs and parachute delivery of newspapers at the air show staged at Teterboro airport here today by the New Jersey Wing of the Civil Air Patrol. The air show will be repeated tomorrow when it is expected that Army planes will participate.

The New England
Journal of Medicine

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Volume 238 JUNE 3, 1948 Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§
ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.‖
BOSTON

JOURNAL OF THE NATIONAL MEDICAL ASSOCIATION
July, 1951 • Vol. 43 • No. 4

ORIGINAL COMMUNICATIONS

An Evaluation of Folic Acid Antagonists in Adults with Neoplastic Diseases: A Study of 93 Patients with Incurable Neoplasms*

JANE C. WRIGHT, M.D., AARON PRIGOT, M.D., BARBARA P. WRIGHT, M.D.
SOLOMON WEINTRAUB, M.D., AND LOUIS T. WRIGHT, M.D.
Cancer Research Foundation, Harlem Hospital, Department of Hospitals, New York City

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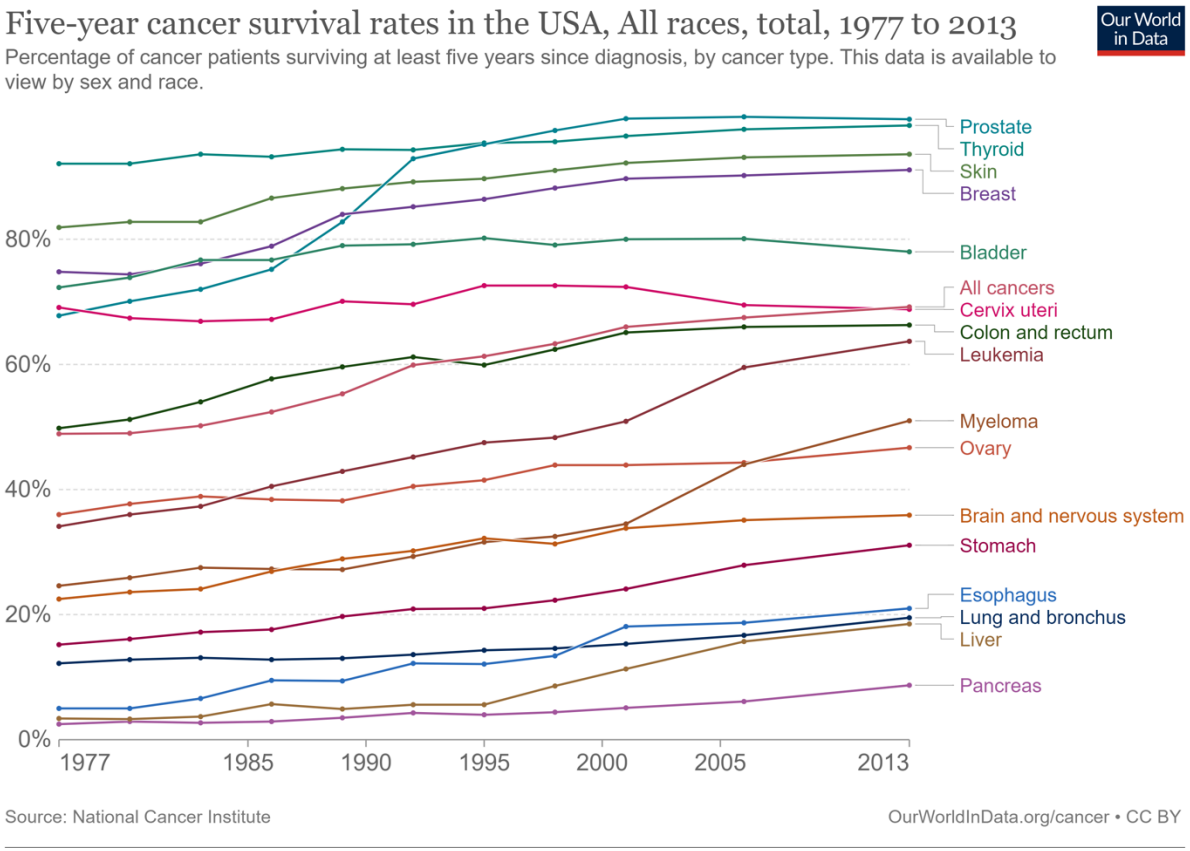
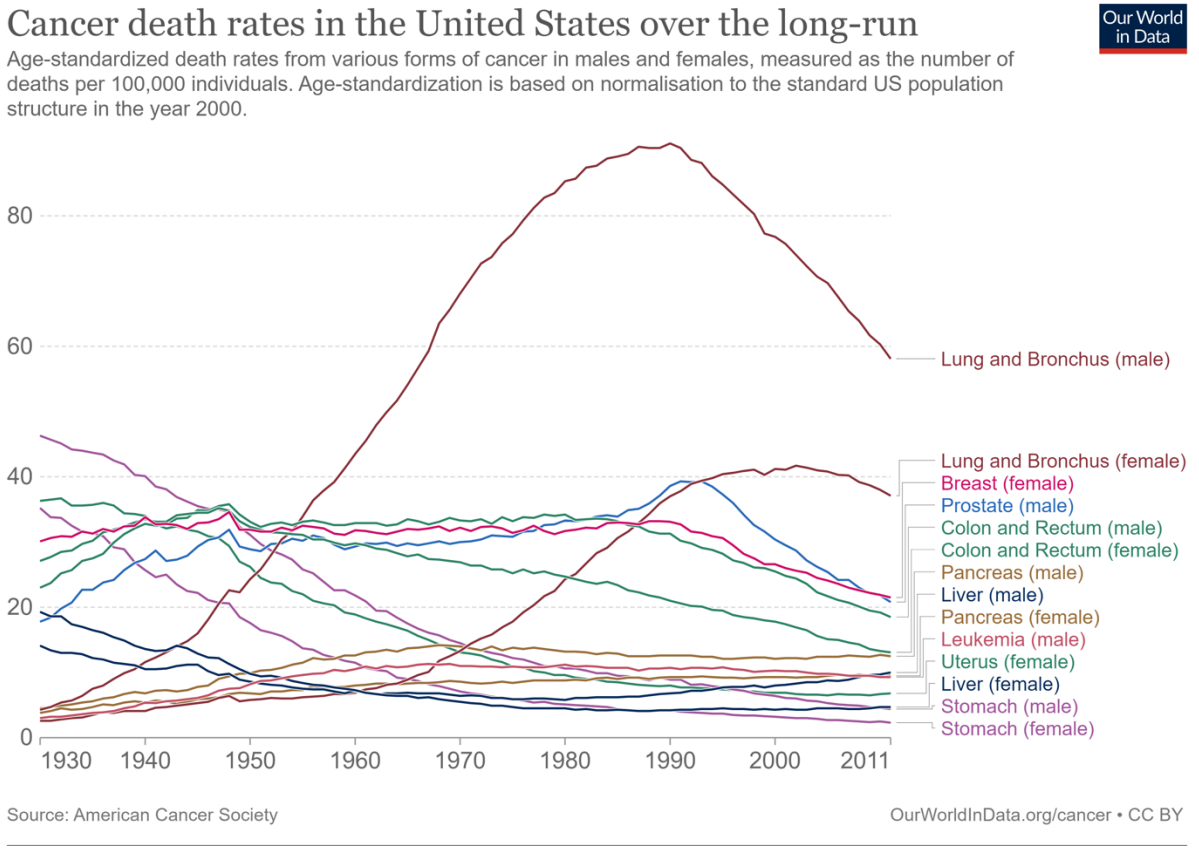
Construction of MD Anderson in 1952

MADE A LOT OF PROGRESS

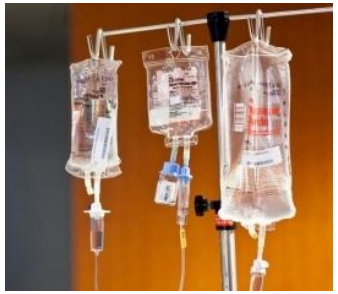




https://ourworldindata.org/

DRUGS / THERAPEUTICS COME IN MANY FLAVORS

Chemotherapy

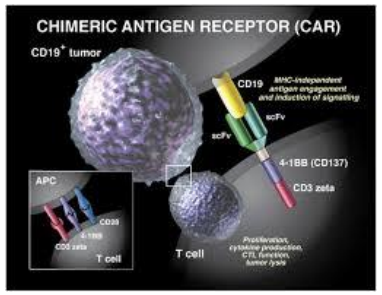


Hormone (endocrine) therapy

Targeted Therapy

Monoclonal antibodies

CAR T-Cell Therapy

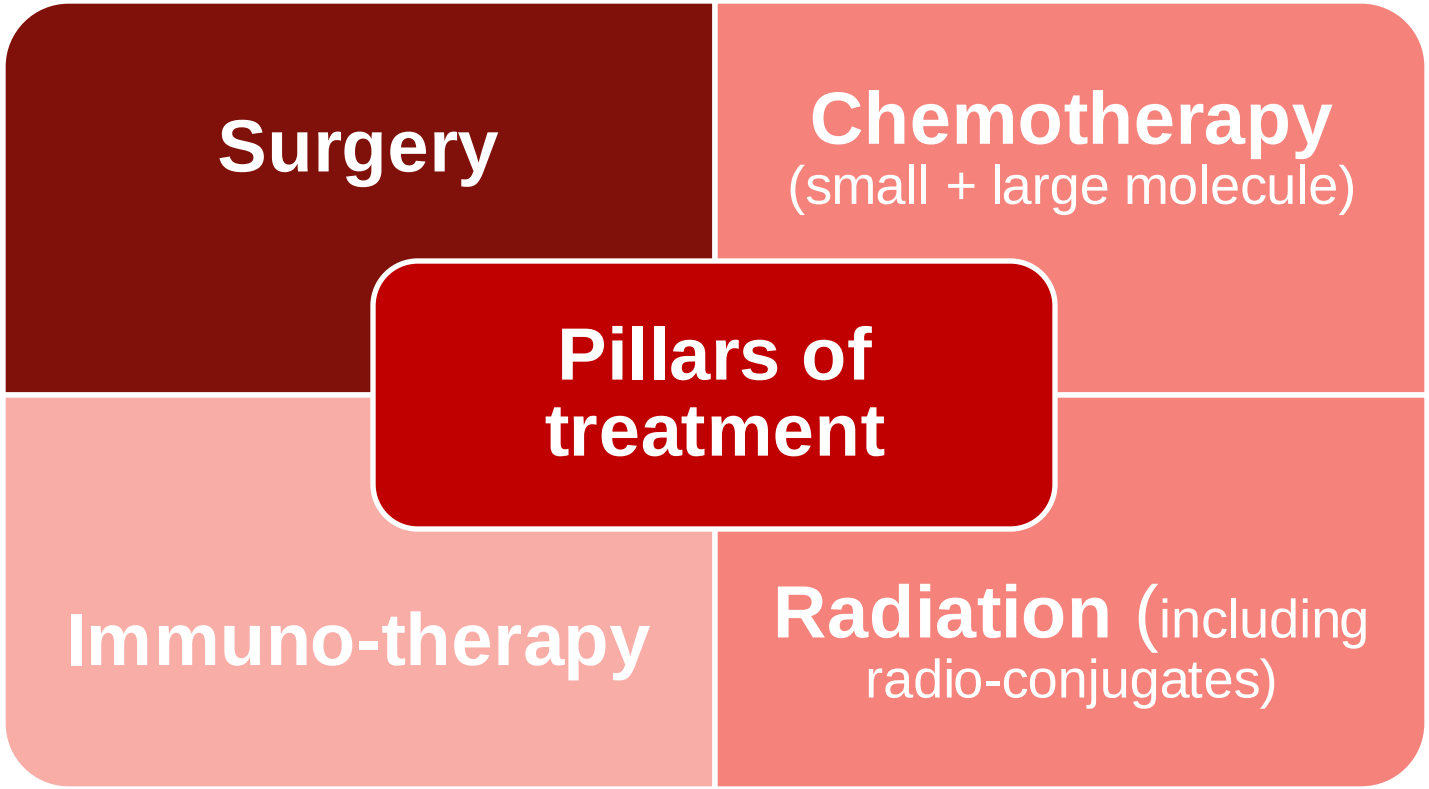


Cancer vaccines

Immune checkpoint inhibitors

Antibody-drug conjugates

EMBRACE MULTI-MODALITY THERAPY WITH "CURATIVE INTENT" FOR DURABLE RESPONSE



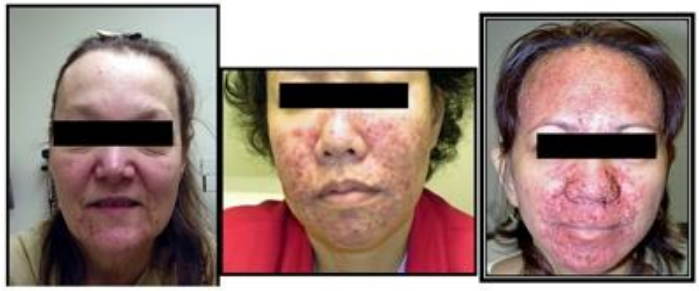
STILL GOT A LOT TO DO

- Not everyone responds

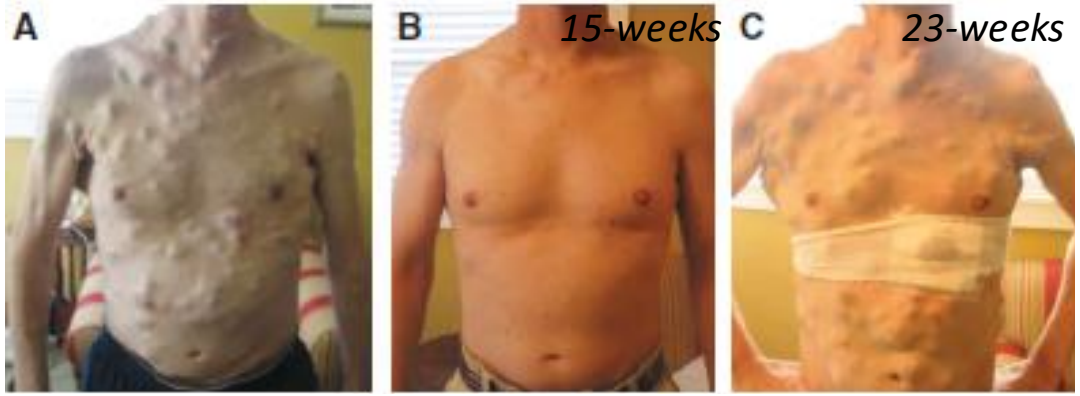
NEJM 2018, 378, 2078-2092

- Narrow therapeutic index

BLACK BOX WARNINGS:
- **CARDIOMYOPATHY**
- **HEPATOTOXICITY**
- **NEPHROTOXICITY**



- Resistance

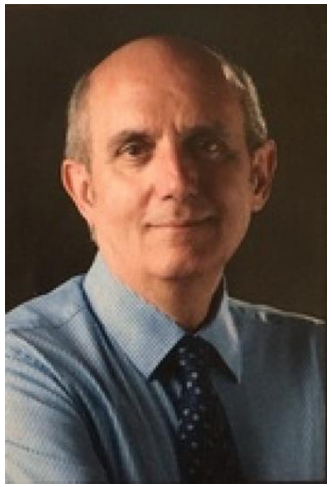


J. Clin. Oncol. 2011, 29, 3085-96

- Chemotherapy induced peripheral neuropathy (CIPN), & "Chemobrain"

I cannot distinguish between car accelerator or brake, have difficulty tying shoes, and fall often. I cannot write; cannot hold small objects." **– Mr. Book**

ALL GOT OUR OWN PERSONAL STORIES







What does it take to have a successful drug discovery & development project?

