TKI inhibitors and new drugs in lung cancer: omics driven prescription and combination with radiation oncology

Dr C Le Pechoux

- Better combined modality treatments: CTRT, CTRT+consolidation IO
- Adjuvant or neo adjuvant CT in st II,III NSCLC

Technical innovations++

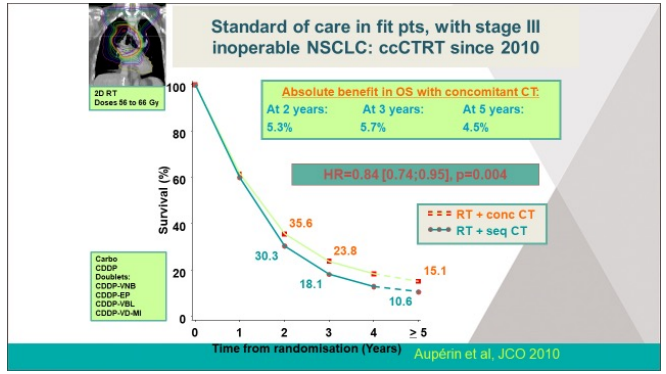
Genomics ++++

- TKI inhibitors
- Immunotherapy (Check Point Inhibitors)
- Combined CT-IO

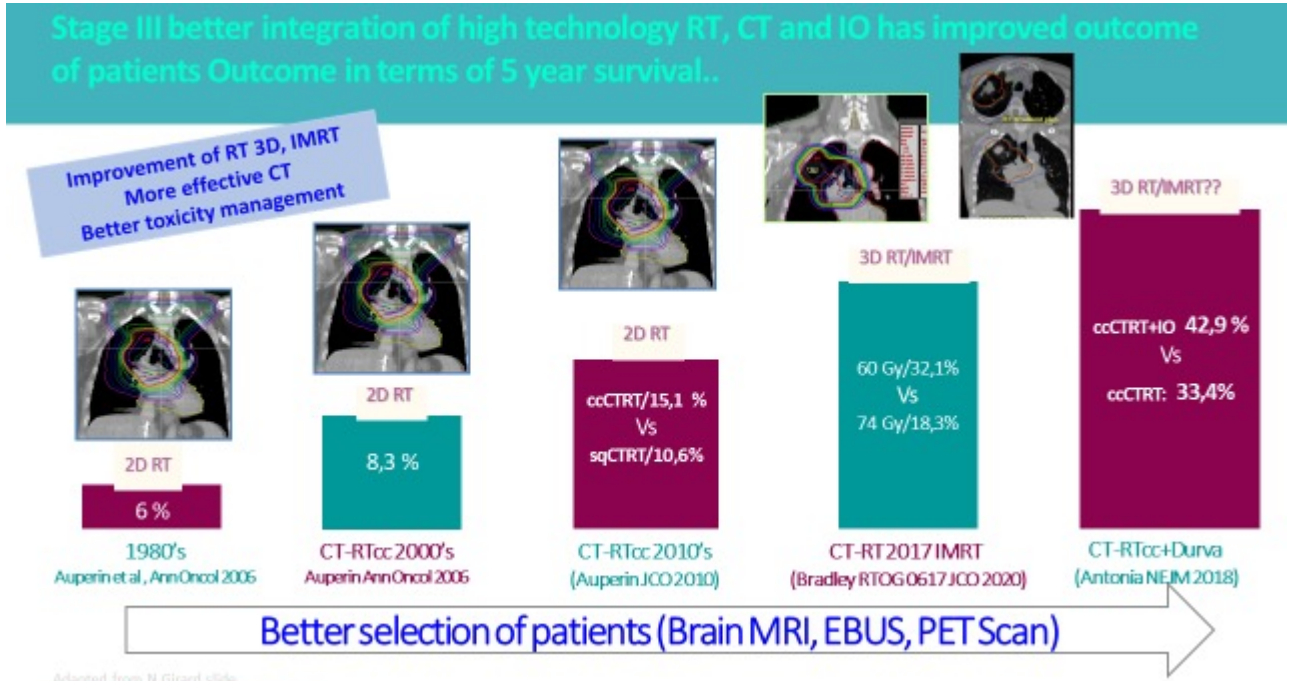
RT has become more « high tech » and an important component in the management of lung cancer at all stages

Schenk Oncologist 2021, Rami-Porta 2020

Stage III NSCLC: Technical ameliorations over recent years, but few changes in terms of systemic treatment to complement radiotherapy until 2017



- Combined modality treatment: improved local tumour control, better management of toxicities (Lung, Esophagus, Heart..), and patient survival in Lung Cancer



Combination of TKI in the pre-omics era…

- Preclinical evidence suggested that TKI (gefitinib) enhanced the radioresponse of NSCLC cells by suppressing cellular DNA repair
- Concomitant use of EGFR inhibitor and radiotherapy demonstrated a

significantly increased overall survival compared with radiotherapy

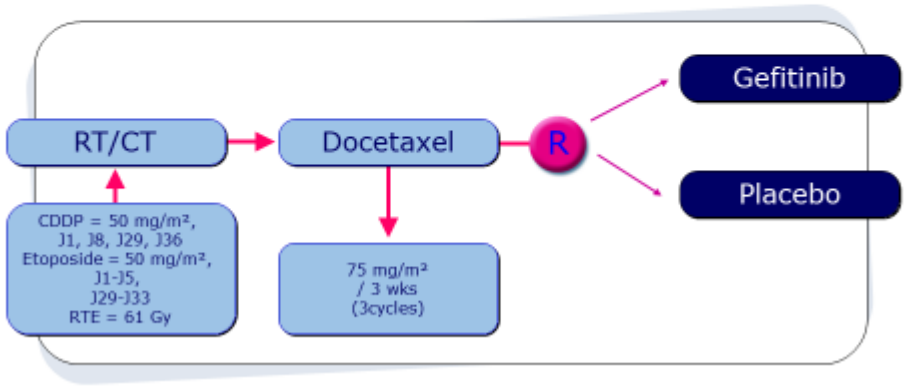
alone in one randomized controlled trial in head and neck cancer

Tanaka Cancer Research 2008; Bonner NEJM 2006

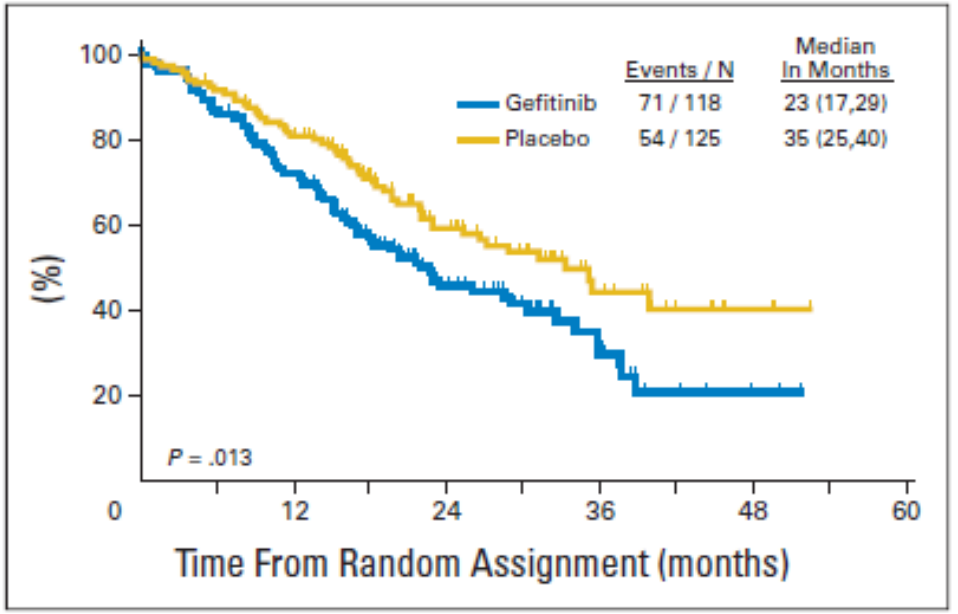
Study	Phase	Patients *N*	EGFR+ *N (%)*[*]	RT *(Gy)*	Chemotherapy	PFS *(med. m)*	OS *(med. m)*	Toxicity ≥G4[b] *(%)*
					Gefitinib			
Ready	II	PR:29 GR:21	13 (26)	66	PR: none GR: Conc Ca Txl	PR: 13.4 GR:9.2	PR: 19 GR: 13	PR:0 GR: G5 pneumonitis (8) G4 neutrop (36)
Niho	II	38	NS	60	Ind CDDP Vin	11.2	28.5	G4 HLE increase (6)
Stinchcombe	II	23	NS	74	Ind Ca Txl Iri Conc Ca Txl	9	16	G4 embolism (4.8) G4 thrombopenia (4.8)
Okamoto	II	9	2 (29)	60	None	NS	NS	None
Center	I	16	NS	70	Conc+Cons Txt	7.1	21	G5 pneumonitis (13)
Rothschild	I	Step 1: 9 Step 2: 5	NS	63	Step 1 : none Step 2 : CDDP	6m: 42.9%	6m: 85.7%	G4 dyspnea (7)
Current	*II*	*16*	*0*	*66*	*Cons CDDP Vin*	*5*	*11*	*G5 pneumonitis (6.3)* *G4 pneumonia (6.3)* *G4 dehydration (6.3)*
					Erlotinib			
Lilenbaum	II	75	0	66	Ind Ca nab-Txl	11	17	G4 blood (8) G4 fatigue (1)
Komaki	II	48	4 (8)	63	Conc+Cons Ca Txl	14	36.5	G4 pneumonitis (2)
Socinski	I/II	45	NS	74	Ind+Conc Ca Txl Bev +Cons Bev	10.2	18.4	G4 neutrop (18) G4 esophagitis (2)
					Cetuximab			
Bradley	III	147 110	NS	60 74	Conc+Cons Ca Txl idem	10.8	25	G4 blood (46) G4/5 dyspnea (2) G4 pneumonitis (1) G4 dehydration (2) G4 dysphagia (1)
Blumenschein[a]	II	93	NS	63	Conc+Cons Ca Txl	2y FR : 44.8%	22.7	G5 pneumonitis (2) G5 ARDS (1)
Hallqvist	II	75	NS	68	Ind CDDP Txt	NS	17	G5 pneumonitis (1.4) G4 hypersens (2.8)
Ramalingam	II	40	NS	73.5	Cons Ca Txl	9.3	19.4	G4 infection G4 infusion reaction G4 embolism G4 feb neutrop (9.8)
Govidan	II	53	NS	70	Conc Ca Pem	12.3	25.2	G5 pneumonitis (4) G5 embolism (2)

