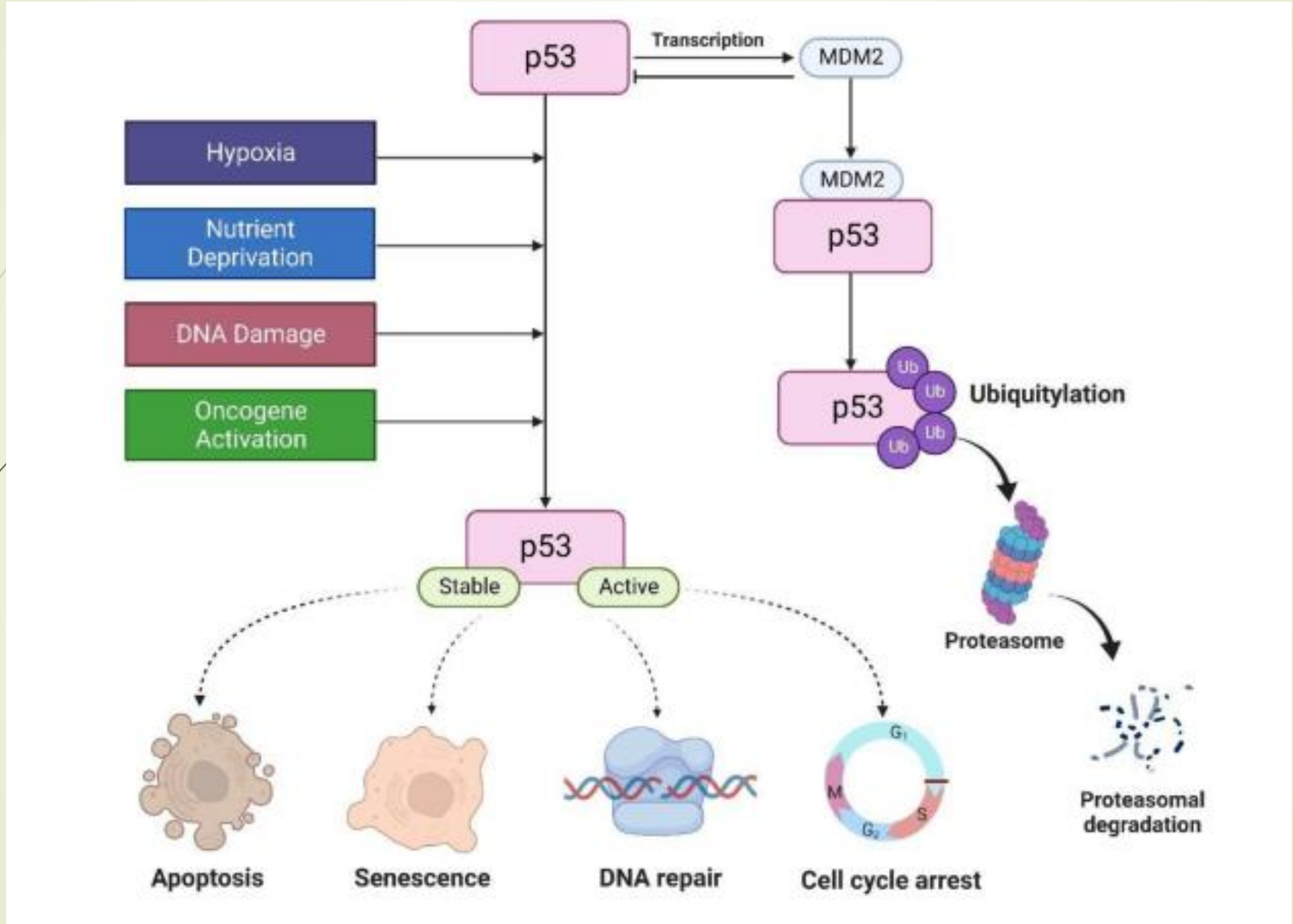
