Neues vom SABCS (und aus 2024)

Medikamentöse Tumortherapie

Neue Zulassungen und Medikamente

Rudolf Weide
Praxis für Hämatologie und Onkologie
Neversstrasse 5
56068 Koblenz

Übersicht:

- Ribociclib in der Adjuvanz

- Inavolisib beim HR+/Her2- metastasierten Mammakarzinom

- Finden der individuell richtigen Medikamentendosis

- Medikamente der Zukunft

FDA Special Session: new drug approvals

SAN ANTONIO BREAST CANCER SYMPOSIUM

BR

NATALEE Trial Design

FDA

Adults with HR+, HER2-neg EBC at high recurrence risk, defined as:

- Anatomic Stage Group IIB-III, or
- Anatomic Stage Group IIA that is either:
  - Node positive or
  - Node negative, with:
    - Histologic grade 3, or
    - Histologic grade 2, with any of the following criteria:
      - Ki67 ≥ 20%
      - High risk by gene signature testing

R
1:1

Ribociclib 400 mg (3 wks on/1 wk off) +
NSAI (anastrozole 1 mg or letrozole 2.5 mg) +/- goserelin 3.6 mg
(N=2549)

Stratification:

- Anatomic Stage
- Prior treatment
- Menopausal status
- Region of the world

Treatment duration:

- Ribociclib: up to 36 months
- NSAI: up to 5 years

Primary Endpoint:

- local iDFS per STEEP 1.0 in ITT

Secondary Endpoint:

- OS (descriptive)

NSAI +/- goserelin
(N=2552)

HR+: hormone receptor positive; HER2: human epidermal growth factor receptor 2; EBC: early breast cancer, iDFS: invasive disease-free survival; ITT: intent-to treat; OS: overall survival

Ribociclib bei frühem Brustkrebs: NATALEE

Studiendesign: Die NATALEE-Studie (Phase-III-Studie, NCT03701334) vergleicht die zusätzliche Gabe von Ribociclib adjuvant über 3 Jahre mit Placebo, jeweils in Kombination mit einem nichtsteroidalen Aromatasehemmer (Letrozol oder Anastrozol) über mindestens 5 Jahre. Die Patientinnen (und Patienten) der Interventionsgruppe nehmen 400 mg Ribociclib täglich in Tablettenform ein, immer für 3 Wochen, gefolgt von 1 Woche Pause. Prämenopausale Frauen und an Brustkrebs erkrankte Männer erhalten zusätzlich ein GnRH-Analogon (Goserelin). Die Teilnehmenden durften vor Studienbeginn bereits bis zu 12 Monate einer (neo)adjuvanten endokrinen Therapie erhalten haben. Außerdem durften sie eine (neo)adjuvante Chemotherapie erhalten haben.

Für wen geeignet: Aufgenommen in die NATALEE-Studie wurden Frauen und Männer mit frühem, Hormonrezeptor-positivem (Östrogen- und/oder Progesteronrezeptor-positiv), HER2-negativem Brustkrebs im Stadium II oder III. Falls im Stadium IIA kein Lymphknotenbefall (N0) vorlag, musste noch Folgendes gegeben sein: hohes Grading (G3) oder aber mittleres Grading (G2) und Ki-67 ≥ 20 % oder aber ein hohes Risiko in einem Genexpressionstest.

Weniger Rückfälle unter Ribociclib: Bei Zugabe von Ribociclib kam es in der bisherigen Nachbeobachtungszeit seltener zu einem Rückfall der invasiven Erkrankung, Tod oder Zweittumor (primärer Studienendpunkt: invasive disease-free survival, iDFS): Zusätzliches Ribociclib reduzierte das Risiko für einen Rückfall der invasiven Erkrankung, Tod und einen Zweittumor um relativ 25,2 %. Absolut führte Ribociclib zu einer Verbesserung des 3-Jahres-iDFS um 3,3 % (90,4 % versus 87,1 % unter Aromatasehemmer allein, Hazard Ratio (HR) 0,75, 95 %-KI 0,62 – 0,91, p = 0,0014, Kaplan-Meier-Schätzungen).

Was bedeutet Hazard Ratio?

Risikoverhältnis, von engl. “hazard”: Gefahr, Risiko, und “ratio”: Verhältnis. Die Hazard Ratio (HR) ist ein Maß zum Vergleich zweier Gruppen im Hinblick auf das Risiko, dass ein bestimmtes Ereignis eintritt. Eine HR von 0,75 bedeutet, dass das betreffende Ereignis (z. B. Nebenwirkung, Todesfall) in der einen Gruppe um 25 % seltener ist als in der Vergleichsgruppe.

Quelle: KID, 10.12.24

FDA Special Session: new drug approvals

SAN ANTONIO BREAST CANCER SYMPOSIUM®

BR

Drug Effects on the Mechanisms of Female Fertility

DRUG CLASS	DRUG PRODUCT	TARGETED PATHWAY	RELEVANT FUNCTION
Immunotherapy Anti-CTL-4, anti-PD-1, anti-PDL1	Ipilimumab, pembrolizumab, nivolumab, atezolizumab	**Enhance infiltration of immune cells and expression of tumor necrosis factor in the ovary**	**Primary hypogonadism, reduction in oocytes, secondary hypogonadism – damage to the HPG axis – impaired production of viable oocytes or sperm**
EGFR/HER Inhibitors	Erlotinib, gefitnib, osimerinib, labatnib, afatinib, neratinib, trastuzumab, pertuzumab, cetuximab	Receptor tyrosine kinases signaling through Ras/Raf/MEK/ERK, PI3K/Aktt/mTor and JAK/STAT pathway; also, direct nuclear translocation	**Oocyte maturation, cumulus expansion and ovulation**
BRAF/MEK inhibitors	Vemurafenib, dabrafenib, encorafenib/trametinib, binimetinib, cobimetnib	Serine/threonine kinase signaling through RAS/RAF/MEK/ERK	Follicle growth, cumulus cell-oocyte complex expansion, oocyte maturation and luteinization
PI3K/Akt/m TOR inhibitors	Rapamycin, temsirolimus, everolimus	PI3K/Akt/mTOR pathways regulate cellular growth, motility, survival, metabolism and apoptosis	Primordial follicle dormancy/ growth activation, granulosa cell proliferation, follicle survival, possible chemoprevention
JAK/STAT inhibitors	Ruxolitinib, fedratnib, tofacitinib, baricitinib	Cytokine signal transduction through STAT phosphorylation, crosstalk withPI3K pathway	Primordial follicle growth activation, follicle survival
BCR-Abi	Imatinib, asciminib	MAPK, PI3K/Akt/mTOR, and JAK/STAT signaling	Primordial follicle survival/apoptosis, possible chemoprotection
CDK4/6 inhibitors	Palbociclib, ribociclib, abemaciclib,	**Cell cycle transition from G1 to the S phase of the cell cycle**	**Ovulation, corpus luteum formation**
PARP inhibitors	Olaparib, rucaparib, niraparib, talazoparib	**DNA repair including single-strand breaks, nucleotide excision repair, non-homologous end joining, homologous repair, and DNA mismatch repair**	**Direct damage and death of primordial follicle oocytes, granulosa cell dysfunction/follicle growth**
Anti-angiogenesis	Bevacizumab, ramucirumab, nintedanib, pazopanib, sorafenib	VEGF, FGF, PDGF receptor tyrosine kinase signaling	Possibly primordial follicle activation, antral follicle growth, corpus luteum function