Stage III inoperable NSCLC: SWOG 0023 Role of maintenance after CTRT with EGFR-TKI in unselected population

- Phase III randomised (SWOG 0023) stage III NSCLC (n=571)
- Place of maintenance Gefitinib (n=243 randomised)



K. Kelly et al, JCO 2008



Survival	Gefitinib	Obs	p
PFS **(mo)**	8	12	0,17
MS **(mo)**	23	35	0,013
S1Y **(%)**	73	81	
S2Y **(%)**	46	59	

K. Kelly et al, ASCO 2007, JCO 2008

NSCLC: frequent cancer but ….addition of rare cancers (adenocarcinoma..) identification of actionable targets through genomic molecular profiling clinical benefit (in stage IV)

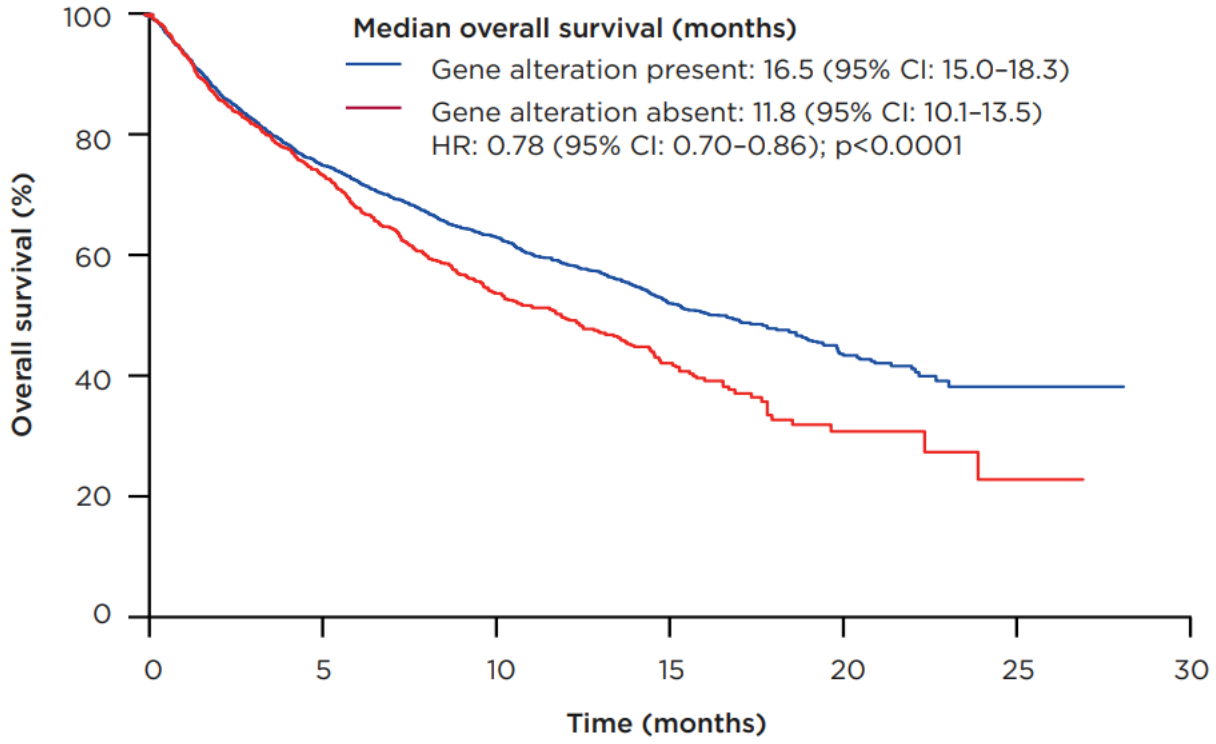
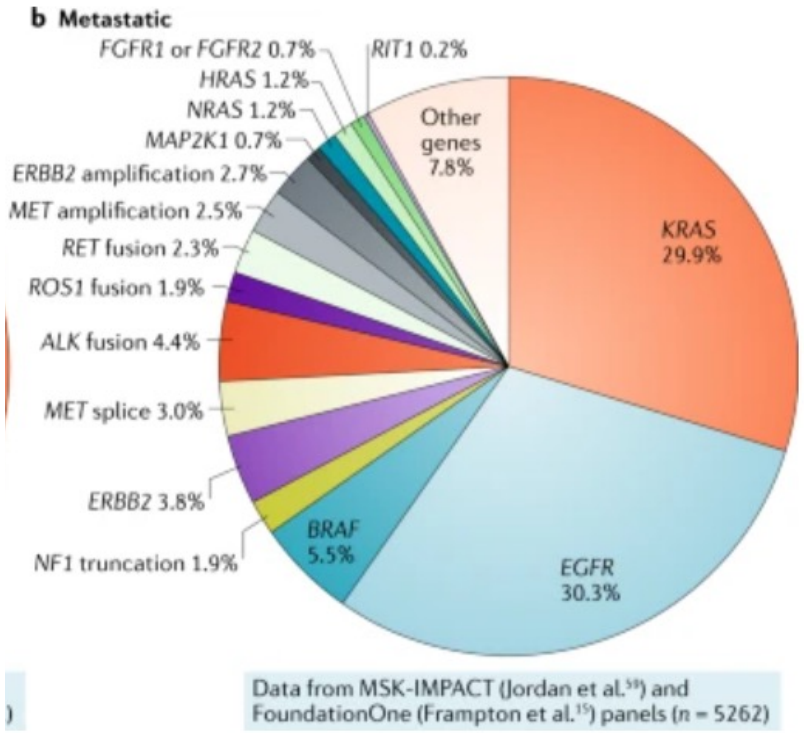


Figure 2: Median overall survival of patients who underwent molecular analysis for genomic alterations.
CI: confidence interval; HR: hazard ratio.
Adapted from Barlesi et al.[15]



Lung Adenocarcinoma

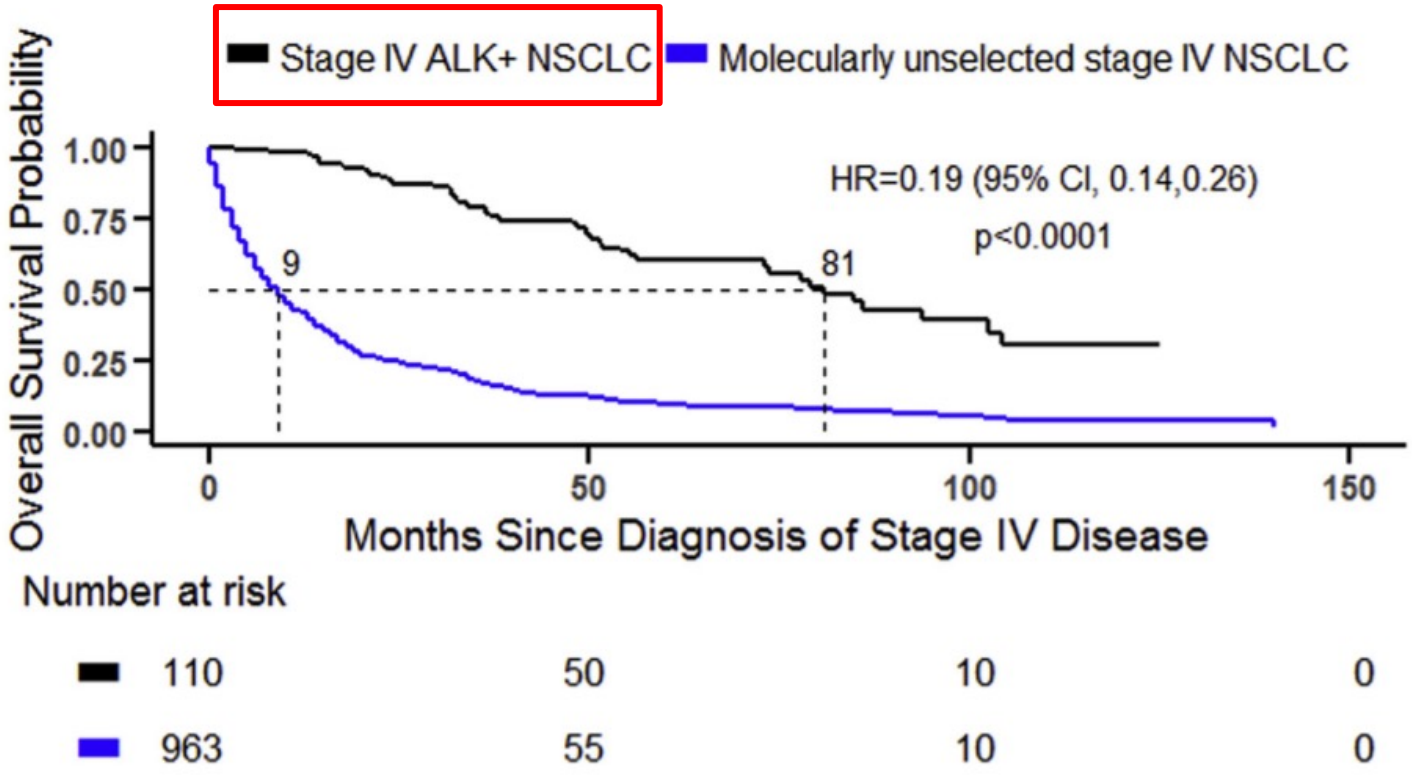
Presence of a genetic alteration associated with improved overall survival