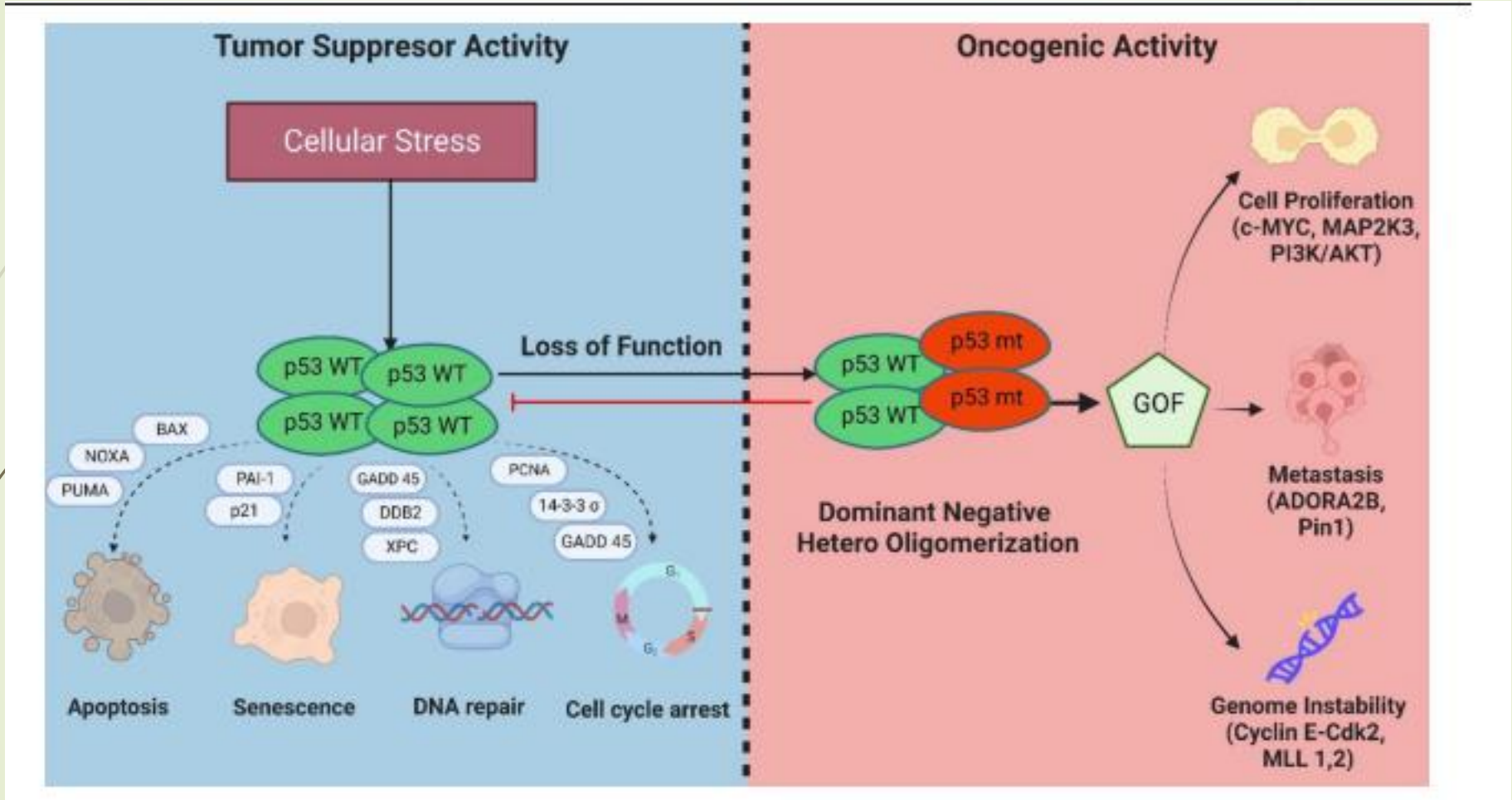
Tp53