GEORGE W. MERCK

"…We try never to forget that medicine is for the people. ….. **The profits follow**, and if we have remembered that, they have never failed to appear. **The better we have remembered it, the larger they have been**."

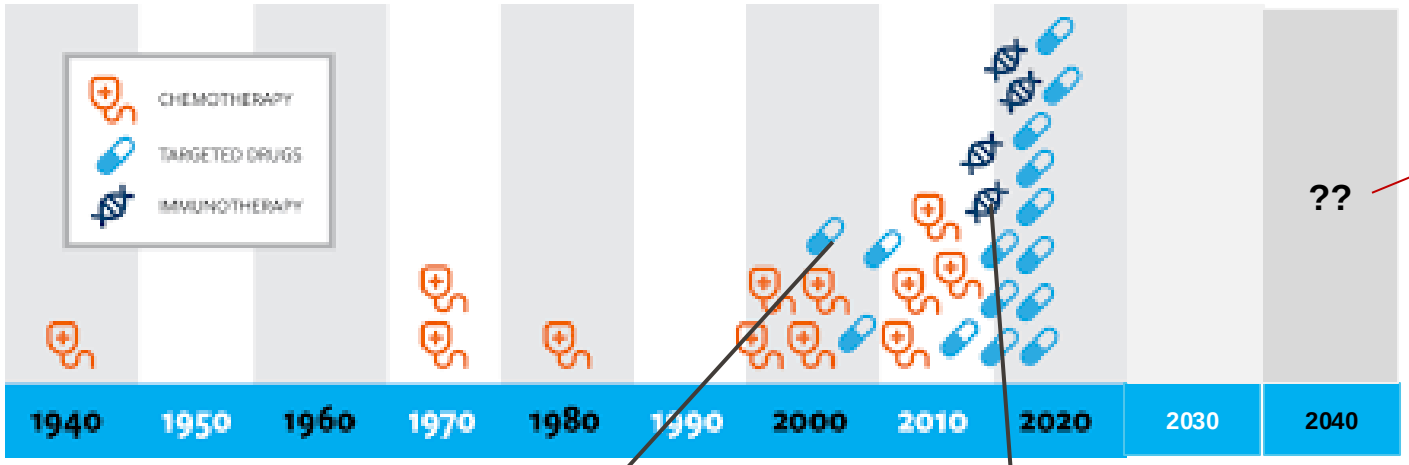
What is the unmet medical need you are targeting?

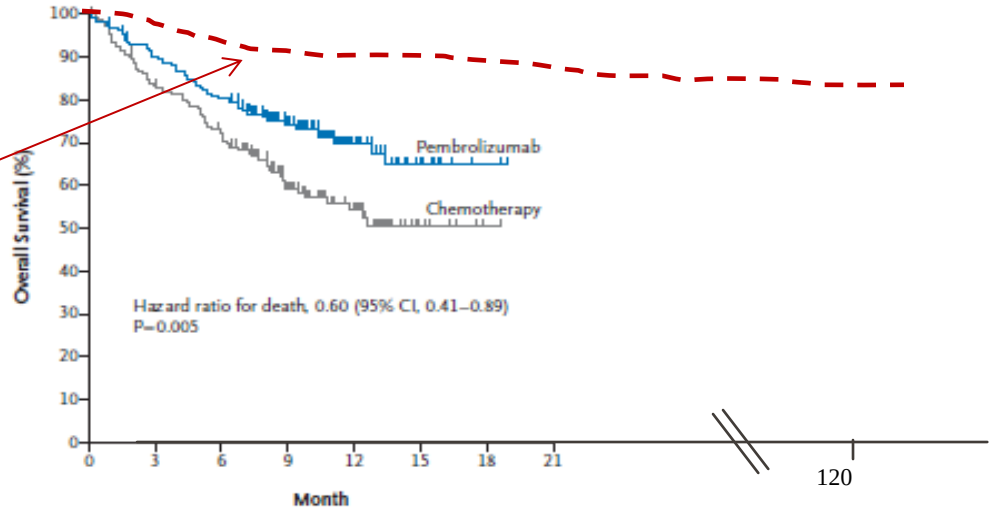
Thinking about playing field 3-7 years from now

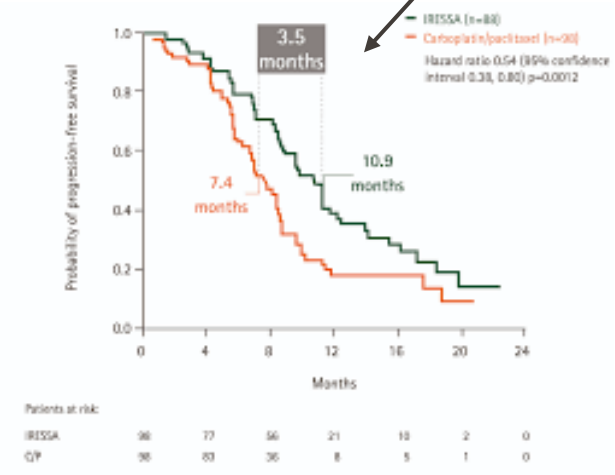
Monitor your competition during the lifetime of your project

CLINICAL LANDSCAPE CHANGES WITH TIME

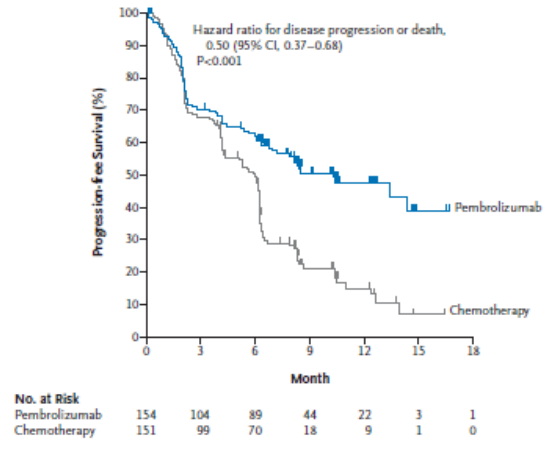
Approved therapeutics for non-small cell lung cancer







Pembro vs. Chemo for PD-L1+ NSCLC

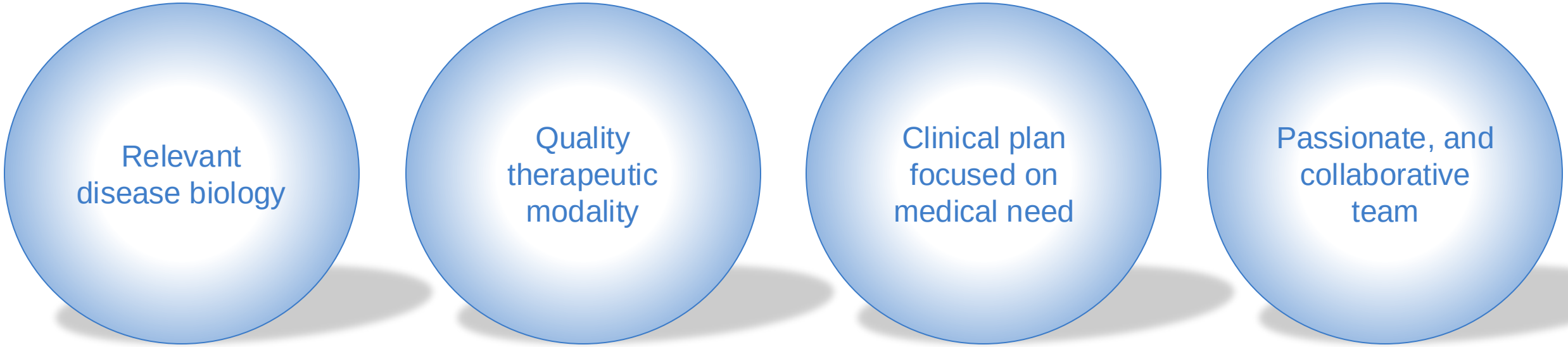


Maintaining high quality of life

Similar progress in other malignancies

N Engl J Med 2016; 375:1823-1833

BEHIND EVERY SUCCESSFUL PROJECT THERE ARE FOUR KEY PIECES



Comprehensive understanding about how a target impacts on disease

Has all the attributes to make it succeed in the humans

Early proof of biology and activity response read-outs
Distinct clinical populations

Focus and alignment on task/issue to hand, with strong camaraderie

WHAT DO WE MEAN BY DRUG DISCOVERY & DEVELOPMENT?

- Hypothesis testing:
  - Changing the abundance or activity of a “target” [usually a protein or RNA] through an intervention of some sort, will impact or cure a disease, or ameliorate its symptoms

WHERE DO IDEAS COME FROM?

Clinical Research

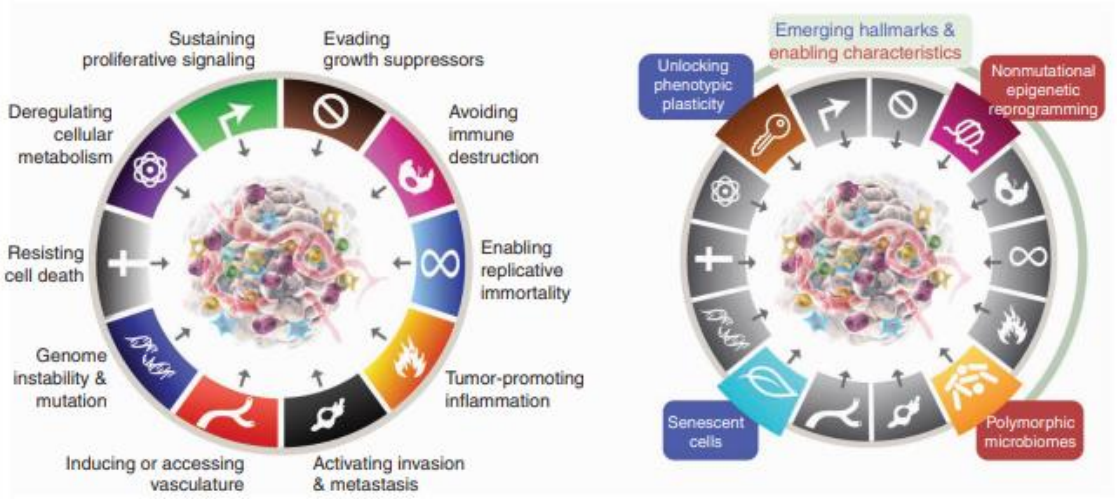
- Driver mutations/fusions
- Mechanism of resistance
- Impact of tumor microenvironment
- “-omics” profiling

Basic scientific discovery

- Understanding of fundamental biological processes
- High-throughput functional genomic screens

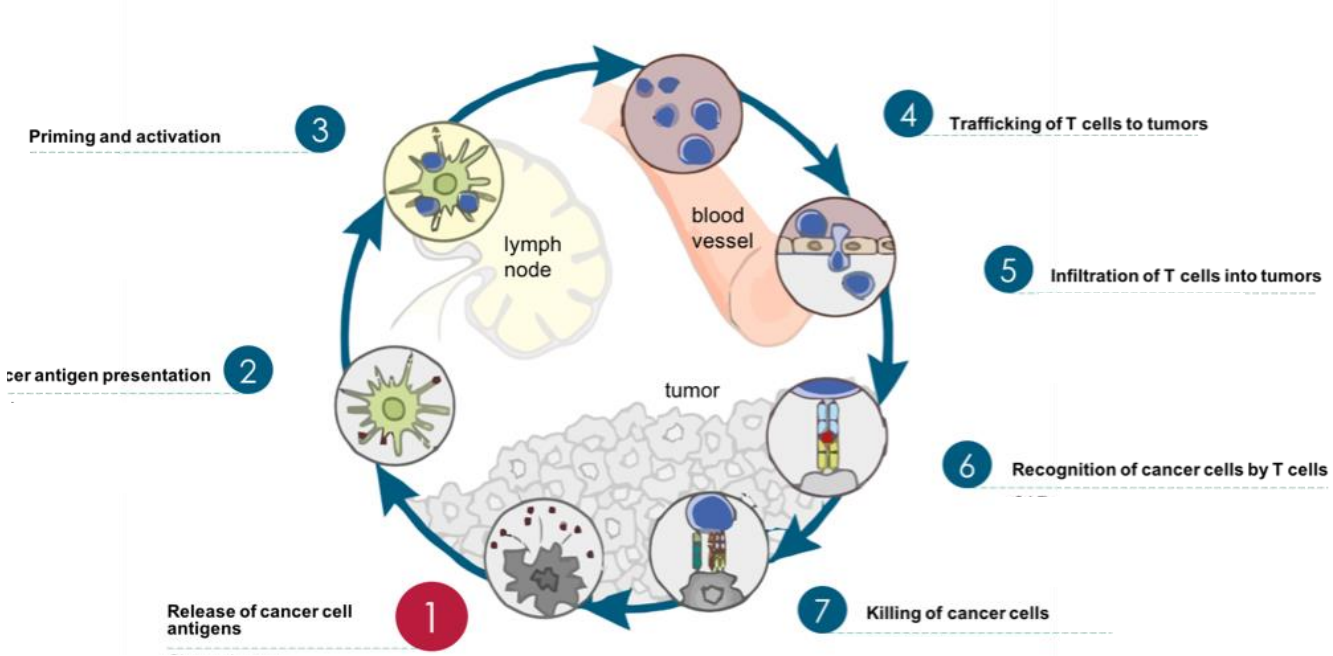
DISEASE RELEVANT BIOLOGY - IDEALLY SOMETHING THAT HAS MEANINGFUL IMPACT ON THE DISEASE

Hallmarks of Cancer



Cancer Discovery 2022, 12, 31

Cancer Immune Cycle



Immunity 2013, 39, 1

TARGET PROFILE: WHAT IS A GOOD DRUG TARGET?

