Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

INTEGRAZIONE DI TERAPIA BIOLOGICA E RADIOTERAPIA NEL TUMORE DELLA MAMMELLA.

Andrea Guerini
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Associazione Italiana Radioterapia e Oncologia clinica
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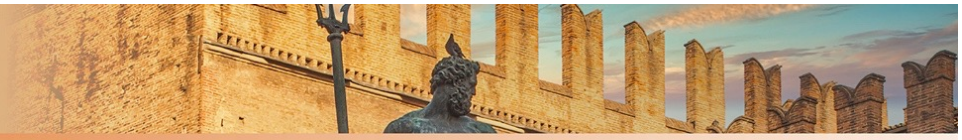


DICHIARAZIONE

Relatore: ANDREA GUERINI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Consulenza ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Partecipazione ad Advisory Board (NIENTE DA DICHIARARE)
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)

Metastatic breast cancer

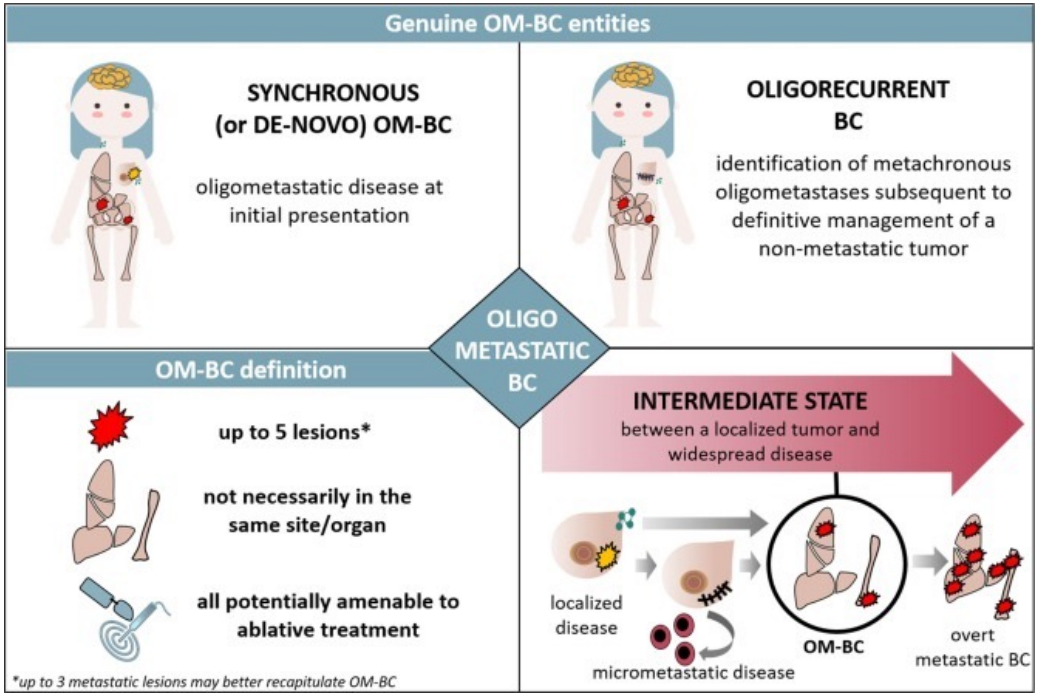
About 6% of pts de novo metastatic disease, about 8% diagnosed in earlier stages develop metastatic disease

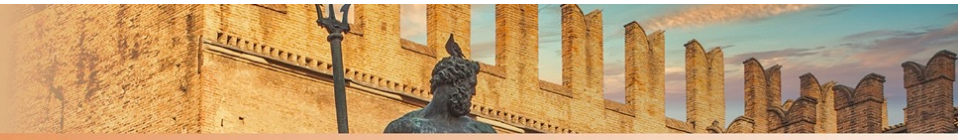
5-year disease specific survival exceeds 50% for de novo disease

Solid tumor for which the highest number of drugs have been authorized: since the 90s about 30 drugs approved

New drugs: hormonal treatments, new chemotherapy drugs and modified formulations of already used molecules, biologic agents, small molecules and targeted therapy

Miglietta et al. Cancer Treatment Reviews Volume 110, November 2022, 102462





Radiotherapy in metastatic breast cancer

RT central role: >50% bone involvement, brain M1 increasingly common secondary to prognosis improvement

IR + systemic treatment: synergy vs increased toxicity
Unanswered issues:
possible contraindications due to increased toxicity
best timing of the association
unexpected acute or chronic side effects

Under-reported, few published data
Different mechanisms of action unpredictable interactions
Few data + isolated case reports of high grade toxicity unnecessary drug suspension vs withhold radiotherapy

Systemic treatment in metastatic breast cancer

DOI:10.1158/0008-5472.CAN-12-4617

Metastatic breast cancer

Microtubule Inhibitors
- Irreversible mitotic block
- Eribulin Mesylate, Vinorelbine (November 15, 2010)

Monoclonal Antibody
- Trastuzumab acts against HER2 (September 25, 1998)
- Bevacizumab inhibits VEGFR (February 26, 2004)

Epothilone
- Bind to tubulin, cell cycle arrest
- Ixabepiline (October 16, 2007)

Taxane
- Inhibit mitosis
- Cabazitaxel (June 17, 2010)

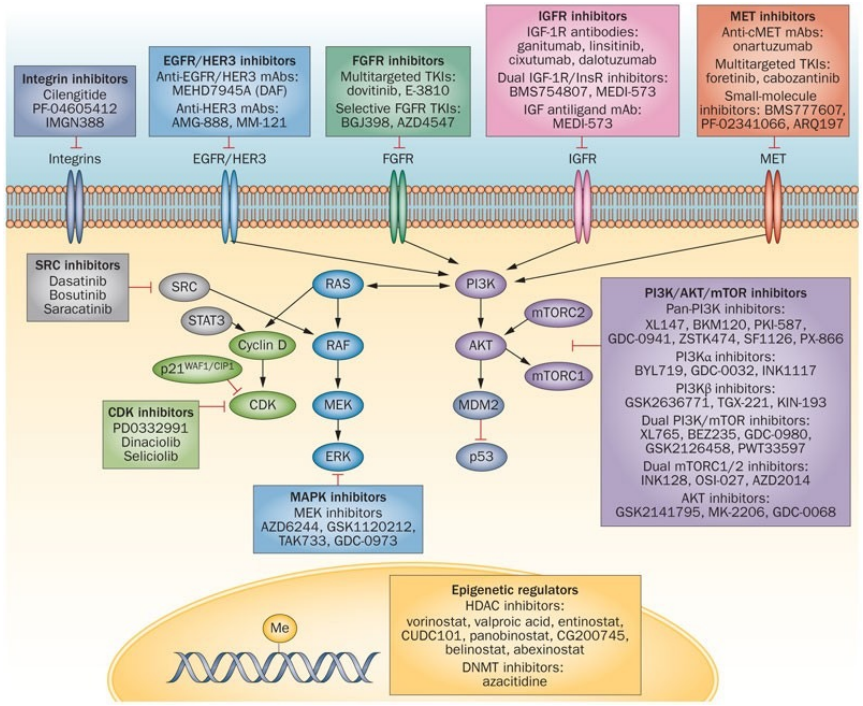
Tyrosine kinase inhibitor
- Inhibits VEGFR, PDGFR
- Motesanib

PARP1 inhibitor
- Inhibits PARP1 leading to cell death
- Iniparib

Antiestrogen
- Blocks, degrades estrogen, progesterone receptor
- Fulvestrant (April 25, 2002)

Antimetabolite
- It is converted to 5 FU which impair the growth
- Capecitabine (April 30, 1998)

Nature Reviews Clinical Oncology volume 10, pages191–210 (2013)



Concurrent definition: half life

- eribulin (Halaven); half life about 40 hours (allowed interval 200 hours – 8 days) [18]
- nab-paclitaxel (Abraxane); half life 13-27 hours (allowed interval 135 hours – 5.5 days) [19]
- Caelyx; half life 73.9 hours (allowed interval 370 hours – 15 days) [20]
- Myocet; half life 52.6 hours (allowed interval 263 hours – 11 days) [21]
- olaparib (Lynparza); half life 15 hours (allowed interval 75 hours – 3 days) [22]
- talazoparib (Talzenna); half life 58-90 hours (allowed interval 450 hours – 19 days) [23]
- neratinib (Nerlynx); half life 10-17 hours (allowed interval 85 hours – 3.5 days) [24]
- everolimus (Afinitor) half life 30 hours (allowed interval 150 hours – 6 days) [25]
- trastuzumab (Herceptin); half life 4-5 weeks (allowed interval 20 weeks) [26]
- pertuzumab (Perjeta); half life 18 days (allowed interval 90 days) [27]
- trastuzumab emtansine (Kadcyla); half life 4 days (allowed interval 20 days) [28]
- lapatinib (Tyverb); half life 24 hours (allowed interval 120 hours – 5 days) [29]
- bevacizumab (Avastin); half life 18 days (allowed interval 90 days) [30]

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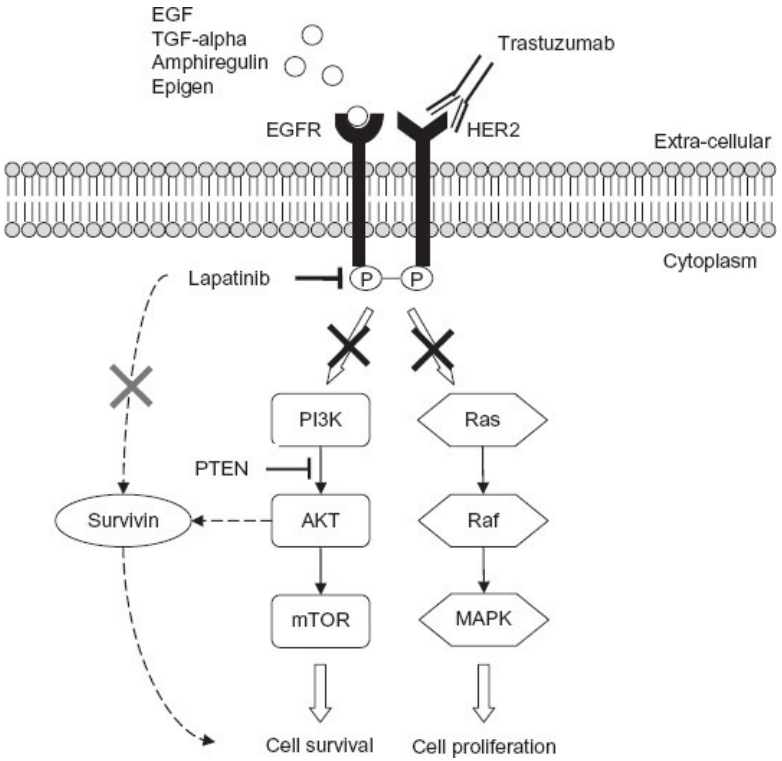


Lapatinib

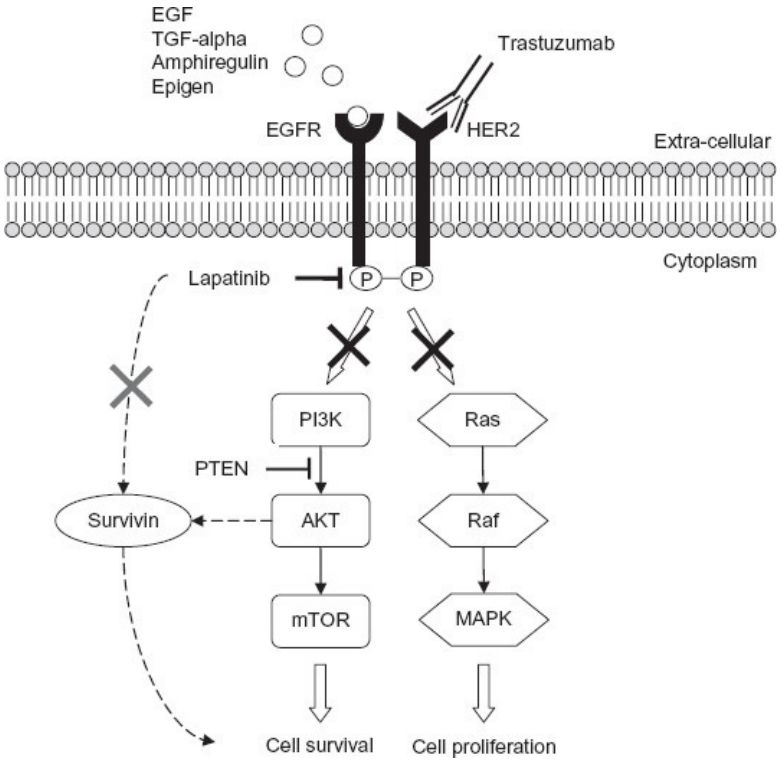
dual-targeted small molecule inhibitor

intracellularly binds to the cytoplasmic ATP-binding sites of EGFR/HER1 and HER2 receptors

block of tyrosine kinase phosphorylation

reduced signal transduction PI3K/Akt/mTOR and Ras/Raf/MAPK pathways

Tsang RY et al. Clinical Medicine Insights: Therapeutics. 2011;3.



