MRO. ART
INNOVATIVE TREATMENTS AND PATIENTS COMPLIANCE
31° RESIDENTIAL COURSE

Does drug innovation change compliance in combined treatments?

MONOCLONAL ANTIBODIES AND SMALL MOLECULES

Dott. Fabio Marazzi
UOC Radioterapia
Fondazione Policlinico Gemelli IRCCS - Roma

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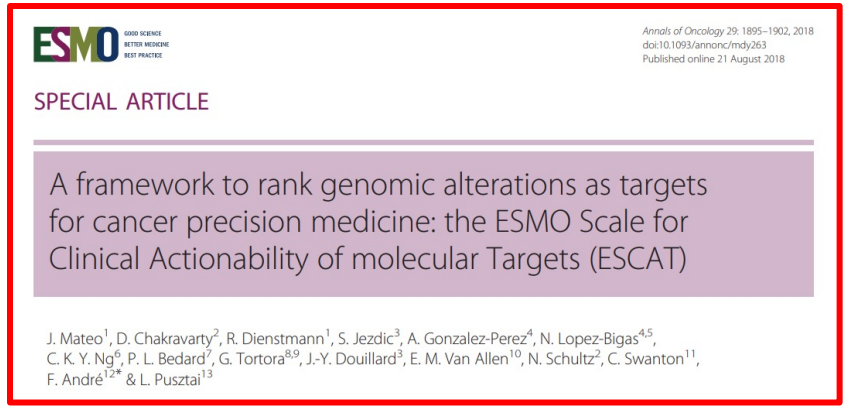
- Introduction
- Monoclonal antibodies and radiotherapy: adjuvant and metastatic setting
- Small molecules and radiotherapy: adjuvant and metastatic setting
- Conclusion

Introduction

SISTEMIC THERAPY EVOLUTION IN CANCER TREATMENT



CYTOTOXIC DRUGS

- ANTRACICLINE
- TAXANES
- ALKILANTS
- FLUOROPIRIMIDINE
- PLATINUM COMPAUNDS
- VINKA ALCALOIDES
- MICROTUBLE INIBITORS

TARGET THERAPIES

- ORMONAL THERAPIES
- HER2 TARGET THERAPIES
- PARP INHIBITORS
- CDK4/6 INHIBITORS
- PI3KCA ALFA INHIBITORS
- PI3KCA BETA SPARING
- ANTI-EGFR
- ANTI-TKI
- ANTIBODY DRUGS CONIUGATE ADC

IMMUNOTHERAPY

- ANTI PD1/PDL1
- CTLA4

CAR-T CELL THERAPY

DIAGNOSTIC MORPHOLOGICAL AND MOLECULAR EVOLUTION

NEW DRUGS IN THE ERA OF PRECISION MEDICINE → ESSENTIAL ROLE OF PREDICTIVE AND PROGNOSTIC MARKERS

Introduction

- **In 2021 FDA approved 43 drugs**
- **15 drugs were approved for cancer treatment**
- 10 small molecules (1 anti-CDK4/6, 1 c-MET inhibitor, 1 PI3K inhibitor, 4 anti-TKI, 1 KRAS inhibitor, 1 enzyme, 1 interferon)
- 1 drug-conjugate small molecule (1 peptide)
- 2 monoclonal antibodies (1 anti-PD1, 1 biphasic anti EGFR-anti MET)
- 2 drug-conjugate monoclonal antibodies (1 anti-CD19, 1 anti-TF)

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date*
43	Besremi	ropeginterferon alfa-2b-njft	11/12/2021	To treat polycythemia vera, a blood disease that causes the overproduction of red blood cells Press Release
42.	Scemblix	asciminib	10/29/2021	To treat Philadelphia chromosome-positive chronic myeloid leukemia with disease that meets certain criteria
41.	Tavneos	avacopan	10/7/2021	To treat severe active anti-neutrophil cytoplasmic autoantibody-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapy, including glucocorticoids
40.	Livmarli	maralixibat	9/29/2021	To treat cholestatic pruritus associated with Alagille syndrome
39.	Qulipta	atogepant	9/28/2021	To prevent episodic migraines
38.	Tivdak	tisotumab vedotin-tftv	9/20/2021	To treat recurrent or metastatic cervical cancer with disease progression on or after chemotherapy
37.	Exkivity	mobocertinib	9/15/2021	To treat locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor exon 20 insertion mutations
36.	Skytrofa	lonapegsomatropin-tcgd	8/25/2021	To treat short stature due to inadequate secretion of endogenous growth hormone
35.	Korsuva	difelikefalin	8/23/2021	To treat moderate-to-severe pruritus associated with chronic kidney disease in certain populations
34.	Welireg	belzutifan	8/13/2021	To treat von Hippel-Lindau disease under certain conditions
33.	Nexviazyme	avalglucosidase alfa-ngpt	8/6/2021	To treat late-onset Pompe disease Press Release

Novel Drug Approvals for 2021 | FDA

Introduction

TARGET THERAPIES

Monoclonal Antibodies

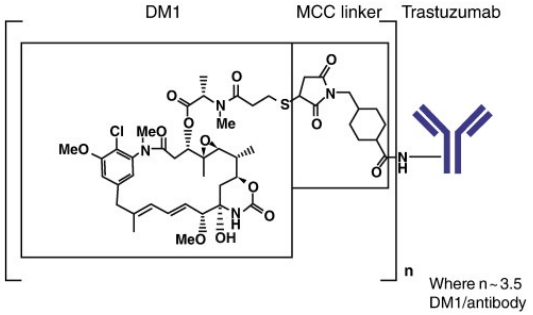
Small-molecules

RADIOTHERAPY SINERGIC EFFECT

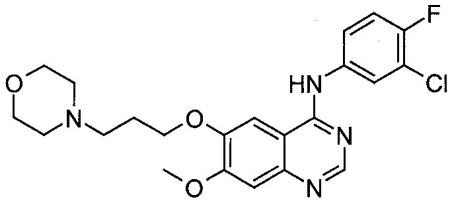
Antibody-drug conjugates (ADCs)

Small molecule drug-conjugates (SMDCs)

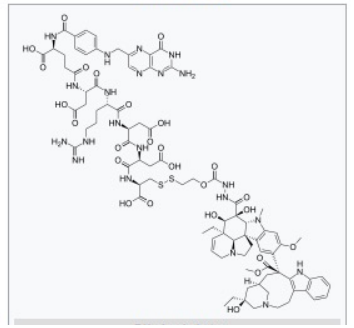
Trastuzumab



Gefitinib



Vintafolide



[Targeted Therapy for Cancer - National Cancer Institute]

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

TRASTUZUMAB: clinical evidences

Radiotherapy
Breast Cancer
the NCCTG P

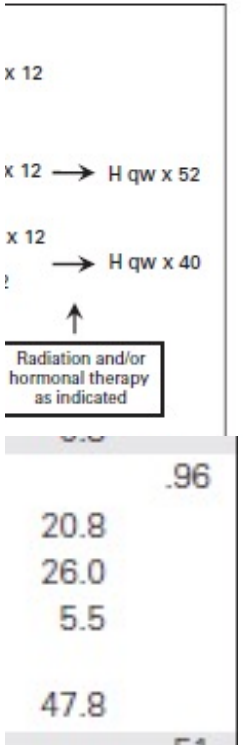
Michele Y. Halyard, Thon
Larry Marks, Nancy Davi
and Edith A. Perez

Type of RT
- Whole-breast RT
- Whole-breast plus regior
- Postmastectomy chest v
- Postmastectomy chest v lymphatic RT

Table 2. Incidence of RT-Related Adverse Events (grade ≥ 1 and ≥ 3)

Adverse Event	% of Patients				AC-T *v* AC-T-H*		AC-T *v* AC-TH-H*	
	AC-T (n = 521)	AC-T-H (n = 543)	AC-TH-H (n = 439)	P*†	OR	95% CI	OR	95% CI
Grade ≥ 1								
Radiation dermatitis	84	84	85	.79	0.97	0.69 to 1.34	1.09	0.76 to 1.55
Pneumonitis or pulmonary infiltrates	0.6	1.1	1.1	.59	1.93	0.48 to 7.75	1.97	0.47 to 8.31
Dyspnea	1.9	2.4	2.3	.86	1.25	0.55 to 2.88	1.18	0.49 to 2.87
Cough	2.9	2.4	2.3	.81	0.83	0.39 to 1.76	0.78	0.35 to 1.75
Radiation dysphagia (esophageal)	1.6	1.5	2.7	.30	0.96	0.36 to 2.58	1.79	0.72 to 4.42
Leukocytes	7.2	12.8	10.3	.01	1.89	1.25 to 2.88	1.47	0.93 to 2.32
Neutrophils or granulocytes	3.7	6.5	5.0	.12	1.81	1.02 to 3.21	1.37	0.73 to 2.57
Grade ≥ 3								
Radiation dermatitis	5.6	5.9	4.3	.51	1.06	0.63 to 1.78	0.76	0.42 to 1.38
Pneumonitis or pulmonary infiltrates	—	0.2	—	—	—	—	—	—
Dyspnea	0.6	—	—	—	—	—	—	—
Cough	—	—	—	—	—	—	—	—
Radiation dysphagia (esophageal)	—	—	—	—	—	—	—	—
Leukocytes	0.2	0.6	1.1	.23	2.87	0.30 to 27.69	5.91	0.69 to 50.78
Neutrophils or granulocytes	0.2	—	0.5	.78	—	—	2.35	0.21 to 25.98