- Relevance
  - Good understanding of biological function, including substrates & signaling pathways. Supporting “omics” data, & cross species relevance. **Strong preclinical validation**
- Tractability
  - Druggability, viable screening cascade, appropriate preclinical models
- Clinical development path
  - Clinical need, biomarkers, clear clinical hypothesis for POC
- Issue Awareness
  - Therapeutic window, competition/differentiation, intellectual property
- Clear Go/No-Go decision points
  - Key executable experiments with unambiguous results

YOU CARE ABOUT THE "LABEL" THE FDA/EMEA ARE GOING TO GIVE YOU

INDICATIONS AND USAGE

ZEJULA is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. (1)

The trial demonstrated a statistically significant improvement in PFS for patients randomized to ZEJULA as compared with placebo in the g*BRCA*mut cohort and the non-g*BRCA*mut cohort (Table 6, and Figures 1 and 2).

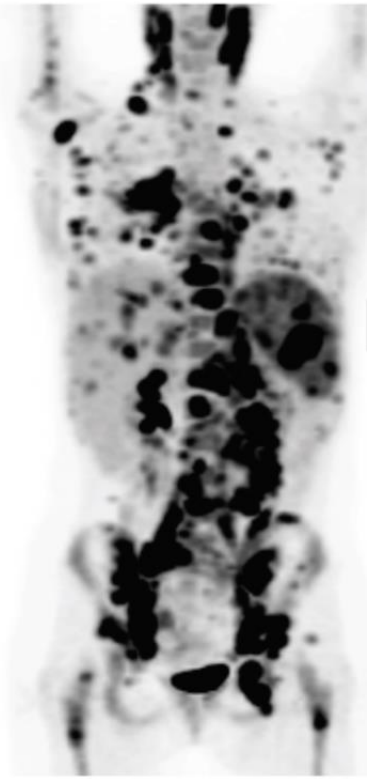
Trial 1 (NOVA) was a double-blind, placebo-controlled trial in which patients (n=553) with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer were randomized 2:1 to ZEJULA 300 mg orally daily or matched placebo within 8 weeks of the last therapy. All patients had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen.

What is clinical readout people (regulatory, payers, patients) care about?

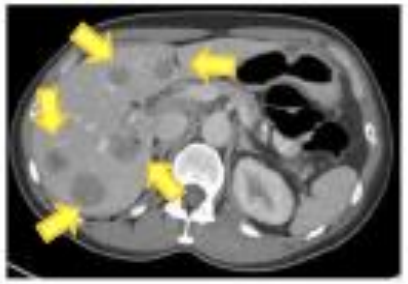
i.e. What is the endpoint of your pivotal clinical trial?

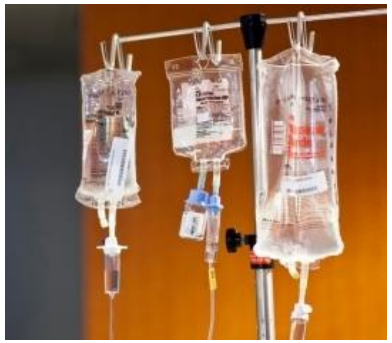
Reimbursement from payers depends on the label

HOW ARE YOU GOING TO KILL CANCER CELLS IN PATIENTS SELECTIVELY WITH A THERAPEUTIC?



Pre-Treatment



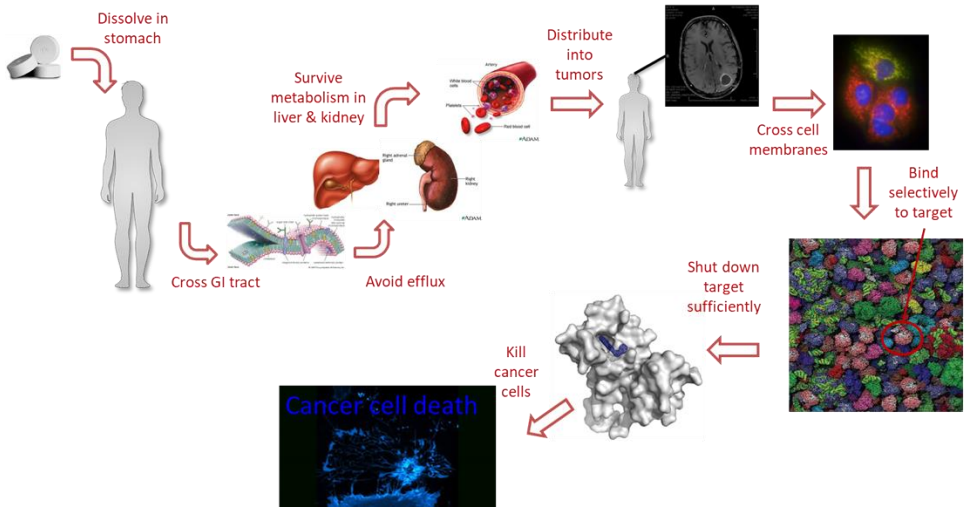


Significant engineering problem

QUALITY THERAPEUTIC MODALITY

- Need an agent that can effectively modulate the target in the desired manner
  - *Where in a cell, and in the human body, does it need to get?*
    - *There are a lot of physical barriers to be overcome*

- Need to think about
  - Potency
  - Selectivity
  - PK profile
    - Need fast on/off action, or sustained exposure?
  - Safety profile
  - Route of administration/convenience
  - Dosage
  - And more….



KNOW AT ONSET WHAT YOU ARE TRYING TO DO – TARGET PRODUCT PROFILE (TPP)

	Clinical Candidate
Biochemical potency (IC_{50} nM)	≤ 50 nM
Cell Target Engagement (IC_{50} nM)	≤ 250 nM
Cell Phenotypical (CC_{50} nM)	≤ 250 nM What disease relevant phenotype?
Non-responder (CC_{50} nM)	> 10000 nM
Desired selectivity profile	100 fold over anti-targets; Is selectivity within family good or bad?
Kinome / CEREP selectivity	What can you tolerate?
hERG patch clamp (IC_{50} uM)	>30 uM
Safety-pharmacology	Clean at 10 uM
PhysicoChemical properties	• Solubility: > 60uM (pH 7) • $Permeability_{WT}$ A-B/B-A(x10^6 cm/s):>10 • Efflux: No
PK	What human PK do you want? How long do you need to hit target?
PD/Efficacy	• Which model? • What is compelling efficacy? • What checks and balances on pharmacological audit trail?
Tolerability	Well tolerated at efficacious doses How large window do you need?

Does it modulate target in vitro

Does it modulate target in cells, & modulate the biology

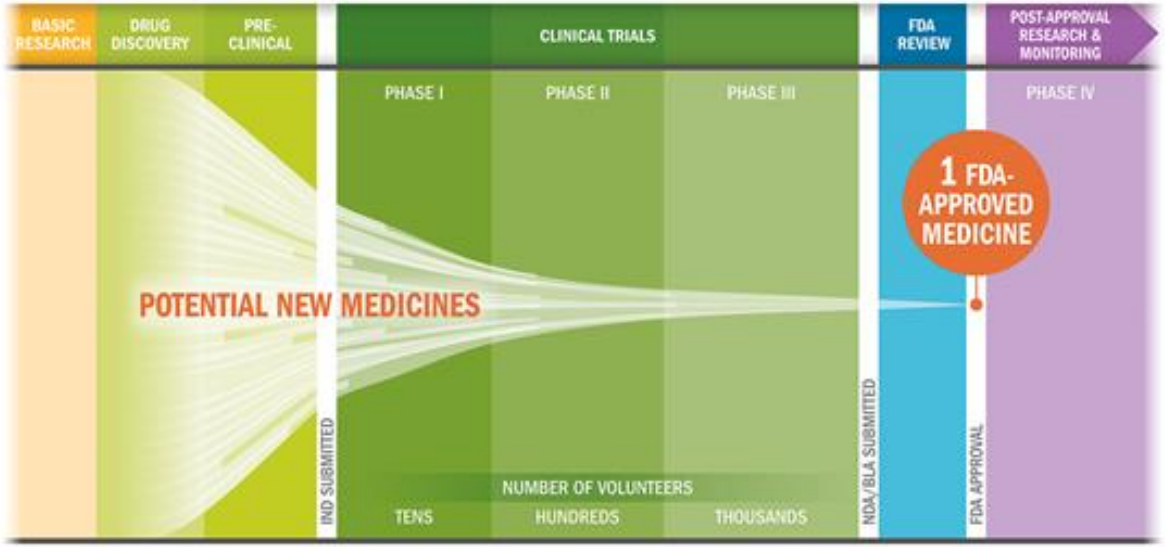
Is it selective?
Does it have unwanted off-targets?

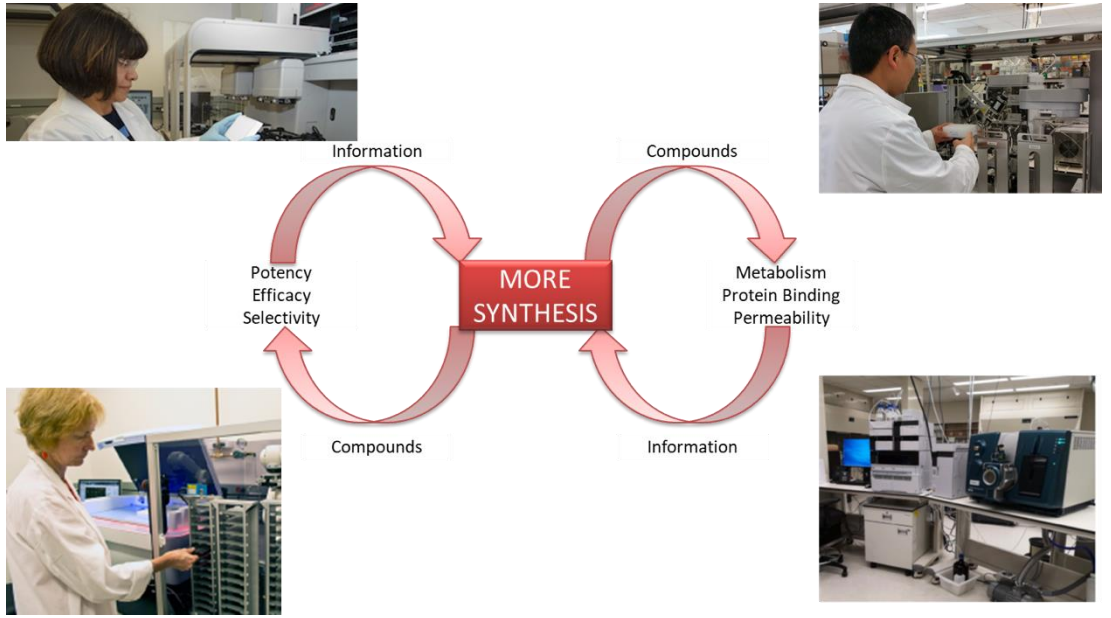
Does it have adequate PK properties?

Does it modulate the disease in preclinical in vivo models?
What dose and exposure?

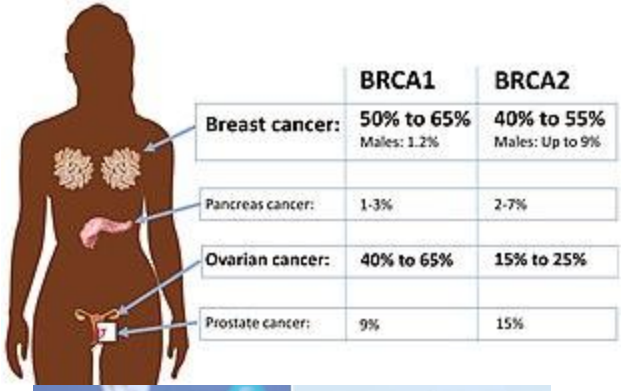
Is it safe?

DRUG DISCOVERY & DEVELOPMENT IS A LONG PROCESS. ALL ABOUT GETTING THE BEST THERAPEUTIC POSSIBLE





PARP INHIBITORS AS CONTEXT-SPECIFIC ANTI-CANCER AGENTS



	BRCA1	BRCA2
Breast cancer:	50% to 65% Males: 1.2%	40% to 55% Males: Up to 9%
Pancreas cancer:	1-3%	2-7%
Ovarian cancer:	40% to 65%	15% to 25%
Prostate cancer:	9%	15%

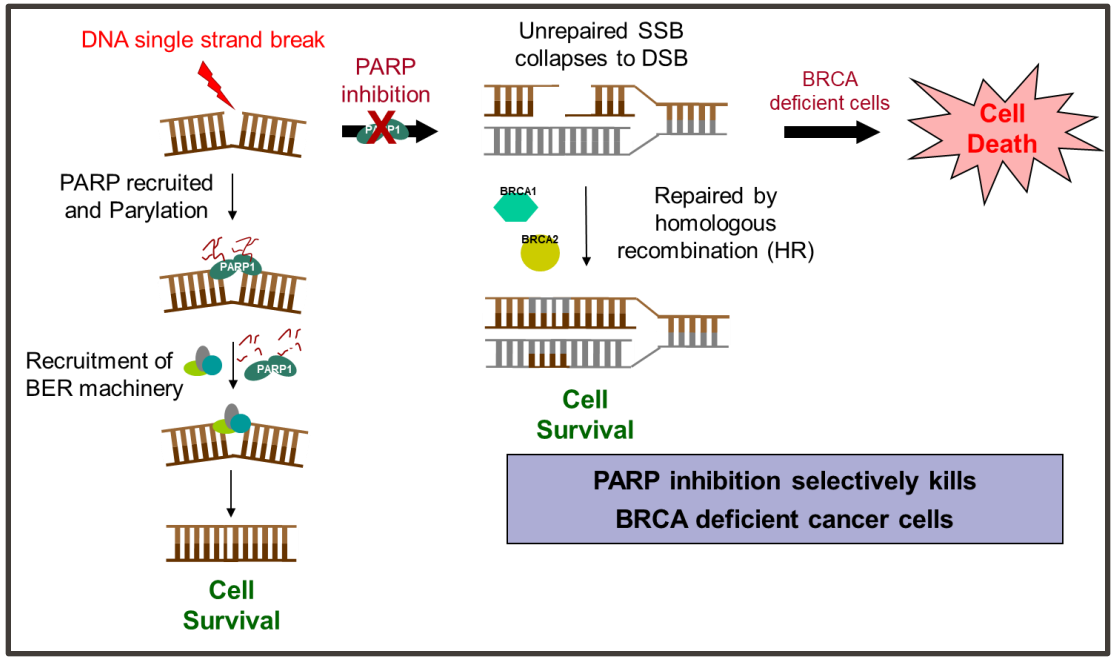
Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Helen E. Bryant[1], Niklas Schultz[2], Huw D. Thomas[3], Kayan M. Parker[1], Dan Flower[1], Elena Lopez[1], Suzanne Kyle[3], Mark Meuth[1], Nicola J. Curtin[3] & Thomas Helleday[1,2]

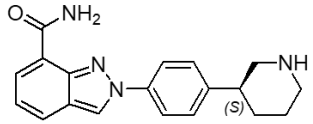
Nature, April 2005.

Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy

Hannah Farmer[1,2*], Nuala McCabe[1,2*], Christopher J. Lord[2*], Andrew N. J. Tutt[2,3], Damian A. Johnson[2], Tobias B. Richardson[2], Manuela Santarosa[2†], Krystyna J. Dillon[4], Ian Hickson[4], Charlotte Knights[4], Niall M. B. Martin[4], Stephen P. Jackson[4,5], Graeme C. M. Smith[4] & Alan Ashworth[1,2]



EVENTUALLY YOU WILL HAVE A THERAPEUTIC WITH ALL THE DESIRABLE ATTRIBUTES



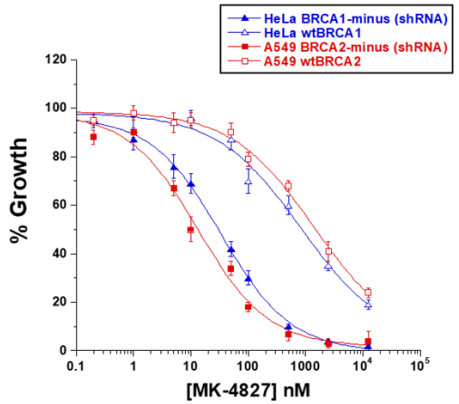
MK-4827

PARP-1 IC_{50} (nM)	3.8
PARP-2	2.1
PARP-3	1300
v-PARP	330
TANK-1	570
PARylation EC_{90} (nM)	45
BRCA1- CC_{50} (nM)	33
BRCA1wt CC_{50} (nM)	860

25-fold

Rat PK

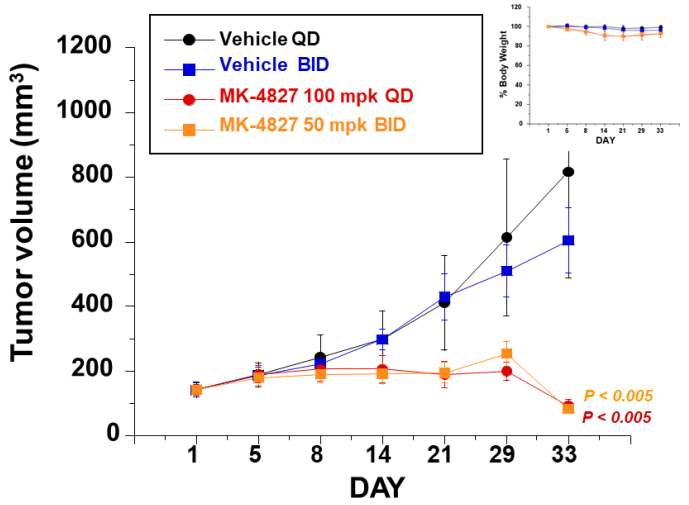
Cl (mL/min/kg)	28
F (%)	65



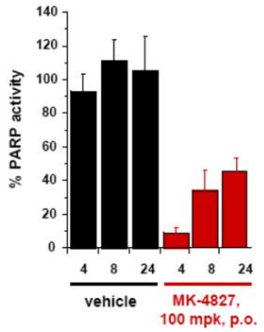
	CC_{50}(nM)
HeLa BRCA1-minus (shRNA)	33
HeLa BRCAwt	860
A549 BRCA2-minus (shRNA)	10
A549 BRCAwt	1,300
UACC-3199 (BRCA1-hypermethylated)	45
BT-20 BRCAwt	2,200
CAPAN-1 (BRCA2-mut)	90
DoTc2-4510 (BRCA2-mut)	23
MDA-MB-436 (BRCA1-mut)	18
SUM149PT (BRCA1-mut)	20
SUM1315MO2 (BRCA1-mut)	20
Renal Epithelial	3,200
Prostate Epithelial	> 5,000
Mammary Epithelial	> 5,000

Predicted human PK - ***Low Cl, Good %F***
High Vd => Long $T_{1/2}$

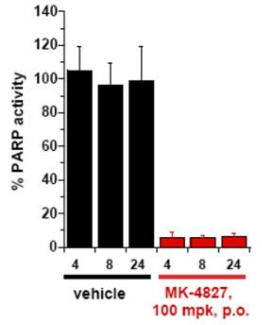
MDA-MB-436 (BRCA1mut) xenograft



Target engagement in PBMCs

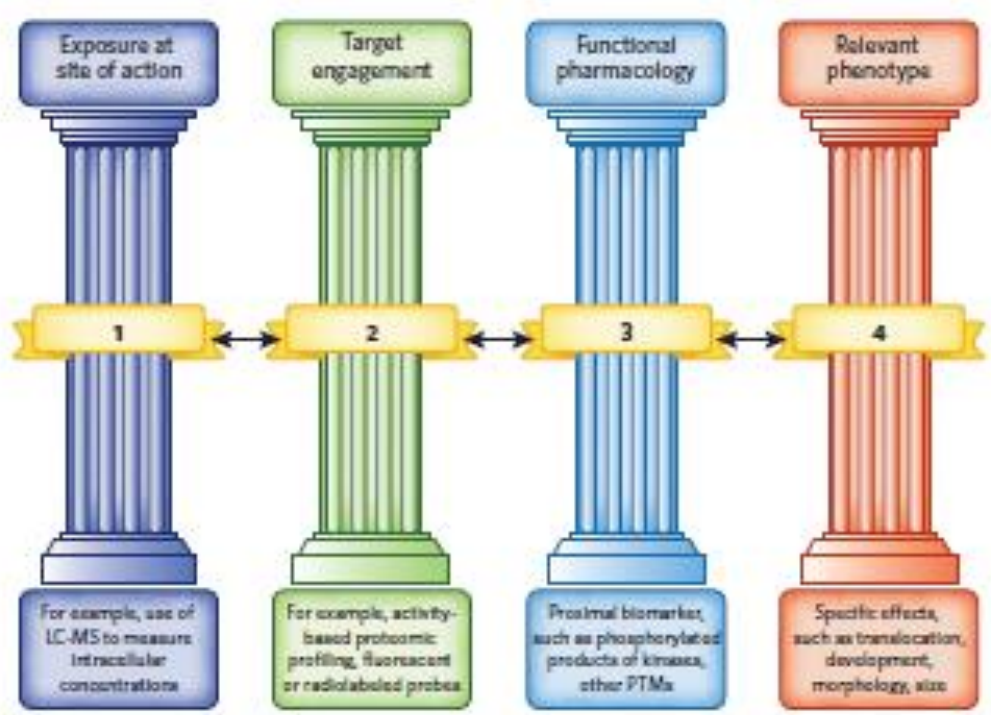


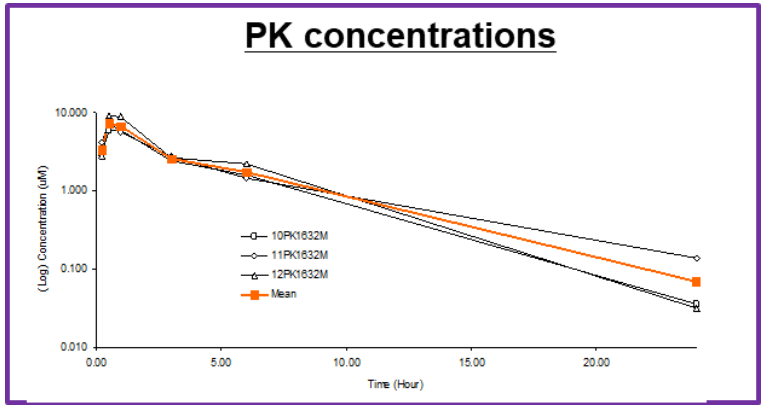
Target engagement in tumor

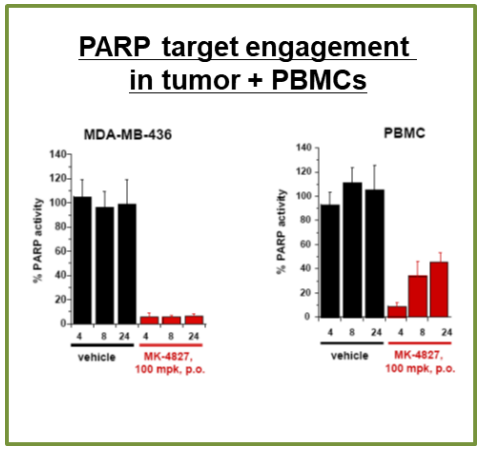


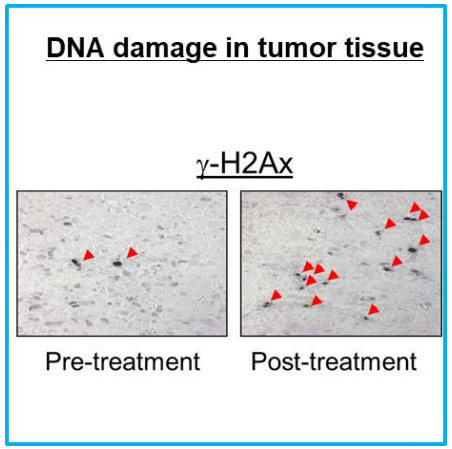
PHARMACOLOGICAL AUDIT TRAIL

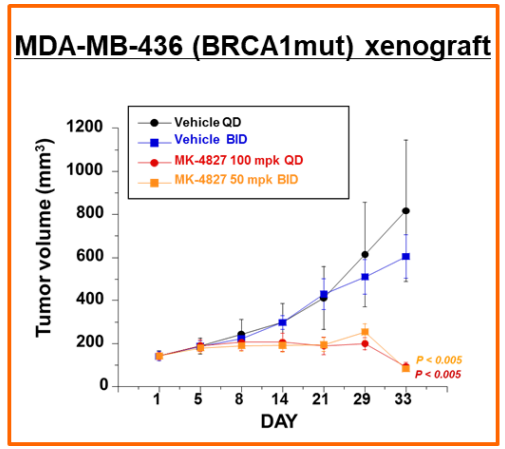
CONNECTS CONCENTRATION OF YOUR DRUG WITH ITS EFFECT











Nature Chemical Biology, 2013, 9, 195

CLINICAL DEVELOP PLAN FOCUSED ON MEDICAL NEED

Ensure test the hypotheses well

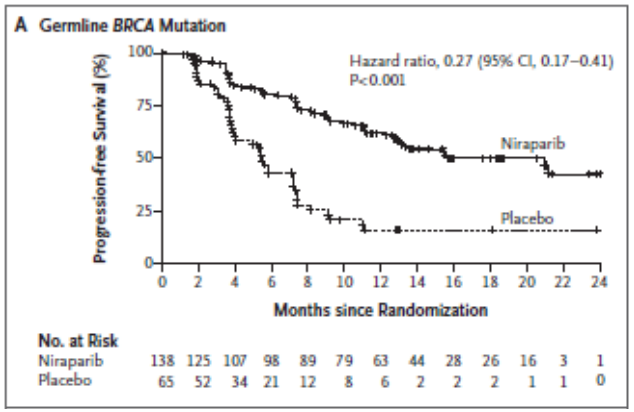
- Well thought out experiment
- Do good science
- Stratify patients
- Quantitative endpoints
- Establish PK - PD – efficacy relationships

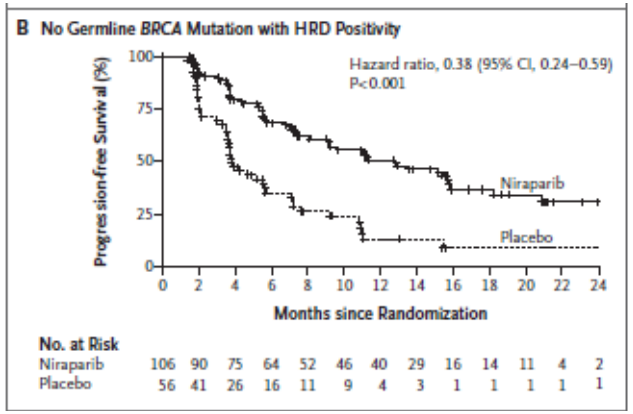
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

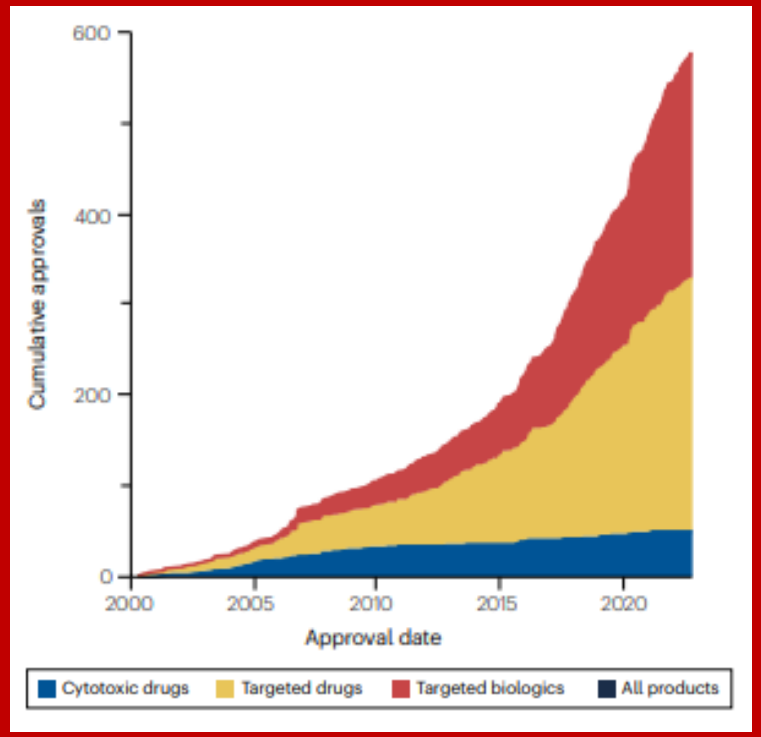
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