Source: Modified from Rosario et al (2022) Reproduction and Fertility 3, R147-R162

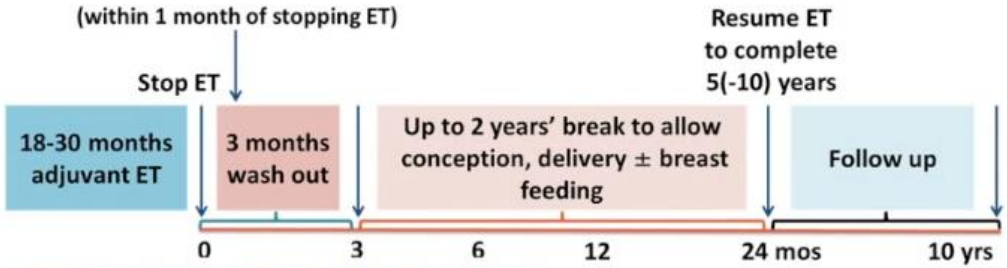
Adapted from Hoberman & Bowman, Oct 2024 FDA-ASCO Workshop on Toxicity in Reproductive Organs

FDA Special Session: new drug approvals

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer

Authors: Ann H. Partridge, M.D., M.P.H., Samuel M. Niman, M.S., Monica Ruggeri, Fedro A. Peccatori, M.D., Ph.D., Hatem A. Azim, Jr., M.D., Ph.D., Marco Colleoni, M.D., Cristina Saura, M.D., Ph.D., +33, for the POSITIVE Trial Collaborators† Author Info & Affiliations



PREGNANCY OUTCOMES – MOST PARTICIPANTS HAD A LIVE BIRTH

	N	% of 497	% of 368
Secondary endpoint population	497	100%	
At least one on trial pregnancy	368	**74%**	100%
At least one live birth (full-term or preterm)	317	**64%**	**86%**
At least one miscarriage	93	19%	25%
At least one elective abortion	16	3%	4%
At least one stillbirth/neonatal death	1/1	0.2% / 0.2%	0.3% / 0.3%

NOTE: 110 women had more than one pregnancy, and may contribute information to more than one row

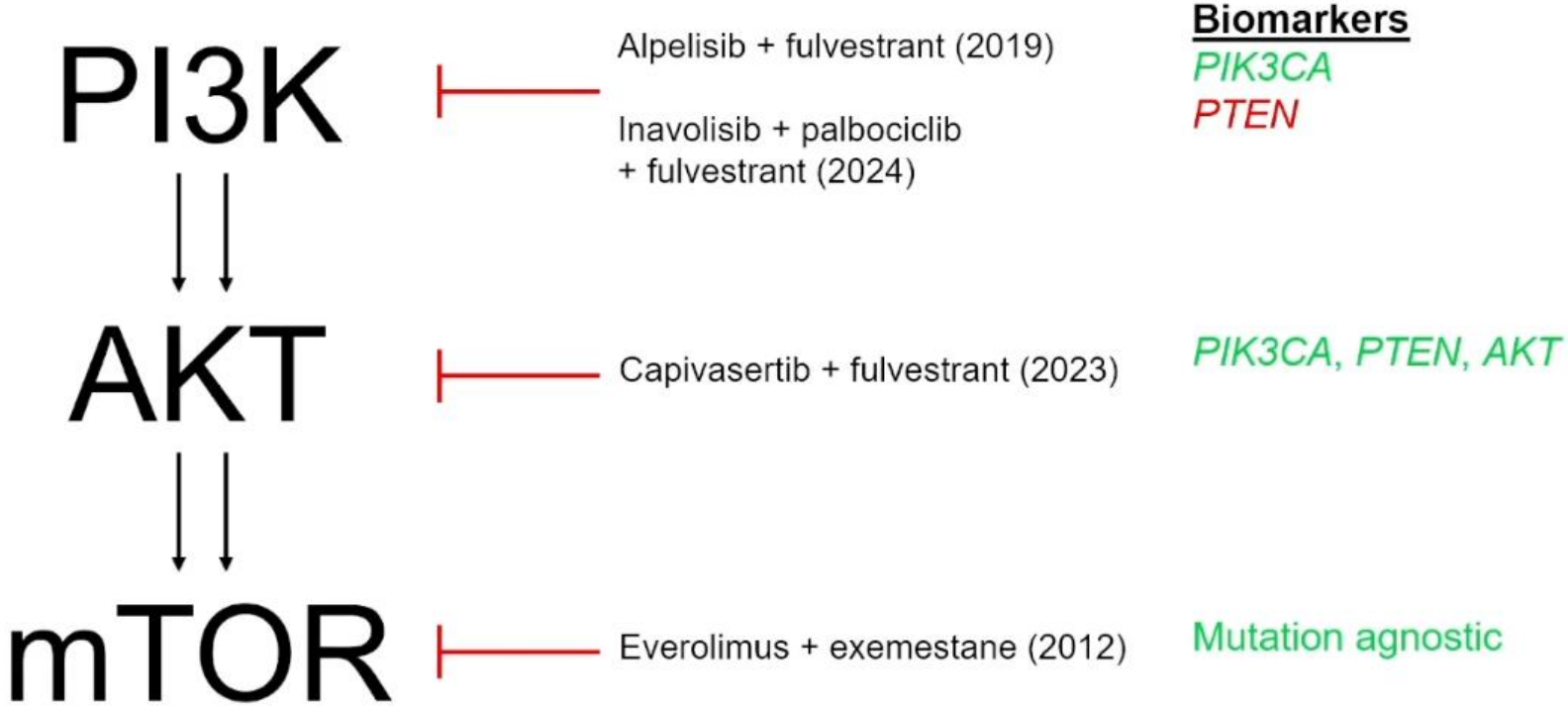
Adapted from Partridge et al, NEJM 2023 PMID 37133584