Mok NEJM 2009; Barlesi Lancet 2016

For ALK+ NSCLC M+: what TKI brought

- ✓ Excellent objective responses
- ✓ Rapid responses
- ✓ Clinical improvement despite a poor PS
- ✓ Improved overall survival

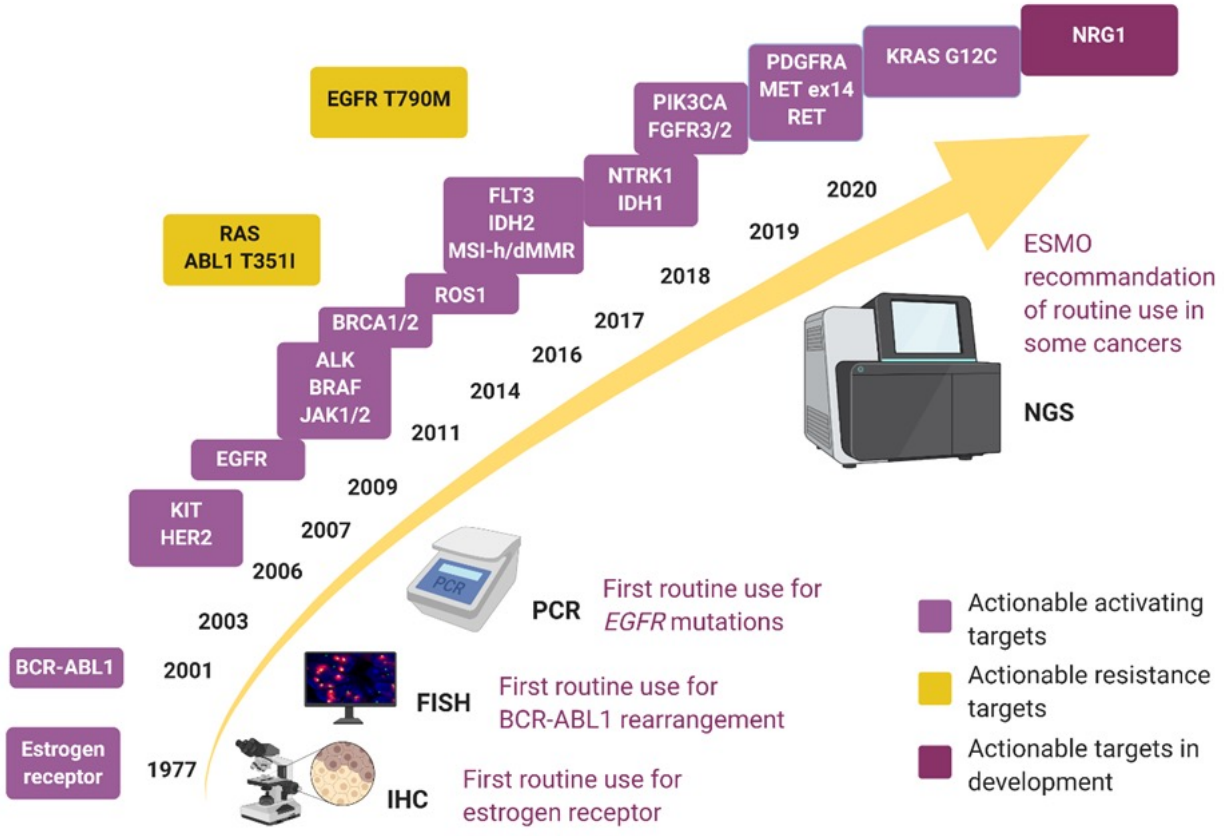
Molecular selection: 7 years !
No molecular selection: 0.75 years



Courtesy of Dr M Aldea

Pacheco *et al*, JTO 2021

Great acceleration with NGS (Next Generation Sequencing) which allows to test many genes in a tumour sample simultaneously, changing the classification and outcomes of NSCLC among others..



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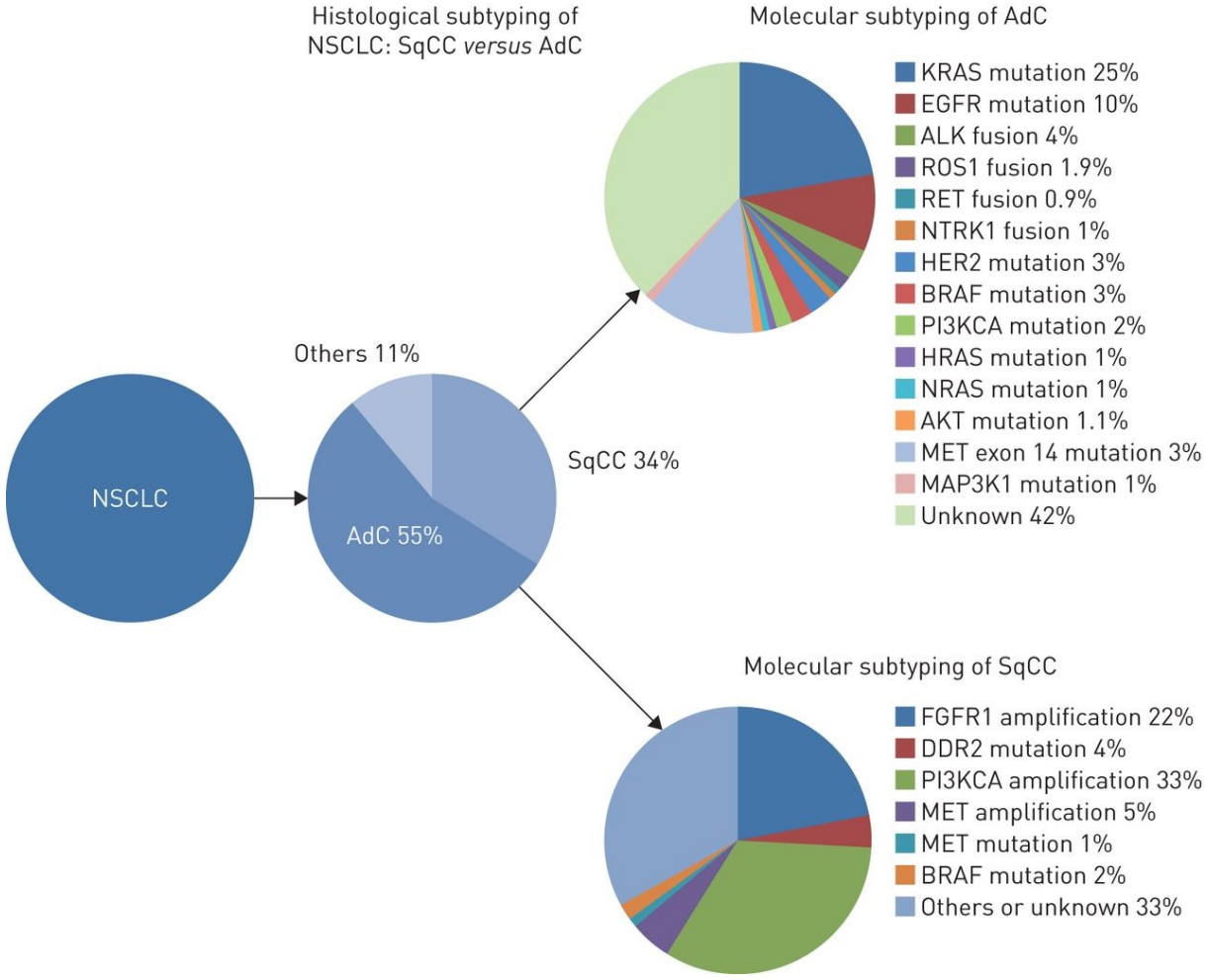
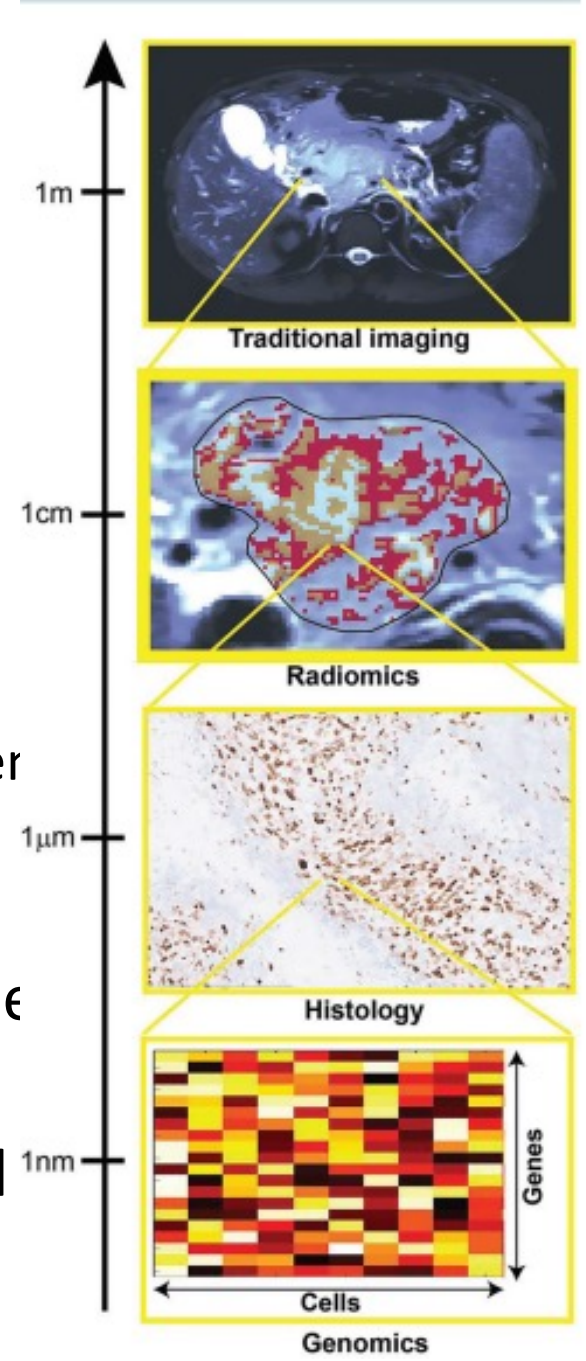
Courtesy of Dr M Aldea