Tums E- workshop on breast cancer management

Tumor protein (*TP53*)

- is a tumor suppressor gene that encodes tumor protein p53.
- The p53 protein is situated in the cell nuclei and binds directly to DNA.
- p53 participates in : the regulation of cell cycle checkpoints, DNA repair and apoptosis regulates the repair process in response to damaging factors, including chemicals, radiation and ultraviolet rays from sunlight


p53
Transcription
MDM2
Hypoxia
Nutrient Deprivation
DNA Damage
Oncogene Activation
MDM2
p53
p53
Ub
Ub
Ub
Ub
Ubiquitylation
Proteasome
Proteasomal degradation
p53
Stable
Active
Apoptosis
Senescence
DNA repair
Cell cycle arrest


Tumor Suppresor Activity
Oncogenic Activity
Cellular Stress
p53 WT
p53 WT
p53 WT
p53 WT
Loss of Function
p53 WT
p53 mt
p53 WT
p53 mt
BAX
NOXA
PUMA
PAI-1
p21
GADD 45
DDB2
XPC
PCNA
14-3-3 σ
GADD 45
Dominant Negative
Hetero Oligomerization
GOF
Cell Proliferation
(c-MYC, MAP2K3,
PI3K/AKT)
Metastasis
(ADORA2B,
Pin1)
Genome Instability
(Cyclin E-Cdk2,
MLL 1,2)
Apoptosis
Senescence
DNA repair
Cell cycle arrest

Inherited *TP53* gene mutations increase the risk of numerous cancer

- Breast cancer, soft tissue and bone sarcoma (>50% of tumors), followed by adrenocortical carcinomas and brain tumors
- Hematological, gastric, colorectal and ovarian cancer, occur earlier in *TP53* mutations carriers than in the general population
- Rare cancers in *TP53* germline mutation carriers: choroid plexus carcinoma and papilloma (at <15 years old), Wilms' tumor and malignant phyllodes tumor

NCCN guidelines: gene summary:

TP53	Primary breast cancer • Absolute risk: >60%[3,67-69] • Management: Li-Fraumeni Syndrome Management • Strength of evidence of association with cancer: Very strong[70] Contralateral breast cancer[j] • 10-year cumulative risk: 18-49%[37,69,71] • Strength of evidence of association with cancer: Strong	Evidence of increased risk: No established association	Pancreatic cancer • Absolute risk: ~5%[68] • Management: Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A. • Strength of evidence of association with cancer: Limited Other cancers[n] • Classical LFS spectrum cancers (in addition to breast): soft tissue sarcoma, osteosarcoma, CNS tumor, ACC • Many other cancers have been associated with LFS, especially melanoma, colorectal, gastric, and prostate. • Li-Fraumeni Syndrome Management
	Comment: See Discussion for information on hypomorphic variants.		

Testing for TP53 is recommended

- in females with breast cancer diagnosis <35 years old and without *BRCA1/BRCA2* mutations.
- the option of a risk-reducing mastectomy is recommended regarding *TP53* mutations
- Therapeutic radiotherapy should be used with caution in patients with *TP53* mutations due to increased sensitivity to radiation

NCCN guideline for LFS& TP53 mutation:

- BSF from 18, CBE (6-12m) from 20-25, mammo or MRI from 30 (til 75, after 75 individual decision)
- Additionally, the NCCN recommends annual breast MRI with contrast or mammogram from the age of 20 or when breast cancer is diagnosed in cases with a family history of breast cancer prior to the age of 20. Breast cancer examination should start at the age of 18
- Patients of both genders with LFS should have annual physical examinations, skin cancer screenings, brain MRIs and colonoscopies every 2-5 years from the age of 25. Whole body MRIs should also be considered

Somatic mutation TP53

- 15–71% breast tumors
- Higher in BRCA1&2
- 75% missense ,frameshift insertions and deletions (9%), nonsense (7%) and silent mutations (5%)

Patients whose tumors harbored p53 missense mutations had

increased tumor PD-L1 expressions (compared to wild type) and had a better response rate to