Tsang RY et al. Clinical Medicine Insights: Therapeutics. 2011;3.

Lapatinib

M1 HER2+ in PD after antracycline+taxane and/or trastuzumab

1000-1500 mg daily per os +/- trastuzumab or cape

Characteristic tox: diarrhea and rash; cardiac toxicity rarely seen

Lapatinib

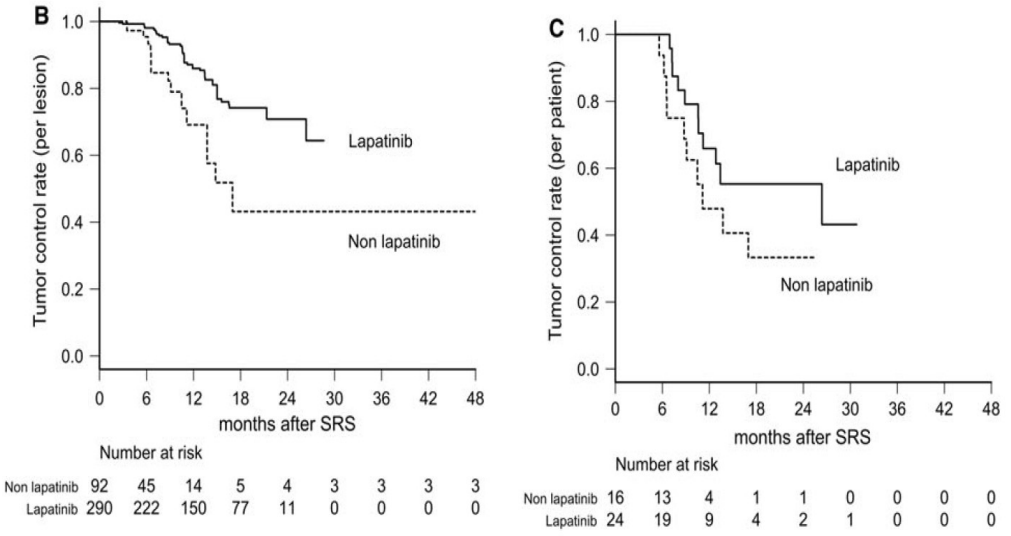
J Neurooncol (2013) 112(2):199–207. 10.1007/s11060-013-1046-1

Yomo S et al - 2013

40 pts with HER2-overexpression
gamma knife SRS (10–24 Gy, median: 20 Gy)

lap (24 pts) vs no lap (16 pts)

lapatinib-based therapy better LC (P = 0.002) and 1-year LC rate (86 vs. 69 %, P < 0.001).



Lapatinib

Miller JA et al – 2017 Parsai S et al - 2019

126 pts SRS, 479 HER2-amplified lesions

47 pts lap, 24 pts lap concurrent (within 5 h-l) with brain SRS (Gamma Knife)

lap reduce 12 mo LF (5.7% vs 15.1%, p < 0.01)

lap lower RN vs SRS alone (1.3% vs 6.3%, p < 0.01)

rate remained low in largest lesions (> 75th percentile, 12-month rate 4.8%).

J Neurosurg. 2019 Feb 8;132(2):503-511. doi: 10.3171/2018.10.JNS182340.

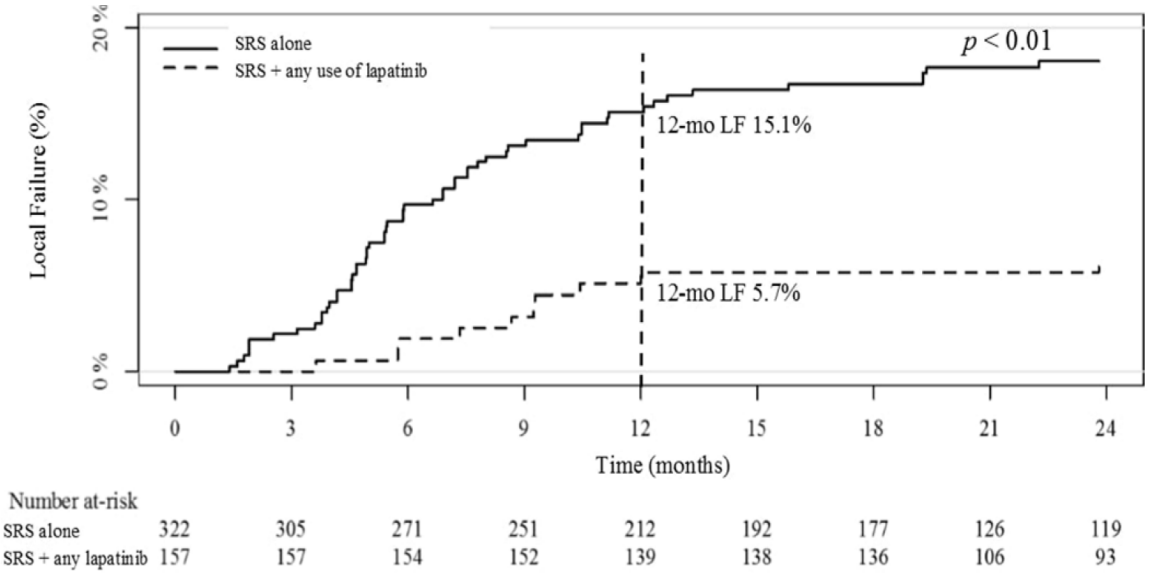


FIG. 2. Cumulative incidence of local failure (LF) stratified by use of SRS with or without the use of concurrent lapatinib.

Lapatinib

Kim JM et al. - 2019

Neuro Oncol. 2019 May; 21(5): 659–668.

84 pts 487 brain M1 SRS (median dose 24 Gy)

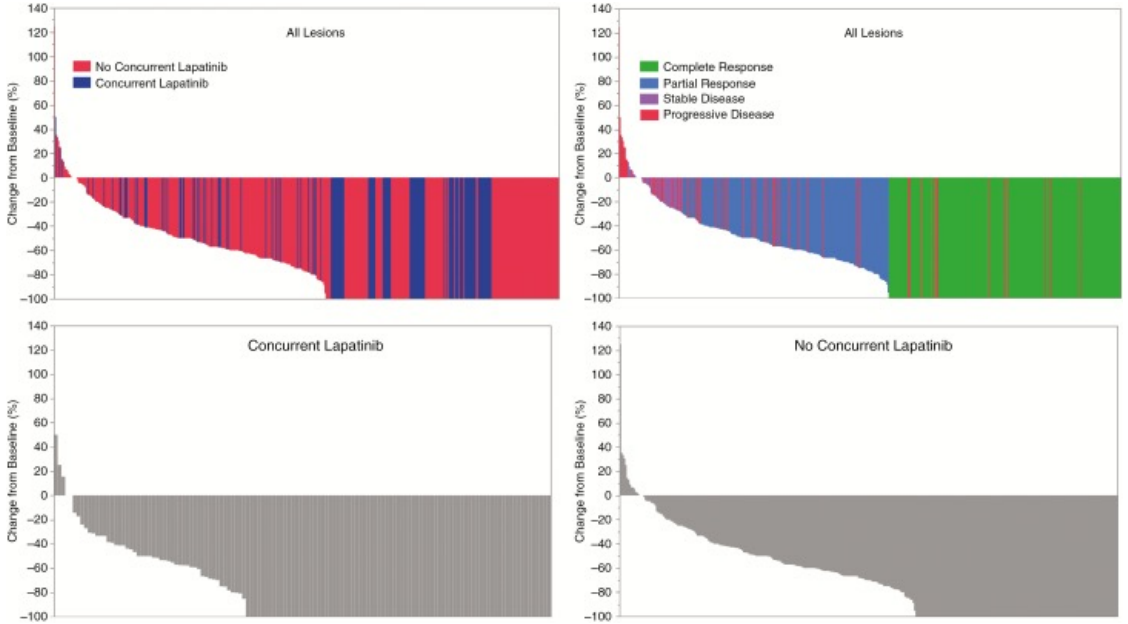
132 lesions (27%) SRS + concurrent (+/- 5 days) LAP

best OR median 100% vs 70% reduction (P < 0.001)
CR 57% vs 38% (p < 0.001)

Median ORR at 6-, and 12-month: 100 vs. 60% (p < 0.001), and 100 vs. 71% (p < 0.001).

no ↑ risk of G≥2 RN (1.0% LAP vs 3.5% no LAP, P = 0.27)

24-mo local failure 12% vs 19% (P = 0.071)



Lapatinib

Khan M et al. - 2020

Front Oncol
. 2020 Nov 6;10:576926. doi: 10.3389/fonc.2020.576926.

Local control was significantly increased with SRS plus lapatinib based on the meta-analysis of three studies (HR 0.47 [0.33, 0.66], p = 0.0001)

6 studies with 843 HER-2 positive breast cancer patients; 279 patients had received lapatinib in addition to HER-2 antibody (trastuzumab)

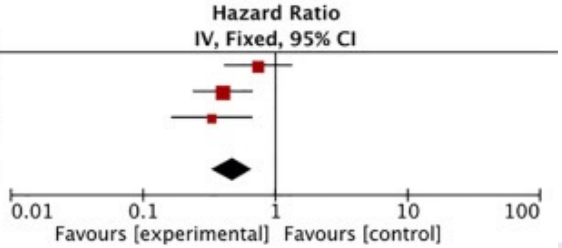
Miller et al. concurrent HER2/LAP + SRS ↓ RN 12mo rate (1.3 vs. 6.3%, p = 0.001)

Shireen et al. ↓ RN 6-mo (0.0 vs. 4.1%), 12-mo (1.3 vs. 6.3%), and 24-mo (1.9 vs. 8.2%)

Kim et al G≥2 RN similar (1.0 vs. 3.5%, p = 0.134).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Kim, et al.	-0.30110509	0.30210912	33.4%	0.74 [0.41, 1.34]
Miller, et al.	-0.91629073	0.26567701	43.2%	0.40 [0.24, 0.67]
Yomo, et al.	-1.10866263	0.36149643	23.3%	0.33 [0.16, 0.67]
Total (95% CI)			**100.0%**	**0.47 [0.33, 0.66]**

Heterogeneity: $Chi^2 = 3.58$, df = 2 (P = 0.17); $I^2 = 44\%$
Test for overall effect: Z = 4.33 (P < 0.0001)



Lapatinib

Kim al. - 2020

QUICK PITCH ORAL ABSTRACT | VOLUME 108, ISSUE 3, SUPPLEMENT , S174-S175,
NOVEMBER 01, 2020

PDF [337 KB] Save Share Reprints

NRG Oncology/RTOG 1119: PHASE II Randomized Study of Whole Brain Radiotherapy/Stereotactic Radiosurgery with Concurrent Lapatinib in Patients with Brain Metastases from HER2-Positive Breast Cancer — A Collaborative Study of NRG and KROG (NCT01622868)

I.A. Kim • J. Moughan • P.W. Sperduto • ... M.M. Kim • M.P. Mehta • J.R. White • Show all authors

randomized 1:1 to WBRT (37.5 Gy/3 weeks) or SRS (size-based dosing) +/- concurrent L (1000 mg daily x 6 weeks), 6 pts on each arm received SRS, the rest WBRT.