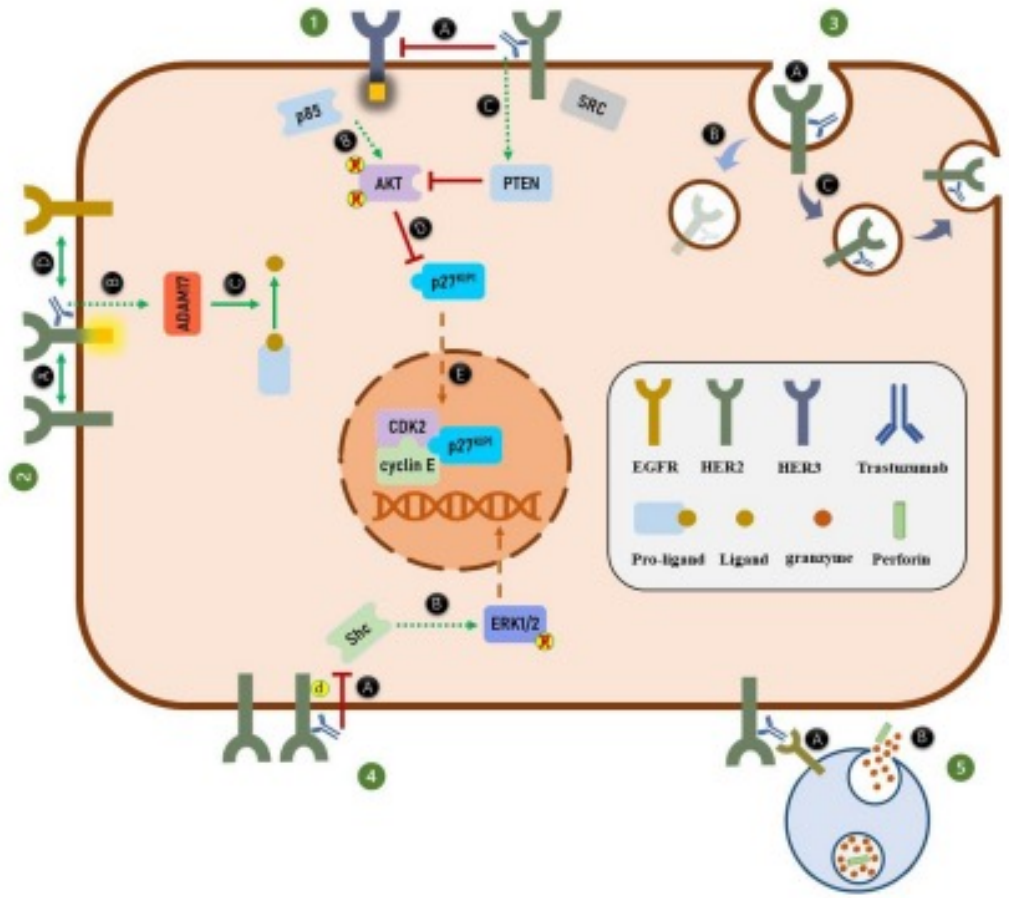
Abbreviations: RT, radiotherapy; AC, doxorubicin and cyclophosphamide; H, trastuzumab; T, paclitaxel; OR, odds ratio.
*Based on a logistic regression model of the given adverse event containing a single predictor variable (arm: AC-T *v* AC-T-H *v* AC-TH-H).
†Wald χ^2 *P* value for overall arm effect.



NCCN Clinical Practice Guidelines – Breast Cancer – v.08.2021
10.1200/JCO.2008.17.9549 Journal of Clinical Oncology 27, no. 16 (June 01, 2009) 2638-2644

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

TRASTUZUMAB: biomolecular effect



Molecular effect

- Blocking of the proteolytic cleavage and dimerization of the HER2 receptor, thereby blocking the ligand-independent signaling and downstream signaling pathways (inhibition of PI3K-Akt and MAP kinase signaling pathways)

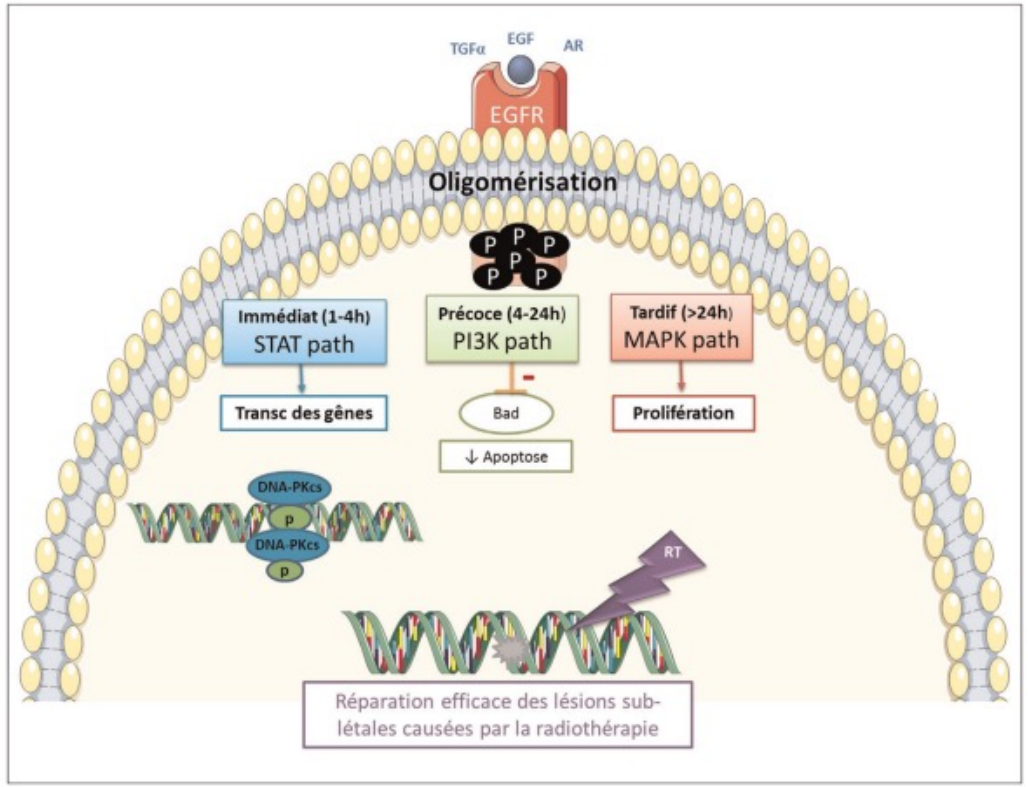
Immune effect

- Stimulation of innate cellular immunity by recruiting natural killer cells and macrophages (ADCC) by recognition of FcγRs

Cancers 2021, 13, 3540. https://doi.org/10.3390/cancers13143540

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

<u>TRASTUZUMAB:</u> biomolecular effect and radiotherapy



Molecular sinergic effect

- Trastuzumab reduces phosphorylation hence the inactivation of the different signaling pathways causing radioresistance
- In vitro association, showed a 4,5 times implementation of apoptosis

Possible side effects

- HER2 receptor has a cardioprotector role -> its inhibition can cause a slow reparation of cardiomyocites
- Trastuzumab can activate apoptosis in cardiomyoctes

https://doi.org/10.1016/j.bulcan.2020.12.012

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

PERTUZUMAB: clinical evidences

APHINITY: 2nd INTERIM OS ANALYSIS
SABCS 2019

docetaxel or 12 weekly cycles of paclitaxel; or 6 cycles (every 3 weeks) of docetaxel plus carboplatin. Patients with hormone-receptor–positive tumors received standard endocrine therapy starting at the end of chemotherapy; the endocrine therapy was planned to continue for at least 5 years. Radiotherapy was given as clinically indicated at the end of chemotherapy and concomitantly with anti-HER2 treatment.

A physical examination and an assessment of safety and concomitant medications were con-

89.2% was assumed for the placebo group, on the basis of the results of the Breast Cancer International Research Group 006 trial,[3] and a rate of 91.8% was assumed for the pertuzumab group, with approximately 379 events required for the primary analysis.