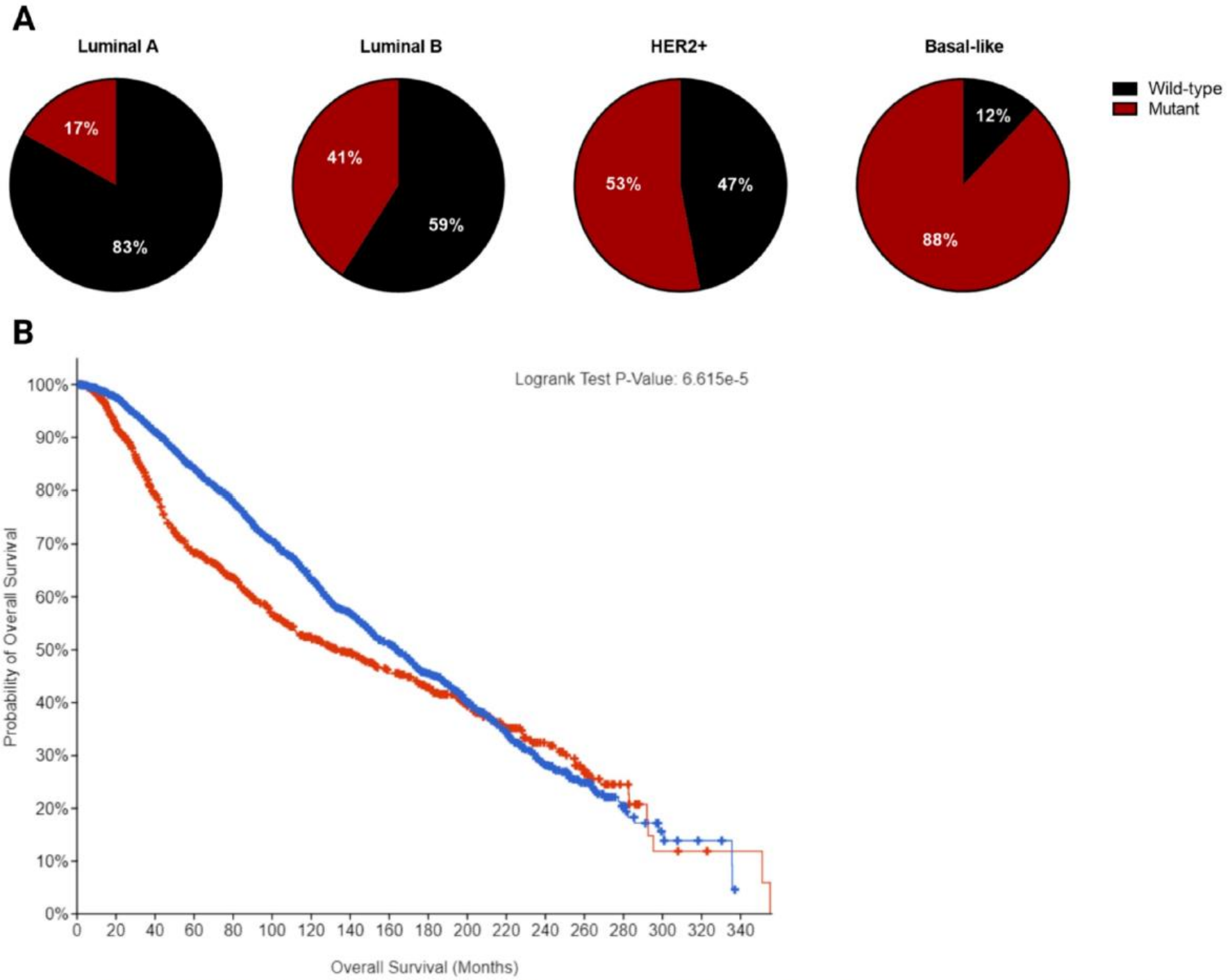
anti-PD-1/PD-L1

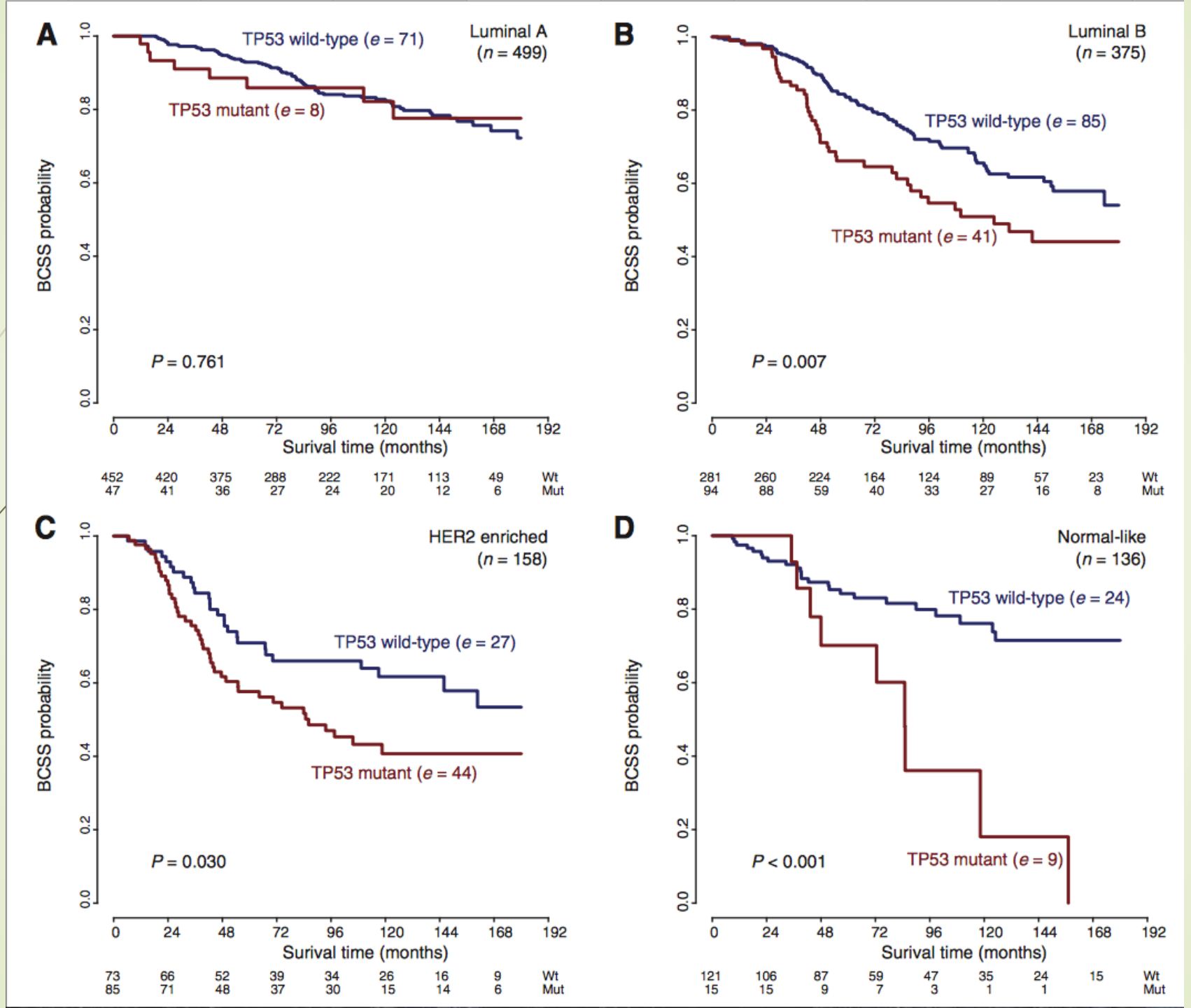
TP53 mutations as a prognostic factor

- Tp53 mutation = poor prognosis in several trials:
- The combination of *TP53* mutation &PR- (worse prognosis)
- risk factor of disease recurrence and mortality in LN-&her2+
- Higher frequency in LN=+& larger size & ER-
- *TP53* mutation status was revealed to be associated with basal-like breast cancer