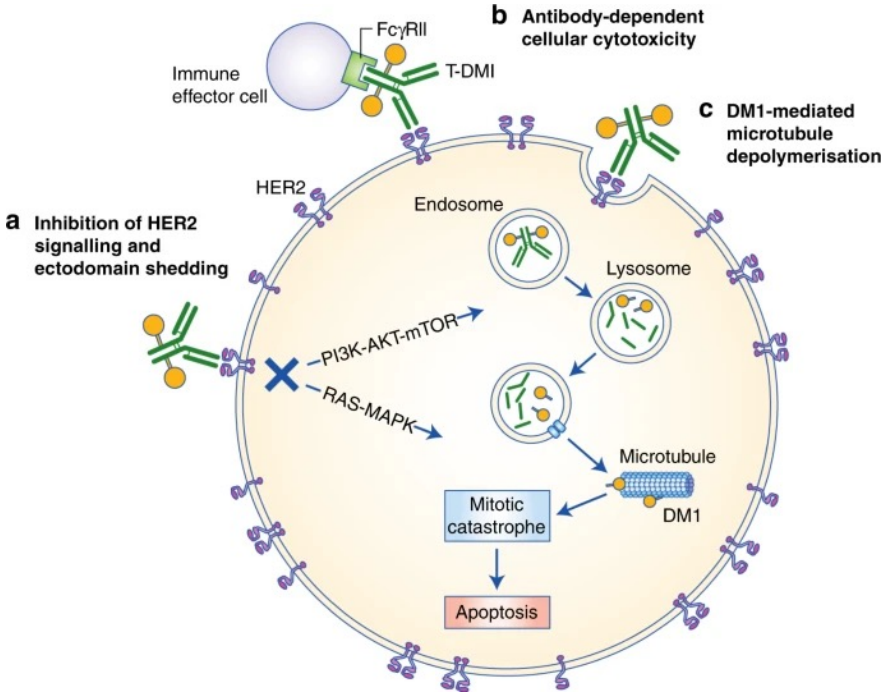
143 pts; 114 evaluable for 12-wk CR (52 RT, 62 RT+L)

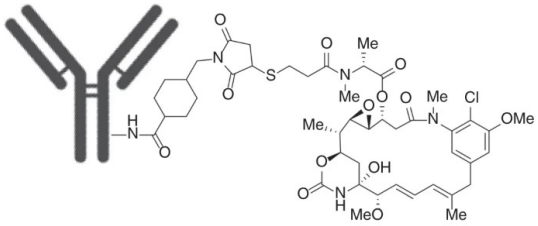
G3 and G4 AEs 8% and 0% RT vs 29% and 6% RT+L

12 and 4wk CR rates 5.8% vs 0% and 3.6% vs 1.5% ($p = 0.97$ and $p = 0.77$)

RECIST ORR at 4wk 42 % and 56% ($p = 0.059$)
WHO ORR at 4 wk 40% and 58% ($p = 0.027$)

Trastuzumab emtansine – T-DM1





HER2 antibody-drug conjugate
Trastuzumab (humanized anti-HER2 IgG1) + emtansine

T-DM1 binds HER2 receptor endocytosis lysosome degradation DM1 release DM1 inhibits microtubule assembly

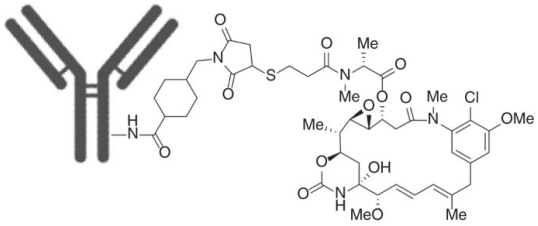
Hunter FW et al. British Journal of Cancer volume 122, pages603–612 (2020)

Trastuzumab emtansine – T-DM1

M1 or LABC, monotherapy after trastuzumab + taxane - concurrent or not

most common AEs: nausea, fatigue, thrombocytopenia, headache, constipation, diarrhea, elevated liver enzymes, anorexia, and epistaxis

IV infusion q21



Hunter FW et al. British Journal of Cancer volume 122, pages603–612 (2020)

Trastuzumab emtansine (T-DM1)

Carlson JA et al. - 2014. Neuro Oncol. 2014 Jul;16(7):1006-9. doi: 10.1093/neuonc/not329.

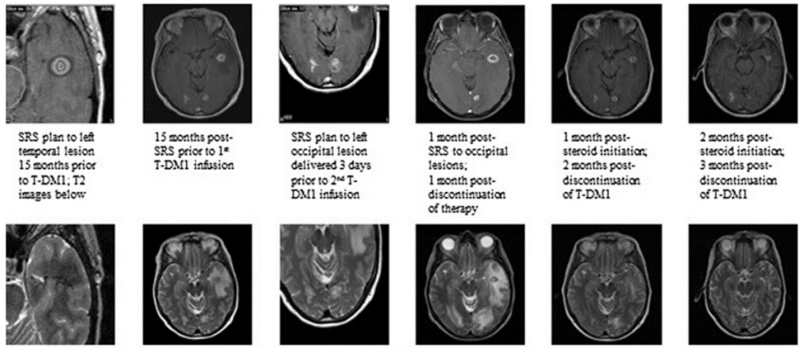
SRS to one or more BM, median 8 days before T-DM1 infusion

2 pts sympt immediately after infusion, one at 5th one at 7th

All clinical and radiographical improvement with steroids

3 stopped T-DM1, one surgery (radionecrosis)

Other 3 SRS+T-DM1 no RN → 57% VS ~ 10% reported in literature



Clinical and treatment characteristics for 7 patients with HER2+ breast cancer treated with SRS and T-DM1 over a 2-year period

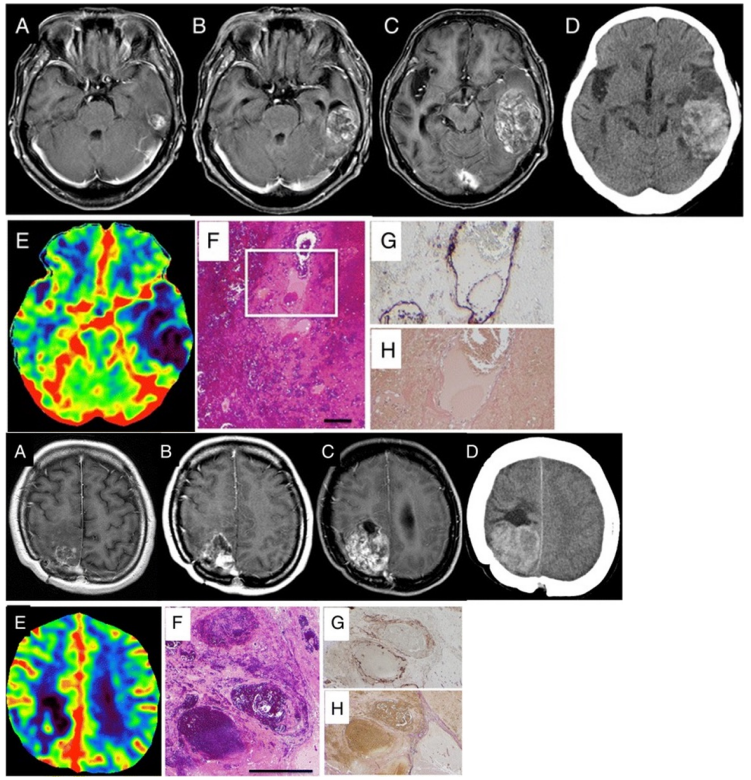
Patient	Age (years)	CSRN	Prior Systemic Therapy	Total no. Cycles T-DM1	T-DM1 On-Trial	Total no. Treated BM	SRS Dose (Gy)	Maximum Size of Treated Lesion (cm^3)	Interval to CSRN From T-DM1 (days)
1	37	Yes	T, S	1	No	4	24	1.1	10
2	56	Yes	AC, ET	7	Yes	1	18	1.6	7
3	57	Yes	APx, XT, TV, GTCaL	5	No	5	16-20	0.9	35
4	57	Yes	ACPx, T, S	2	No	5	24	4.5	3
5	49	No	TPx, AC, DPT	4	No	3	20	0.5	N/A
6	46	No	TaPT, CaL	2	Yes	2	20	0.9	N/A
7	57	No	AC,TPx, PTPx, V, L	31	Yes	2	18	5.0	N/A

Trastuzumab emtansine (T-DM1)

Mitsuya K et al. 2016. BMC Cancer. 2016 Jul 4;16:391. doi: 10.1186/s12885-016-2464-1.

Cae 1: 8 mm M1 left temporal lobe → SRS 25 Gy → 5.5 years after SRS T-DM1 → 8 mo after MRI nodular lesion → resection: radiation necrosis → improved sensory aphasia after surgery.

Case 2: 10 mm M1 right parietal lobe → SRS 25 Gy → 12 mo later recurrence → surgery + post-op SRT 30 Gy/5 fr → 5.5 years after SRT T-DM1 → 9 mo after MRI cyst increasing in size, mild disorientation → surgical resection hematoma/necrosis



Trastuzumab emtansine (T-DM1)

Kolarichet al - 2014. Acta Oncol. 2014;53: 1434-1436.
WBRT 39.8Gy/22fr → 12 mo later SRS 17.5 Gy 8 lesions → 2 years later T-DM1 → 1 week after T-DM1 start hyponatremia, after 6 cycles hemorrhage in a treated M1 parietal lesion

Geraud A et al. – 2017 J Neurooncol . 2017 Jan;131(1):69-72.
4 pts treated for BM with T-DM1 and concurrent SRS +/- WBRT: 75% response rate (1CR,1PR,1SD). No RT interruption, 50% RN

Ricciardi GRR et al. - 2018 BMC Cancer. 2018 Jan 25;18(1):97.
brain and leptomeningeal M1, T-DM1 + concomitant WBRT 30Gy/10fr
CR after 3 cycles (lasting over 13 mo), no relevant toxicities

Vilela et al – 2018 World Neurosurg. 2018 Mar;111:109-114.
april 2016 WBT 30Gy/10fr → june 2016 12 Gy SRS cerebellar boost → september 2016 start T-DM1 → since october 2016 enlarging hematoma → june 2017 neurol sympt, surgical resection (hematoma, anomalous vessels)

Trastuzumab emtansine - T-DM1

Stumpf et al. - 2019 Clin Cancer Res. 2019 Jul 1;25(13):3946-3953

MBC, age ≤45 years regardless of HER2 or had HER2+ disease regardless of age
SRS (median 1fr, 20 Gy) to a median of 5 lesions
per-lesion rate of CSRN in overall cohort was 7.1% (19/268 lesions)

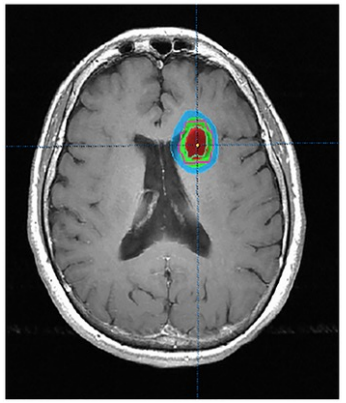
45 pts, 23 pts T-DM1 (16 concurrent)
10 pts clinically significant RN, 9 received T-DM1(6 concurrent)
6 surgery (confirmed RN)

CSRN 39.1% SRS + T-DM1 vs 4.5% no T-DM1

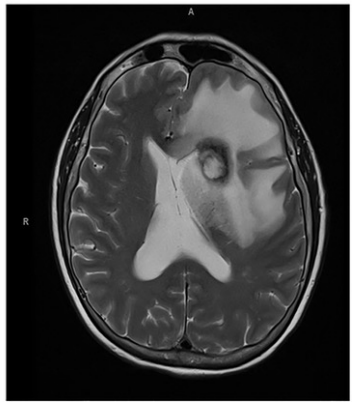
T-DM1 13.5-fold (P = 0.02) increase in CSRN.

median time from SRS to CSRN 16 mo, from T-DM1 to CSRN 8–532 days

SRS Plan to 18Gy in a single fraction



MRI Brain: Axial T2 sequence 6 months after completion of SRS



Trastuzumab emtansine - T-DM1

Said et al. - 2022 J Neurooncol. 2022 Aug;159(1):177-183.

HER2 + MBC SRS for BM + T-DM1

67 pts, 223 BM; 21 pts T-DM1 post SRS (14 within 12mo)

predictors of RN.
equivalent dose in 2 Gy fractions (EQD2) > 90 Gy2 (HR 2.4, p = 0.02)
T-DM1 treatment post-SRS (hazard ratio (HR) 2.5, 95% CI 1.2-5.3, p = 0.02)

overall probability of RN post-SRS 21.6%
1 and 2 year risk was 6.7% and 15.2%

T-DM1 + SRS 29.9% probability of RN, 25.2% (95% CI 12.8-37.6%)
risk at 1- and 2 years post-T-DM1.