Secondary End Points

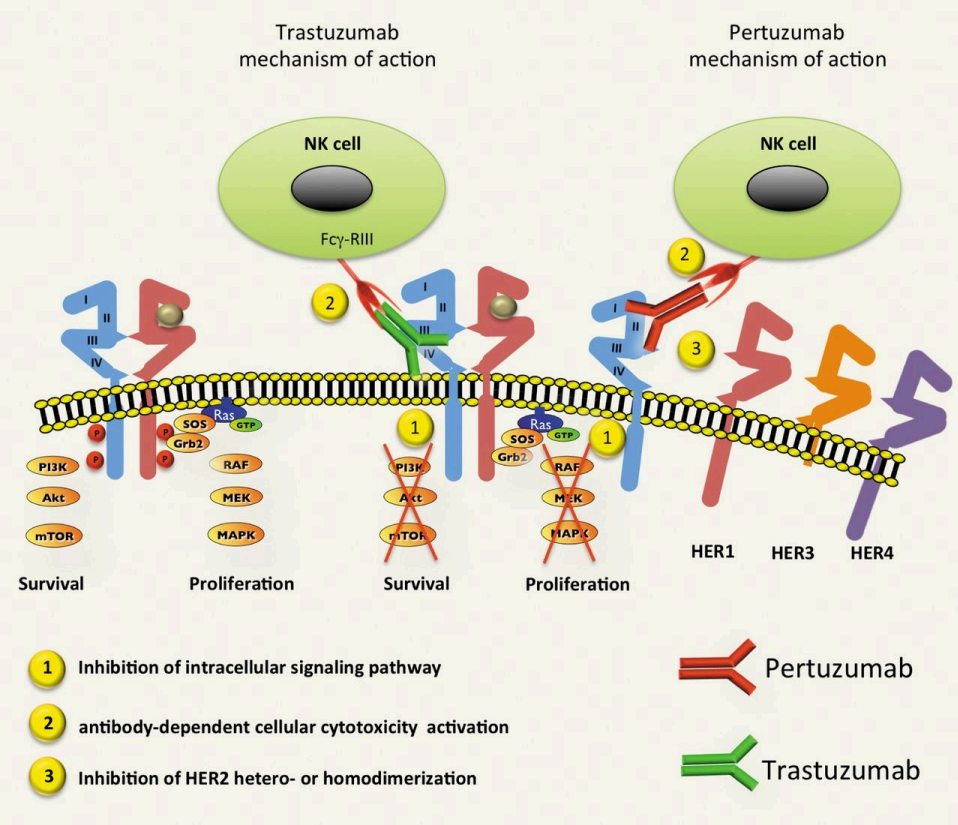
The secondary end points included overall survival, disease-free survival (including noninvasive breast cancers), invasive-disease–free survival (in-

124 N ENGL J MED 377;2 NEJM.ORG JULY 13, 2017

NCCN Clinical Practice Guidelines – Breast Cancer – v.08.2021
J Clin Oncol. 2021 May 1;39(13):1448-1457. doi:10.1200/JCO.20.01204

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

PERTUZUMAB: biomolecular effect



Molecular effect

- Prevention of potent ligand-dependent HER2/HER3 heterodimerization
- Suppression downstream PI3K,
- Suppression MAPK pathways

Immune effect

- Stimulation of innate cellular immunity by recruiting natura killer cells and macrophages (ADCC)

Am J Cancer Res 2020;10(4):1045-1067 www.ajcr.us /ISSN:2156-6976/ajcr0109526

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

PERTUZUMAB: biomolecular effect and radiotherapy

Very FEW DATA -> pertuzumab is always associated with trastuzumab during irradiation

Molecular sinergic effect

- Association of pertuzumab and trastuzumab with radiotherapy probably further reduces radioresistance of HER2+ tumors

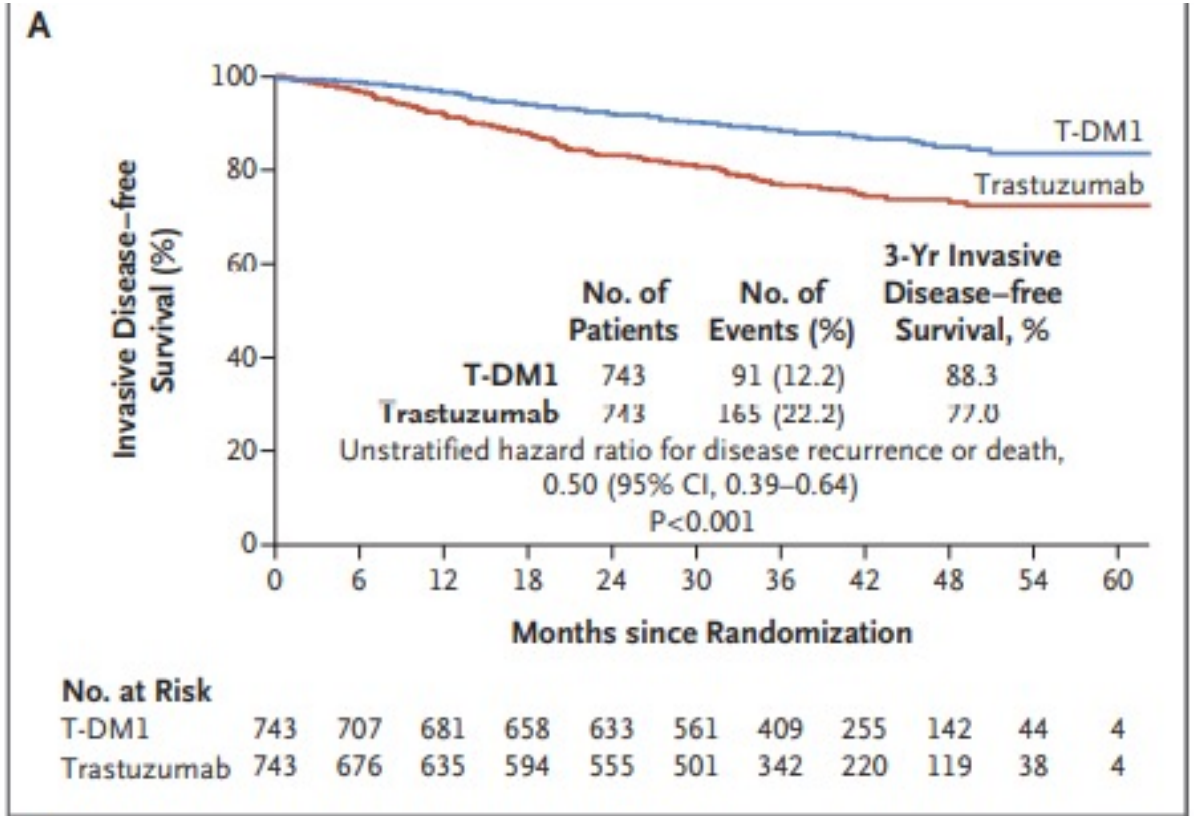
Possible side effects

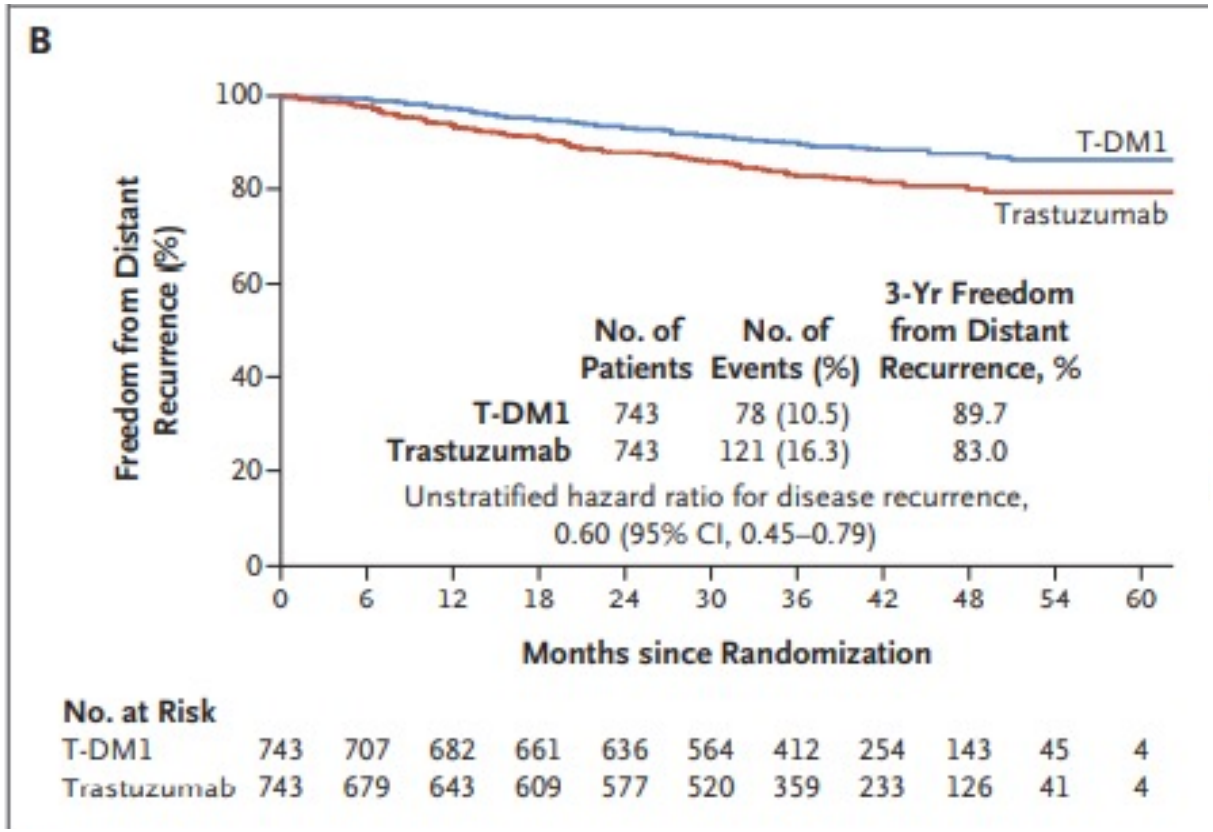
- HER2 receptor has a cardioprotector role -> its inhibition can cause a slow reparation of cardiomyocites
- Dual blockage + radiotherapy -> compared to an increased fear of toxicity rate clinical data are reassuring
    - Ajgal Z et al. 2016: 23 pts -> 1 case of asymptomatic <50% LVEF; 1 case of grade 3 radiodermitis
    - Aboudaram A. 2021: 55 pts -> 3 cases of grade 3 radiodermitis (5.4%), but no significant gastrointestinal or cardiac toxicity
    - APHINITY Trial 2021: 4805 pts -> primary cardiac events remain < 1% in both the treatment groups