INAVOLISIB

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Therapeutic symmetry in targeting the PI3K pathway in 2024

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research



SAN ANTONIO BREAST CANCER SYMPOSIUM®

INAVO120 Trial Design

FDA

Enrolled Population

- HR+/HER2 neg advanced/metastatic BC
- PIK3CA mutation in tumor tissue or ctDNA
- Progression during or within 12 mos of completion of adj endocrine tx
- No prior tx for met dz
- No prior fulvestrant, SERD, PI3K, AKT or mTOR inhibitor
- HbA1c<6% and FBG<126

R: 1:1

Inavolisib 9mg QD
palbociclib 125mg QD 21/7
fulvestrant 500mg IM

n=161

Placebo QD
palbociclib 125mg QD 21/7
fulvestrant 500mg IM

n=164

Stratification:

- Visceral disease (y/n)
- Endocrine resistance (primary vs secondary)*
- Region

Primary endpoint:

- PFS by investigator assessment

Key secondary endpoints:

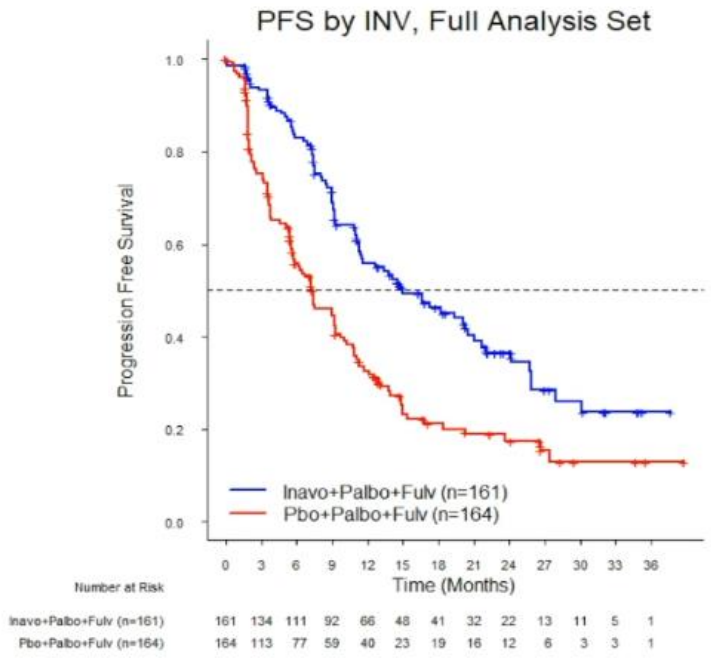
- ORR
- OS

*Primary endocrine resistance: relapse while on the first 2 years of adjuvant endocrine therapy (ET); Secondary endocrine resistance: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Progression Free Survival (INV)

FDA



Endpoint	Inavo + Palbo + Fulv N=161	Pbo + Palbo + Fulv N=164
Number of events	82 (51%)	113 (69%)
Progressions	75 (47%)	105 (64%)
Deaths	7 (4%)	8 (5%)
Median PFS, months (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
HR (95% CI); P-value	0.43 (0.32, 0.59); p<0.001	

PFS by BICR results were supportive of the primary endpoint.
Inavo=inavolisib; Palbo=palbociclib; Fulv=fulvestrant; Pbo=placebo; BICR=blinded independent committee review

SAN ANTONIO BREAST CANCER SYMPOSIUM®

FDA

Adverse Events of Special Interest

- **Hyperglycemia:** 9 pts with grade 3/4 events, no grade 5 events, DKA, HHNK
  - 74 pts tx with oral anti-hyperglycemic; 11 pts tx with insulin
  - Discon in 2 pt, reduction in 4 pts, interruption in 45 pts
- **Stomatitis:** 9 pts with grade 3 events, no grade 4 or 5 events; no SAEs
  - Discon in 1 pt, reduction in 6 pts, interruption in 16 pts
- **Rash:** No grade 3-5 events; no SAEs
  - Discon in 0 pts, reduction in 1 pt, interruption in 2 pts
- **Diarrhea:** 6 pts with grade 3 events; no grade 4 or 5 events, 2 SAEs
  - Discon in 0 pts, reduction in 2 pts, interruption in 11 pts

DKA=diabetic ketoacidosis; HHNK=hyperglycemic hyperosmolar nonketotic coma; discon=discontinuation; pt=patient; tx=treatment; SAE=serious adverse event