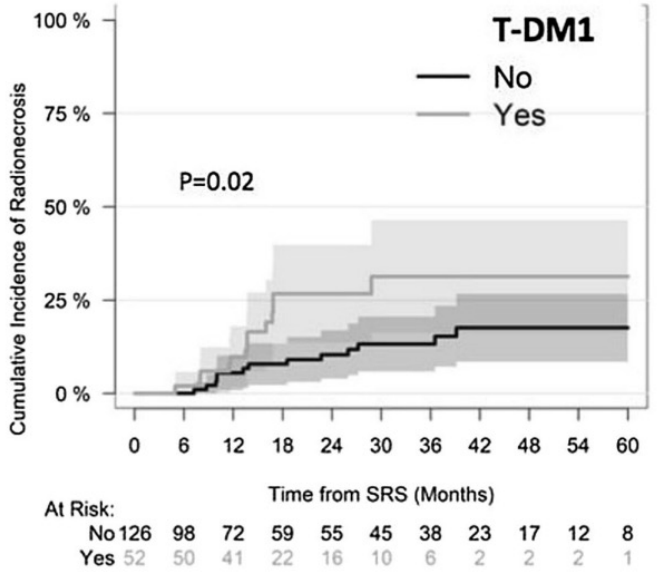


Fig. 2 Probability of RN according to T-DM1 status

71% of RN symptomatic (treated with steroids/beva), median time to RN of 13.2 mo from SRS and 4.8 mo from T-DM1 (80% within 12 mo)

Trastuzumab emtansine - T-DM1

Geraud et al. - 2016 Preliminary results of the concurrent use of radiotherapy for bone metastases andtrastuzumab emtansine in patients withHER2-positive metastatic breast cancer

	Patient 1	Patient 2	Patient 3
Initial disease			
Age	35 years	30 years	53 years
Histology (grade)	Invasive ductal carcinoma (III)	Invasive ductal carcinoma (II)	Invasive ductal carcinoma (II)
Tumour stage	T1 N2 M0	T3 N1 M0	T4N1M1
Local and systemic treatment	Lumpectomy + lymph node dissection Radiotherapy breast + boost (66) + supraclavicular (50) Mastectomy for disease recurrence Adjuvant chemotherapy, hormonal therapy and trastuzumab	Mastectomy + SN Radiotherapy breast (50) + internal mammary chain and supraclavicular (45) Adjuvant and neoadjuvant chemotherapy, adjuvant hormonal therapy and trastuzumab	Mastectomy + lymph node dissection Breast (45), supraclavicular (45) Chemotherapy and trastuzumab before surgery/radiotherapy
Bone metastatic evolution			
Age at bone metastatic localizations	50 years	38 years	58 years
Others metastatic sites	Brain, liver, lung	Brain	Brain, liver
Systemic treatment	Chemotherapy, trastuzumab	Chemotherapy, lapatinib, trastuzumab	Chemotherapy, hormonal therapy, lapatinib, trastuzumab
Trastuzumab emtansine duration	4 months	11 months	5 months
Stop: yes or no (cause)	Stopped after liver progression	Continued	Continued
Bone radiotherapy			
Localization	Dorsal vertebras	Sacrum	Left shoulder
Type of treatment	D3–D7		
Dose	15 Gy 5 fractions	15 Gy 5 fractions	8 Gy 1 fraction
Symptoms before radiation	Motor deficit, pain	Pain	Pain
Pain control after radiotherapy	Good pain relief	Good pain relief	Good pain relief
Neurologic evolution after radiotherapy	Partial response	N/A	N/A
Side effects related to the concurrent use of radiotherapy and trastuzumab emtansine	No side effects (12 months after treatment)	No side effects (9 months after treatment)	No side effects (3 months after treatment)

Trastuzumab emtansine - T-DM1

HER2-positive Historical published data lower rates of significant RN varying from 5–17%

Kondziolka et al, 350 women SRS 1535 lesions: 6% sympt RN
Minniti et al, SRS for brain M1: 10% sympt RN, 5.8% G3-4
Yang et al, SRS for brain M1: pathologic RN 8.6%
RTOG 90-05: 2-year rate of RN 11%

Mechanisms of toxicity

T-DM1 trastuzumab antibody + cytotoxic agent mysantine (DM1) (activity similar to vinca alkaloids)

Mechanisms of cell death include cellular lysis, apoptosis and mitotic catastrophe

ErbB2 plays a role in glial cell formation, preclinical data upregulation of erbB2 in response to neuronal injury.

→ inflammatory response → increased levels of glutamate, release of cytokines including tumor necrosis factor and interleukins

Trastuzumab emtansine - T-DM1

Stumpf et al. - 2019 Clin Cancer Res. 2019 Jul 1;25(13):3946-3953

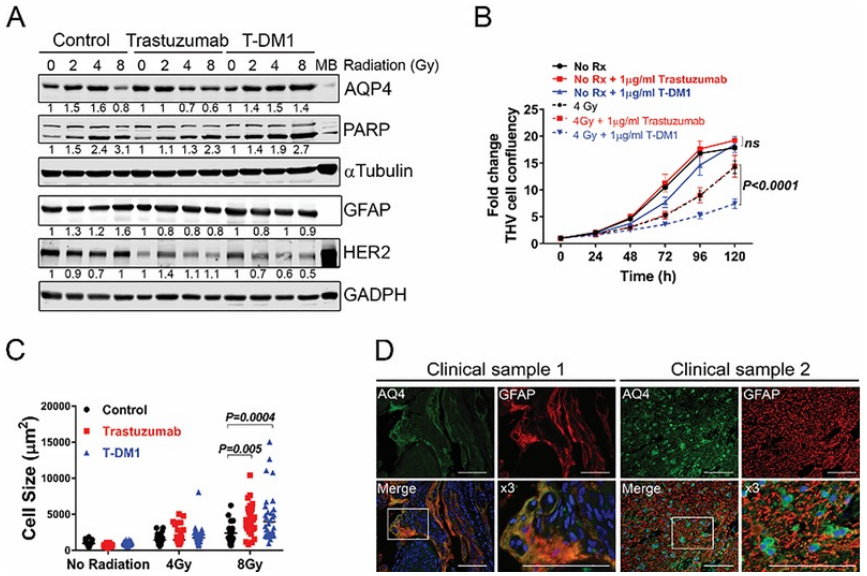
HER2-positive reactive astrocytes → T-DM1 uptake → ↑ RT-induced cytotoxic edema

T-DM1 target reactive astrocytes, ↑ radiation-induced cytotoxicity and astrocytic swelling via upregulation of Aquaporin-4 (Aqp4).

Aqp4 indices neuroinflammation and oedema

Reactive astrocytes modulators of neuroinflammatory response, regulate water flow with Aqp

In vitro T-DM1 exacerbated RT-induced Aqp4 upregulation and cytotoxic effect



lower dose fSRS?

anti-epileptic drugs that target Aqp4?

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

ER+, HER2 - metastatic or advanced BC + AI or fulvestrant

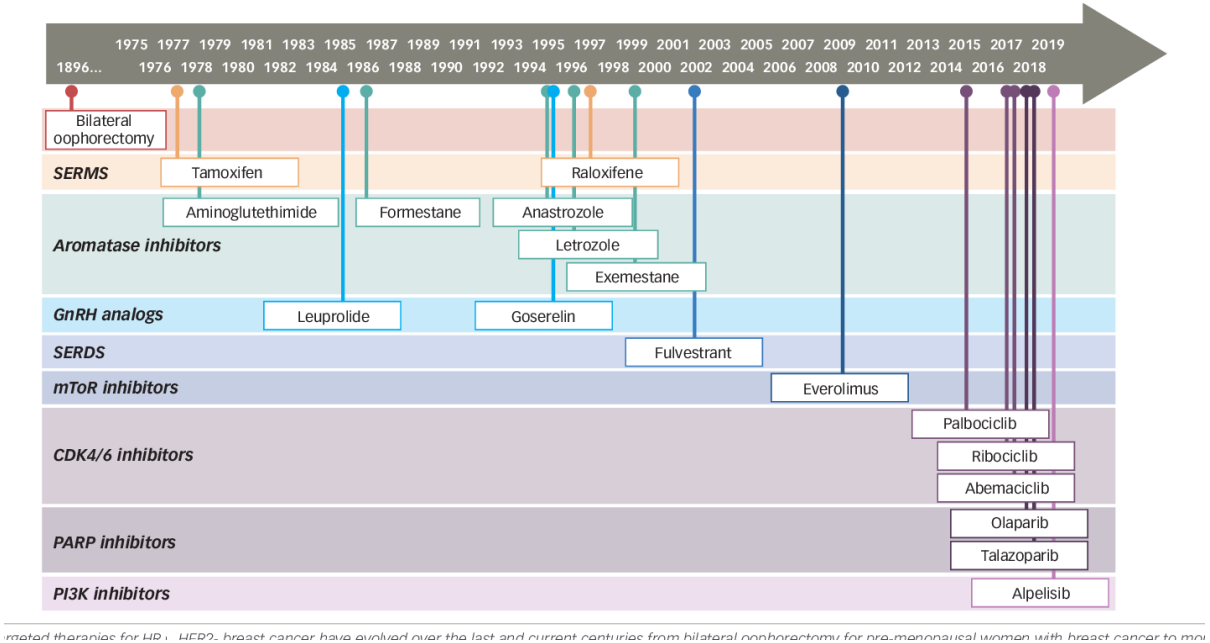
Palbociclib (2016) Ribociclib (2017)

Abemaciclib (2018)

Palbociclib and ribociclib G 3–4 neutropenia

Abemaciclib lower rates vs higher frequence of G 3–4 diarrhea

Oncology & Hematology Review (US). 2020;16(1):23-9 DOI: https://doi.org/10.17925/OHR.2020.16.1.23



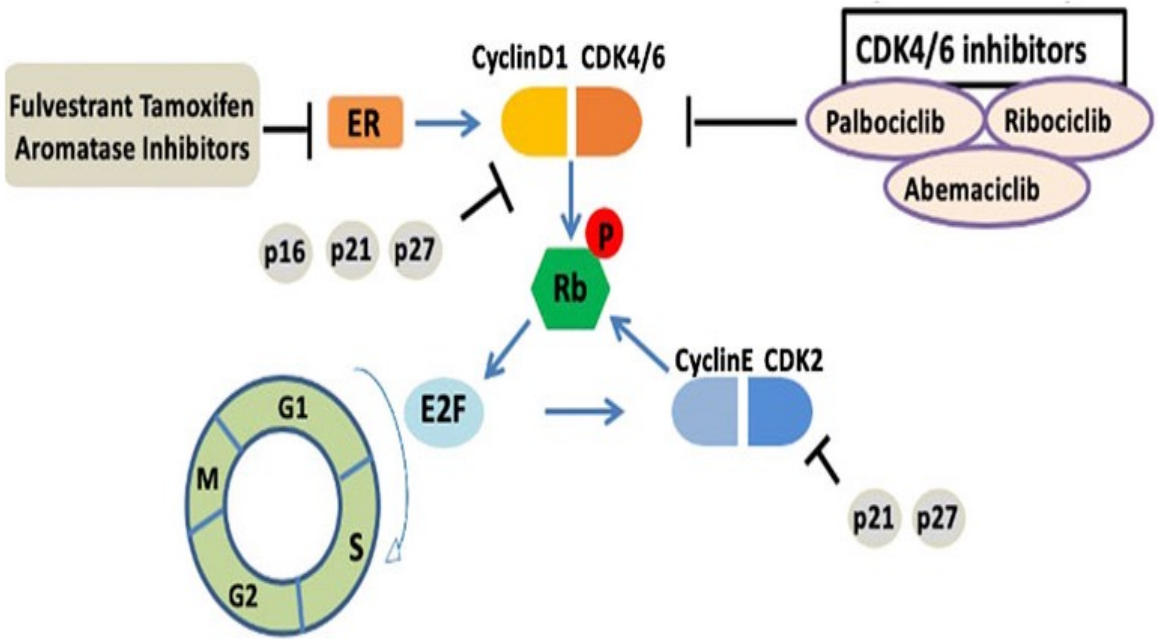
...rgeted therapies for HR+, HER2- breast cancer have evolved over the last and current centuries from bilateral oophorectomy for pre-menopausal women with breast cancer to mo...