Ajgal Z. et al. Cancer Radiothérapie 21 (2017) 114-118
Aboudaram, A et al. Cancers 2021, 13, 4790. https://doi.org/10.3390/ cancers13194790
J Clin Oncol. 2021 May 1;39(13):1448-1457. doi:10.1200/JCO.20.01204

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

TRASTUZUMAB EMTASINE (T-DM1): clinical evidences



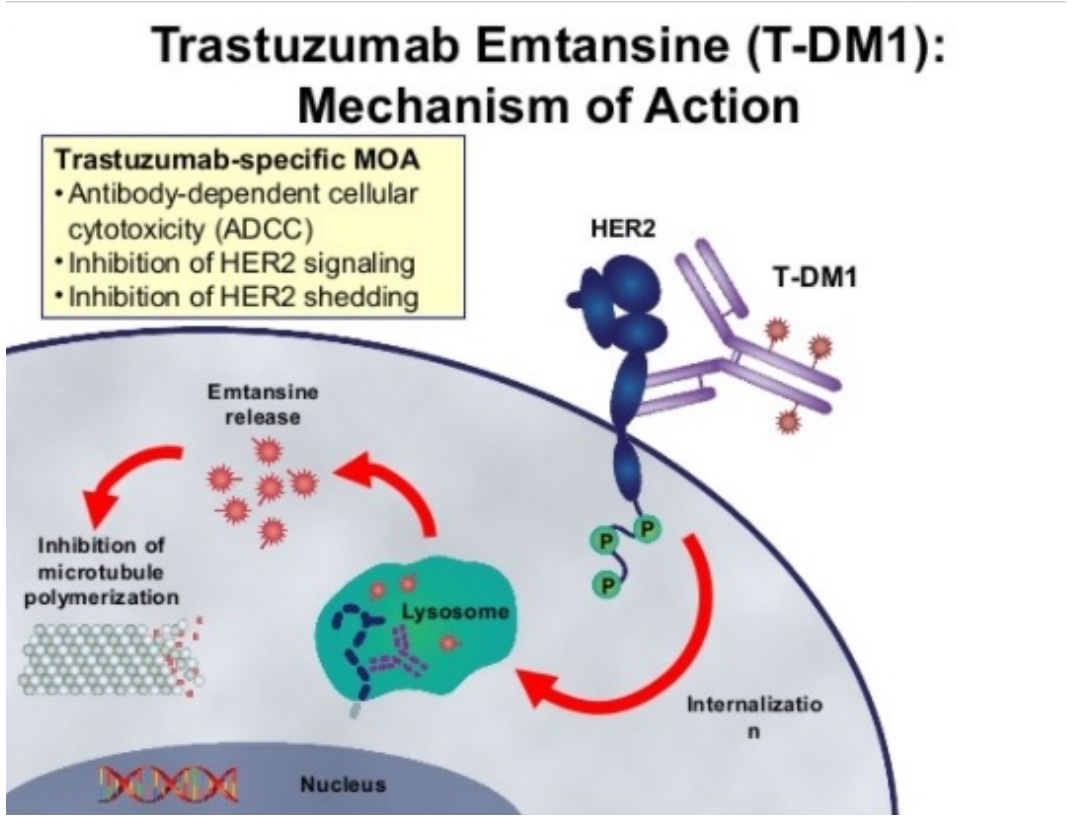


T-DM1 reduces the risk of IDFS of 50% respect trastuzumab

NCCN Clinical Practice Guidelines – Breast Cancer – v.08.2021
Von Minckwitz G et al. N Engl J Med 2019; 380:617-628

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

T-DM1: biomolecular effect



Molecular effect

- T-DM 1 retains all mechanisms of action of anti-HER2 monoclonal antibodies drugs
- Through lysosome internalization Emtasine inhibits microtubule polymerization blocking cells and leading them to mitototic arrest, apoptosis, mitotic catastrophe and disrupted intracellular trafficking

Immune effect

- T-DM1 retains also stimulation of innate cellular immunity by recruiting natura killer cells and macrophages (ADCC)

LoRusso PM et al. Cliln Cancer Res 2011
Barok et al. Breast Cancer Research 2014, 16:209

MONOCLONAL ANTIBODIES AND RT: ADJUVANT SETTING

T-DM1: biomolecular effect and radiotherapy

Molecular sinergic effect

- Anti-HER2 + RT sinergic effects are retained
- Anti-tubulin drugs have a comprovate radiosensitizing role
- Emtasine delivery directly into tumor cells allows to radiosensitize only tumor

Possible side effects

Overall Safety

During T-DM1 therapy (n = 148), the most common any-grade AEs were nausea (37.8%; n = 56) and headache (37.2%; n = 55; Table 4). Fifty-seven patients (38.5%) experienced grade 3 AEs, and four (2.7%) experienced grade 4 AEs; there were no grade 5 AEs. The most common grade ≥ 3 AEs were thrombocytopenia (8.1%; n = 12), increased ALT (7.4%; n = 11), and increased AST (7.4%; n = 11; Table 4). Fifteen patients (10.1%) experienced serious AEs during T-DM1 therapy, with atrial fibrillation (n = 2), pyrexia (n = 2), and device-related infection (n = 2) occurring in > one patient. No was the only grade 3 AE reported in ≥ two patients administered concurrent hormonal therapy.

During concurrent T-DM1 and radiotherapy (n = 39), three patients (7.7%) had grade 3 AEs (one each: neutropenia, asthenia, erythema), and one patient (2.6%) experienced radiotherapy-associated pneumonitis (grade 2). During sequential radiotherapy (n = 77), two patients (2.6%) had grade 3 AEs (neutropenia, radiotherapy pneumonitis), and one additional patient had grade 2 radiotherapy pneumonitis; thus, in total, 2.6% of patients experienced radiotherapy-associated pneumonitis. No grade 4 AEs were reported during concurrent or sequential radiotherapy.

Table 2. Summary of Adverse Events in the Safety Population.*

Event	Trastuzumab Group (N=720)	T-DM1 Group (N=740)
	no. of patients (%)	
Any adverse event	672 (93.3)	731 (98.8)
Grade ≥3 adverse event	111 (15.4)	190 (25.7)
Adverse event leading to death†	0	1 (0.1)
Serious adverse event	58 (8.1)	94 (12.7)
Adverse event leading to discontinuation of trial drug‡	15 (2.1)	133 (18.0)
Grade ≥3 adverse event that occurred in ≥1% of patients in either group		
Decreased platelet count	2 (0.3)	42 (5.7)
Hypertension	9 (1.2)	15 (2.0)
Radiation-related skin injury	7 (1.0)	10 (1.4)
Peripheral sensory neuropathy	0	10 (1.4)
Decreased neutrophil count	5 (0.7)	9 (1.2)
Hypokalemia	1 (0.1)	9 (1.2)
Fatigue	1 (0.1)	8 (1.1)
Anemia	1 (0.1)	8 (1.1)

Adams SR et al. Nature Communications 7: 13019

Von Minckwitz G et al. N Engl J Med 2019; 380:617-628

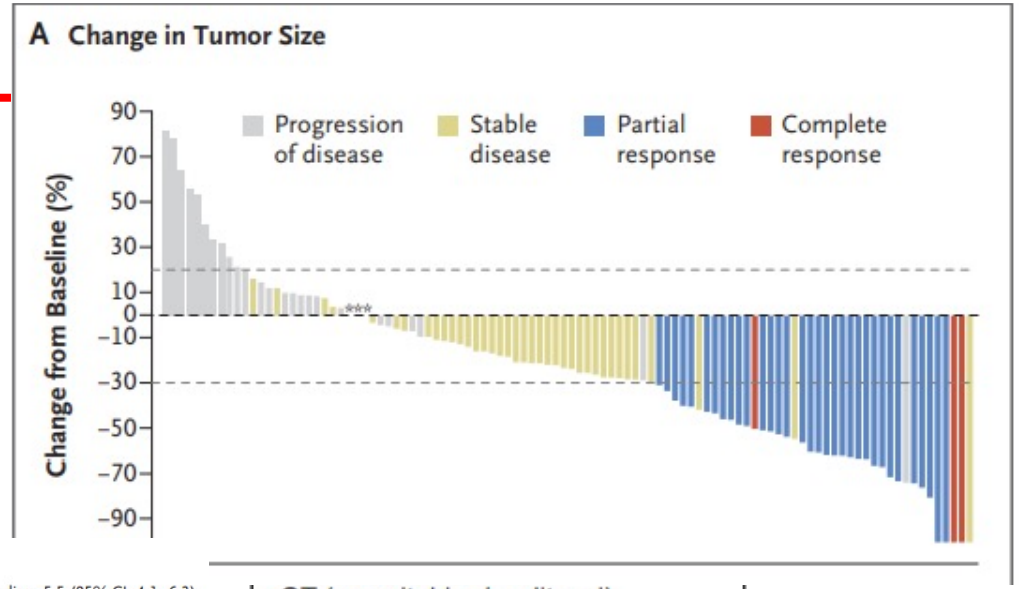
MONOCLONAL ANTIBODIES AND RT: METASTATIC SETTING