Frequency of mutant P53 in breast cancer

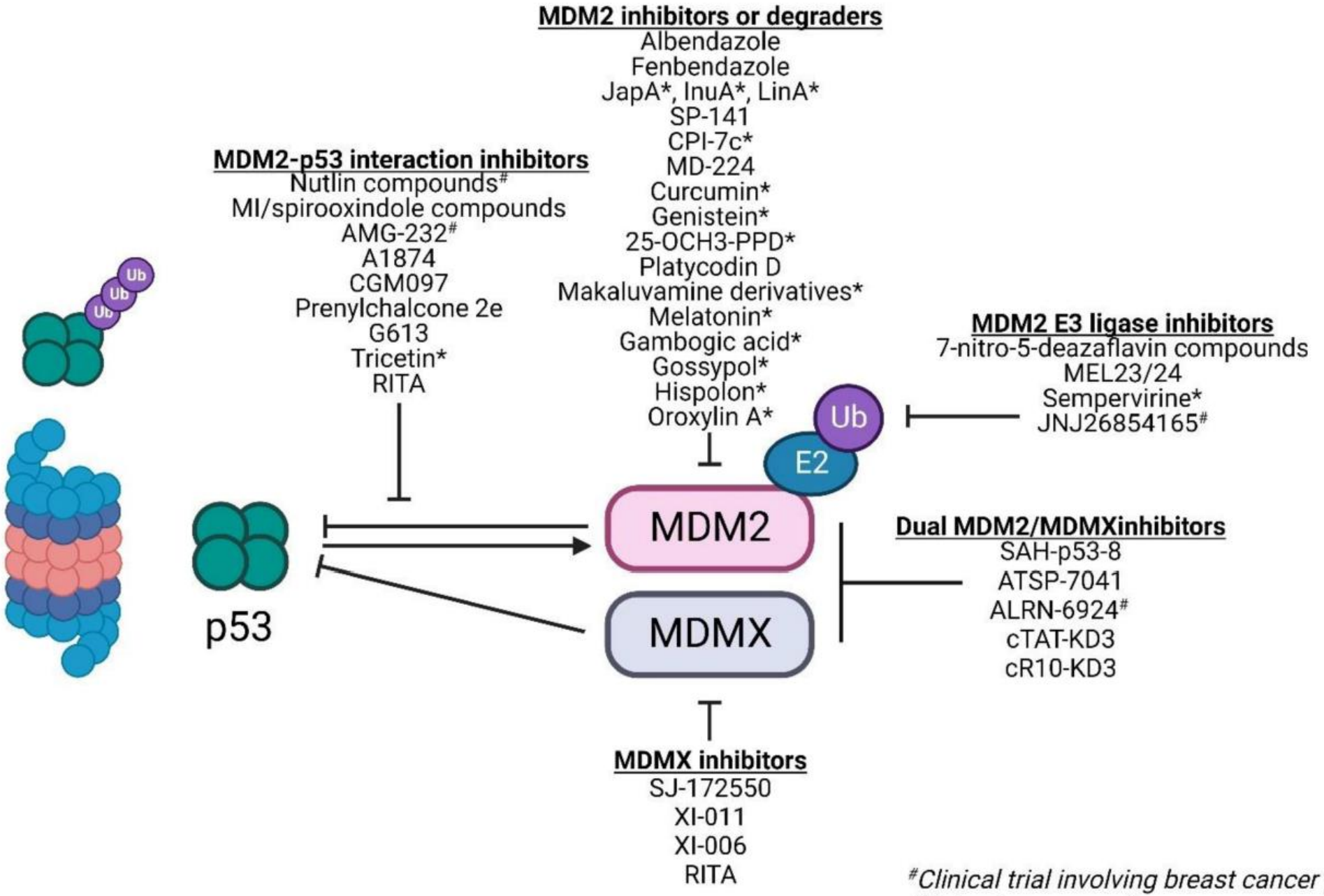
- Luminal A(14%) luminal B(41%) her2+(53%) basal like(88%)
- IBC (50%) > non inflammatory breast cancers (20-30%)
- Higher frequency in advancd stage
- Higher frequency in higher grade tumor