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

block tumor suppressor retinoblastoma protein phosphorylation

prevent the transition of cancer cells from G1 to S phase

inhibition of cell cycle and proliferation



Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

Hans et. al. Radiother. Oncol. 2018;126(1):181. doi: 10.1016/j.radonc.2017.09.010

5 MBC palbo + cRT: no TOX increase, symptom relief

Meattini et al. Breast. 2018;42:1–2. doi: 10.1016/j.breast.2018.08.096

5 MBC ribo+RT to bone M1: no RT suspension, one pts G3 vomit/diarrhea

Chowdhary et al. Adv. Radiat. Oncol. 2019;4(3):453–457. doi: 10.1016/j.adro.2019.03.011.

16 MBC palbo + RT (median interval 5 days): not TOX increase vs palbo alone, all pain control and no local failures

Ippolito et al. Breast. 2019;46:70–74. doi: 10.1016/j.breast.2019.05.001.

16 MBC (24 treatments) palbo/ribo + RT (69% palliative to bone - median dose 30Gy; 31% oligoM1 median dose 50 Gy): no myelosuppr increase, all pain relief, no failure in oligoM1

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

Figura et al - 2019 J Neurooncol. 2019 doi: 10.1007/s11060-019-03260-6

15 pts SBRT (various 20Gy/5fr to 24Gy SF) on 42 brain M1
Median dose 21 Gy (range 18–30 Gy), 62% SRS, median PTV 0.6 cm3

6 mo pre-post (43% lesions concurrent) palbo (n=10) or abem (n=5)

2 cases of radionecrosis (dose and drug not reported) managed with steroids and bevacizumab.

No other treatment-related neurologic toxicities

12 mo LC 88%

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

doi: 10.1016/j.clbc.2020.05.013. Epub 2020 May 26.

Ratosa et al - 2020

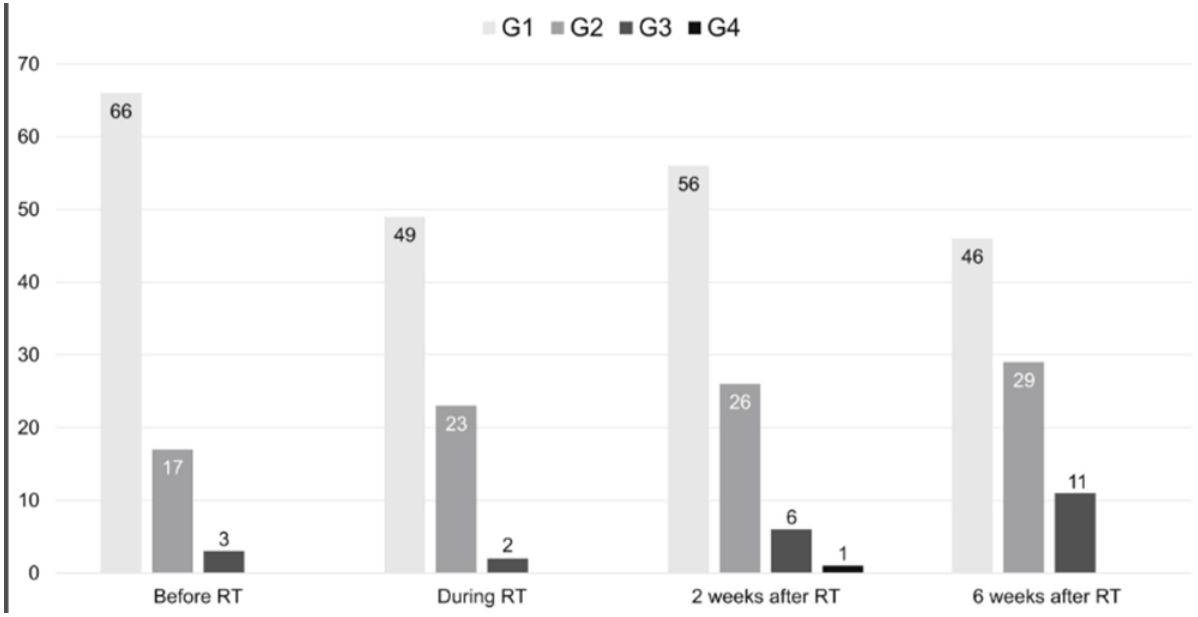
46 pts MBC + CDK4/6i (30 palbo, 15 ribo, 1 abem), 62 lesions (50 bone, 7 visceral, 3 brain, 2 breast)

LC 98% 6 mo, 90% 12 mo

Pain relief 80%

16 pts (34.8%) concurrent CDK4/6i + palliative RT

one G2 and one G3 diarrhea, soon after RT end and resolved without complications.



Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

Beddok et al - 2020

30 pts MBC RT+concurrent palbo

35 sites: M1 20Gy/5fr (n = 13), 30Gy/10fr (n=10) and 8Gy/1fr (n=3) 18Gy/1FR (brain)
9 LR RT (50Gy/25fr)

2 pts RT stop due to TOX: G3 dermatitis + febrile neutropenia and G2 dysphagia in pts with local treatment both large PTV (~1607 cc)

No late TOX

BJC British Journal of Cancer www.nature.com/bjc

BRIEF COMMUNICATION
Clinical Study

Concurrent use of palbociclib and radiation therapy: single-centre experience and review of the literature

Arnaud Beddok[1], Hao Ping Xu[2], Alexandre Arsène Henry[1], Baptiste Porte[3], Alain Fourquet[1], Paul Cottu[3] and Youlia Kirova[1,4]

Table 1. Characteristics of the nine locoregional irradiations.

Patient	Sites	CTVcc	PTVcc	Dose	Technique	Grade ≥ 2 acute toxicity	Pa du
1	Left thoracic wall + left L1–L4 and IP	223	392	50 Gy (2 Gy/f)	Tomo	0	0
2	Right thoracic wall + right L2–L4, IP, and IMN	362	669	50 Gy (2 Gy/f)	VMAT	Neutropenia	0
3	Left breast + left L1–L4 and IP	566	820	50 Gy (2 Gy/f)	Tomo	0	0
4	Right breast + right L1–L4 and IP SIB	1082	1285	50.4 Gy (1.8 Gy/f) SIB: up to 64.4 Gy (2.3 Gy/f)	Tomo	0	0
5	Right thoracic wall + right L1–L4 and IP	395	725	50 Gy (2 Gy/f)	Tomo	0	0
6	Right thoracic wall + right L1–L4 and IP	511	805	50 Gy (2 Gy/f)	Tomo	0	0
7	Left thoracic wall + left L2–L4 and IP	533	778	50 Gy (2 Gy/f)	Tomo	0	0
8	Left breast + left L2–L4 and IP SIB	1355	1607	50.4 Gy (1.8 Gy/f) SIB: up to 64.4 Gy (2.3 Gy/f)	VMAT	Dermatitis, neutropenia and dysphagia	1
9	Bilateral thoracic walls + bilateral L1–L4 and IP	1019	1607	50 Gy (2 Gy/f)	Tomo	Dermatitis, neutropenia and pain	1

L1–L4 axillary level 1–3 and supraclavicular region (level 4), *IP* interpectoral (Rotter) nodes, *IMN* internal mammary nodes, *SIB* simultaneous integrated boost, *2 Gy/f* 2 Gy per volumetric modulated arc therapy.

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

https://doi.org/10.1038/s41598-020-70430-2

Guerini et al - 2020

18 patients (32 treated sites)

50% palbociclib, 33.3% ribociclib and 16.7% abemacliclib. All concurrent.

Acute non-hematologic toxicity only G1, with the only exception of a patient who developed G3 ileitis.

Pain control complete 88.2% 3 mo after RT

94.4% local control of disease

grade 3–4 neutropenia within 6 cycles after RT 61.1% ≈ palbo alone
no RT susp, no definitve CDK4/6 susp, median temporary susp 7 days

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

Kim et al - 2021 Breast. 2021 Dec;60:163-167. doi: 10.1016/j.breast.2021.10.001.

30 pts, 36 RT courses (brain n=5, spine n=19, pelvis n=9, others=10)

RT within 14 days of CDK4/6i (8 concurrent, 21 after CDK4/6i)(palbo n=34, abem n=2)

median dose 30 Gy (8-40Gy)

No G≥3 non-hematologic TOX

No increased hematologic TOX

29/30 pts sympt relief, LC 94.4%-91.7% 6mo-12mo

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The Breast
journal homepage: www.elsevier.com/brst
THE BREAST

Safety of cyclin-dependent kinase4/6 inhibitor combined with palliative radiotherapy in patients with metastatic breast cancer

Kristine N. Kim [a], Payal Shah [b], Amy Clark [b], Gary M. Freedman [a], Sana Dastgheyb [a], Andrew R. Barsky [a], Alexandra D. Dreyfuss [a, c], Neil K. Taunk [a, *]

AL Rashdan A et al - 2022

RADIATION ONCOLOGY • BIOLOGY • PHYSICS ASTRO
CLINICAL INVESTIGATION | VOLUME 114, ISSUE 3, P399-408, NOVEMBER 01, 2022

Radiation Therapy With Cyclin-Dependent Kinase 4/6 Inhibitors: A Multi-institutional Safety and Toxicity Study

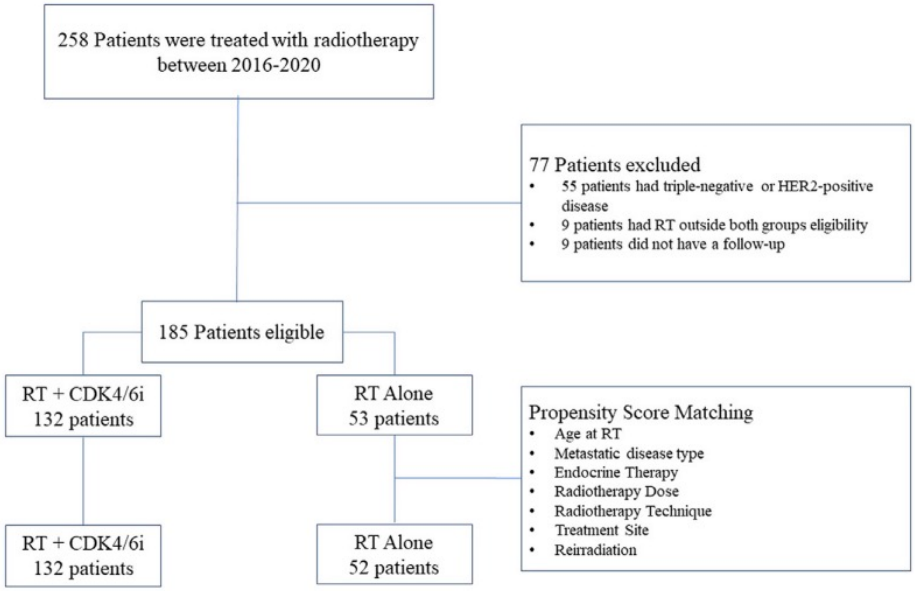
Abdulla Al-Rashdan, MD • Sarah Quirk, PhD, MCCPM • Michael Roumeliotis, PhD, MCCPM • ...