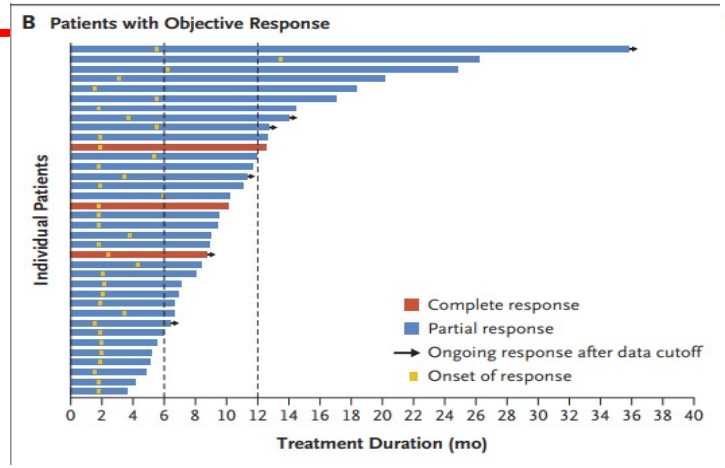
MONOCLONAL ANTIBODIES AND RT: METASTATIC SETTING

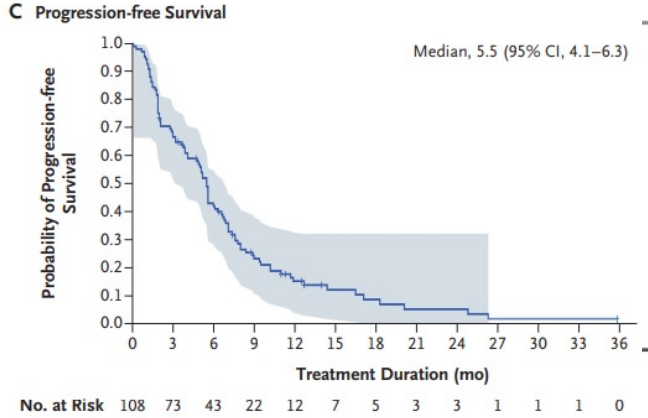
SACITUZUMAB GOVITECAN: clinical evidences

Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer

A. Bardia, I.A. Mayer, L.T. Vahdat, S.M. Tolaney, S.J. Isakoff, J.R. Diamond, J. O'Shaughnessy, R.L. Moroose, A.D. Santin, V.G. Abramson, N.C. Shah, H.S. Rugo, D.M. Goldenberg, A.M. Sweidan, R. Iannone, S. Washkowitz, R.M. Sharkey, W.A. Wegener, and K. Kalinsky







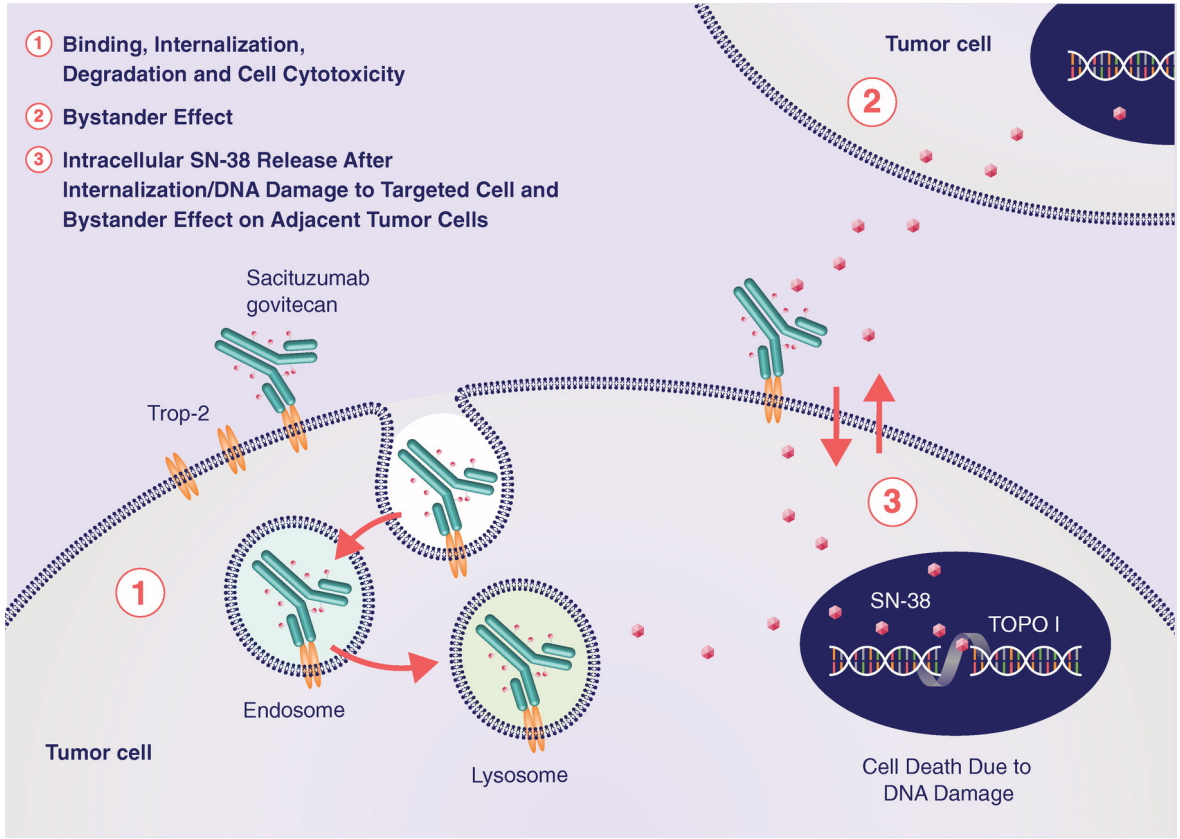
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[h,i]
- Carboplatin + paclitaxel or albumin-bound paclitaxel

NCCN Clinical Practice Guidelines – Breast Cancer – v.08.2021

Bardia A et al. N Engl J Med 2019; 380(8):741-751

MONOCLONAL ANTIBODIES AND RT: METASTATIC SETTING

Sacituzumab Govitecan: biomolecular effect



Molecular effect

- TROP-2 is a signal trasducer that play a role in cell growth, migration and invasion
- In solid epithelial cancers is highly overespressed
- Sacituzumab link TROP-2 to selectively deliver SN-38 (active metabolite of irinotecan) into tumor cell
- SN-38 delivered inside cell targets Topoisomerase I with damage and cellular apoptosis
- Due to its permeability, free SN-38 can leave the cell and give antitumor effects in adjacent tumor cells

Rugo HS et al. Future Oncology, 16;12

MONOCLONAL ANTIBODIES AND RT: METASTATIC SETTING

<u>Sacituzumab Govitecan:</u> biomolecular effect and radiotherapy

Increment in apoptosis? ?

Increment in SN-38 release?

Increased cell permeability?

?

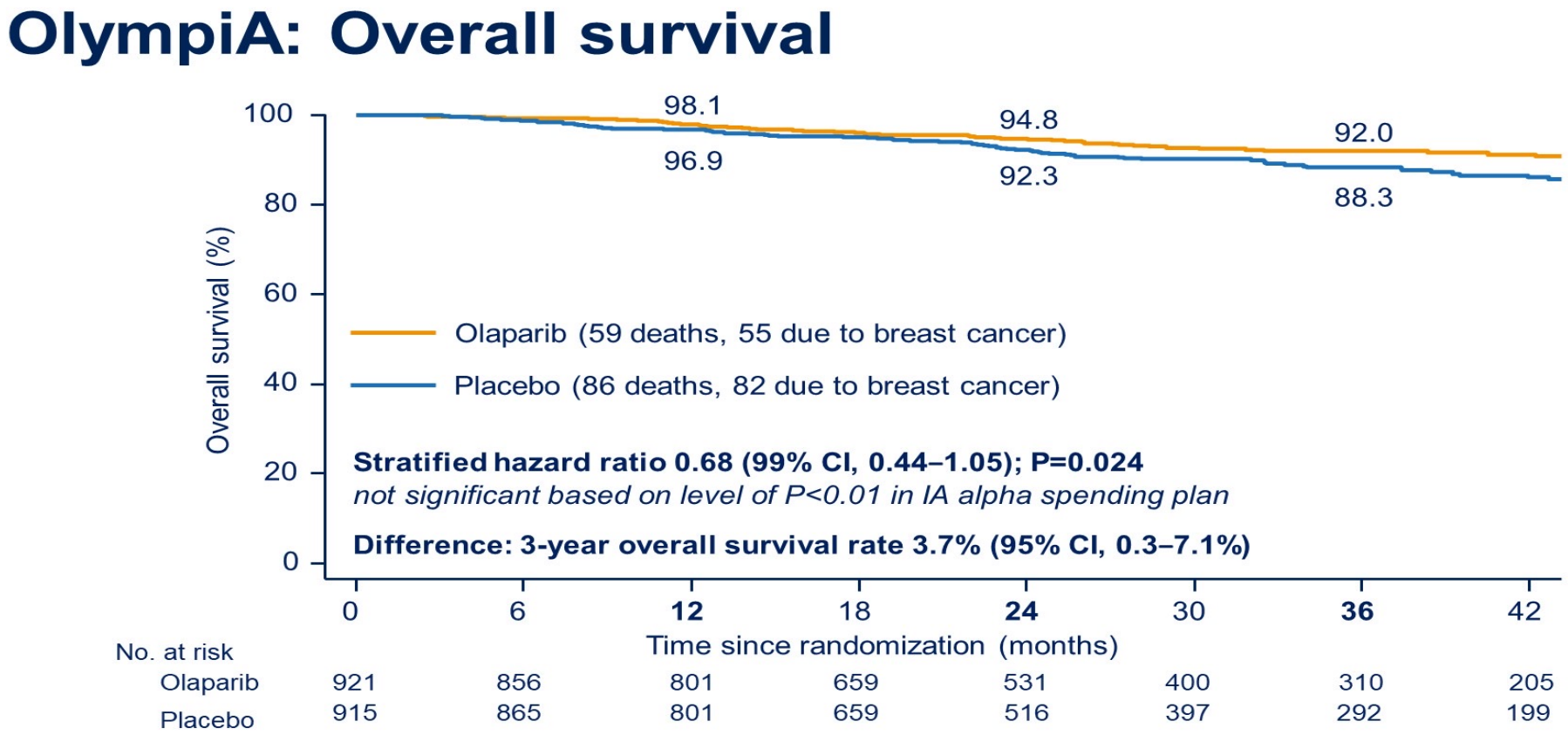
NEED OF MORE CLINICAL DATA

Sacituzumab Govitecan +/- Pembrolizumab In HR+ / HER2 - MBC - Full Text View - ClinicalTrials.gov