Bubendorf *et al*, ERJ 2017

Radiomics in lung cancer

- Utility of radiomics as a noninvasive approach to predict lung cancer treatment response to
  - tyrosine kinase inhibitors (Khorrami 2019, Aerts 2017)
  - platinum-based chemotherapy (Khorrami 2019)
  - neo-adjuvant chemoradiation (Coroller 2017)
  - stereotactic body radiation therapy (Huynh 2017 and Mattoner 2016)
  - immunotherapy (Tunali 2019 2021, Sun 2018 Champiat 2017).
- Highly predictive biomarkers of immunotherapy response are an unmet clinical need…
- Combination of IO and CT has now become the standard

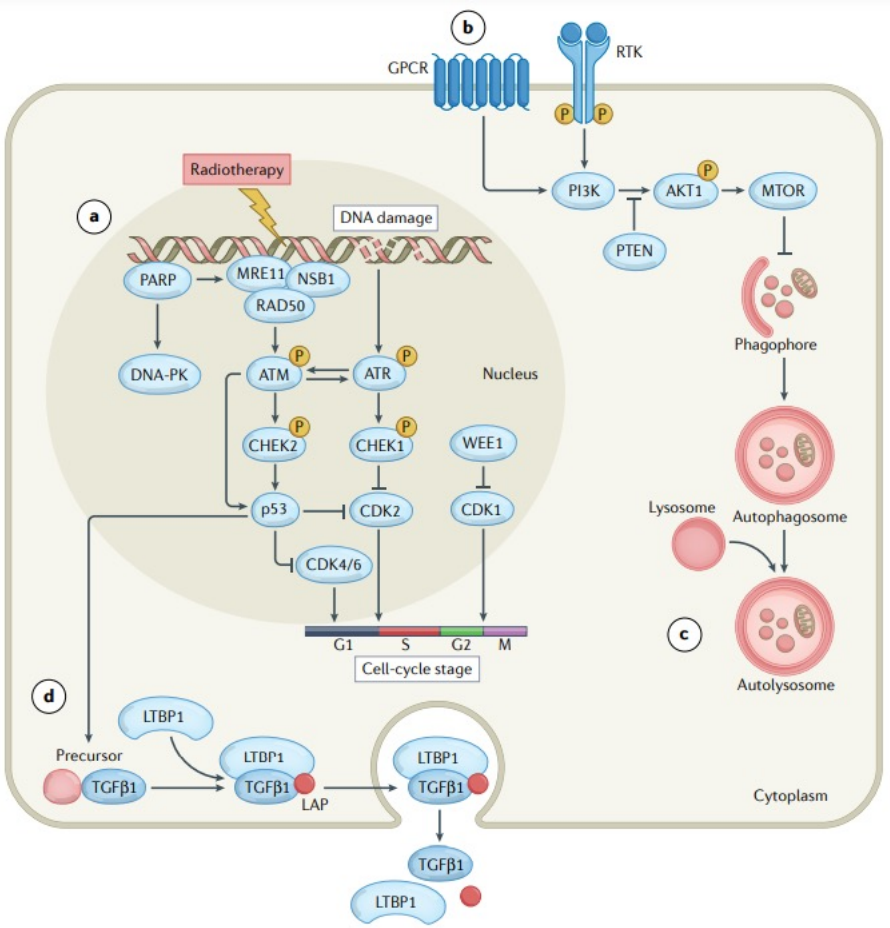


Potential role of RT in metastatic disease when TKIs have less effectiveness

- Tumours can be intrinsically resistant to targeted anticancer agents
  - because not all malignancies harbour genetic alterations
  - because such signal transduction pathways emerge from epigenetic alterations or stress-responsive transcriptional programmes that are either not present or inactive at baseline
- Both situations result in a lack of targetable alterations

Cytoprotective pathways elicited by RT

- RT frequently used in more than 50% cancer Pts - Prominent cytostatic and cytotoxic effects on malignant cells.
- A wide panel of cytoprotective pathways can be activated by radiotherapy, thus limiting therapeutic efficacy.
- However, these signal transduction cascades can be effectively inhibited with targeted anticancer agents, potentially supporting superior treatment efficacy.
- Radiotherapy stands out as a promising tool to elicit clinically actionable signaling pathways in cancer.



Petroni et al Nature Reviews Clin Oncol 2022

Stage III: combined modality treatment and omics driven prescription at recurrence

- Molecular profiling (leading to omics driven prescription for EGFR mutation and ALK rearrangement) has become a standard procedure in advanced NSCLC
- Predictive value of EGFR and ALK is well known for advanced NSCLC, but Ongoing debate regarding the prognostic value of mutations
- Objective: Explore the prognostic value of specific gene alteration in stage III NSCLC population (190 consecutive patients treated with radiotherapy (RT) +/- chemotherapy (CT) between 2002 and 2013)

Boros et al, 2016

Mutations prevalence Stage III vs. Stage IV in Gustave Roussy patients

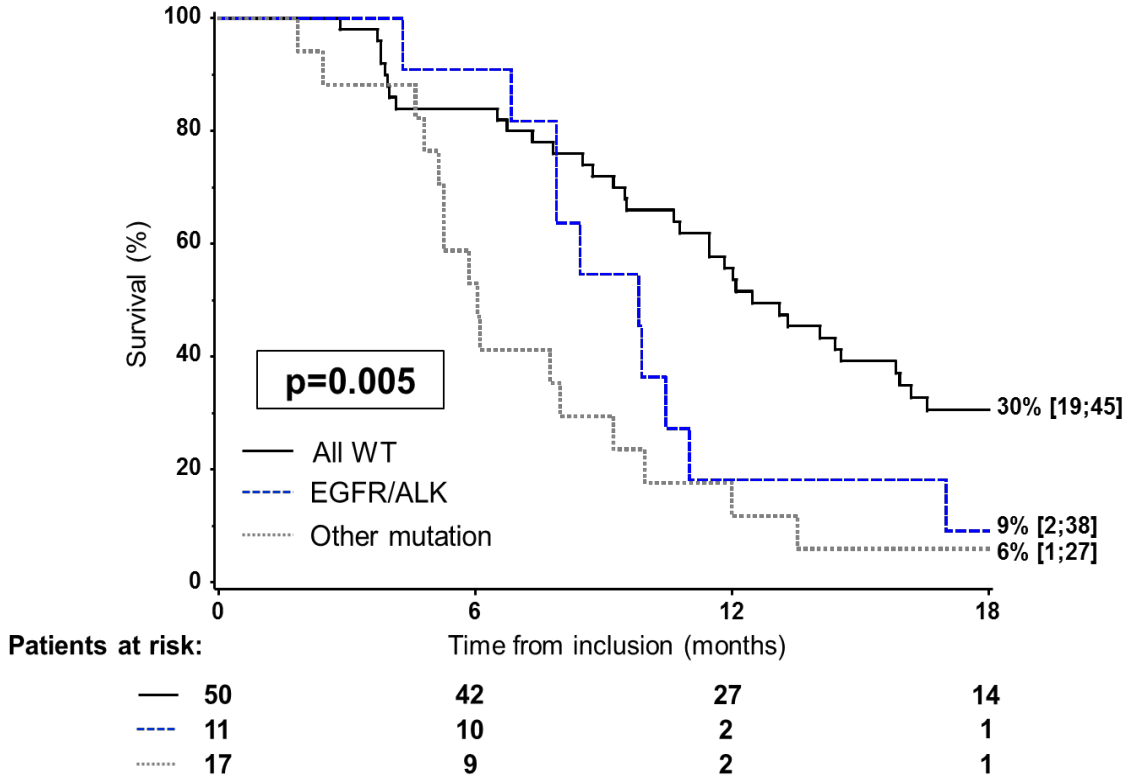
	Stage III		Stage IV	
	N	%	N	%
EGFR	9 / 78	***11.5***	47 / 362	***13***
KRAS	12 / 78	***16***	122 / 362	***34***
BRAF	3 / 78	***4***	6 / 311	***2***
PI3KCA	1 / 78	***1***	6 / 185	***3***
HER2	0 / 78	***0***	4 / 216	***2***
ALK	2 / 78	***2.5***	19 / 216	***9***
NRAS	1 / 78	***1***	1 / 126	***1***
AKT1	0 / 78	***0***	0 / 123	***0***