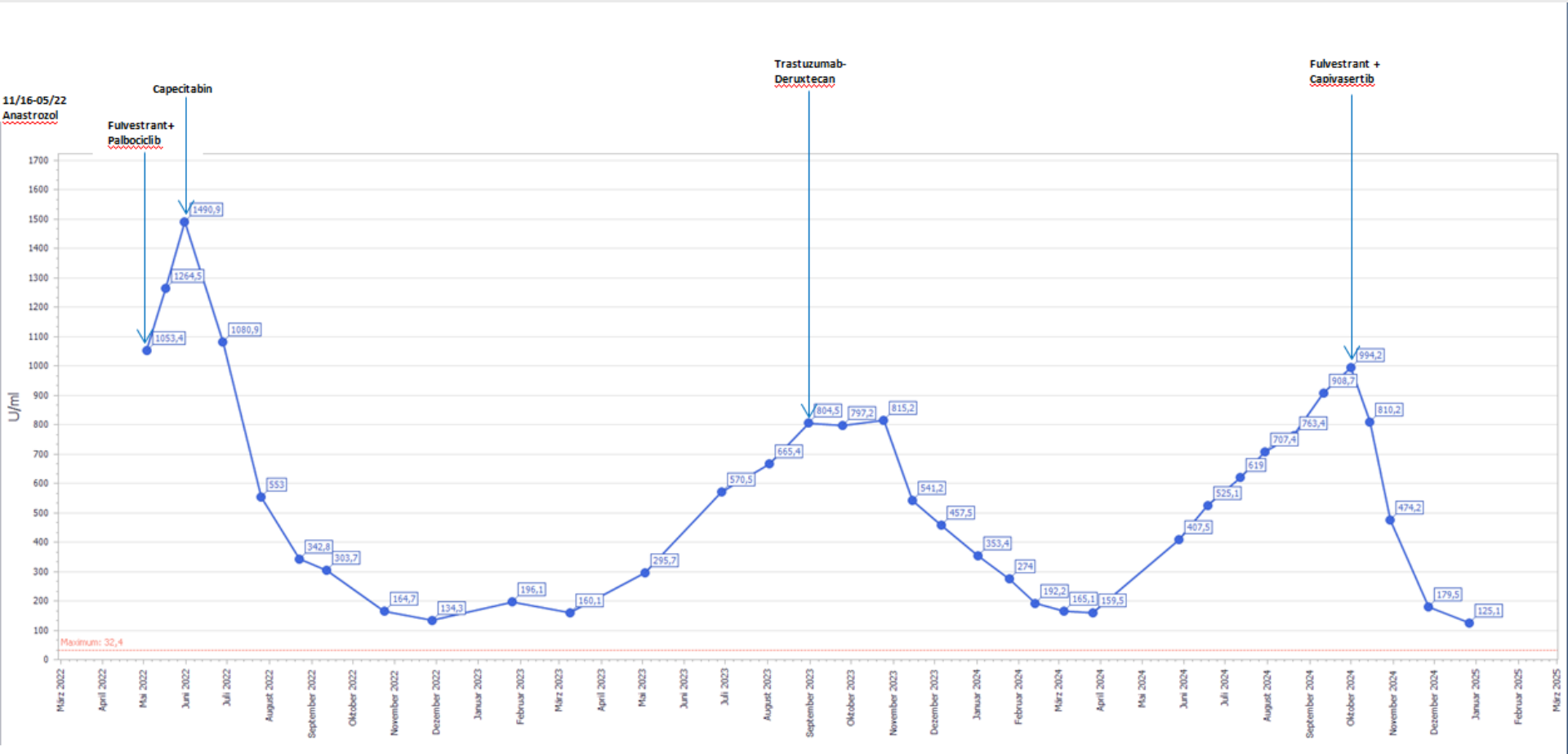
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Patient Reported Outcomes (PROs)

FDA

- Patient-reported tolerability (select PRO-CTCAE items and Modified Bother Index) assessed every two weeks through cycle 3 day 15, then day 1 of every other 28-day cycle.
- Completion rates in both arms were generally high (>80%).
- Treatment with inavolisib showed worsening of patient-reported diarrhea, nausea, vomiting, fatigue, mouth sores, decreased appetite, rash, and overall side effect impact.
- FDA focused on these descriptive tolerability results.

Aktuell: 85-jährige Patientin
-04/22 ED Skelettmetastasierung
-ER 85%, PR 0%, Her2/neu Low (Score 2), PIK3CA-Mutation

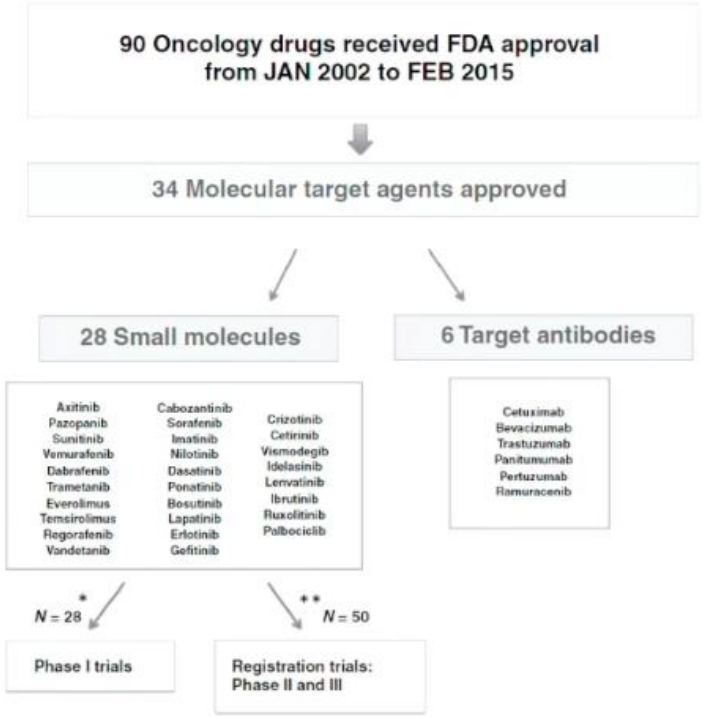


Wie finden wir die individuell richtige Medikamentendosis?

SAN ANTONIO BREAST CANCER SYMPOSIUM

Are we even getting the dose right in phase I?