SMALL MOLECULES AND RT: ADJUVANT SETTING

SMALL MOLECULES AND RT: ADJUVANT SETTING

OLAPARIB: clinical evidences

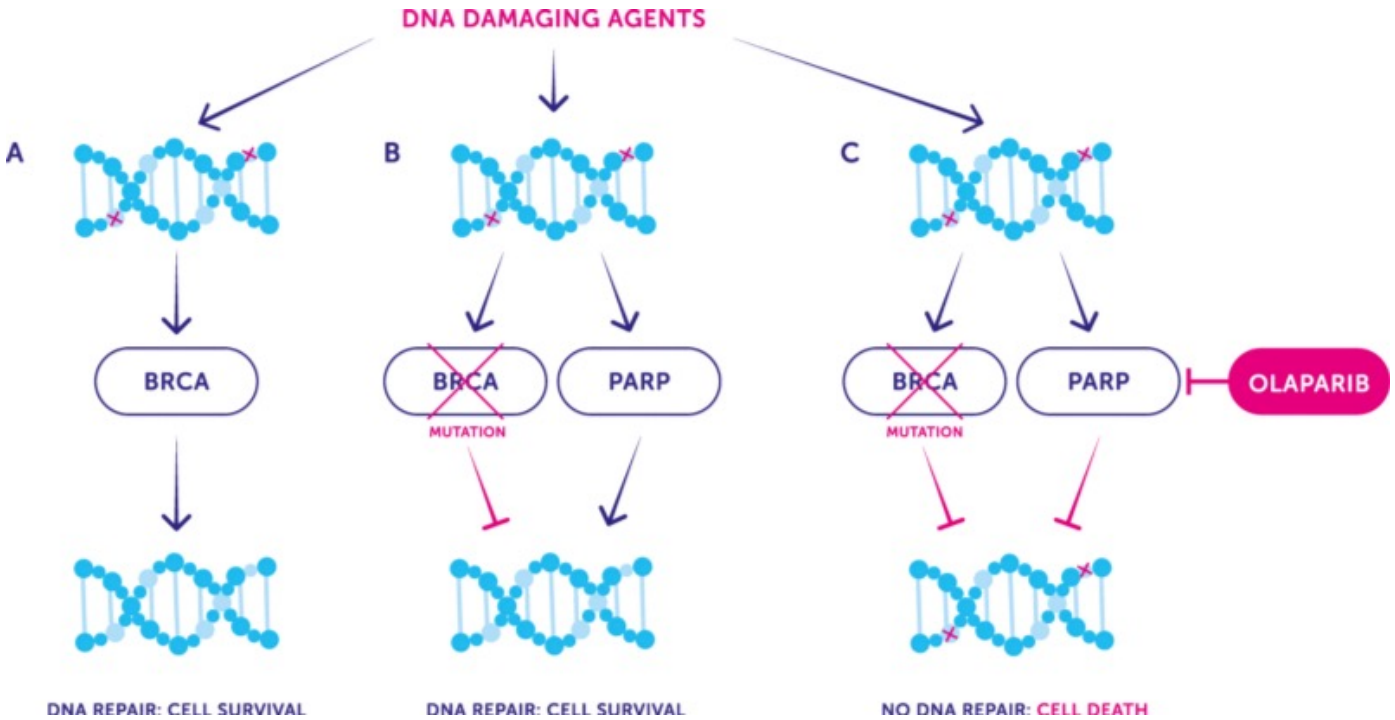


NCCN Clinical Practice Guidelines – Breast Cancer – v.08.2021

10.1200/JCO.2021.39.15_suppl.LBA1 Journal of Clinical Oncology 39, no. 18_suppl

SMALL MOLECULES AND RT: ADJUVANT SETTING

OLAPARIB: biomolecular effect



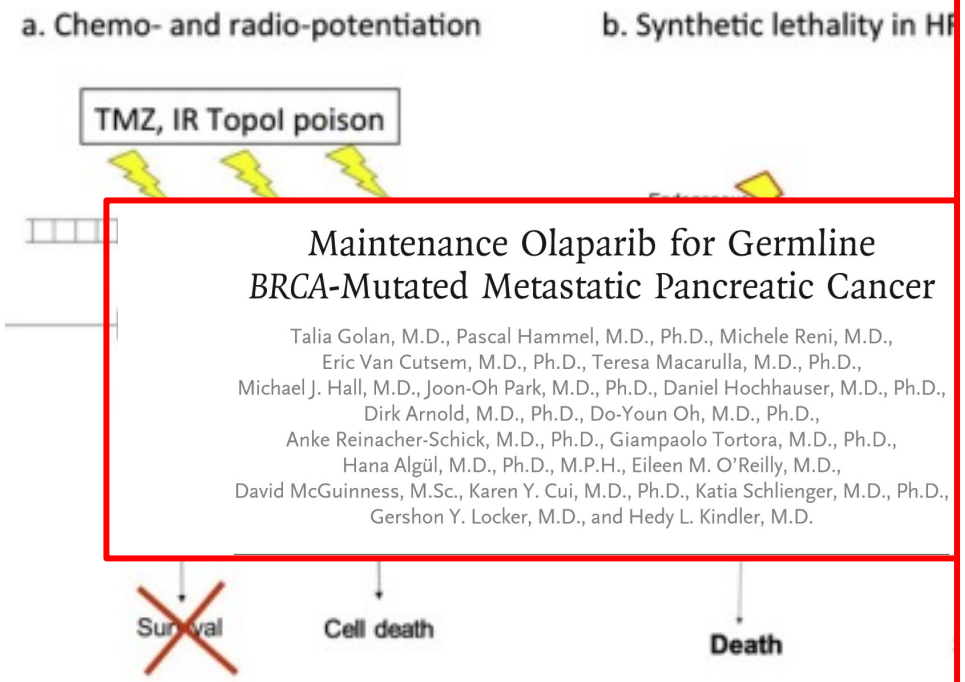
Molecular effect

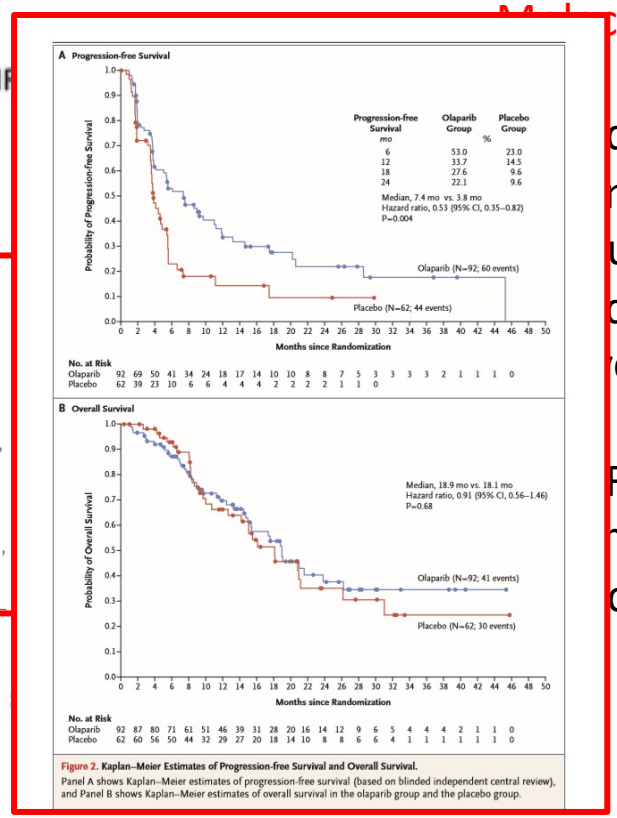
- PARP inhibitor block poly-polymerase enzymes (PARP1, PARP2 and PARP3)
- PARP enzymes partecipates to DNA trascription, cell cycle regulation and DNA repair
- When a BRCA mutation is present, PARP inhibition induces increment of formation of double stranded DNA breaks, disruption of cellular homeostasis and cell death

Olaparib: realising the promise of synthetic lethality | by Research at CRUK | Medium

SMALL MOLECULES AND RT: ADJUVANT SETTING

OLAPARIB: biomolecular effect and radiotherapy





Molecular effect

diotherapy causes different DNA mages (base modifications, single and uble-strand breaks) that lack of BRCA d PARP inhibition are conditions not vourable for repair

RP inhibitors and RT have a mprovate sinergic effect in promotion cell death

Curtin NJ et al. Anticancer therapy and beyond. Mol. Asp. Med. 2013, 34, 1217–1256