Adenocarcinoma

Stage III: 49%

Stage IV: 81%

Progression-free survival (PFS)



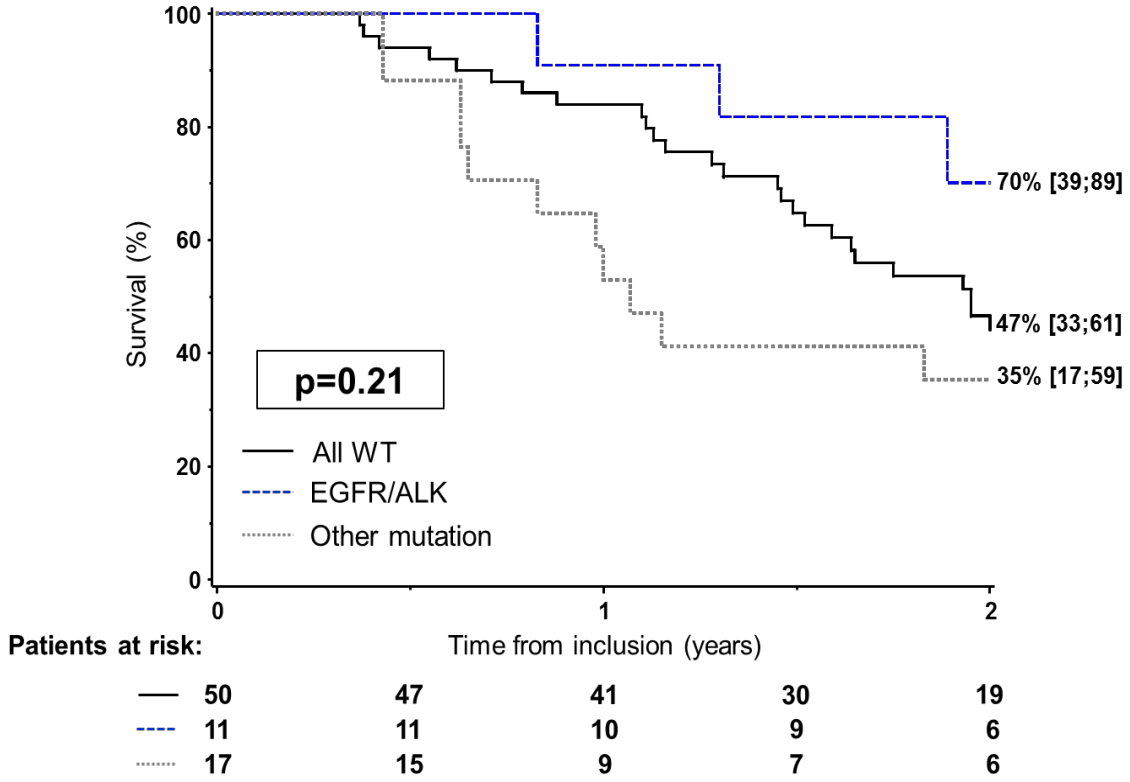
Poor PFS for EGFR/ALK and other mutations group

	Median (months) [95% CI]
Wild-type	12.5 [10.6;15.9]
EGFR/ALK	9.8 [6.8;11.0]
Other mutation	6.0 [4.8;9.2]

Multivariable Cox model adjusted on: performance status, stage, radiotherapy dose, thoracic surgery and mutation groups

	No. events / No. patients	Hazard Ratio [95% CI]	p-value
Wild-type	41 / 50	Reference	
EGFR/ALK	10 / 11	1.8 [0.8;3.8]	**0.004**
Other mutation	16 / 17	2.8 [1.5;5.1]	

Overall survival (OS)



No significant difference between the three groups

	Median (years) [95% CI]
Wild-type	1.9 [1.5;2.5]
EGFR/ALK	2.4 [1.3;not reached]
Other mutation	1.1 [0.6;2.5]

Multivariable Cox model adjusted on: performance status, stage, radiotherapy dose, thoracic surgery and mutation groups

	No. deaths / No. patients	Hazard Ratio [95% CI]	p-value
Wild-type	34 / 50	Reference	
EGFR/ALK	6 / 11	0.7 [0.3;1.9]	0.23
Other mutation	13 / 17	1.7 [0.9;3.3]	

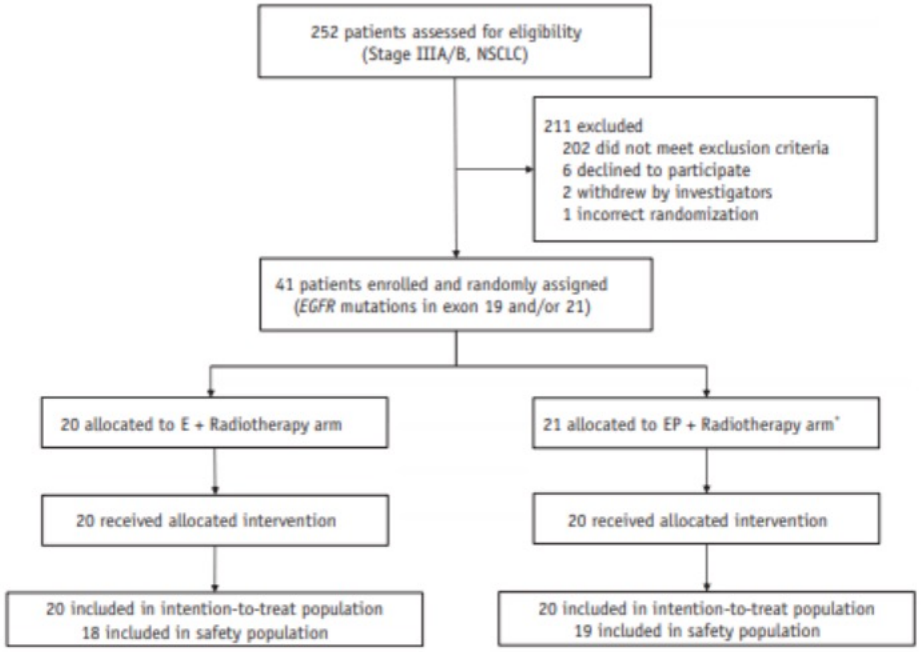
Outcome in unresectable stage III NSCLC after omics driven combined modality treatment

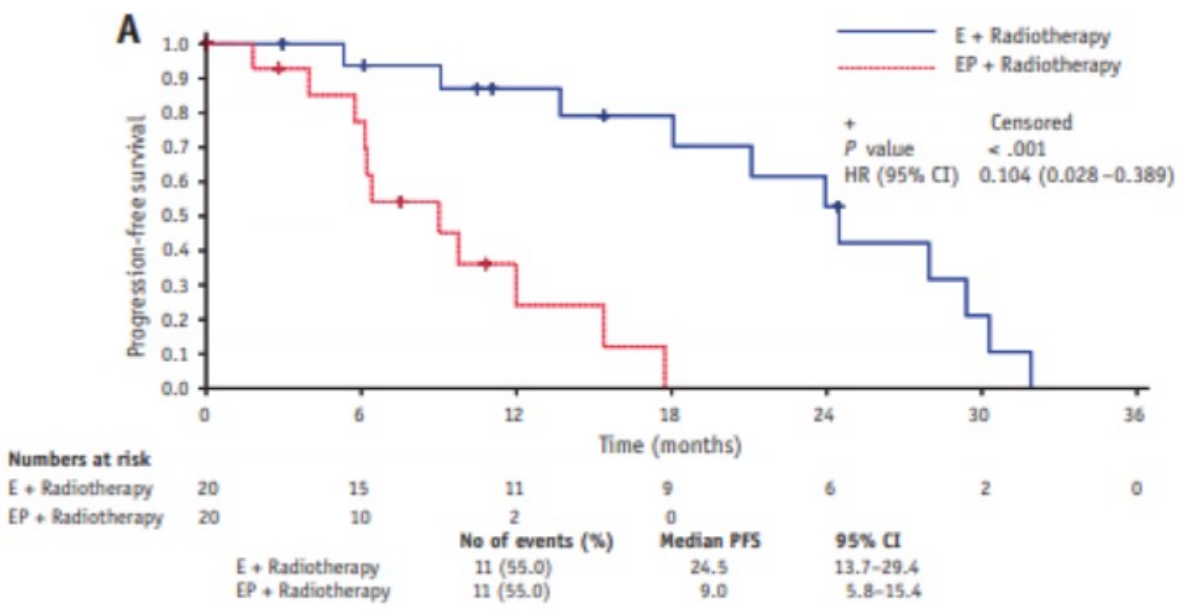
Author/ Trial Name	Design	Period	Histology	No. of pts	Regimen	% ORR	% 2-year PFS	% Local rec.	% Distant rec.	% Brain rec.	% 2-year OS
<EGFR-mutant population>											
Tanaka K	retro.	'06–'13	ad	28	P-based CRT	72.4	*	14	76	35	*
Yagishita S	retro.	'01–'10	nonsq	34	P-based CRT	79	(10–25)	4	80	16	(around 80)
Nakamura M	retro.	'06–'16	nonsq	34	P-based CRT	-		53	85	29	
Akamatsu H	retro.	'02–'09	ad	13	P-based CRT	76.9		15	69	46	
Ours	**p2**	**'11–'17**	**nscc**	**20**	**Gefitinib followed by DP-conc. RT**	**85.0**	**36.9**	**10**	**65**	**30**	**90**
<EGFR-mutation-unselected population>											
OLCSG0007	p3	'00–'05	nscc	101	DP-conc. TRT	78.8	*	38	37	35	60.3
PROCLAIM	p3	'08–'12	nonsq	301	PP-conc. TRT	35.9	(20–30)	58	50	19	52
WJTOG0105	p3	'01–'05	nscc	156	PC-conc. TRT	63					*(45)
PACIFIC	p3	'14–'16	nscc	473	durvalumab in post-CRT	30.0	*(45)	-	-	5	66.3
				236	placebo in post-CRT	17.8	*(20)	-	-	12	55.6