SAN ANTONIO BREAST CANCER SYMPOSIUM
UT Health San Antonio MD Anderson Cancer Center
AACR American Association for Cancer Research



- Significantly increased G3-4 adverse events with small molecules vs monoclonal antibodies [40% vs. 27%; p=0.038] in phase III studies.
- 9% discontinuation rate

Roda et al, Clin. Cancer Res. 2016

SAN ANTONIO BREAST CANCER SYMPOSIUM

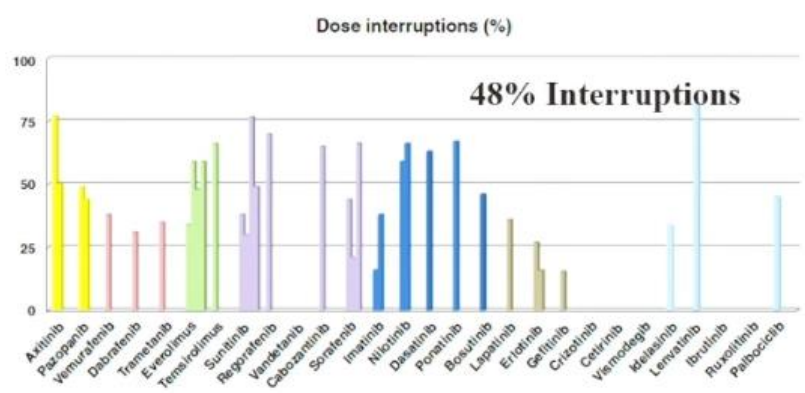
Modalities in Oncology Development

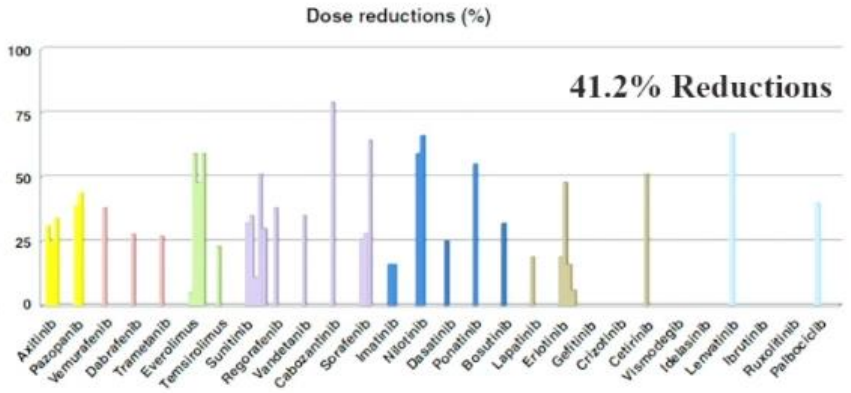
Novel Mechanism of Actions

FIH Dose Selection

SAN ANTONIO BREAST CANCER SYMPOSIUM

45% of patients on small molecules required dose modifications due to drug-related toxicity in phase III trials





Important as combinations will be required for most small molecules to optimize efficacy

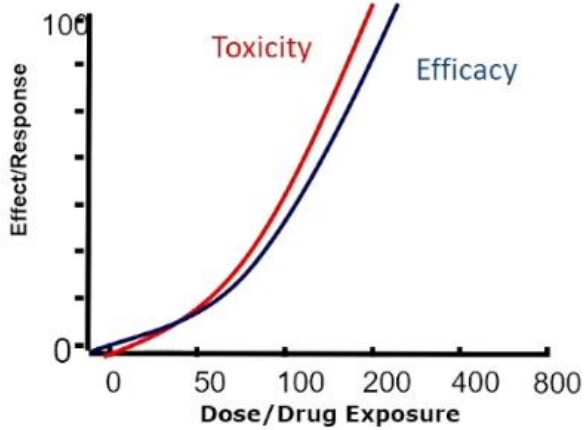
Higher incidence of G3–4 toxicity in phase III trials in combos versus single-agent small molecules (64% vs. 37%; p=0.001).

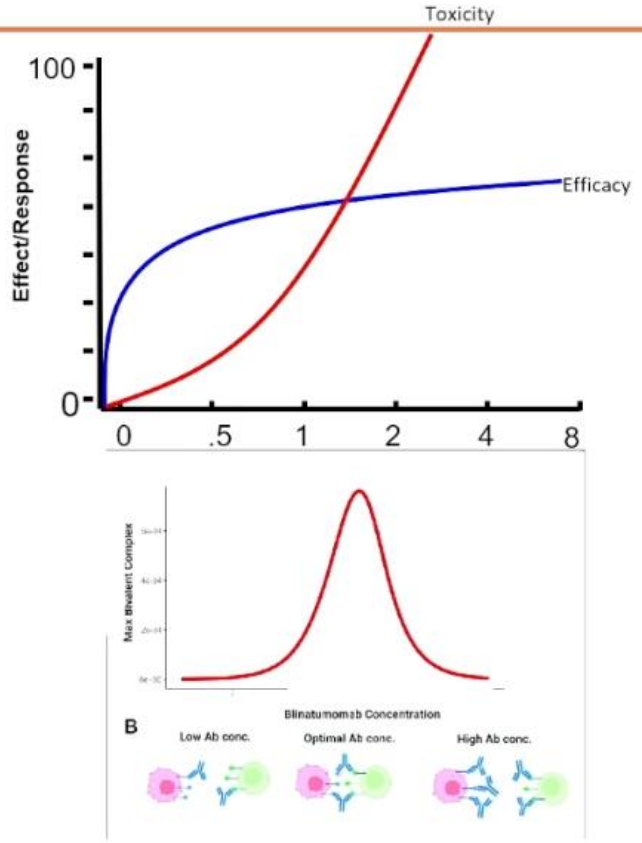
25% SM-MTA Phase I trials recommended Phase II dose below the MTD based on PK/PD data and had fewer dose modifications in subsequent Phase III registration trials (32% vs 50%; RR 0.64; 95% CI 0.43-0.88).