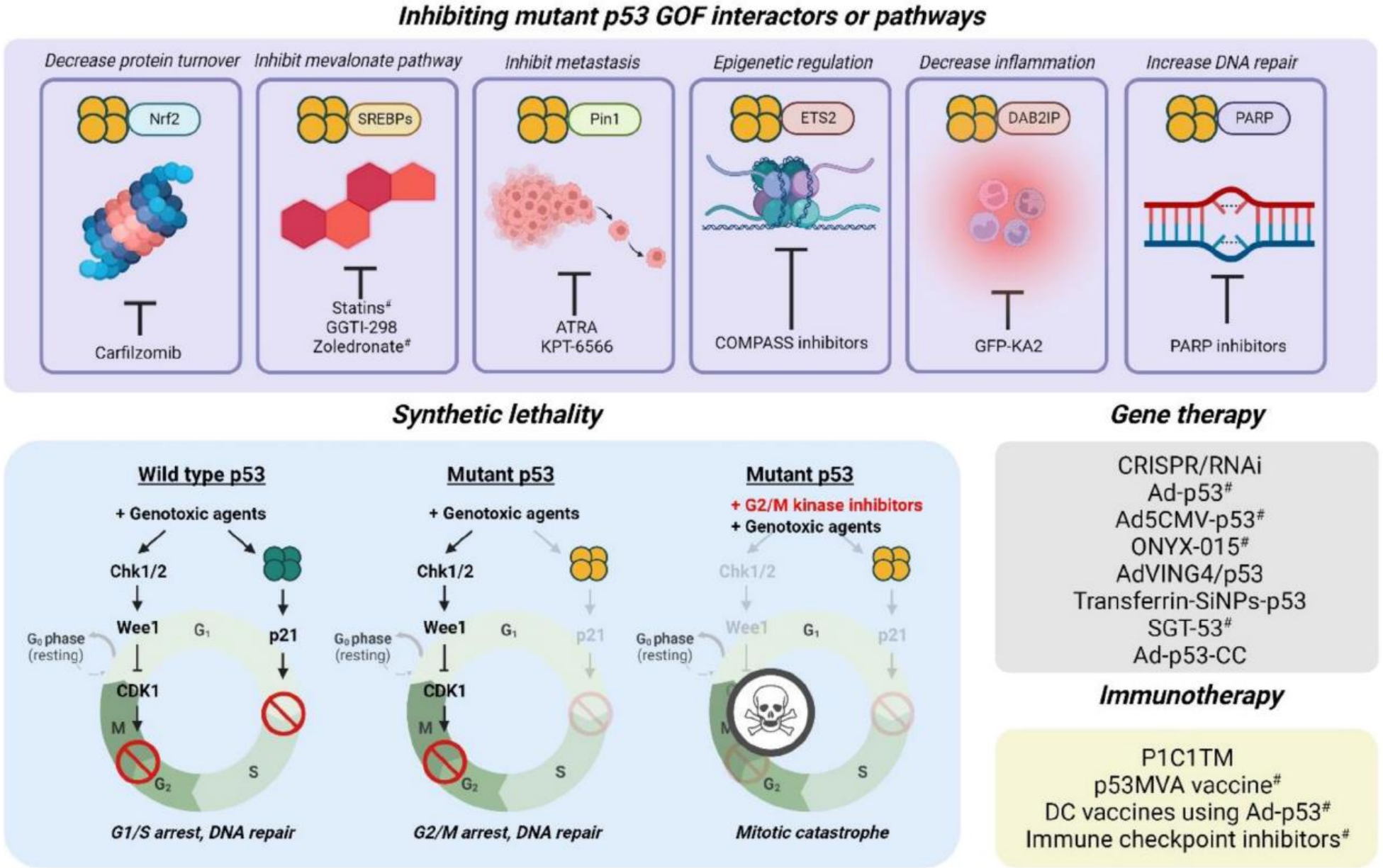

A
Luminal A
Luminal B
HER2+
Basal-like
17%
83%
41%
59%
53%
47%
12%
88%
Wild-type
Mutant
B
Logrank Test P-Value: 6.615e-5
Probability of Overall Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340
Overall Survival (Months)


A
Luminal A
(n = 499)
TP53 wild-type (e = 71)
TP53 mutant (e = 8)
P = 0.761
BCSS probability
Surival time (months)
452 420 375 288 222 171 113 49 Wt
47 41 36 27 24 20 12 6 Mut
B
Luminal B
(n = 375)
TP53 wild-type (e = 85)
TP53 mutant (e = 41)
P = 0.007
BCSS probability
Surival time (months)
281 260 224 164 124 89 57 23 Wt
94 88 59 40 33 27 16 8 Mut
C
HER2 enriched
(n = 158)
TP53 wild-type (e = 27)
TP53 mutant (e = 44)
P = 0.030
BCSS probability
Surival time (months)
73 66 52 39 34 26 16 9 Wt
85 71 48 37 30 15 14 6 Mut
D
Normal-like
(n = 136)
TP53 wild-type (e = 24)
TP53 mutant (e = 9)
P < 0.001
BCSS probability
Surival time (months)
121 106 87 59 47 35 24 15 Wt
15 15 9 7 3 1 1 Mut