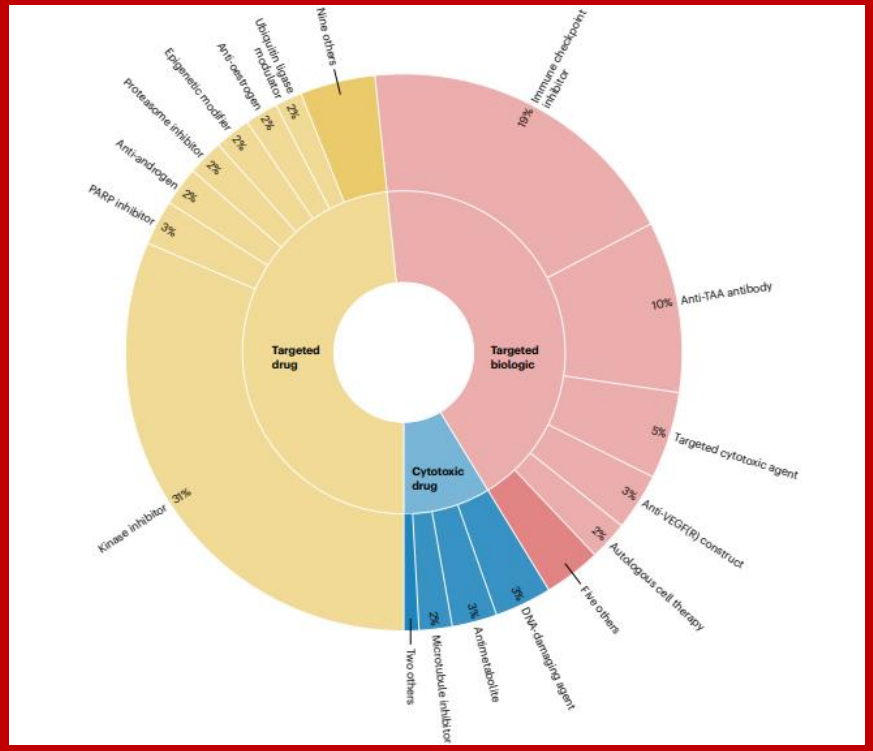
M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, J. Buscema, J.P. Balser, S. Agarwal, and U.A. Matulonis, for the ENGOT-OV16/NOVA Investigators*





LIVING IN GOLD AGE FOR CANCER THERAPEUTIC

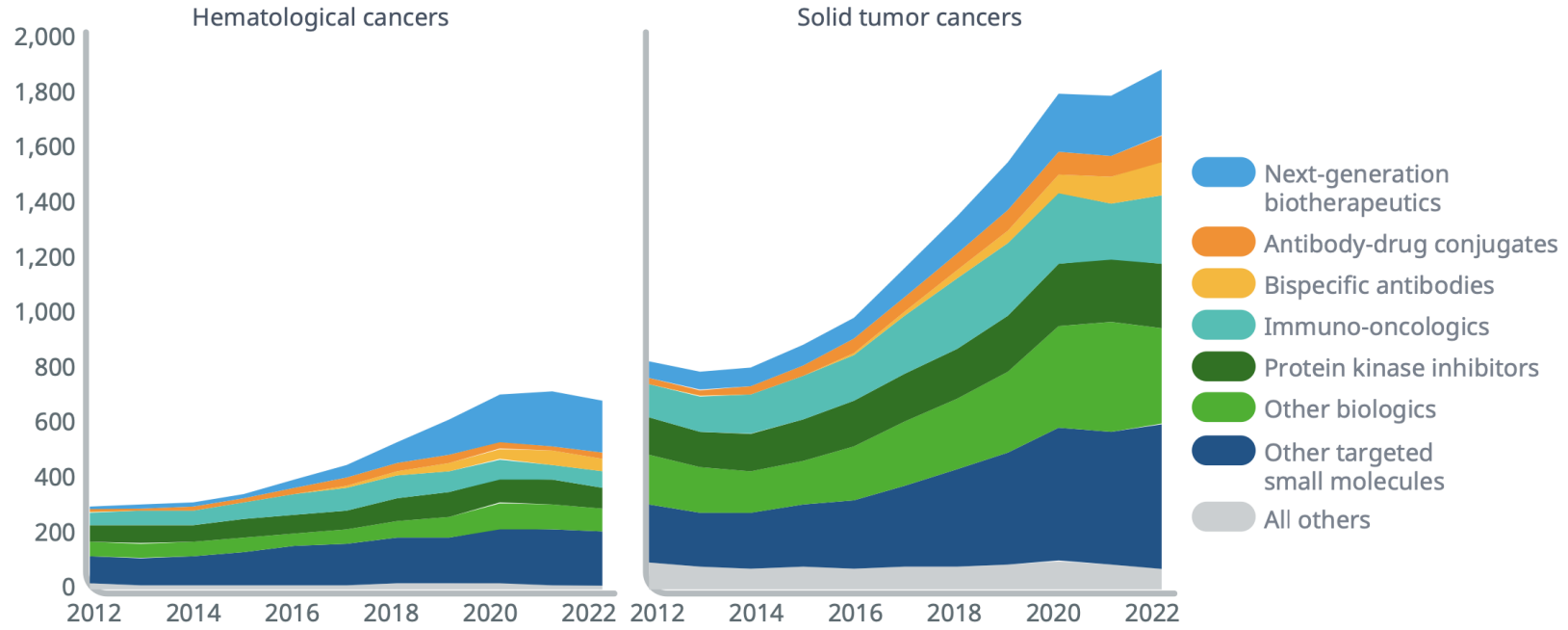




Nature Reviews Drug Discovery, 2023, ***22***, 625

EXPLOSION ON NEW TARGETS AND MODALITIES

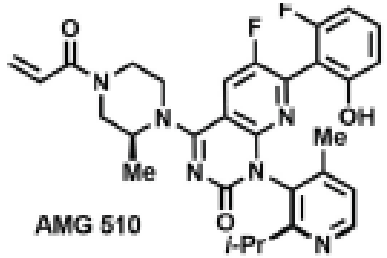
Exhibit 10: Oncology R&D pipeline Phase I to regulatory submission by type, 2012–2022



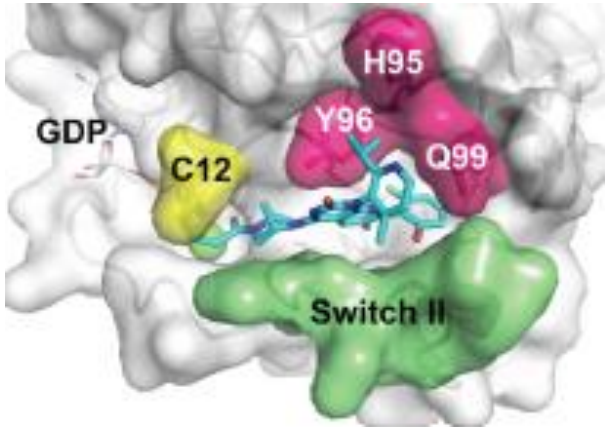
Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Jan 2023.

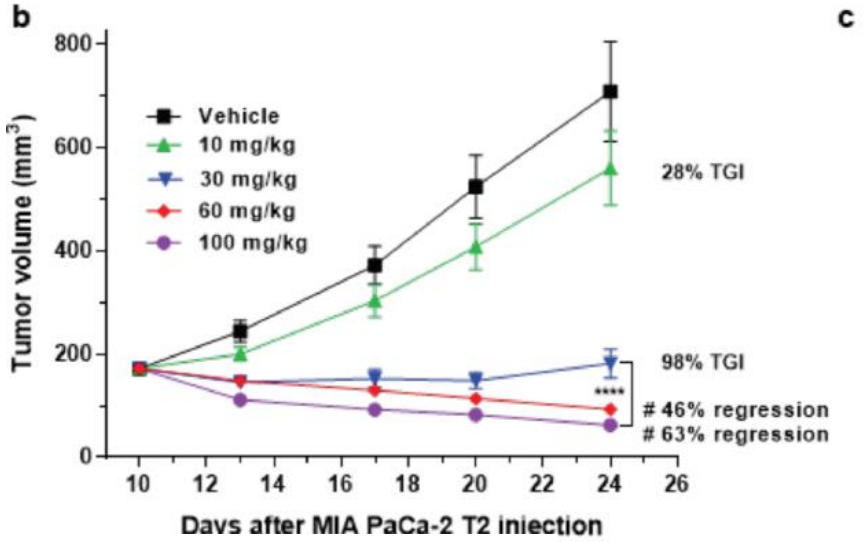
Nature Reviews Drug Discovery, 2023, ***22***, 625

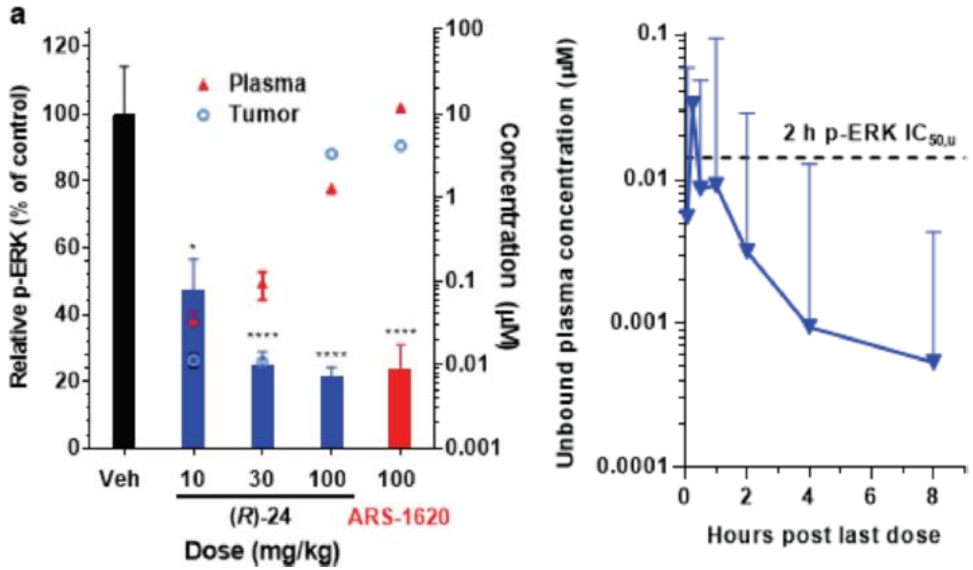
SOTORASIB (AMG-510) – FIRST-IN-CLASS KRAS G12C INHIBITOR



p-ERK IC_{50} (2 h):	68 nM
$KRAS^{G12C}$ k_{inact}/K_i:	9,900 $M^{-1}s^{-1}$
MIA PaCa-2 T2 xenograft:	86% TGI (10 mg/kg), 34% regression (30 mg/kg)

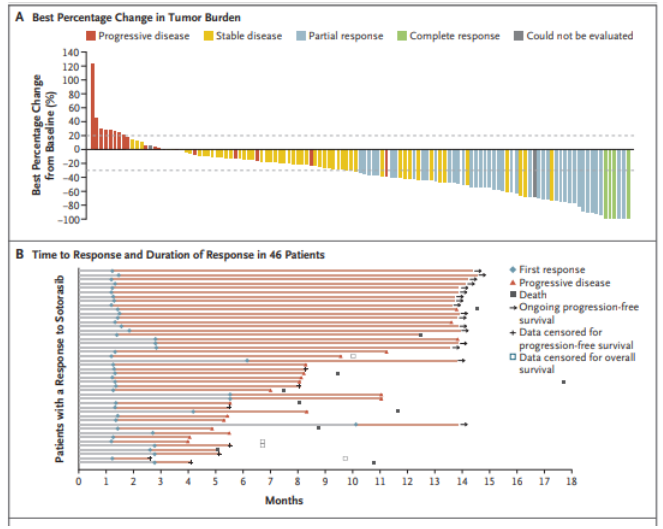






Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

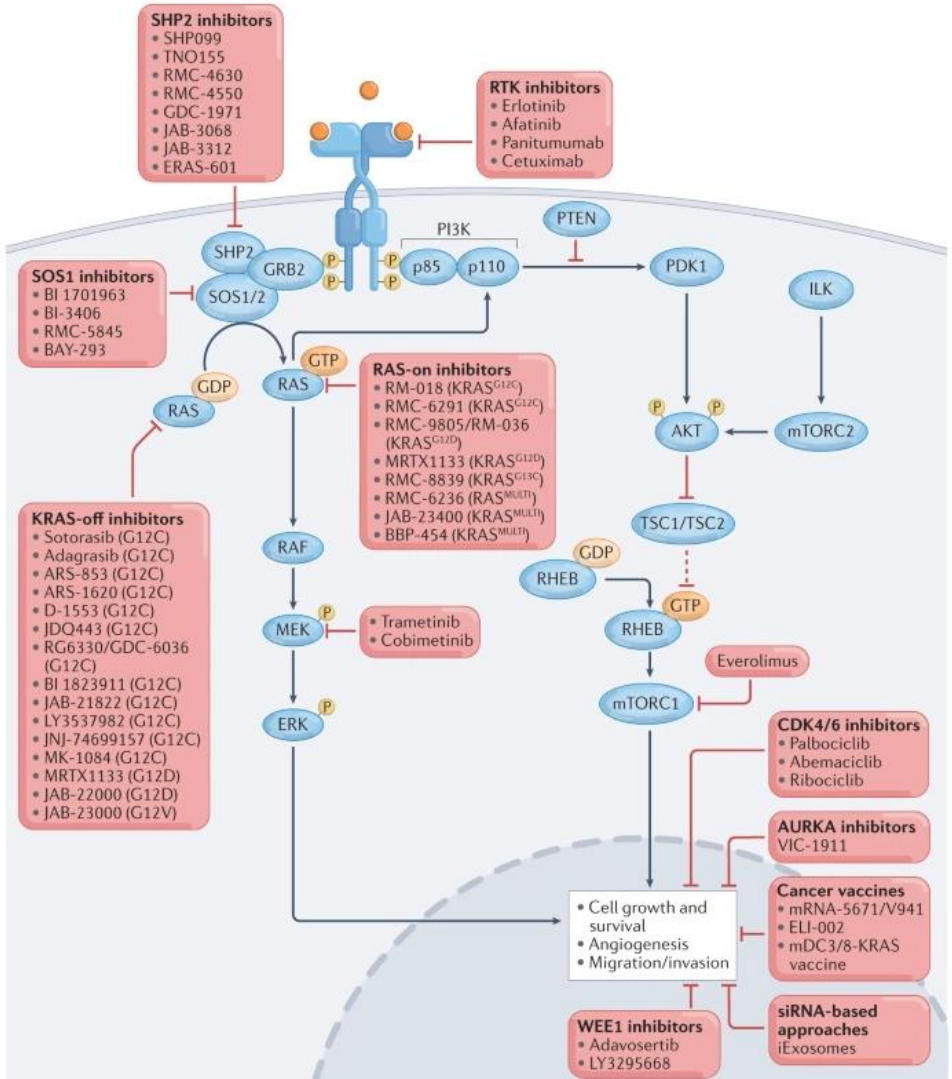
F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan



J. Med. Chem. 2020, 63, 52–65

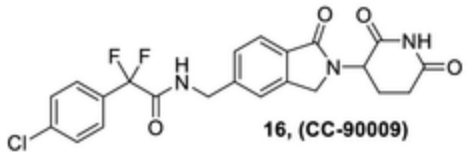
N Engl J Med 2021; 384, 2371-2381

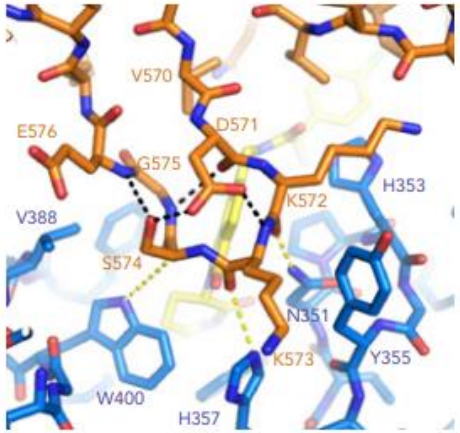
TRIGGERED AN EXPLOSION OF EXCITEMENT IN RAS TARGETING THERAPIES

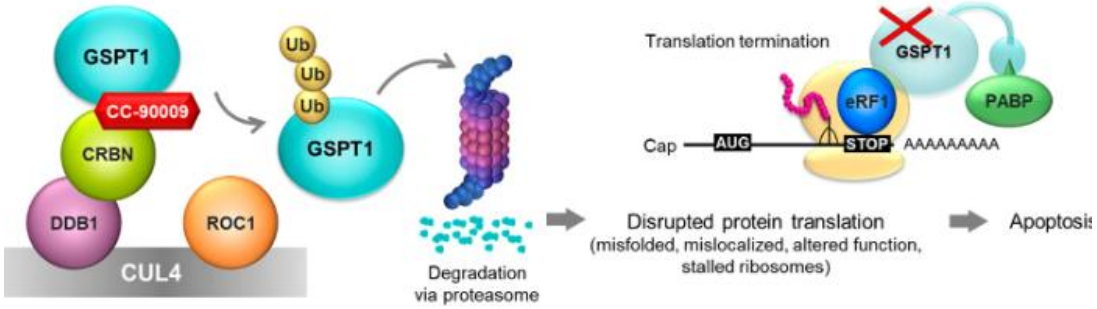


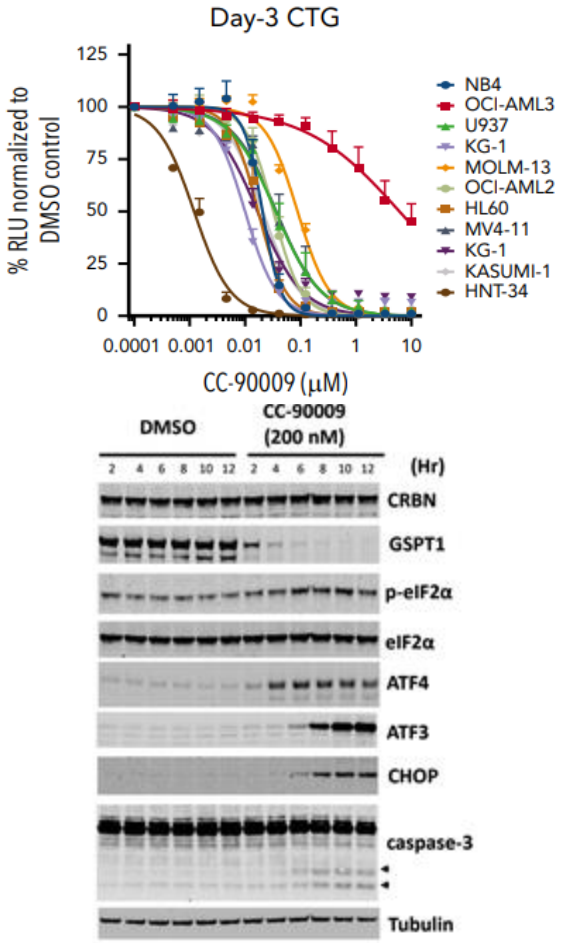
Nature Reviews Clinical Oncology 2022, 19, 637

MOLECULAR GLUES - CC-90009: CEREBLON E3 LIGASE MODULATOR THAT PROMOTES GSPT1 DEGRADATION FOR AML

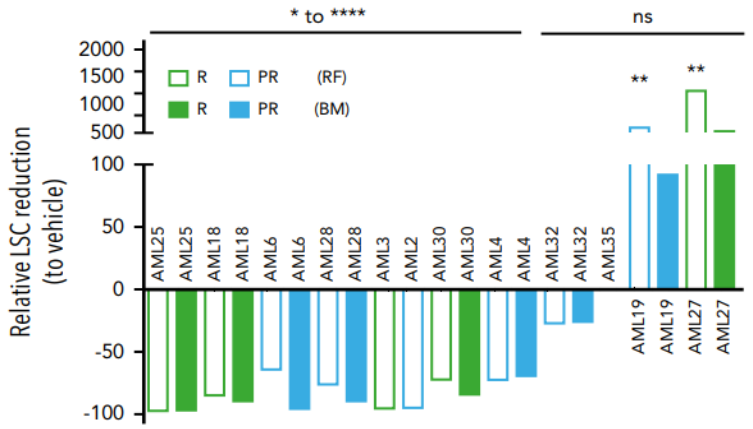






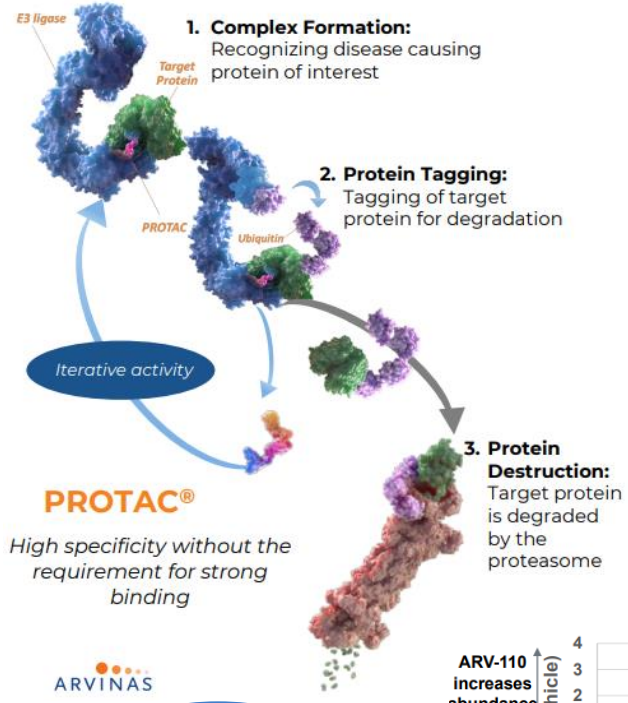


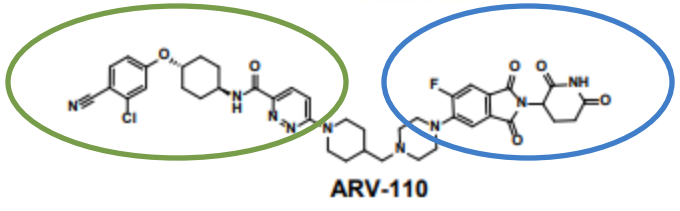
Relative reduction in LSC numbers in mice treated with CC-90009 compared with vehicle

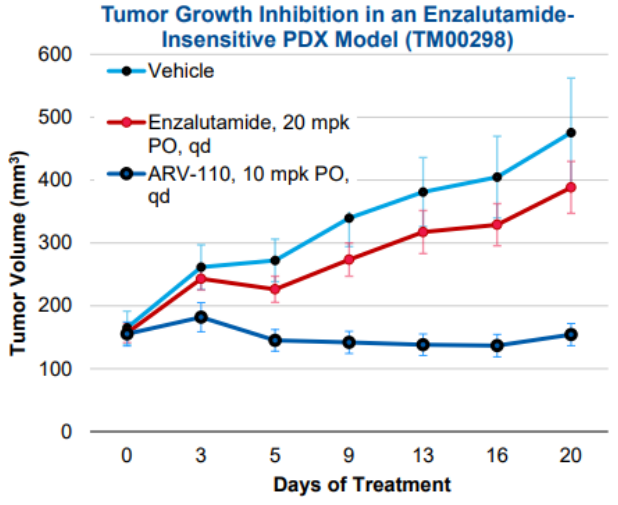


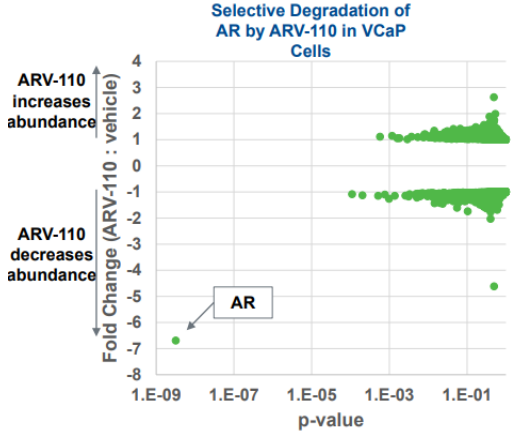
J. Med. Chem. 2021, 64, 1835
Blood 2021, 137, 661

ARV-110 - ANDROGEN RECEPTOR (AR) PROTAC DEGRADER, IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

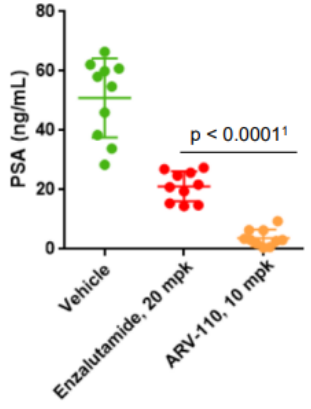




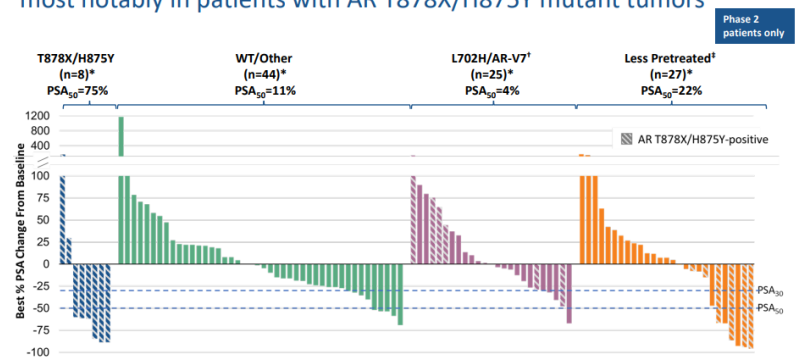




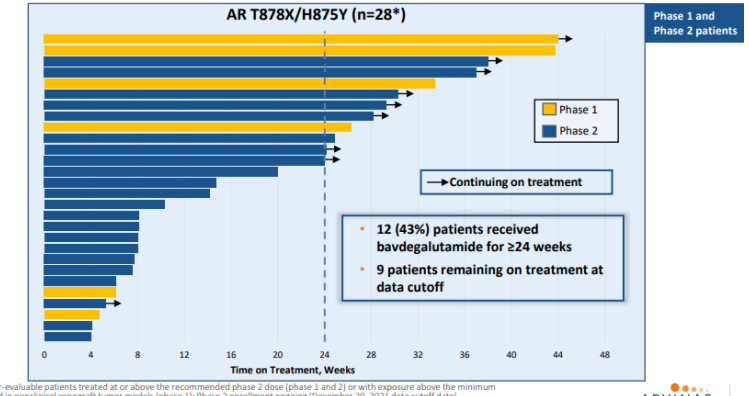
- Plasma PSA levels following ARV-110 treatment significantly decreased vs. mice treated with vehicle or enzalutamide



PSA reductions were seen across all subgroups in the ARDENT trial, most notably in patients with AR T878X/H875Y mutant tumors

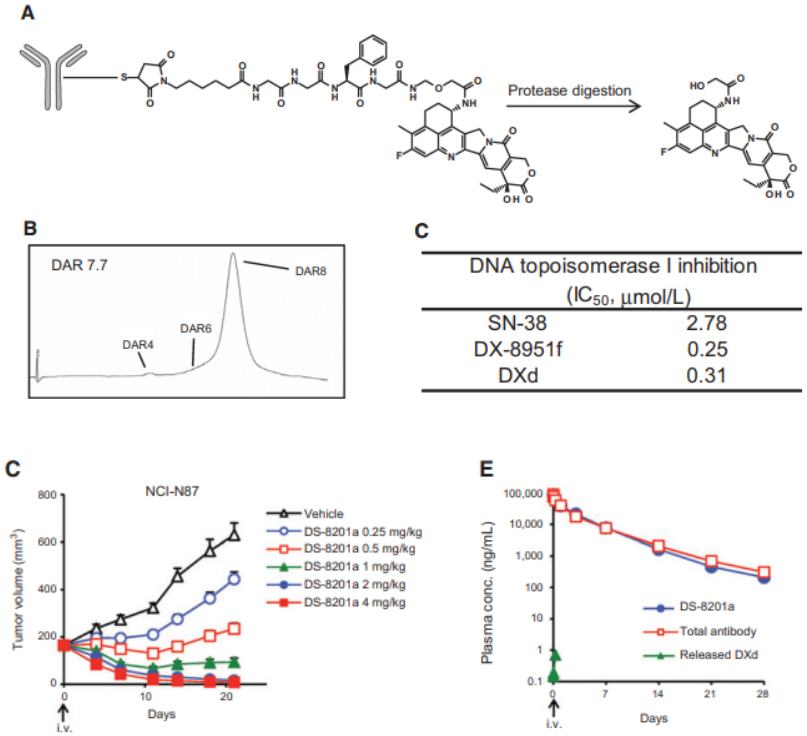


Bavdegalutamide showed robust duration of treatment in Phase 1 and ARDENT trial patients with AR T878X/H875Y mutant tumors