Roda et al, Clin. Cancer Res. 2016

SAN ANTONIO BREAST CANCER SYMPOSIUM

Changing Paradigm





SAN ANTONIO BREAST CANCER SYMPOSIUM®

Capecitabine Phase I Study

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Duration of Treatment

Dose Level, mg/m²/d	No. of Cycles Administered (one cycle = 21 days)	No. of Patients	No. of Cycles Per Patient	
			Median	Range
502	9	3	2	1-6
1,004	13	3	6	1-6
1,657	24	6	5	1-7
2,510	40	9	3	1-12
3,000	42	7	5	2-21+, ongoing at 686+ days
3,514	36	6	4	2-27+, ongoing at 833+ days

Total Patients Treated N=34

DLTs:

1/9

2/6 initial patients

4/6

Mackean et al. JCO. 1998. 16:9

SAN ANTONIO BREAST CANCER SYMPOSIUM®

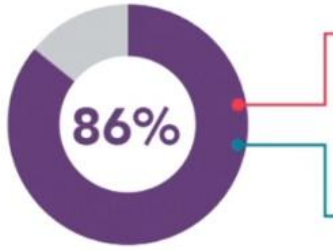
Survey of people living with MBC

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio MD Anderson Cancer Center
AACR American Association for Cancer Research

1,221 patient respondents

Toxicity Is a Significant Issue

Based on a survey[1] of 1,221 patients with MBC:



86% experienced at least one bad treatment-related side effect

20% visited the ER/hospital

43% missed scheduled treatment

83% of patients felt better upon receiving dose reduction for side effect palliation

SAN ANTONIO BREAST CANCER SYMPOSIUM

PCDI: Patient-Centered Dosing Initiative

SAN ANTONIO BREAST CANCER SYMPOSIUM
UT Health San Antonio MD Anderson Cancer Center
AACR American Association for Cancer Research

We are a patient-led initiative created by Anne Loeser in 2019 to question the practice of routinely treating Metastatic Breast Cancer patients **with the highest tolerable dose**.

- MBC isn't curable but can be treated, often for years, in some cases even decades.
- We don't just want to live LONGER. We also want to live WELL.
- Evidence suggests that lower allowed doses of some MBC drugs may be as effective as the Recommended Starting Dose (usually based on MTD).
- Anecdotally, we have seen that several long-term survivors are on reduced doses of medications for various reasons, and that has played a role in how they have been able to tolerate these treatments and stay on these treatments for long periods of time.

Neue Medikamente:

-Glues

-PROTACS (Proteolysis-Targeting-Chimera)

-LYTACS (Lysosome-Targeting-Chimera)

-Biparatopic Antibodies

Educational Session 5: Unlocking New Targets with Molecular Degraders

BRI

SAN ANTONIO BREAST CANCER SYMPOSIUM®

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio Mays Cancer Center

AACR American Association for Cancer Research

DECEMBER 10–13, 2024

HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

Oncology therapeutics discovery:
PROTACs as chemically induced proximity drugs

Stephen M. Hinshaw, Ph.D.
Stanford Cancer Institute
Stanford Dept. of Chemical and Systems Biology
Stanford Center for Therapeutics Discovery
Stanford, CA