Tp53 mutation as a predictive factor

- *TP53* mutation status was a significant prognostic factor for RFS, BCCS & OS in patients recieved CMF *(Andersson Ann oncol 2005)*
- Adjuvant radiotherapy and TMX less effective in patients with LN+ &*TP53 mutation (Bergh Nat Med 1995)*
- association between *TP53* mutations and a reduced response to CAF (Clahsen J Clin Oncol 1998)
- median PFS time following chemotherapy was reduced for patients with a *TP53* mutation in comparison to wild type(Berns Cancer Research 2000)
- patients with *TP53* mutations exhibited a statistically significant improvement in OS following the use of olaparib compared with non-carriers (18 vs 7.5 m) (Matrinez Bueno EZMO 2017)


MDM2 inhibitors or degraders
Albendazole
Fenbendazole
JapA*, InuA*, LinA*
SP-141
CPI-7c*
MD-224
Curcumin*
Genistein*
25-OCH3-PPD*
Platycodin D
Makaluvamine derivatives*
Melatonin*
Gambogic acid*
Gossypol*
Hispolon*
Oroxylin A*
MDM2-p53 interaction inhibitors
Nutlin compounds#
MI/spirooxindole compounds
AMG-232#
A1874
CGM097
Prenylchalcone 2e
G613
Tricetin*
RITA
MDM2 E3 ligase inhibitors
7-nitro-5-deazaflavin compounds
MEL23/24
Sempervirine*
JNJ26854165#
Ub
Ub
Ub
E2
MDM2
p53
MDMX
Dual MDM2/MDMXinhibitors
SAH-p53-8
ATSP-7041
ALRN-6924#
cTAT-KD3
cR10-KD3
MDMX inhibitors
SJ-172550
XI-011
XI-006
RITA
#Clinical trial involving breast cancer patients
*Natural compounds



igure 6. Strategies to treat mutant p53 tumors that have been evaluated in breast cancer

Table 3. List of clinical trials evaluating p53 targeted therapies that involve breast cancer patients in the past decade (2013-2023).

Compound	Intervention	Phase	Status	Conclusion	ClinicalTrial.gov identifier & reference
			Therapies against mutant p53 tumor		
p53MVA	p53MVA (5.6 x 10^8 pfu IM) Pembrolizumab (200 mg IV)	I	Active, not recruiting	3/11 with stable disease, 2 with increased and sustained T cell activity	NCT02432963 [173, 174]
SGT-53	SGT-53 (IV) on day 1, 8, 15 Pembrolizumab (IV) on day 3 Carboplatin (IV) on day 3	I	Withdrawn: funding and drug preparation issues	-	NCT05093387
Zoledronic acid	Zoledronic acid (4 mg IV) every 3 or 4 weeks Atorvastatin (80 mg oral) once daily	II	Unknown	-	NCT03358017
	Zoledronic acid (4 mg IV) 7 days before definitive breast surgery	II	Terminated: low accrual	-	NCT02347163
Ad-p53	Ad-p53 (dose according to tumor size; intratumoral) Clinician recommended ICI	II	Recruiting	Dose of Ad-p53 at above 7 x 10^{10} viral particles/cm^3 of tumor corresponds to better response; improved immune activities	NCT03544723 [180]
PC14586	PC14586 (various doses oral)	I/II	Recruiting	Safe and well-tolerated up to 3000 mg daily; 1 breast cancer patient with partial response	NCT04585750 [116]
			Therapies against wild-type p53 tumor		
Idasanutlin	Atezolizumab (840 mg IV) Idasanutlin (100 mg oral)	Ib	Terminated: low accrual/loss of funding	4 out of 7 patients with disease progression; serious adverse events	NCT03566485
AMG-232	AMG-232 (240 mg MTD oral)	I	Completed	7/12 ER+ patients with stable disease	NCT01723020 [65]
ALRN-6924	Paclitaxel (IV) ALRN-6924 (IV) on day 1, 8, 15	Ib	Recruiting	-	NCT03725436
	ALRN-6924 1.2 mg/kg (IV) Day 0-2 TAC: Doxorubicin 50 mg/m^2 (IV); Cyclophosphamide 500 mg/m^2 (IV); Docetaxel 75 mg/m^2 (IV) Day 1 of every 3-week cycle	Ib	Recruiting	-	NCT05622058

ER+: estrogen receptor-positive; MTD: maximum tolerated dose; Pfu: plaque forming unit; ICI: immune checkpoint inhibitor; IM: intramuscular; IV: intravenous