Hotta, ESMO Open, 2021

Erlotinib Versus Etoposide/Cisplatin With Radiation Therapy in Unresectable Stage III Epidermal Growth Factor Receptor Mutation-Positive Non-Small Cell Lung Cancer: A Multicenter, Randomized, Open-Label, Phase 2 Trial

Ligang Xing, MD, PhD • Gang Wu, MD, PhD • Luhua Wang, MD • ... Baolin Qu, MD • Wanqi Zhu, MD •





Xing, Red J, 2021

Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non–small-cell Lung Cancer: LAURA Trial in Progress

LAURA trial (NCT03521154) is recruiting
First patient enrolled **July 2018**
Primary data readout expected **late 2022**
Study completion **2026**

BACKGROUND

Approximately 30% of patients with NSCLC present with locally advanced, stage III disease at diagnosis; of these, approximately 34% are estimated to have EGFRm NSCLC

Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitizing (Ex19del and L858R) and EGFR T790M resistance mutations, and has demonstrated efficacy in NSCLC CNS metastases

In FLAURA, first-line osimertinib resulted in improvements in PFS and OS in patients with locally advanced/metastatic EGFRm NSCLC, including in patients with CNS metastases. In ADAURA, adjuvant osimertinib showed a statistically significant and clinically meaningful improvement in DFS in patients with stage IB/II/IIIA, resected EGFRm NSCLC

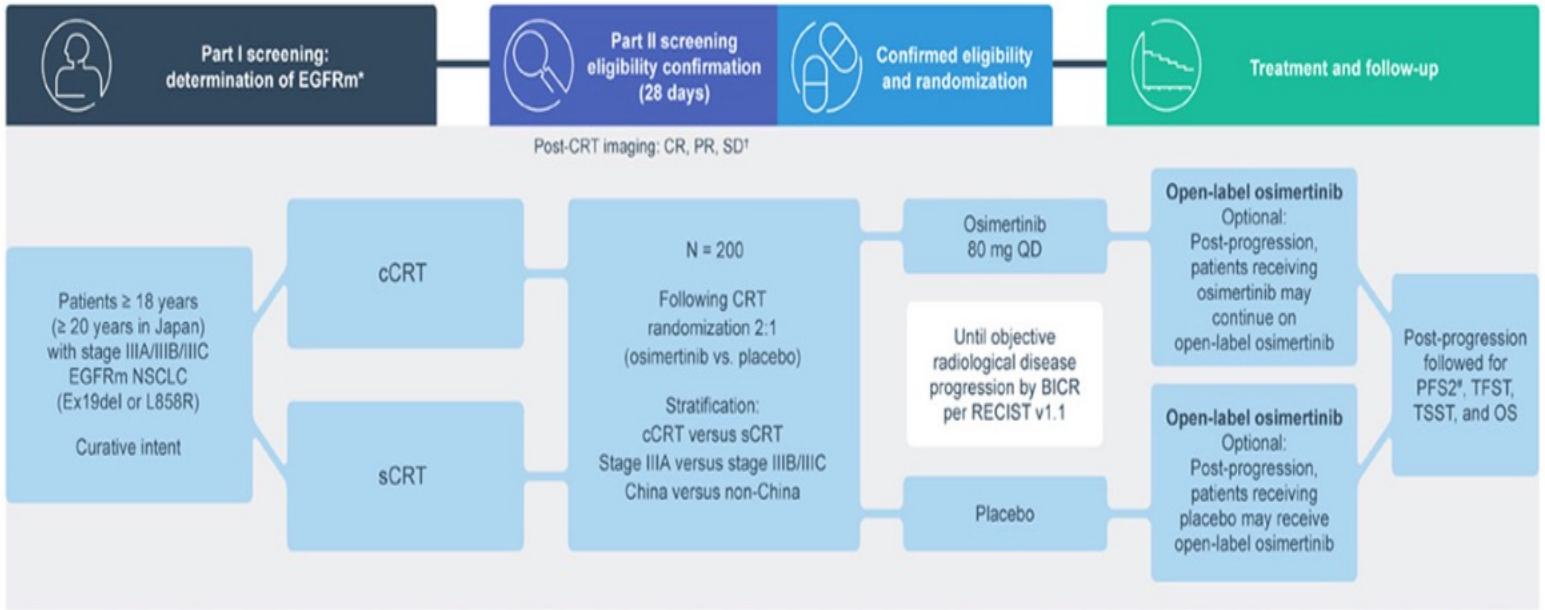
These data indicate that osimertinib could provide benefit in the locally advanced, stage III disease setting of EGFRm NSCLC

TRIAL OVERVIEW

Study design:
Phase III
Double-blind
Randomized
Placebo-controlled

Objective:
To evaluate the efficacy and safety of osimertinib as maintenance therapy in patients with locally advanced, unresectable, EGFRm, stage III NSCLC without disease progression during/ following definitive platinum-based CRT

Primary endpoint: PFS by BICR per RECIST v1.1
Key secondary endpoints:
CNS PFS, OS, PFS by mutation status, and safety (adverse events by CTCAE v5)

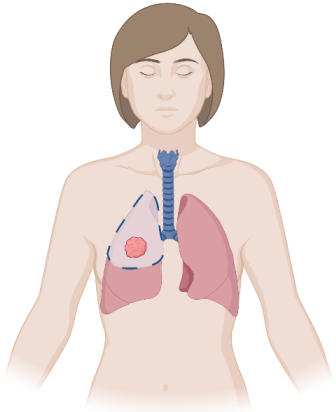


*Patients with a local cobas® EGFR Mutation Test v2 tissue positive result from a CLIA-certified or accredited laboratory do not require part I screening. †Post-CRT imaging performed to assess CR, PR and SD up to 28 days before randomization. ‡Assessment of PFS2 will not be collected after the primary PFS analysis.

BICR = blinded independent central review; cCRT = concurrent chemoradiation therapy; CLIA = Clinical Laboratory Improvement Amendments; CNS = central nervous system; CR = complete response; CRT = chemoradiation therapy; CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease-free survival; EGFRm = epidermal growth factor receptor mutation positive; Ex19del = exon 19 deletion; EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; NSCLC = non–small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression; PR = partial response; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; sCRT = sequential chemoradiation therapy; SD = stable disease; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy

Take home –**Localized EGFR+ NSCLC**

Stage II-IIIA (+/-IB)