Stanford Cancer Institute

Chemical and Systems Biology

Sarafan ChEM-H Stanford University

NIH NATIONAL CANCER INSTITUTE

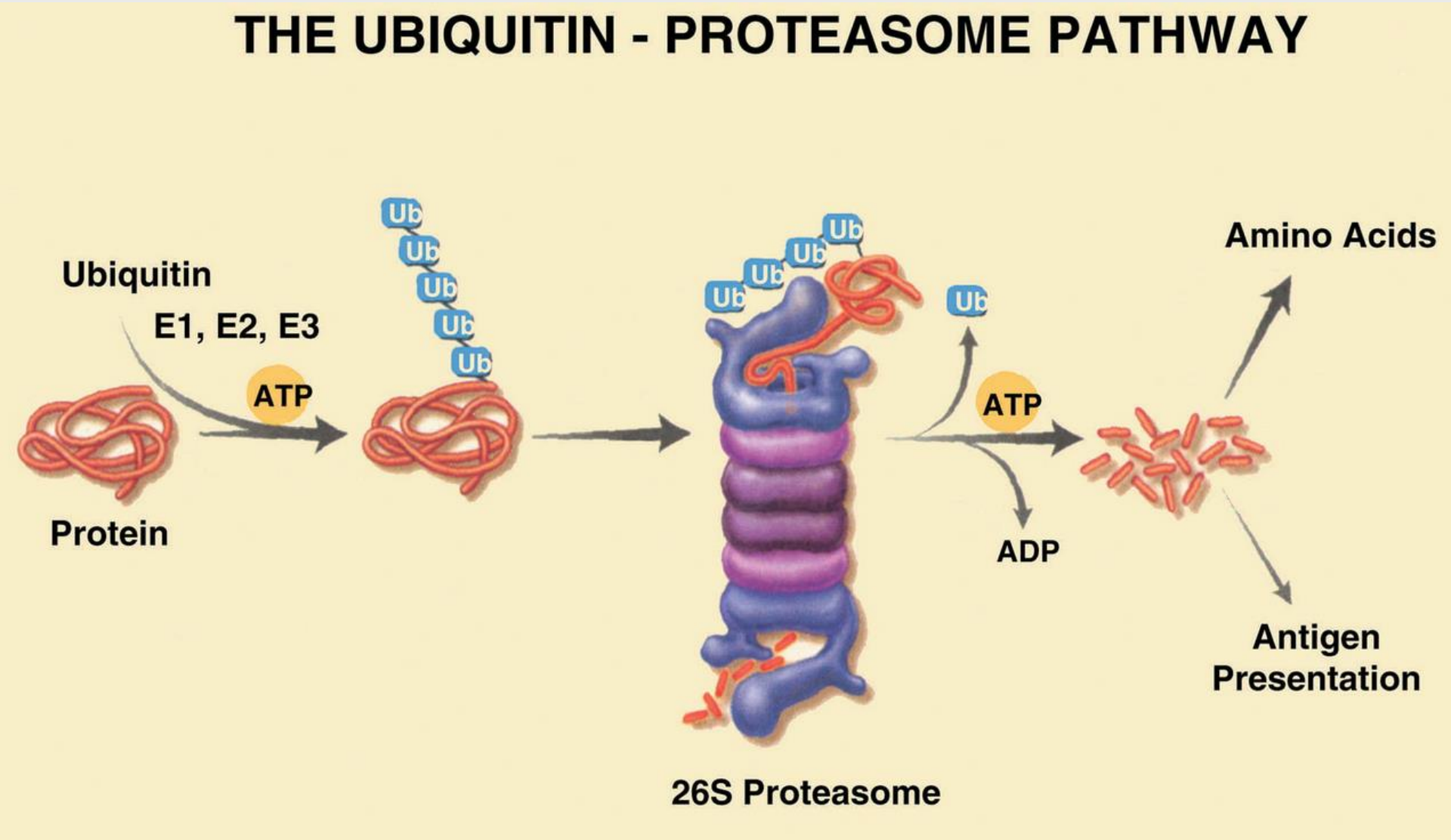
Chemistry & Biology

Volume 8, Issue 8, 2001, Pages 739-758

Review

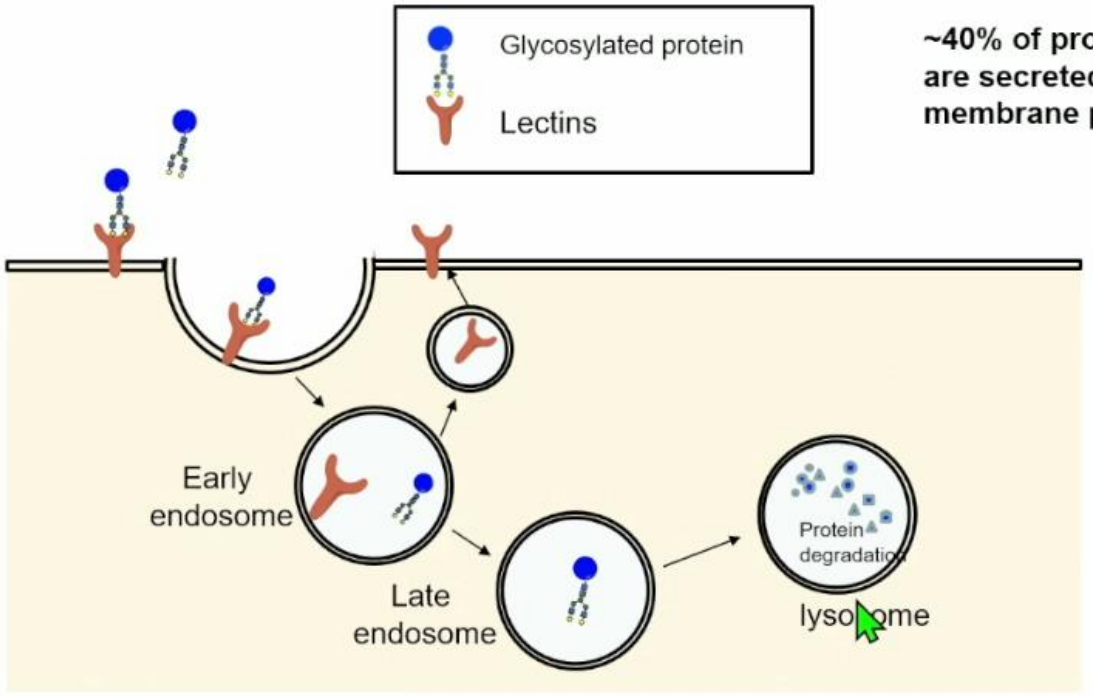
Proteasome inhibitors: from research tools to drug candidates

Alexei F. Kisselev, Alfred L. Goldberg



SAN ANTONIO BREAST CANCER SYMPOSIUM®

Degradation of Extracellular Proteins Mediated by Lectins – A Physiological Process

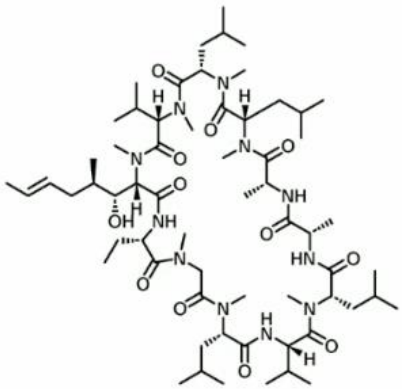


SAN ANTONIO BREAST CANCER SYMPOSIUM®

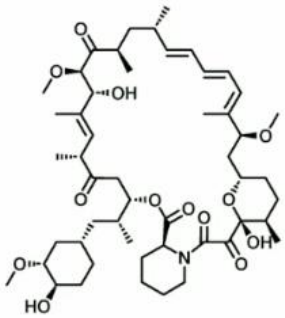
Molecular glues: valuable proximity agents

SAN ANTONIO BREAST CANCER SYMPOSIUM®

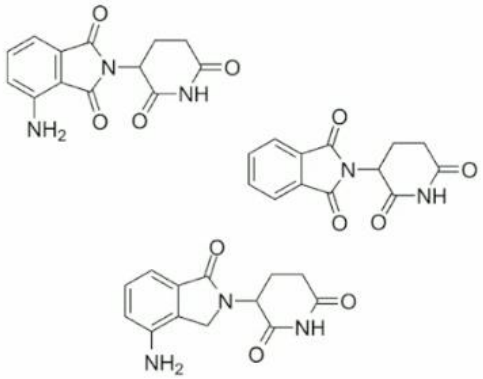
UT Health San Antonio Mays Cancer Center | AACR American Association for Cancer Research



Cyclosporin
FKBP12-Calcineurin
Transplant



Rapamycin
FRB-mTOR
Transplant



Thal-/Len-/Pomalidomide
CRBN- IKZF1/3
Mult. myeloma

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Current Focuses in the Tang Group

LYTACs and Related Degraders

- Lysosomal degradation for extracellular secreted and membrane proteins
- Proteasomal degradation for Intracellular proteins or membrane proteins with a intracellular domain

tissue-specific cell surface receptors and antibody conjugation methods

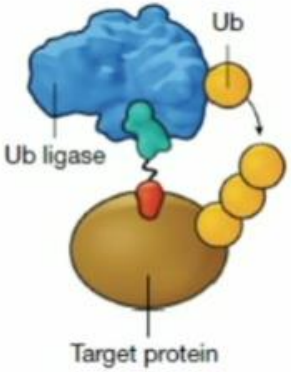
e.g.
BRD4
CARM1
BCR-ABL
RIPK1
NSD2

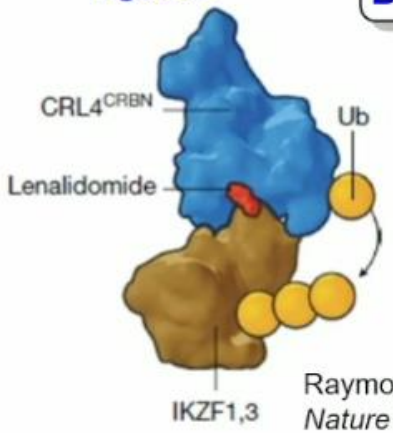
Bifuncitonal PROTACs

E3 ubiquitin ligase ligands

e.g.
IKZF2

Monovalent Molecular Glue Degraders (MMGD)





well-defined small molecule binding sites.