SMALL MOLECULES AND RT: METASTATIC SETTING

SMALL MOLECULES AND RT: METASTATIC SETTING

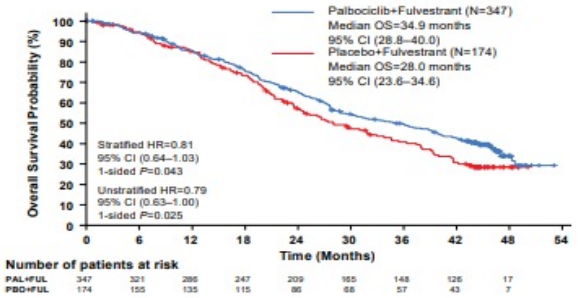
PALBOCICLIB/RIBOCICLIB/ABEMACICLIB: clinical evidences

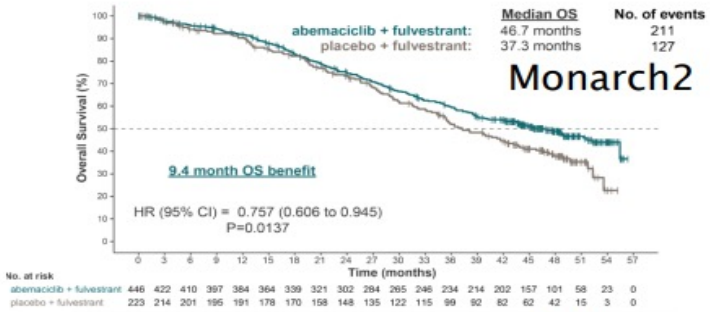
LMU KLINIKUM

HR+ HER2- metastatic breast cancer

Consistent OS advantage for CDK 4/6i

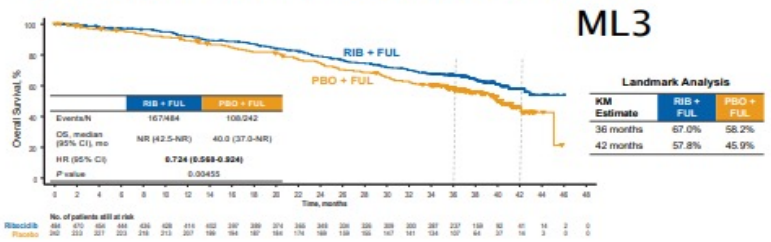
OVERALL SURVIVAL IN PALOMA-3 (ITT)

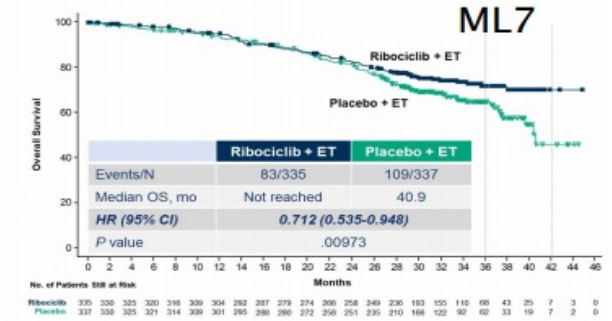




Overall Survival

The reduction in relative risk of death with RIB was 28%





Metastatic breast cancer | LMU breast center | www.lmu-brustzentrum.de | 24.05.2020

Christofanilli et al, 2018; Hurvitz et al, 2019; Slamon et al, 2019; Sledge et al, 2019

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Cristofanilli et al, 2018; Hurvitz et al 2019; Slamon et al 2019; Sledge et al. 2019

SMALL MOLECULES AND RT: METASTATIC SETTING

PALBOCICLIB/RIBOCICLIB/ABEMACICLIB: biomolecular effect and radiotherapy

Clinical and Translational Radia

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Review Article

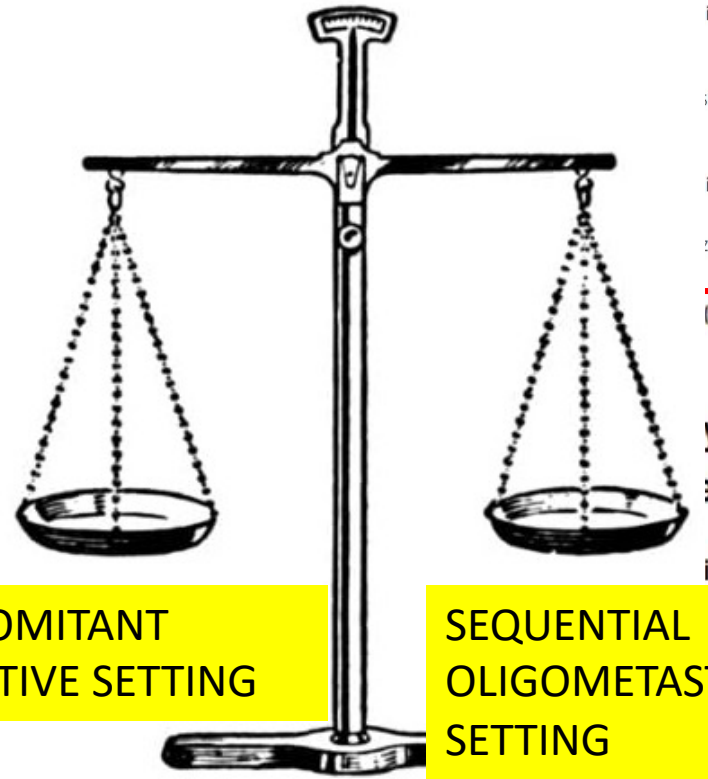
CDK 4/6 inhibitors combined with radiot

Claire Bosacki [a], Wafa Bouleftour [b], Sandrine Sotton [b], Hamza Ouaz [a], Ionel Cojocaru [a], Dariush Moslemi [a], M

[a] Department of Radiation Oncology, Lucien Neuwirth Cancer Institute, 108 bis avenue Al
[b] University Department of Teaching and Research, Lucien Neuwirth Cancer Institute, 108

		(H460)
Tao et al. [30]	Palbociclib and Trametinib	NSCLC (A549)
Huang et al. [45]	Palbociclib	HCC (Huh7)
Li et al. [50]	Ribociclib and CA3	EAC (Flo-1 XTR)
Barton et al. [52]	Palbociclib	Ink4a-ARF- deficient BSG [a] mouse model

[a] BSG, brainstem glioma



CONCOMITANT PALLIATIVE SETTING

SEQUENTIAL OLIGOMETASTATIC/OLIGOPROGRESSIVE SETTING

Table 1 In vitro experimental data of radiosensitization effects

hors	CDK4/6 inhibitor	Human cell line	Efficacy with radiotherapy
iteway et al. [41]	Palbociclib	Medulloblastoma (Daoy) (ONS-76)	SF_2 [a] ↓ SER_{10} [b] 1.6, SER_{50} [c] 1.5 SER_{10} 2.3, SER_{50} 2.3
hizume et al. [42]	Palbociclib	Intracranial ATRT [d] (BT12) (BT16)	DEF [e] 1.16–1.60 DEF 1.18–1.70
ittaker et al. [43]	Palbociclib	Glioblastoma (GBM-L1, HW1, RN1, BAH1)	Colony numbers drop to zero
et al. [44]	Abemaciclib	NSCLC (A549, H460, H820, H1975)	DMF [f] 1.30–1.71

021 April 01; 27(7): 1855–1863. doi:10.1158/1078-0432.CCR-20-3871.

y Delivered before CDK4/6 Inhibitors Mediates erapeutic Effects in ER+ Breast Cancer

itziber Buqué[1], Takahiro Yamazaki[1], Norma Bloy[1], Maurizio Di Liberto[2], Galluzzi[1,4,6]

ng cancer (A549)
lorectal cancer (HCT116)
C [h]
o-1 XTR)
Colony numbers ↓

Lange et al. Endocrine Rel Cancer 2011; Finn Slamon et al. Breast Cancer Res 2009
Yang Y et al. Jour Exper Clin Cancer Resear 2020 39;188

SMALL MOLECULES AND RT: METASTATIC SETTING

ANTI-EGFR and ANTI-TKI: clinical evidences in oligoprogressive I

Table 4 Selected trials of radiotherapy combined with tyrosine kinase inhibitors in oligoprogressive oncogene-driven NSCLC

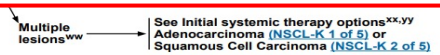
Author, ref.	No pts	Molecular status	Therapy	Median PFS	Median OS	Toxicity
Wang *et al.*, (79)	14	UNK	G, SBRT	7	19	G3 pneumonitis 7%, esophagitis 7%, rash 7%, no G4/5
Iyengar *et al.*, (80)	24	0/13 *EGFR*+, other UNK	E, SBRT	14.7	20.4	G5 1 pt
Yu *et al.*, (81)	18	*EGFR*+	E, G, SBRT	10	41	G4 SBRT-related 1 pt, G4 TKI-related 4 pts
Weickhardt *et al.*, (76)	25	*EGFR*+, *ALK*+	E, C, SBRT	PFS 2–6.2 (from progression on TKIs)	NR	G1/2 fatigue 16%, G1/2 nausea 5%, no G3/4 toxicity
Conforti *et al.*, (82)	15	*EGFR*+	E, G, SBRT	10.9	39	No G3/4 toxicity
Gan *et al.*, (83)	14	*ALK*+	C, SBRT	9.1	39	No >G2 tocixity
Borghetti *et al.*, (86)	50	*EGFR* +, *ALK*+	E, G; C; SBRT, HRT	5.5	19.3	G3 neurologic: 2 pts

ref, reference; pt, patient; UNK, unknown; SBRT, stereotactic body radiotherapy; PFS, progression free survival; OS, overall survival; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; G, Gefitinib; E, Erlotinib; C, crizotinib; HRT, hyperfractionated radiotherapy.