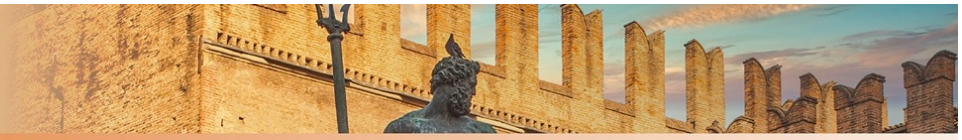
retrospective cohort study mBC, 2016-2020, palliative RT

RT within 30 days (before-after) CDK4/6i vs RT alone
132 pts (220 RT sites) RT + CDK4/6i vs 53 pts (93 RT sites) RT alone

65% vs 75% pts RT on spine/pelvis

acute TOX RT + CDK4/6i vs RT alone OR 3.13 (p .121)





Al Rashdan A et al - 2022

RADIATION ONCOLOGY • BIOLOGY • PHYSICS ASTRO
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acute G≥2 nonhematological TOX 11.5% vs 7% (p = .439)
acute G≥3 TOX 3.7% vs 0% (p = .151).
acute TOX in RT + CDK4/6i group mainly with concurrent treatment (67%)

1 hospital admission
G3 diarrhea concurrent RT

G3 toxicity skin and GI

Table 5 Details for patients with grade 3 toxicity

P	CDK4/6i	RT seq	RT dose (Gy)	RT Fx	RT site	RT technique	Bowel volume within the field (cc)	Bowel volume within 105% or more	Max point in bowel (%)	Admission
1	Ribociclib	C	20	5	Pelvis	3D-CRT	25	<5%	107	Yes
2	Palbociclib	C	20	5	Pelvis	3D-CRT	35	0	99	No
3	Palbociclib	A	20	5	Pelvis	3D-CRT	30	0	104	No
4	Ribociclib	C	30	10	WB	Field in field	NA	NA	NA	No
5	Palbociclib	C	35	12	PB	Combined	NA	NA	NA	No
			30	10	PB	Field in field	NA	NA	NA	
			5	2	Boost	Electrons	NA	NA	NA	

Abbreviations: 3D-CRT = 3D conformal radiation therapy; A = RT-after; C = RT-concurrent; cc = cubic centimeter; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; Fx = fractions; Gy = Gray; NA = not applicable; P = patient; PB = partial breast; RT = radiation therapy; Seq = sequence; WB = whole breast.

Visani et al - 2022


Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com
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Original Article
Safety of CDK4/6 inhibitors and concomitant radiation therapy in patients affected by metastatic breast cancer
Luca Visani [a], Lorenzo Livi [a,b], Ivica Ratosa [c,d], Miha Orazem [c,d], Domen Ribnikar [d,e], Calogero Saieva [f], Carlotta Becherini [b], Viola Salvestrini [a,b], Erika Scoccimarro [a,b], Marianna Valzano [a,b], Cecilia Cerbai [a,b],

132 consecutive pts; RT 57 pts (43.2%) (70 lesions)

concomitant RT no ↑ G ≥ 3 AEs (p = 0.19) or any grade AEs (p = 1.0)

no association with RT and CDK4/6i dose reduction (p = 0.49) and discontinuation rates (p = 0.14)

concomitant RT did not affect PFS (p = 0.71) and OS rates (p = 0.55).

Visani et al - 2022


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palbo 93 (70.5%), ribo 37 (28.0%), abem 2 (1.5%)

RT palliative (n = 56; 77.2%) vs radical intent (n = 14; 22.8%)

2D/3D technique (n = 55; 78.6%) versus an IMRT or CyberKnife (n = 15; 21.4%).

Bone 77.2%

16.6% nausea/vomiting (G3; 2.3%), 14.4% diarrhea (G3; 2.3%)

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

https://doi.org/10.1038/s41598-020-70430-2

Guerini et al - 2020

Bulky (PTV 1854 cc) pelvic localization (L5 vertebra, sacrum and right ischium) 30Gy/10fr

10 days after RT G3 toxicity (diarrhea, pain) → CT scan wall thickening and luminal narrowing of the distal ileum, colonoscopy confirmed ileitis

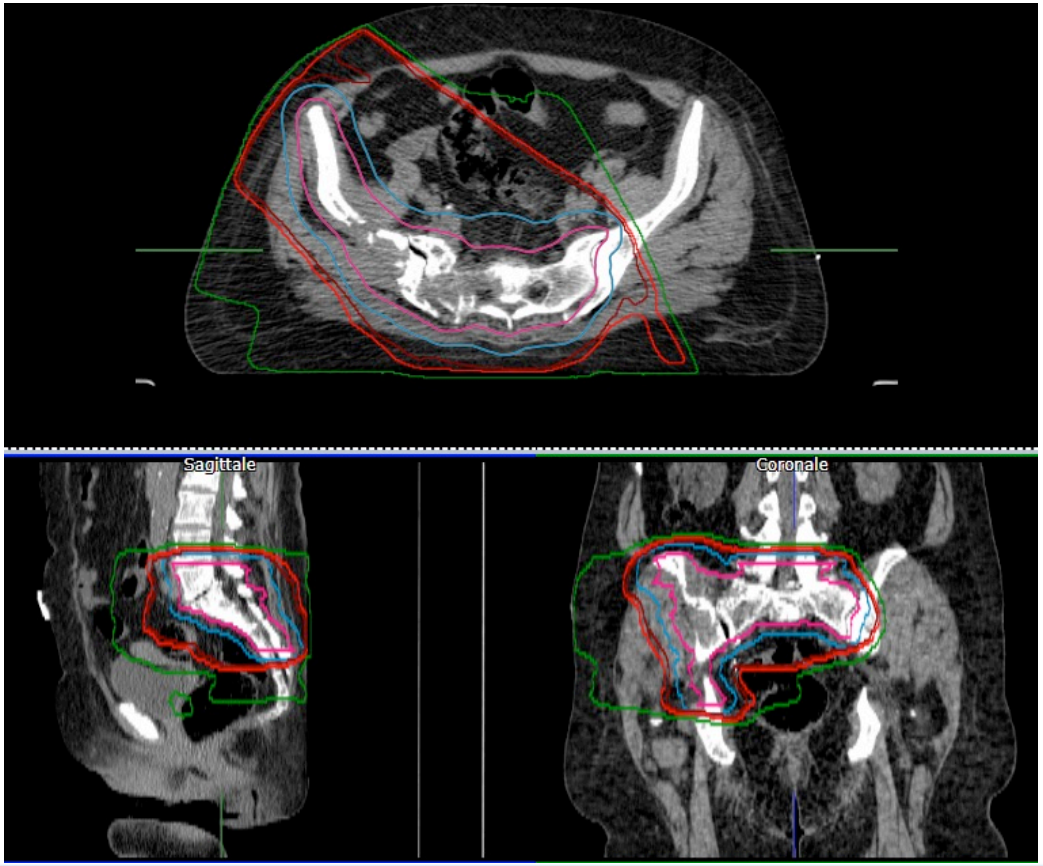
conservative management with antibiotics and anti-inflammatory drugs, toxicity completely resolved after 20 days.

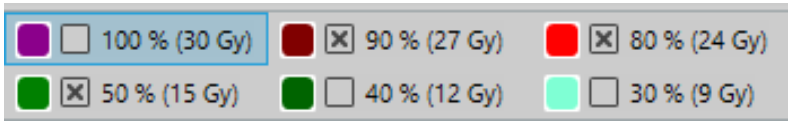
CT-scan performed 3 months later complete radiological resolution of ileitis.

Palbociclib suspended for a cycle and later resumed at full dosage and still ongoing 29 months after

Later SBRT (30 Gy/3 fractions) on C5 vertebra: during this treatment, palbociclib suspended to avoid excessive toxicity.

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors





Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

https://doi.org/10.1038/s41598-020-70430-2

Other seven patients treated to high-volume pelvic sites with similar dosimetric parameters did not develop high grade intestinal toxicity.

Patient	CTV (cc)	PTV (cc)	Intestinal Dmean (Gy)	Intestinal Dmax (Gy)	Intestinal D50 (Gy)	Intestinal V10 (%)	Dose/fraction	Diarrhea
Pt 1: L5 + sacrum + R ilium	944.5	1853.9	10	31	16.7	37	30 Gy/10fr EQD2 32.5	G 3
Pt 2: L5 + sacrum + R sacroiliac joint	545	1,138.9	11.2	30.9	9.2	45	30 Gy/10fr EQD2 32.5	G 1
Pt 4: R ischium + R ilium + S2	491.8	1,053.1	7.7	31.2	2.8	30	30 Gy/10fr EQD2 32.5	G 1
Pt 5: R ilium + R sacral ala	151.7	232.1	1.5	20	0.2	5	20 Gy/5 fr EQD2 23.3	No
Pt 6: L acetabulum + R sacral ala	257.4	666.1	6.7	31.2	1.3	27	30 Gy/10fr EQD2 32.5	No
Pt 7: Sacrum + R ilium	933.7	1819.4					30 Gy/10fr EQD2 32.5	No
Pt 8: S3-S5 tract	36.1	109.7	2.6	30.3	0.2	6	30 Gy/10fr EQD2 32.5	No
Pt 13: L ischium + L pubic bone	89.6	214.9	2.5	8	1.9	0	8 Gy/1fr EQD2 12	No

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

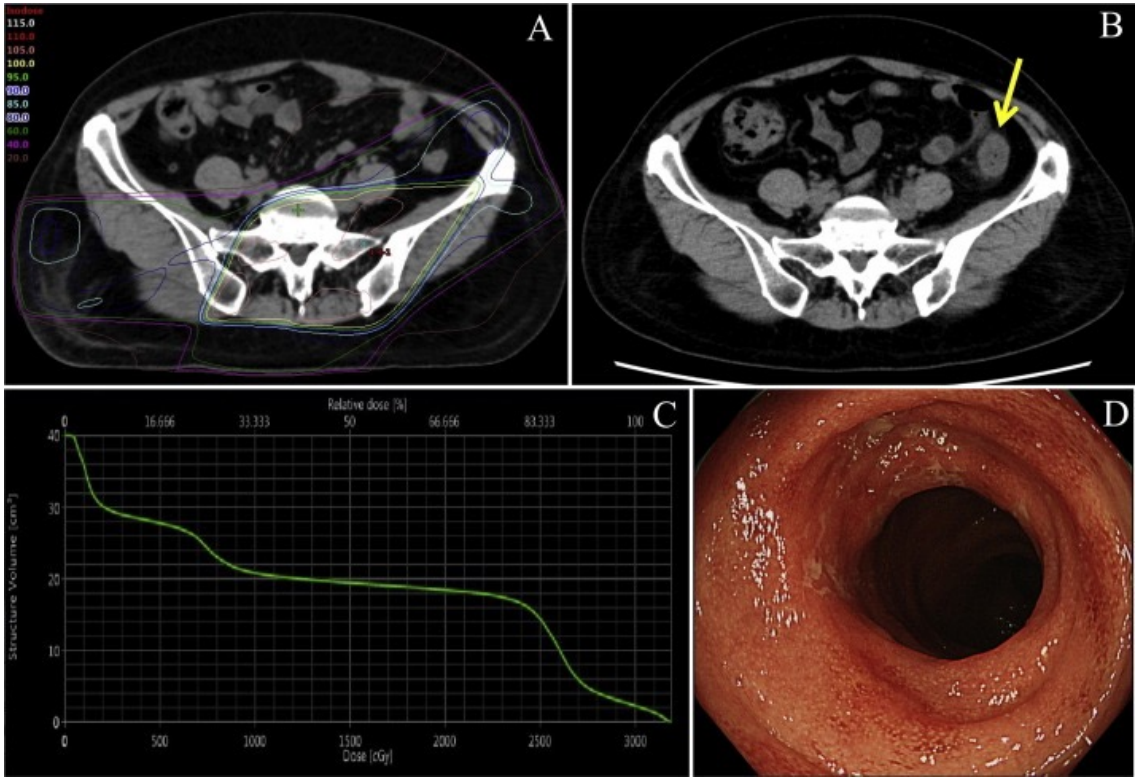
doi: 10.1016/j.radonc.2018.09.020.