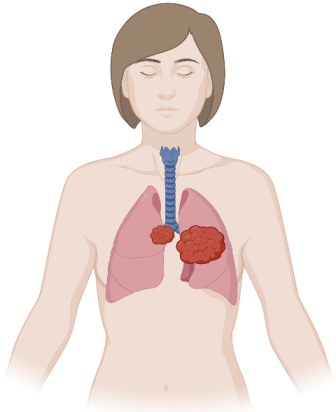


Surgery
+/- adjuvant chemotherapy

Osimertinib

3 years

Unresectable stage III



Chemoradiation

Osimertinib

waiting results LAURA trial

Durvalumab

1 year

ineffective, possibly toxic

Courtesy of Dr M Aldea

Durvalumab for Stage III *EGFR*-Mutated NSCLC After Definitive Chemoradiotherapy

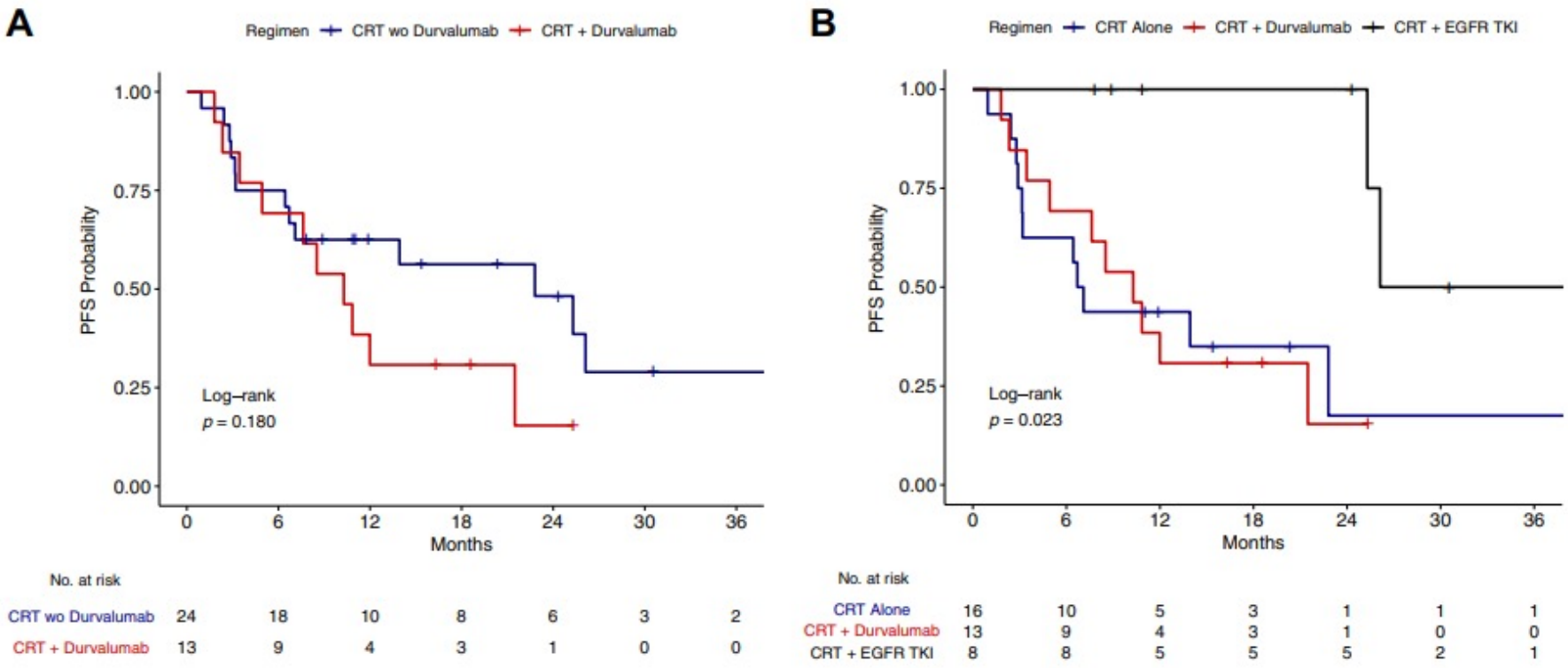


Figure 3. PFS after chemoradiotherapy with or wo durvalumab. (*A*) Median PFS among patients who completed CRT and durvalumab versus CRT wo durvalumab was 10.3 months versus 22.8 months (log-rank $p = 0.180$). (*B*) Median PFS among patients who completed CRT alone versus CRT and durvalumab versus CRT and induction or consolidation EGFR TKI was 6.9 months versus 10.3 months versus 26.1 months (log-rank $p = 0.023$). CRT, chemoradiotherapy; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; wo, without.

Pts with EGFR-m NSCLC
- no benefit with consolidation durvalumab and
- experienced a high frequency of irAEs.

Pts who initiate osimertinib after durvalumab may be susceptible to incident irAEs. Consolidation durvalumab should be approached with caution in this setting and concurrent CRT with induction or consolidation EGFR TKIs further investigated as definitive treatment.

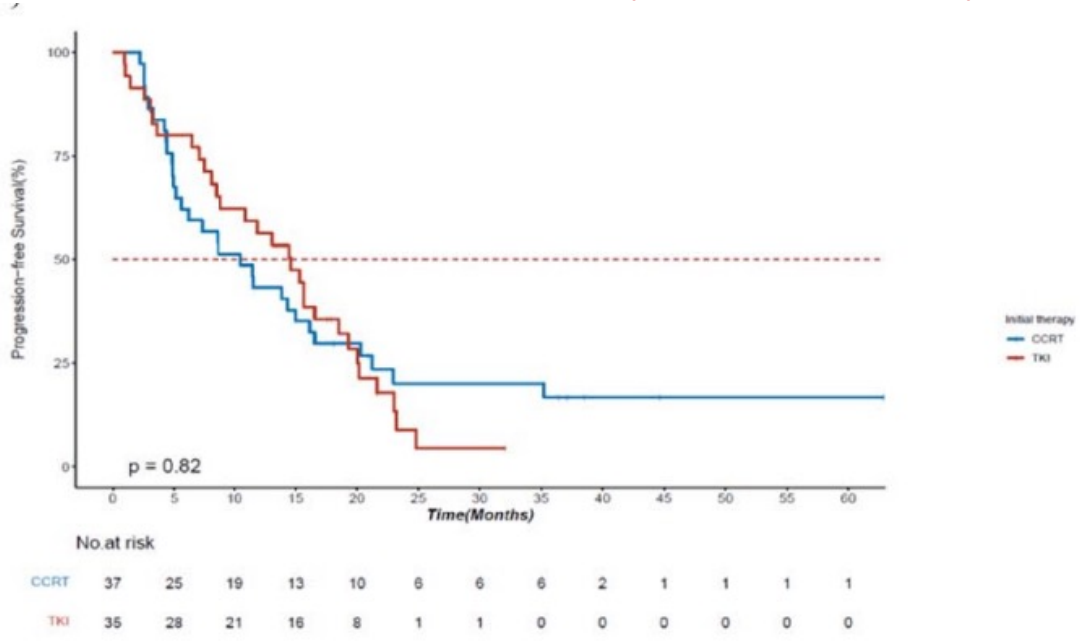
Aredo et al, JTO 2021

Real-world global data on targeting epidermal growth factor receptor mutations in stage III non-small-cell lung cancer: the results of the KINDLE study

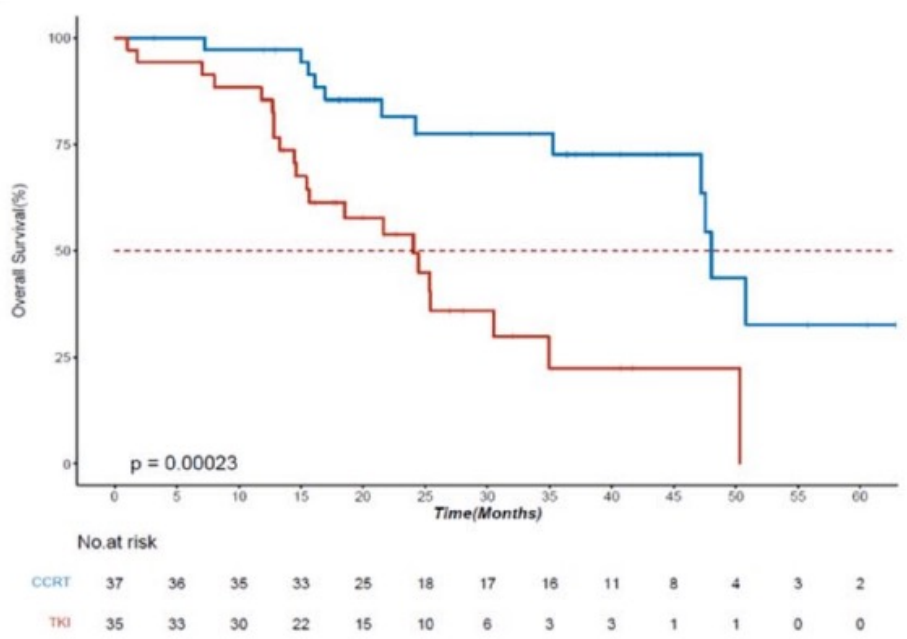
Jazieh et al,Ther Adv Med Oncol 2022

1114 / 3151 patients (35%) tested for EGFRm (46% in Asia, 17% in MENA and 32% in LA)
EGFRm detected in 32% of tested patients (34.3% in Asia, 20.0% in MENA and 28.4% in LA).
Most common initial ttt used in pts with EGFRm : EGFR TKI monotherapy (24%) NOT recommended in guidelines

EGFR mutated pts
mPFS for cCRT: 10.5months (95% CI: 5.6–16.6).
mPFS for TKI alone no RT: 14.6months (95% CI: 8.9–19.3)



EGFR mutated pts **EGFR wt**
mOS for cCRT: 48.0months (95% CI: 47.2–NC). 36.5months (95% CI: 28.9–NC)
mOS for TKI alone no RT: 24.0months (95% CI: 15.7–NC).



Outcomes with EGFR-TKI monotherapy as initial therapy, without any irradiation, were worse.