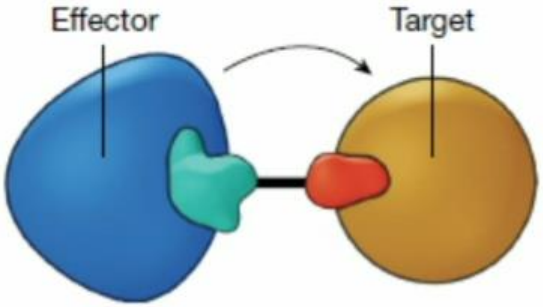
- Targets of PROTACs: Yes
- MMGDs: No

Raymond J. Deshaies
Nature **2020**, *580*, 329.

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Targeted Protein Degradation (TPD)

- one of the main proximity-inducing drug discovery strategies



"**Multispecific drugs herald a new era of biopharmaceutical innovation**" by Raymond J. Deshaies *Nature* **2020**, *580*, 329.

Effector:
E3 Ubiquitin Ligase;
Lysosome Targeting Receptor;

Bi-functional Molecules:
Proteolysis-Targeting Chimera (PROTACs)
Lysosome Targeting Chimeras (LYTACs) and related degraders

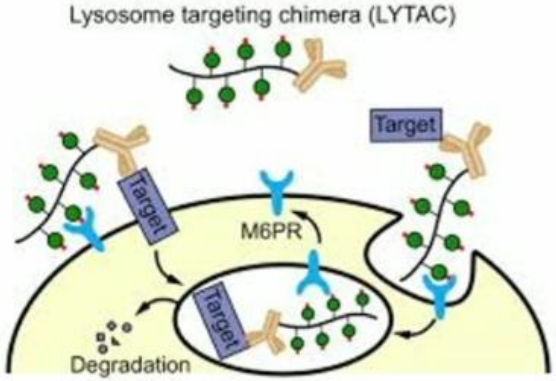
Other PTM: Phosphorylation, dephosphorylation, acetylation, and many more …
In a broad sense, the term "molecular glue" has been used to describe agents that induce proximity between two proteins back in 1992.

"Immunophilin-sensitive protein phosphatase action in cell signaling pathways" by Stuart Schreiber *Cell*, **1992**, *70*, 365.
"The Rise of Molecular Glues" by Stuart Schreiber *Cell*, **2021**, *184*, 3.

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Lysosome-Targeting Chimaeras (LYTACs) for the Degradation of Extracellular Proteins

M6PR or CIM6PR: Cation-independent mannose-6-phosphate receptor, ubiquitously expressed in many cell types.



Bertozzi et al. *Nature* **2020**, *584*, 291.

PROTAC
- **Intracellular protein/domain**
- Ubiquitin-proteasome pathway

LYTAC
- Extracellular protein (e.g. cytokines, immune complexes, amyloid aggregates; receptor tyrosine kinases, integrins, cell adhesion molecules, checkpoint receptors and immune modulatory receptors, etc.)
- Lysosome degradation

Both PROTAC and LYTAC require only a binder, which does not need to be functional.

The binder for PROTAC has to be cell permeable small molecules.

The binder for LYTAC can be antibody, peptides, or small molecules.

SAN ANTONIO BREAST CANCER SYMPOSIUM

Biparatopic Antibodies Targeting FGFR2

Saireudee (Gal) Chaturantabut (Sellers Lab)
The Broad Institute of MIT and Harvard, Cambridge, MA

San Antonio Breast Cancer Symposium

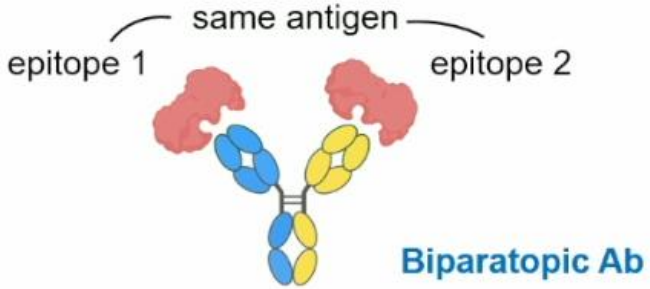
December 11, 2024

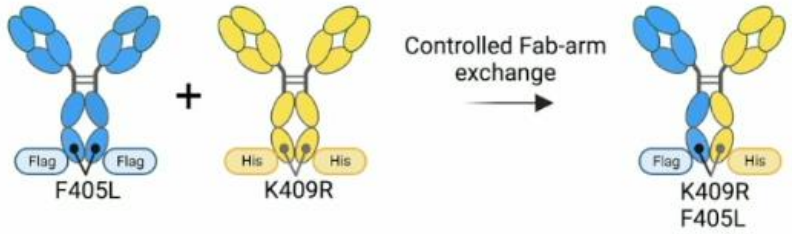
BROAD INSTITUTE

SAN ANTONIO BREAST CANCER SYMPOSIUM®

What is biparatopic antibody?

Generation of FGFR2 biparatopic antibodies





Duobody Technology

- DuoBody Abs are made by controlled Fab arm exchange of matched CH3 mutations
- K409R and F405L are destabilizing mutations in the CH3 interface
- The complementary mutations favor heterodimerization

BROAD INSTITUTE

Zusammenfassung:

-Ribociclib in der Adjuvanz beim HR+/HER2-Mammakarzinom mit hohem Rezidivrisiko bereichert unsere Therapieoptionen

-Inavolisib zeigt Effektivität in Kombination mit Fulvestrant und Palbociclib beim metastasierten HR+/HER2-Mammakarzinom mit PIK3CA-Mutation (bisher nur FDA-Zulassung)

-Das Finden der optimalen individuellen Medikamentendosis ist wichtig

-PROTACS, LYTACS und Biparatopische Antikörper sind neue Medikamente der Zukunft