Kawamoto T et al – 2019

Palbo+RT (30Gy/10fr on iliac bone+S1) →G3 enterocolitis 3 days after RT end, confirmed by CT scan + colonoscopy → resolved after 3 wks conservative treatment

descending colon max dose was 31.9 Gy, 21 mL>10 Gy, 18 mL >20 Gy

30 Gy/10 fr EQD 2 Gy/fr 32.5 Gy → below the normal bowel radiation tolerance

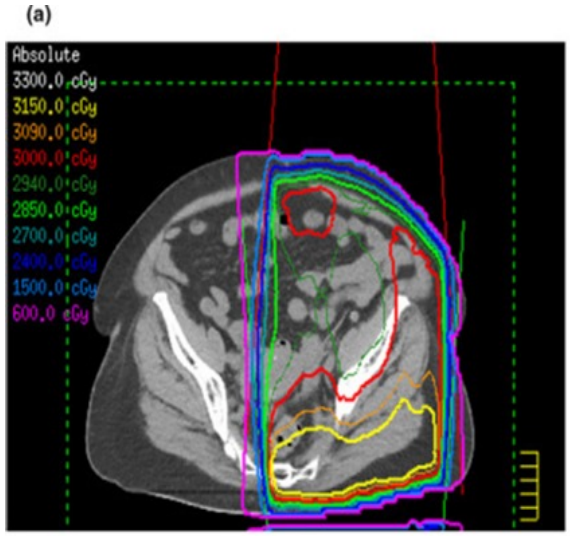


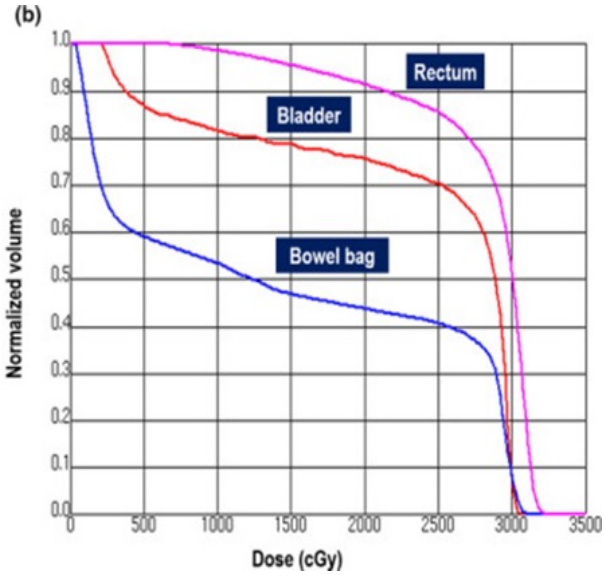
Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

Dasgupta A et al. J Med Radiat Sci. 2021 Mar; 68(1): 96–102.

30Gy/10fr left hemipelvis + proximal femur + concurrent palbo

5 days after RT G3 pancolitis (CT scan confirmed) → 3 w hospitalization, conservative treatment with mesalazine, palbo held → complete resolution





Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

Pract Oncol Radiother. 2019 May-Jun; 24(3): 276–280. doi: 10.1016/j.rpor.2019.03.001

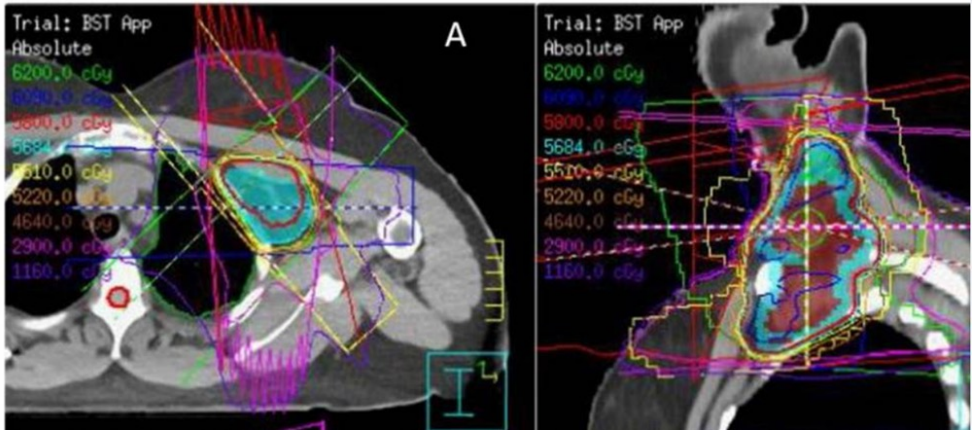
Messer JA et al

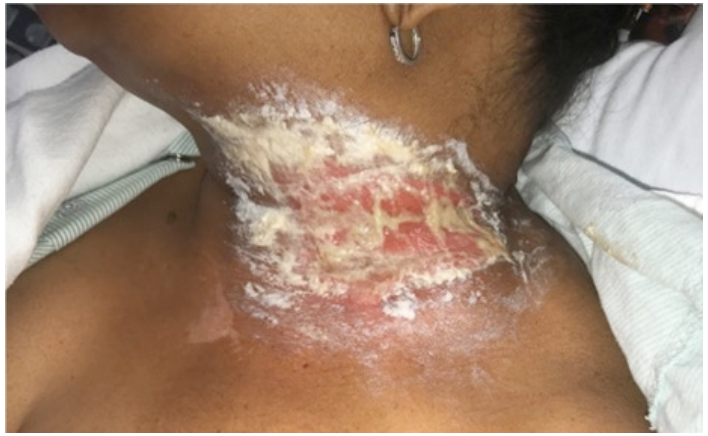
metastatic supraclavicular lymph node 60Gy/30fr + palbo

G3 esophagitis and dermatitis → hospitalized palbo suspended and RT completed

Complete resolution with IV infusion and topical

palbo restarted after 1 mo, at 6 mo CR



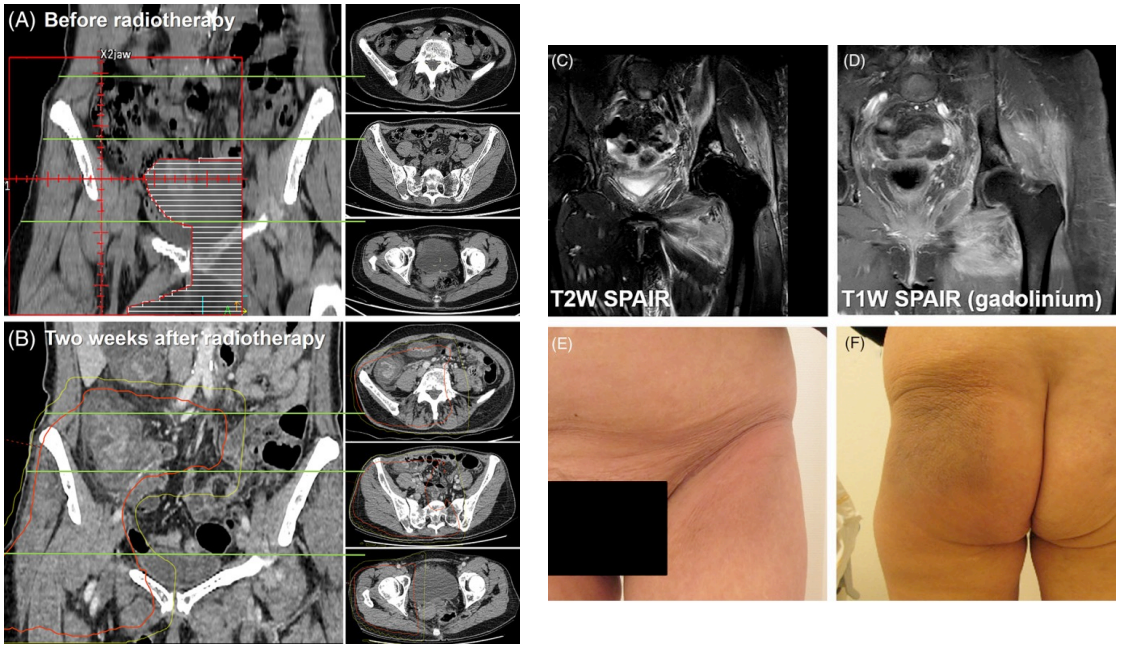


Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

van Aken ESM et al. Cancer Rep (Hoboken). 2022 Feb;5(2):e1470. doi: 10.1002/cnr2.1470.

Case 1: 20Gy/5fr pelvic bone M1 + concurrent palbo EQD2 23 Gy to bowel loops
few days after RT severe enterocolitis (confirmed by CT scan) hospitalized for 10 days
partial remission after 2 months, conservative treatment

Case 2: 8 Gy/1fr left hip → short term pain ctrl → 2 mo later 16Gy/2fr AP-PA + concurrent palbo
4 mo after RT skin discoloration and induration and edema (confirmed by PET and MRI) around RT site with severe pain refractory to treatment

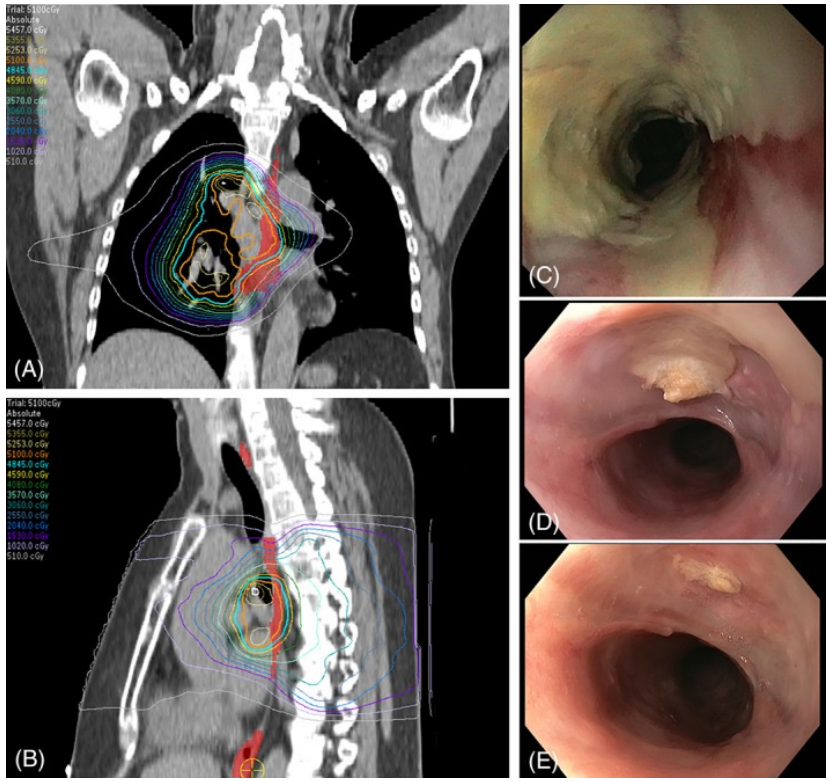


Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

van Aken ESM et al. Cancer Rep (Hoboken). 2022 Feb;5(2):e1470. doi: 10.1002/cnr2.1470.

Case 3: 51Gy/17fr mediastinum and R hilum + palbo last 9 days of RT
G2 dysphagia during and after RT, 3 mo after ulcer with a pinpoint stenosis
resolved after 1.5 mo with palbo suspension, palbo restarted

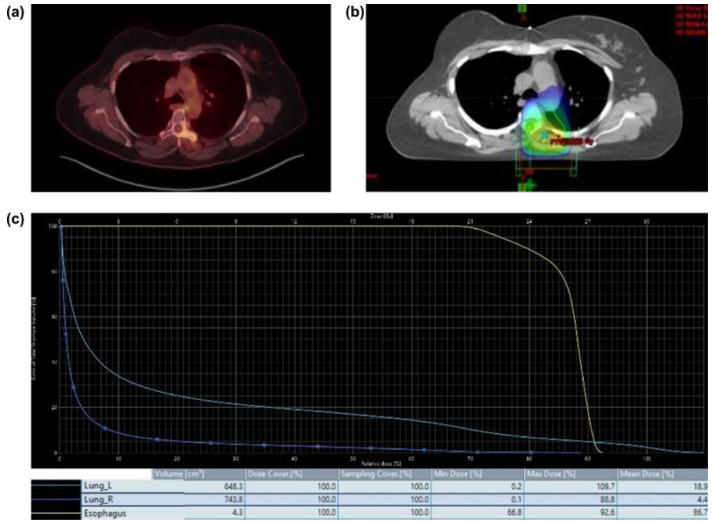
improvement only after discontinuation of palbo → hinders repopulation?