Table 5 Selected trials of radiotherapy combined with tyrosine kinase inhibitors in oligopersistent oncogene-driven NSCLC

Author, ref.	No pts	Molecular status	Therapy	Median PFS (months)	Median OS (months)	Toxicity
Gomez *et al.*, (87)	49	*EGFR*+ 6 *ALK*+ 2 No aberration 41	Systemic therapy + local consolidative therapy	14.2	41.2	G3 in local consolidative therapy group: esophagitis 2 patients, anaemia 1 patient, pneumothorax 1 patient, abdominal pain 1 patient, No G4-5 toxicities
Elamin *et al.*, (90)	12	*EGFR*+	EGFR TKI + SBRT, HRT or surgery	36	NR	No G4 toxicities
Xu *et al.*, (91)	51	*EGFR*+	EGFR TKI + Arm A: SBRT to all residual metastatic sites	20.6	40.9	G≥3, esophagitis 16.9%, pneumonitis 7.7%
			Arm B: SBRT to primary tumor and oligometastatic sites	15.6	34.1	
			Arm C: no SBRT	13.9	30.8	

ref, reference; pt, patient; PFS, progression free survival; OS, overall survival; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; SBRT, stereotactic body radiotherapy; NR, not reached; HRT, hypofractionated radiotherapy.



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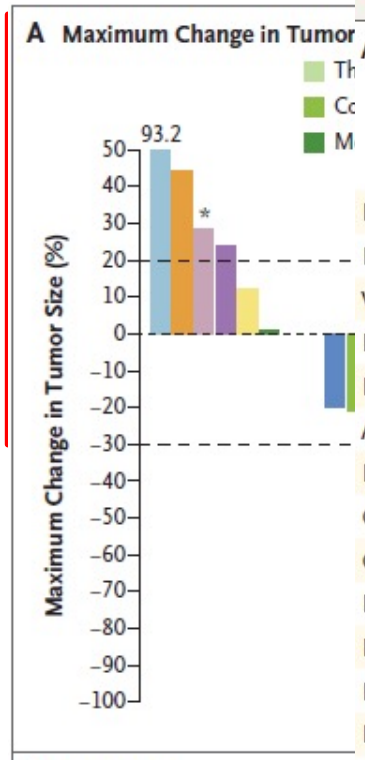
Cristofanilli et al, 2018; Hurvitz et al 2019; Slamon et al 2019; Sledge et al. 2019

SMALL MOLECULES AND RT: METASTATIC SETTING

LAROTRECTENIB: clinical evidences



≥3	19 (35)

Table 3. Adverse Events.*

Adverse Event	Adverse Events, Regardless of Attribution					Treatment-Related Adverse Events		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	percent of patients with event							
Increased ALT or AST level	31	4	7	0	42	5	0	38
Fatigue	20	15	2	0	36	0	0	16
Vomiting	24	9	0	0	33	0	0	11
Dizziness	25	4	2	0	31	2	0	25
Nausea	22	7	2	0	31	2	0	16
Anemia	9	9	11	0	29	2	0	9
Diarrhea	15	13	2	0	29	0	0	5
Constipation	24	4	0	0	27	0	0	16
Cough	22	4	0	0	25	0	0	2
Increased body weight	11	5	7	0	24	0	0	11
Dyspnea	9	9	0	0	18	0	0	2
Headache	13	4	0	0	16	0	0	2
Pyrexia	11	2	2	2	16	0	0	0
Arthralgia	15	0	0	0	15	0	0	2
Back pain	5	9	0	0	15	0	0	0
Decreased neutrophil count	0	7	7	0	15	2	0	9

o Investigator and Central

estigator essment N=55)	Central Assessment (N=55)
percent	
(67–90)	75 (61–85)
64‡	62
16	13
9	13
11	9
0	4

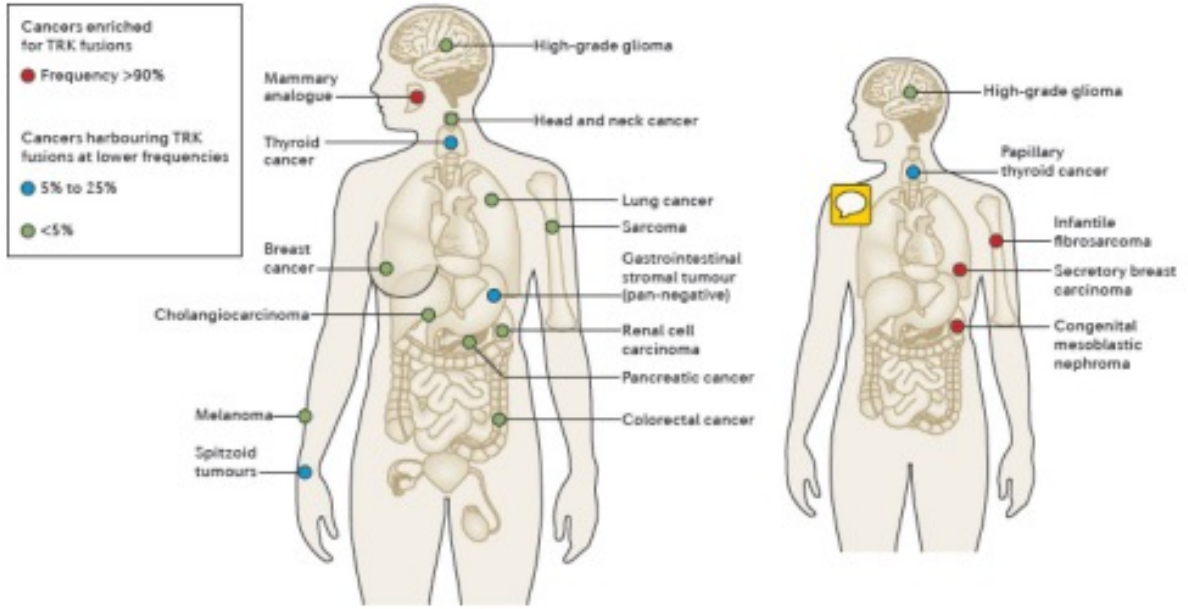
ounding.

Gene driven is N ular profile

Drilon A et al NEJM 2018;378:371:731-9

SMALL MOLECULES AND RT: METASTATIC SETTING

LAROTRECTENIB: biomolecular effect



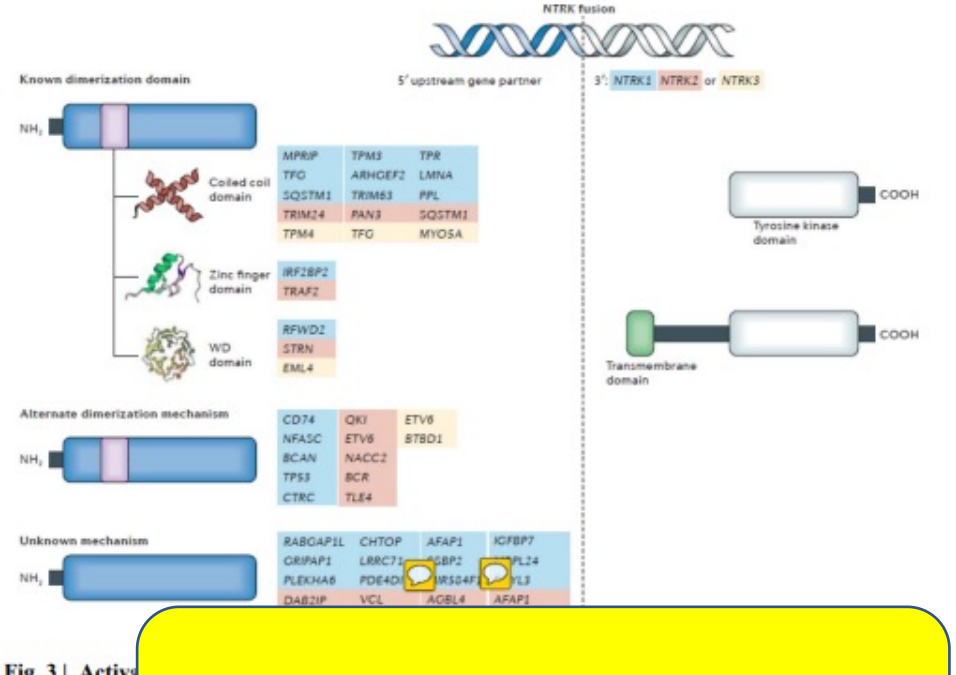


Fig. 3 |. Activa

NEED OF MORE CLINICAL DATA

POSSIBLE ROLE OF RADIOTHERAPY IN OLIGOPROGRESSIVE DISEASE

NTRK fusion-positive cancers and TRK inhibitor therapy (nih.gov)

Conclusion

- Cancer therapies are becoming even more intelligent, tracking a specific driver for damaging cancer cells and reducing systemic side effects
- In some setting, radiotherapy can have a sinergic effect with a good clinical compliance
- Further studies are neeeded, for choicing timing of association and dose of radiotherapy

THANK YOU FOR YOUR ATTENTION