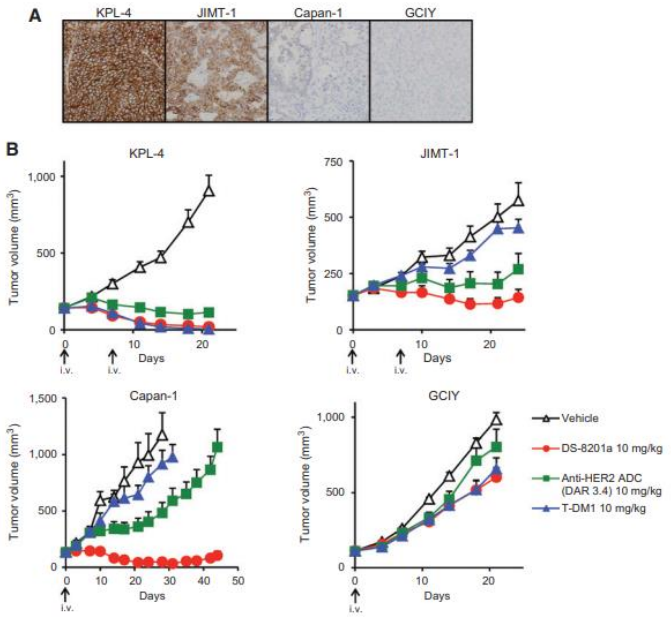


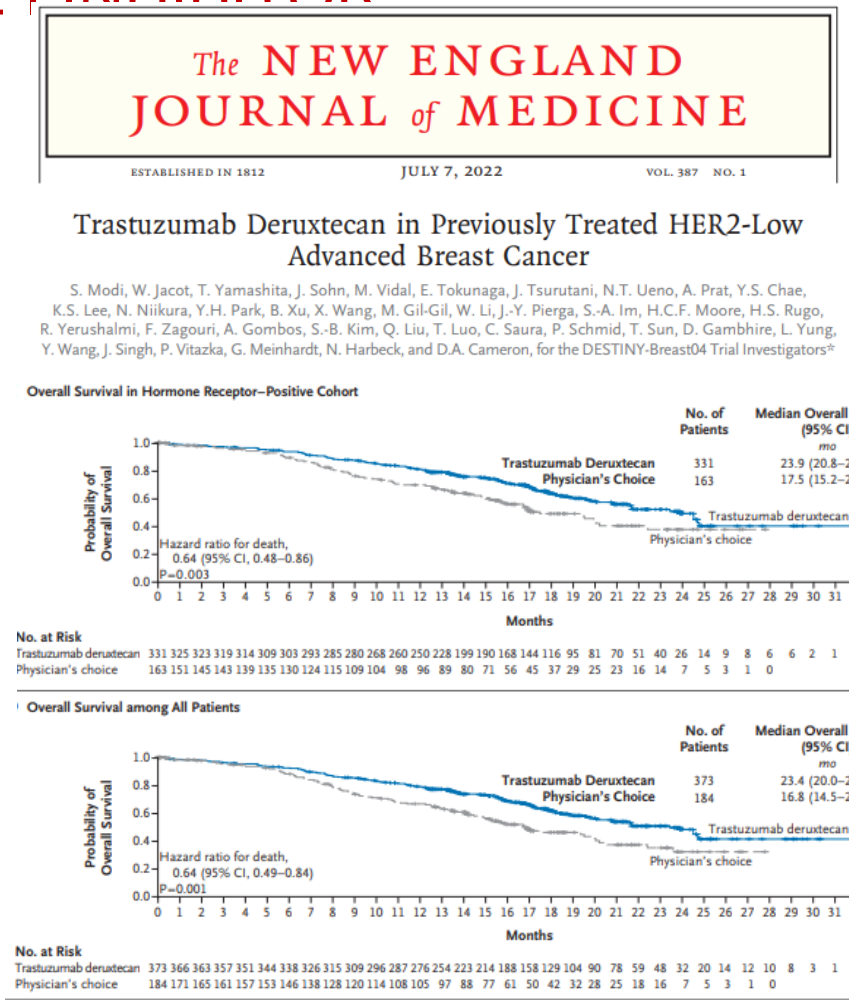
AACR Annual Meeting 2021 and Arvinas website

TRASTUZUMAB DERUXTECAN (T-DXD) FOR HER2-LOW BREAST CANCER - LINKS TRASTUZUMAB, A HER2 MONOCLONAL ANTIBODY, TO DERUXTECAN, A TOPOISOMERASE I INHIBITOR



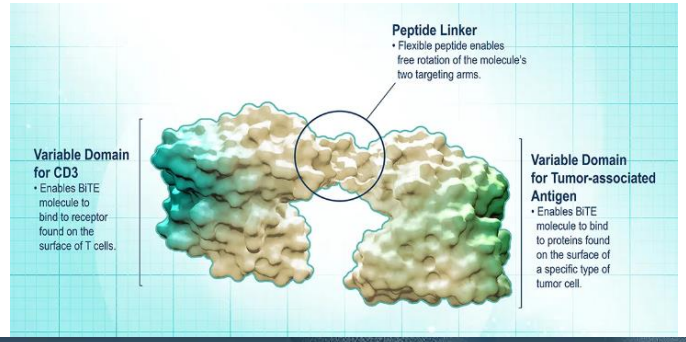
Activity of DS-8201a against tumors with low HER2 levels

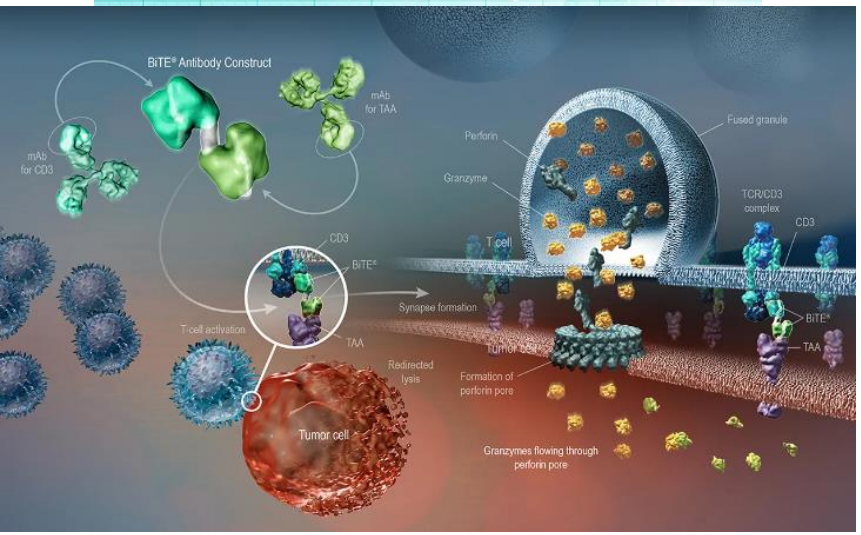




Clin Cancer Res 2016, 20, 5097
N Engl J Med 2022; 387, 9-20

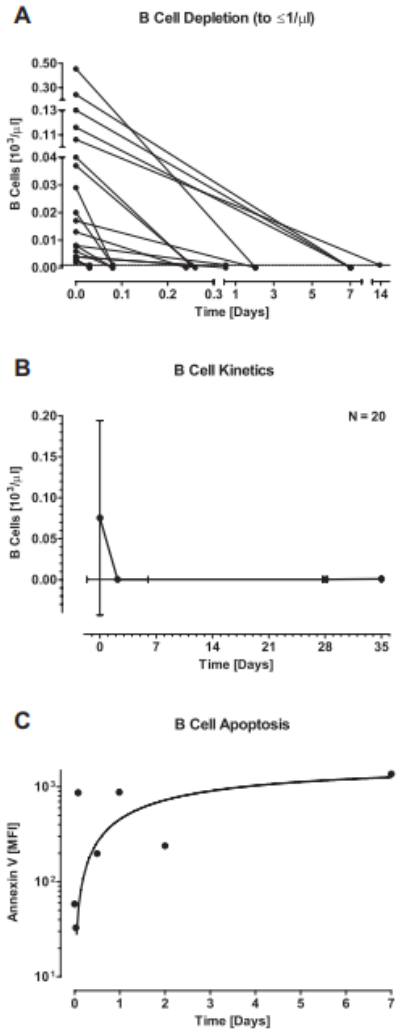
BLINATUMOMAB – CD19 BISPECIFIC T-CELL ENGAGER (BITE)