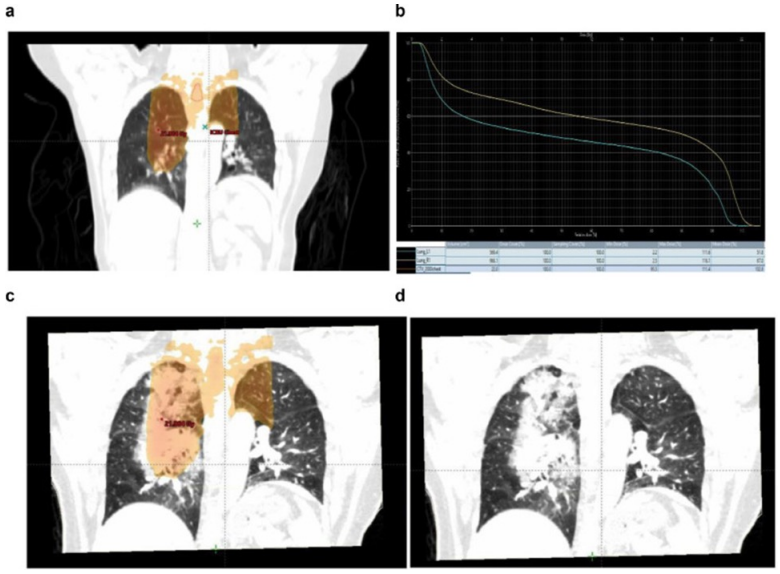


Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

T5+soft tissue M1 30Gy/10fr + concurrent palbo

6 days after RT G3 oesophagitis, hospitalized for supportive care → fully recovered





20 Gy/5 fr AP-PA symptomatic mediastinal nodal metastases

4 mo after started palbo → RT ground glass in previous RT field → G5 radiation recall pneumonitis

David S et al. Transl Oncol. 2021 Jan;14(1):100939.
doi: 10.1016/j.tranon.2020.100939.

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

Nasir UM et al. Anticancer Res. 2020 Sep;40(9):5291-5294. doi: 10.21873/anticanres.14534.

palliative RT T10 20Gy/5fr + palbo

3 days after RT severe odynophagia, and dysphagia and was found to have grade 2-3 esophageal ulcers. 4 days inpatient, after 1 mo restarted palbo, EGDS improved at 2 mo

Kim KN et al J Oncol Pharm Pract. 2022 Aug 5:10781552221118841.

goserelin + tamoxifen + palbociclib

RT 30Gy/10fr postop femur on surgical nail + lumbar spine 20Gy/5fr; palbo stopped 4 days before RT

16 days after RT G3 skin tox, resolved with topic treatment

Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

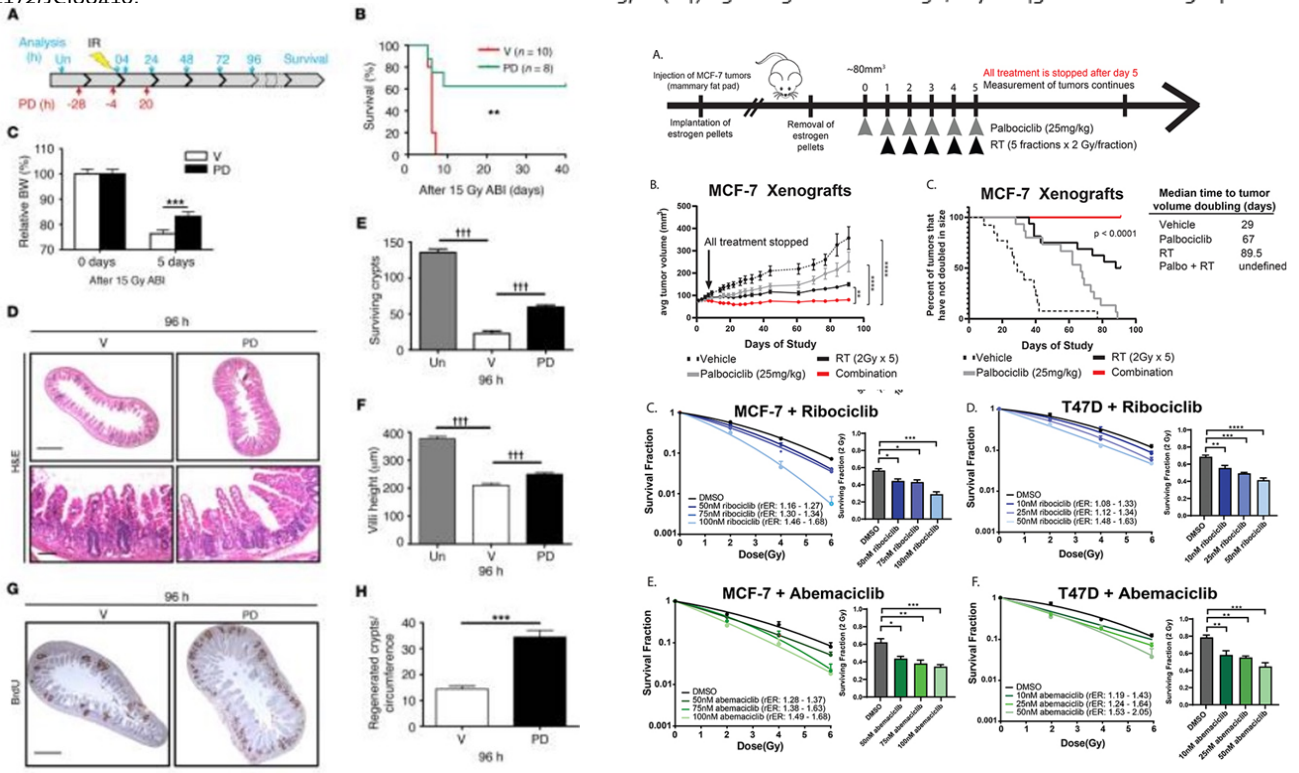
J. Clin. Invest. 2016;126(11):4076–4087. doi: 10.1172/JCI88410.

Clin Cancer Res. 2020 Dec 15;26(24):6568-6580. doi: 10.1158/1078-0432.CCR-20-2269. Epub

cell cycle critically regulates the DNA damage response and survival of intestinal stem cells

G1/S block
cell division pivotal to repair/repopulate normal tissues after radiotherapy

Palbo/ribo/abem significantly radiosensitize ER+ cell lines at low nanomolar, sub IC50 concentrations, suppression of homologous recombination (HR) and non-homologous end joining (NHEJ).



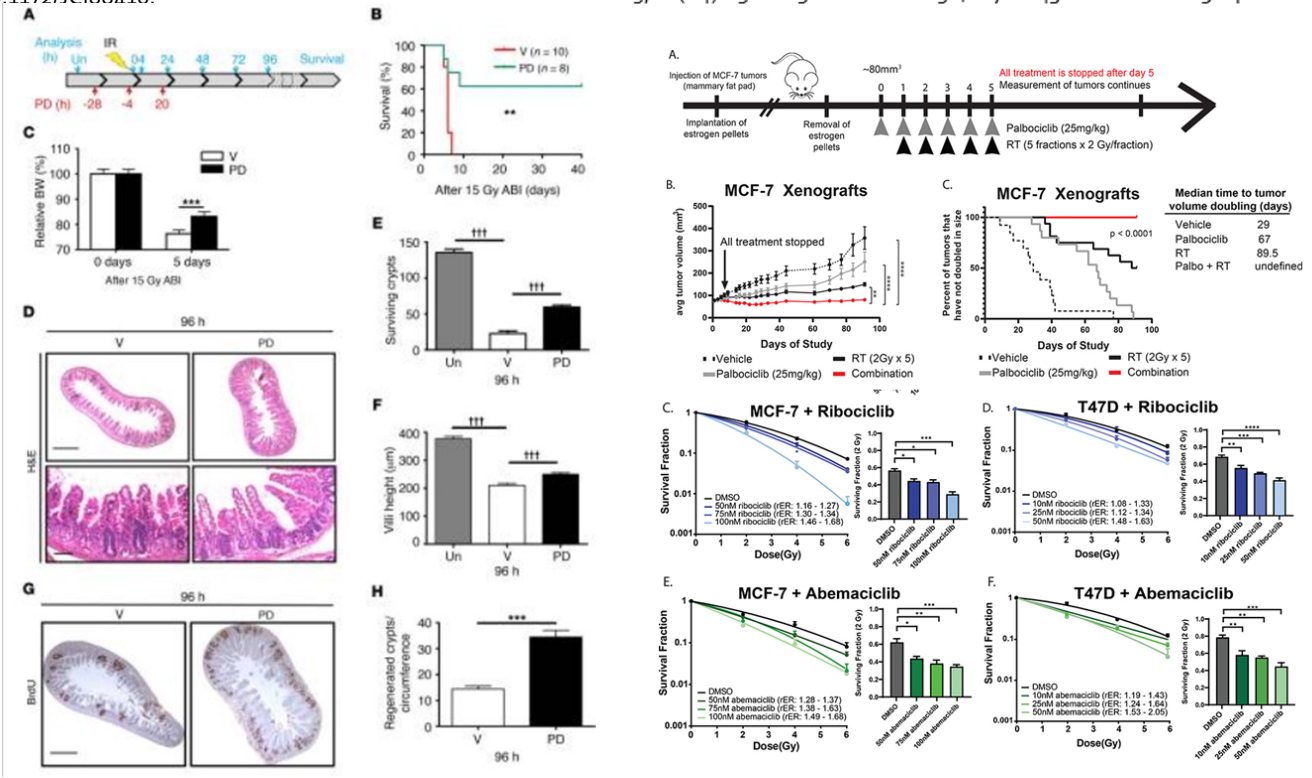
Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

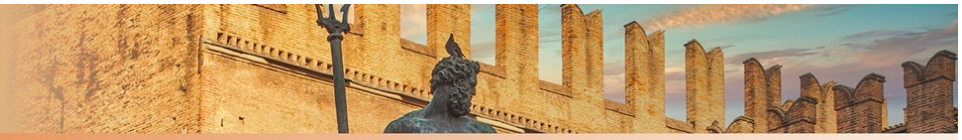
J. Clin. Invest. 2016;126(11):4076–4087. doi: 10.1172/JCI88410.

Clin Cancer Res. 2020 Dec 15;26(24):6568-6580. doi: 10.1158/1078-0432.CCR-20-2269. Epub

radiosensitization enhances DNA damage, halts its repair, blocks cell cycle progression into the radioresistant S phase, and increases the proportion of cells in the radiosensitive G2-M phases.

Lee et al murine model: excessive GI TOX concurrent palbo vs protective before RT





Selective cyclin dependent kinases 4/6 (CDK4/6) inhibitors

INCREASED GI TOX: POSSIBLE SOLUTIONS?

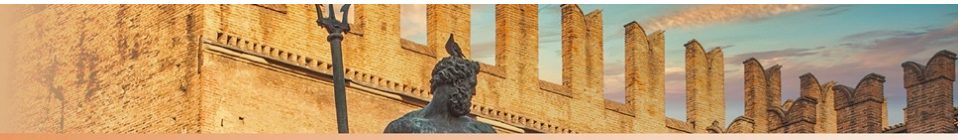
Restrictive constraints to GI structures

Conformal techniques (IMRT/VMAT/Tomo)

Monitor pts with previous GI toxicities and/or risk factors

Consider suspending CDK4/6 inhibitors 1 week before/after RT

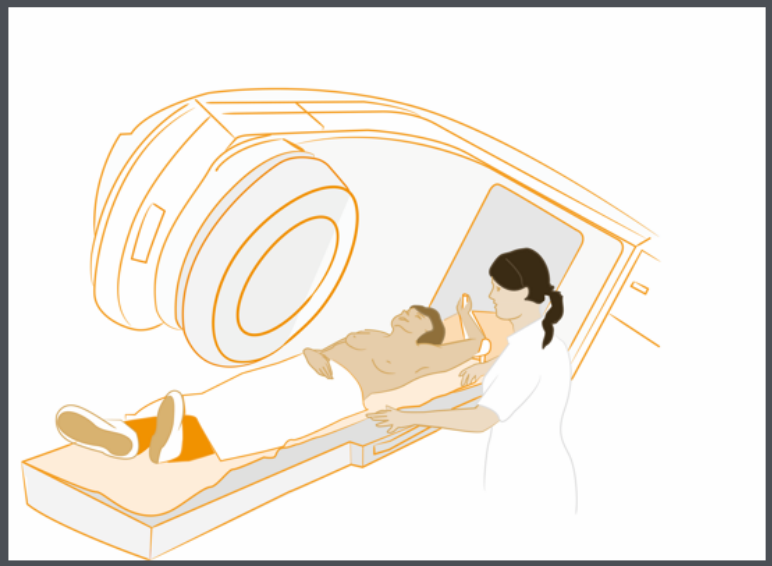
In case of tox consider extending treatment break until all symptoms resolve



Conclusions

- Accurate medical history
- Definition of optimal risk/benefit balance
- Treatment plan tailored according to risk factors
- Specific follow up for patients at higer risk of toxicity
- Gathering data to be published and used for reference

CONCERN-RT-MBC: COncurrent New anticanCER ageNts and Radiation Therapy in Metastatic Breast Cancer patients.




Thank you for the attention
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