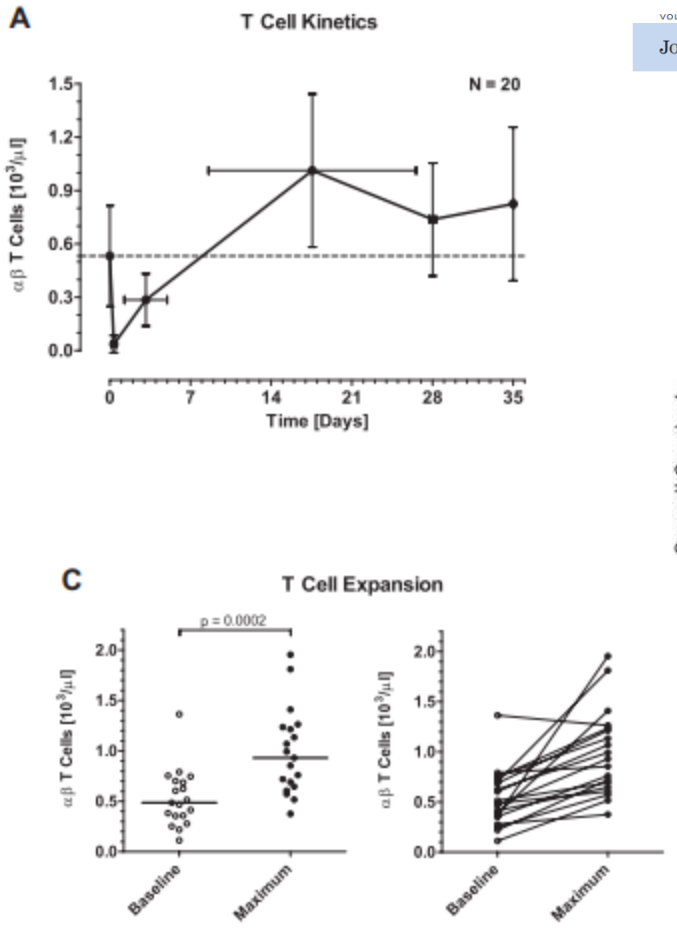


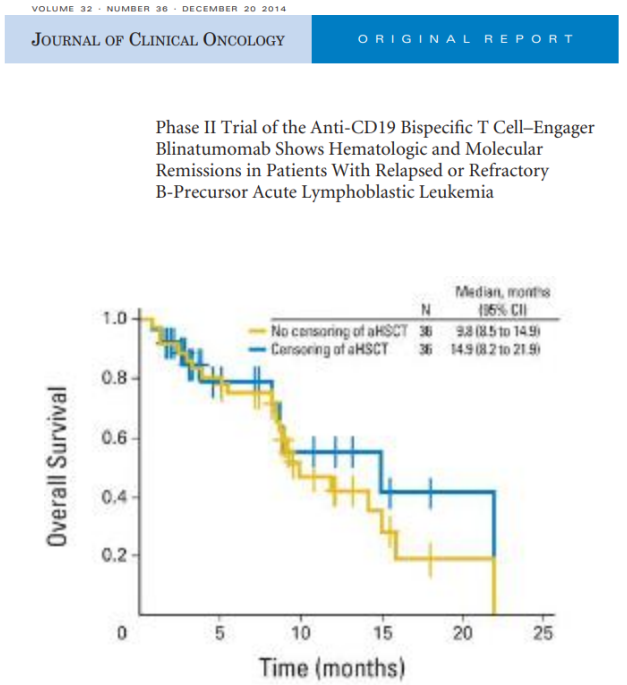
Amgen website

Peripheral B-cell counts and apoptosis



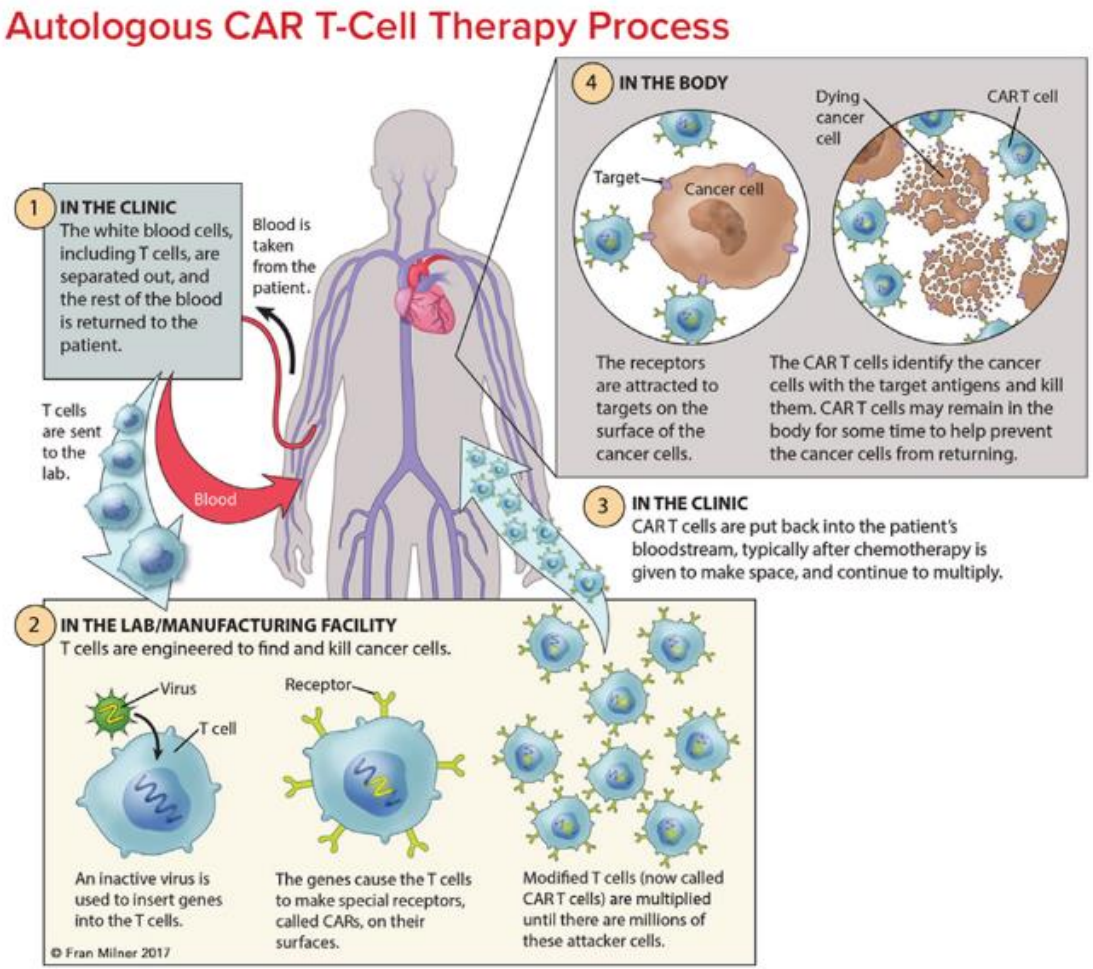
T-cell kinetics



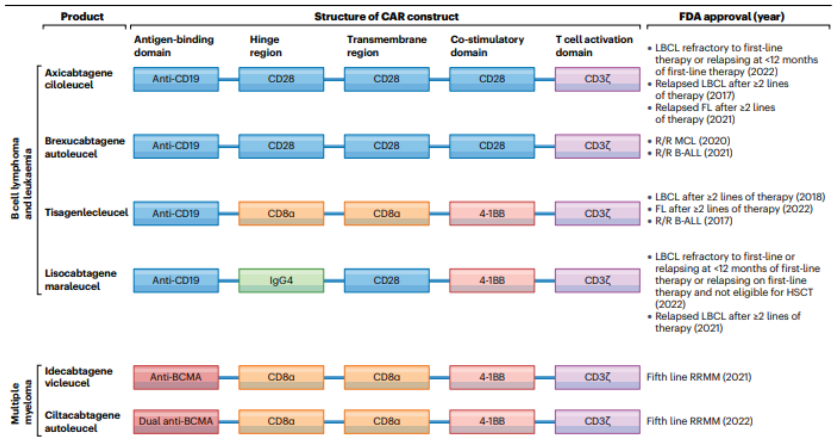


Blood 2012, 119, 6226
J Clin Onc 2014, 36, 4134

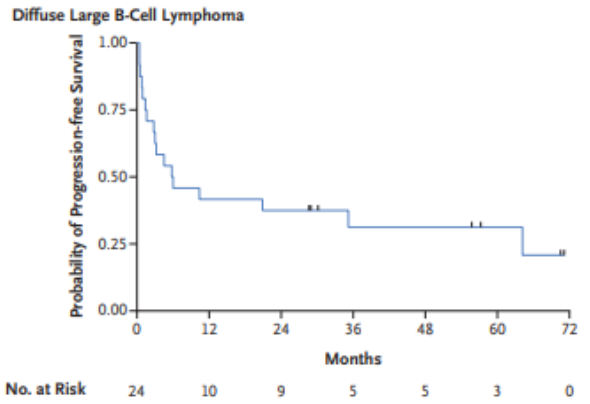
CAR T CELLS: ENGINEERING PATIENTS' IMMUNE CELLS TO TREAT THEIR CANCERS

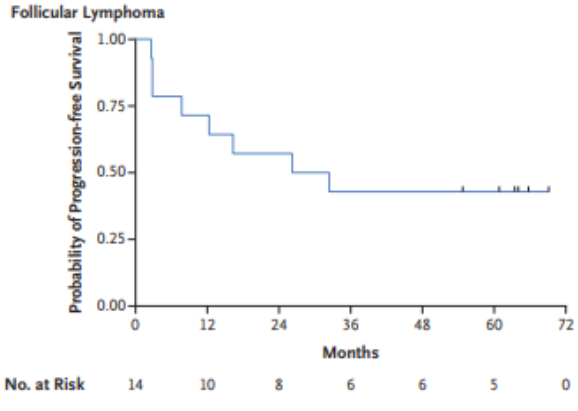


FDA-approved CAR T cell therapies



Five-Year Follow Up to tisagenlecleucel

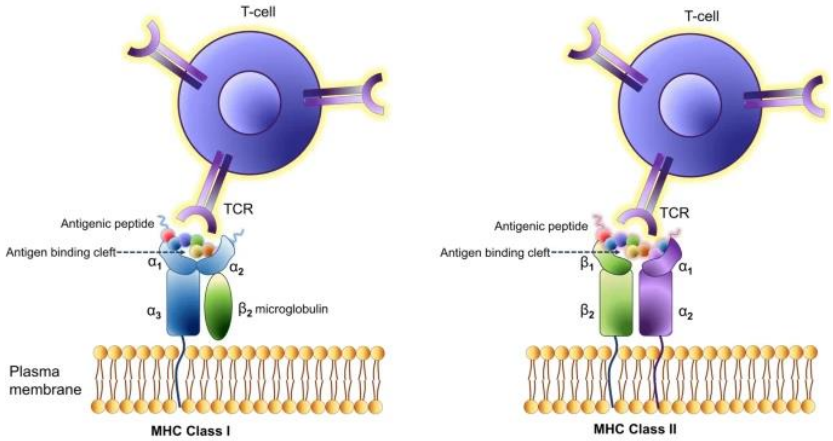




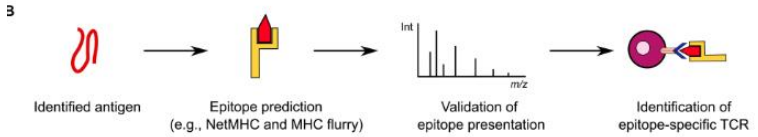
https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

Nature Reviews Clinical Oncology 2023, 20, 359–371. *N Eng J Med*, 2021, 384, 673

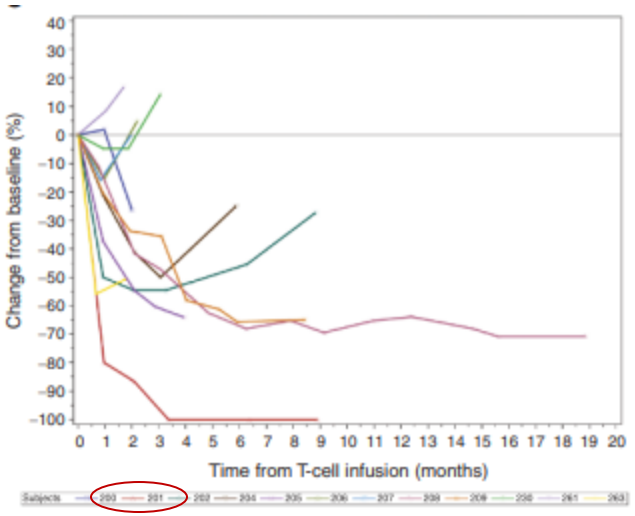
TCR-ENGINEERED T CELL THERAPY IN SOLID TUMORS

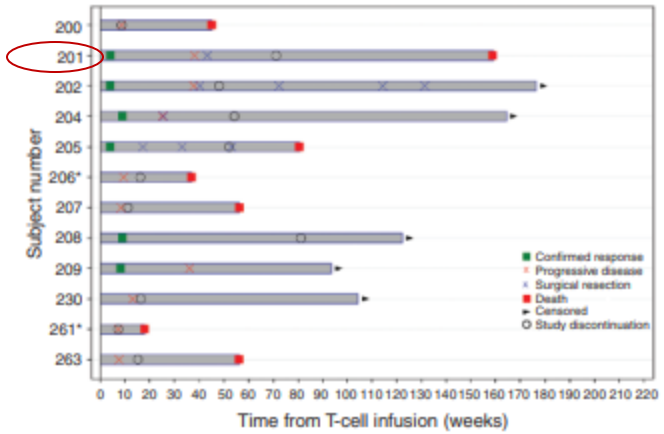


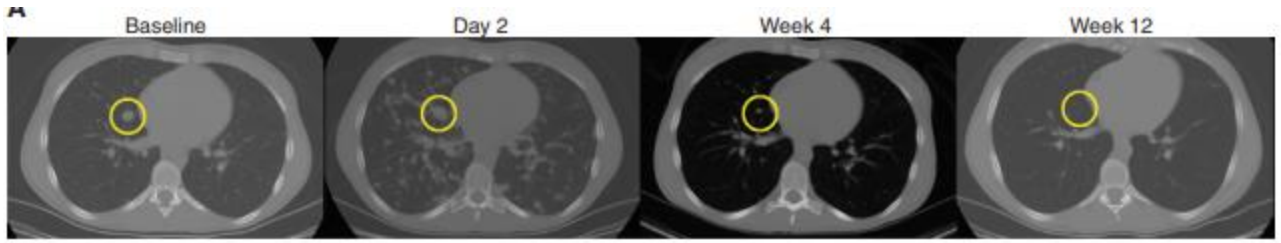
Antigen	Expression in normal tissue	Expression in tumor	Features
Tumor-associated antigen (TAA) Tissue differentiation antigen (TDA) Cancer germline antigen (CGA)		Antigen overexpression	+ Easy assessment of expression profile (RNA-seq, IHC) − Toxicity on normal tissues Potential immune tolerance
Tumor-specific antigen (TSA) Mutation-associated neoantigen Viral antigen Alternative tumor-specific antigen		Tumor-specific expression	+ Tumor-specific, less toxicity Personalized approach − Specific bioinformatic pipeline for alternative antigens



Response of Synovial Sarcoma patients to NY-ESO-1^{c259} T-cell treatment





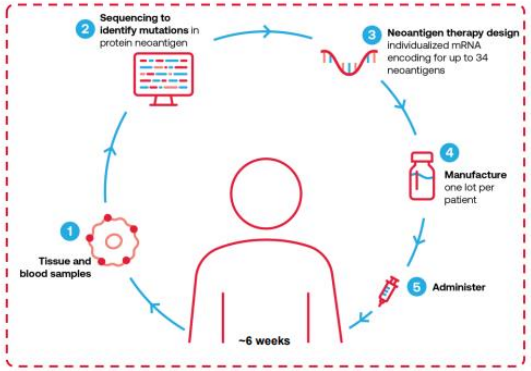


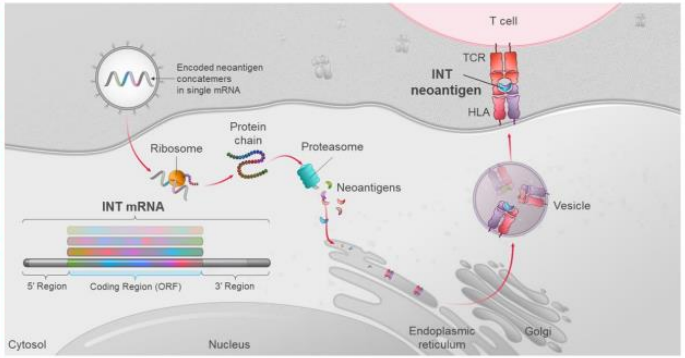
J Hematology and Oncology 2021, 14, 102
Science Advances 2023, 9, 3700
Cancer Discovery 2018, 944

PERSONALIZED CANCER VACCINE, MRNA-4157/V940, TAILORED TO NEOANTIGENS FOUND IN A PATIENT'S TUMOR

mRNA-4157 (V940) Mechanism of Action

- mRNA-4157 (V940) is **an individualized neoantigen therapy** designed to target an individual patient's unique tumor mutations and encodes up to 34 neoantigens[1,2]
- Therapies targeting neoantigens can increase endogenous **neoantigen T-cell responses and induce epitope spreading** to novel antigens with the ability **to drive antitumor responses** and **maintain memory** with cytolytic properties, potentially **producing long-term disease control** for patients[3-7]





mRNA-4157-P201/KEYNOTE-942 (NCT03897881) Study Design

Randomized, phase 2, open-label study in adjuvant resected melanoma patients at high risk of recurrence

Key eligibility criteria
- Resected stage IIIB,[a] IIIC, IIID, or IV cutaneous melanoma
- Complete surgical resection within 13 weeks prior to first pembrolizumab dose
- Disease-free at study entry
- ECOG PS score 0-1
- Tissue available for NGS

2:1 Randomization

Stratified by disease stage[b]

Combination treatment arm: mRNA-4157 (V940) + pembrolizumab
Up to 1 year of pembrolizumab treatment
mRNA-4157 (V940) 1 mg IM Q3W for up to 9 doses + pembrolizumab 200 mg IV Q3W for up to 18 cycles
(n = 107)

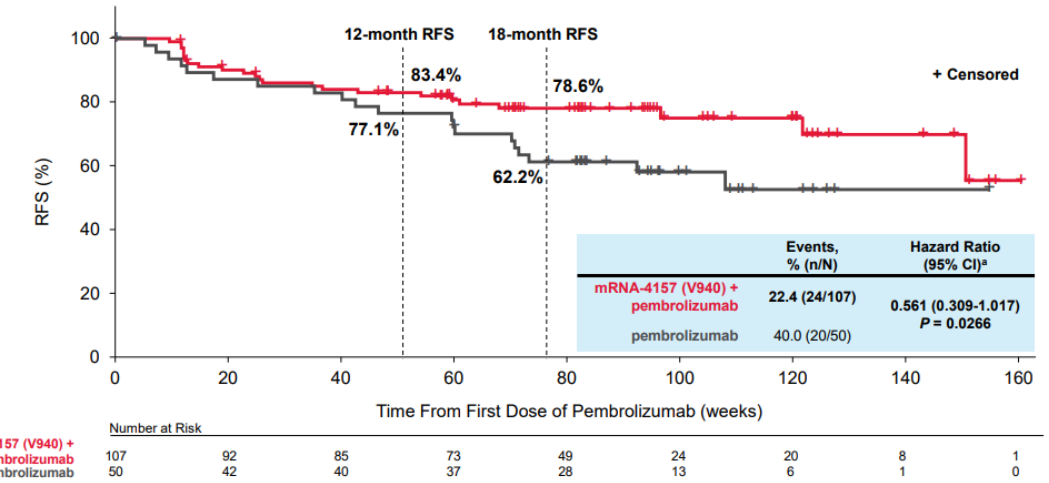
Control treatment arm: pembrolizumab monotherapy
Up to 1 year of pembrolizumab treatment
pembrolizumab 200 mg IV Q3W for up to 18 cycles
(n = 50)

Primary endpoint: RFS[c,d]

Secondary endpoints: DMFS,[e] safety, tolerability

Follow-up: up to 3 years following the first dose of pembrolizumab

Primary Efficacy Endpoint: RFS[1]



Moderna ASCO Investors Presentation

IF YOU ARE INTERESTED IN ADVANCING YOUR SCIENCE AND COMMERCIALIZING, TALK TO YOUR COLLEAGUES

- People who've done it previously
- Your chair and other faculty members
- Your Office Technology Commercialization (OTC)
- BioPharma Community here in Houston and Elsewhere

- Options:
  - **Advance project within your institution** – Internal + External collaborations
  - **Found company with VC** – Small % ownership. Focused effort, Success depends on hiring
  - **License to pharma** – Very small licensing fee, no idea if project will survive portfolio reorgs


THE FUTURE SO BRIGHT

STAY FOCUSED ON UNMET MEDICAL NEED, DO DATA-DRIVEN SCIENCE, AND BE PASSIONATE

THE RESULTS WILL SPEAK FOR THEMSELVES

*Sharon is participating in a clinical trial of MK4827 which is **Merck's PARP inhibitor**. She entered the trial in August 2009 with **4 tumors on her CT scan and CA125 of almost 1,000**. As of her latest follow-up the **four tumors have almost disappeared from her CT scan and her CA125 was 38**. I can confirm from first hand knowledge there are **ZERO side effects** from this PARP inhibitor. Based on my conversations with other researchers conducting trials of other PARP inhibitors, the only side effects reported are mild and the same as cancer symptoms meaning they probably aren't drug related.*

Best of luck to you and yours,

George