History: what TKI brought

The survival of patients with *ALK*+ advanced NSCLC

2000

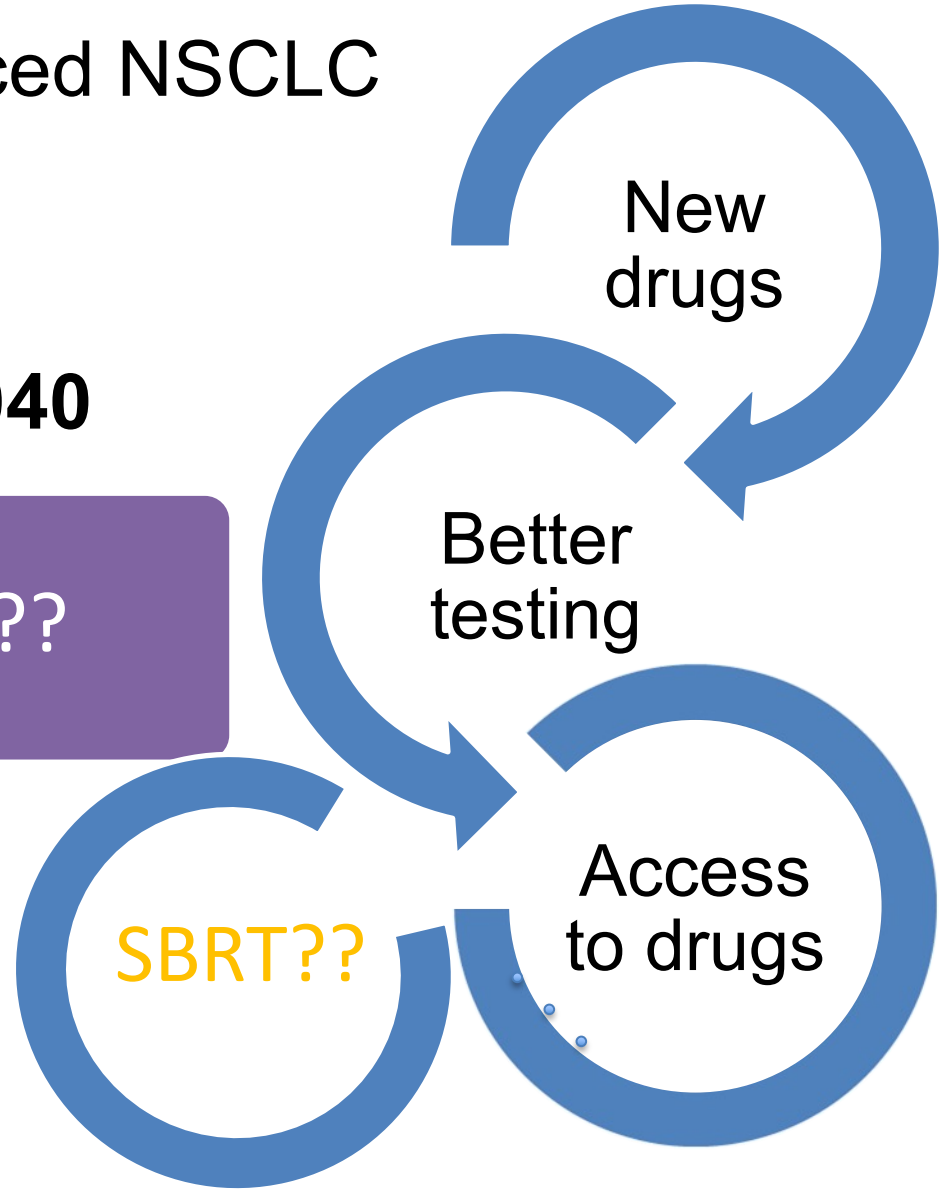
1 year of life

2022

10 years of life

2040

???

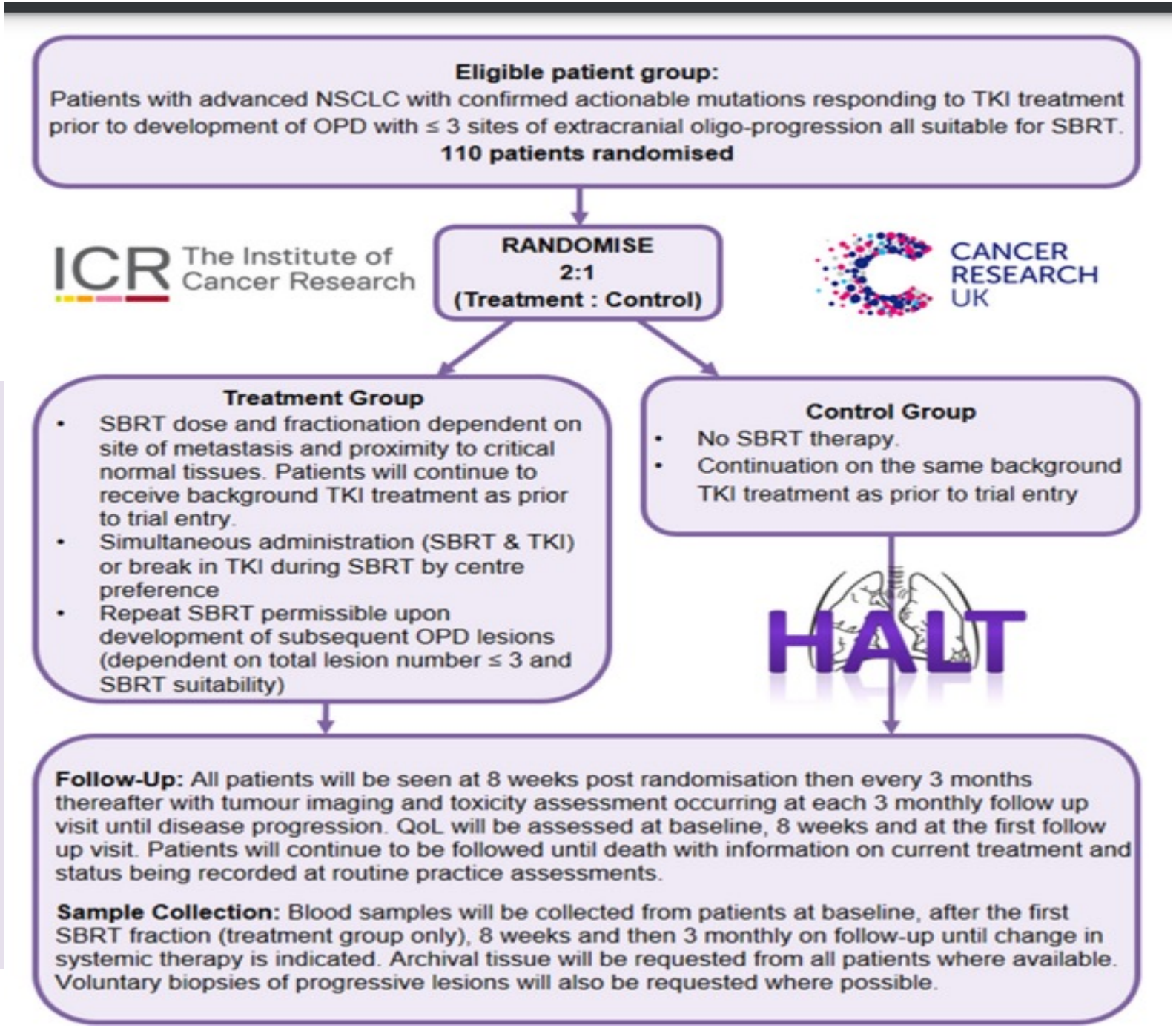


Adapted from Dr M Aldea Slide

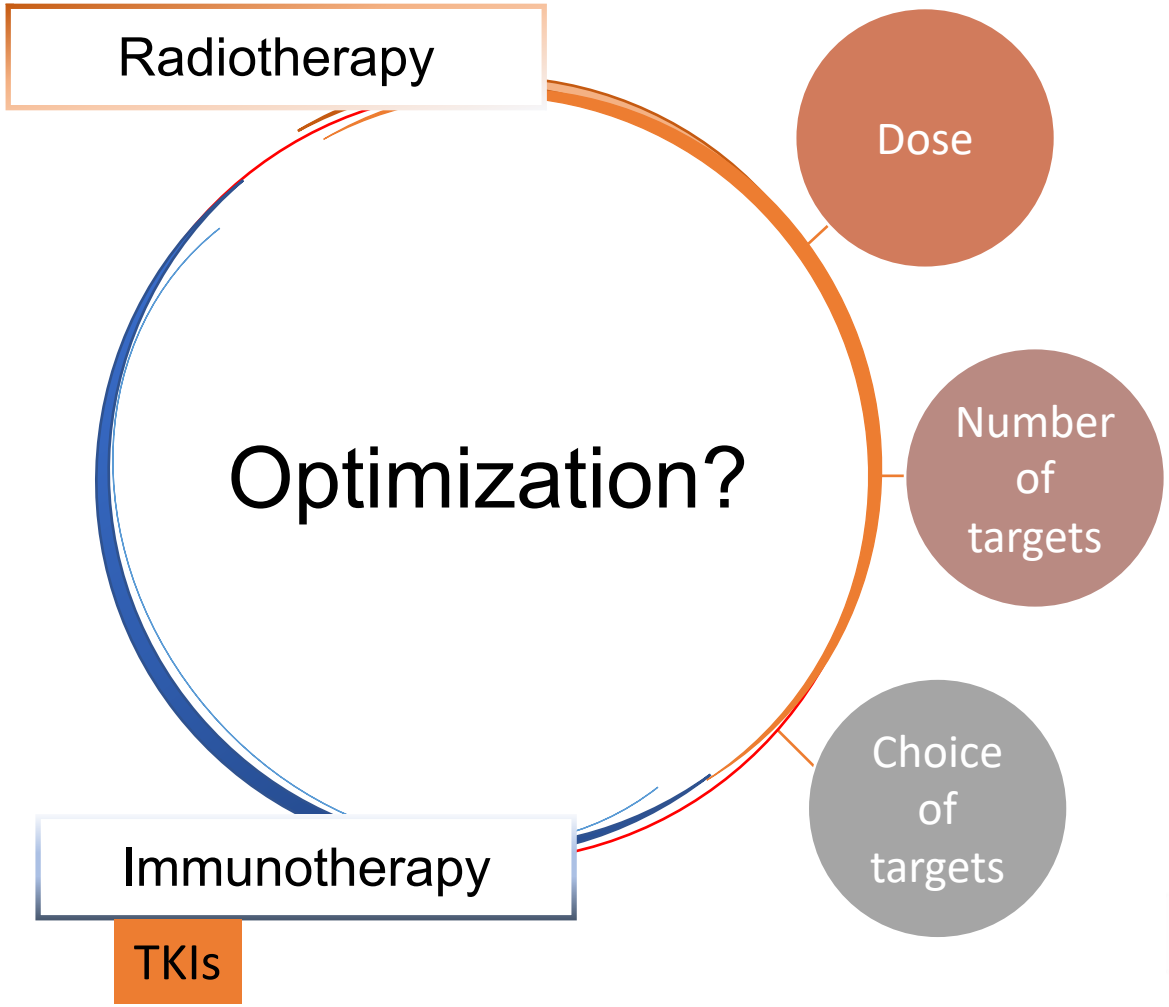
Genomic profiling and SBRT in Oligometastatic disease

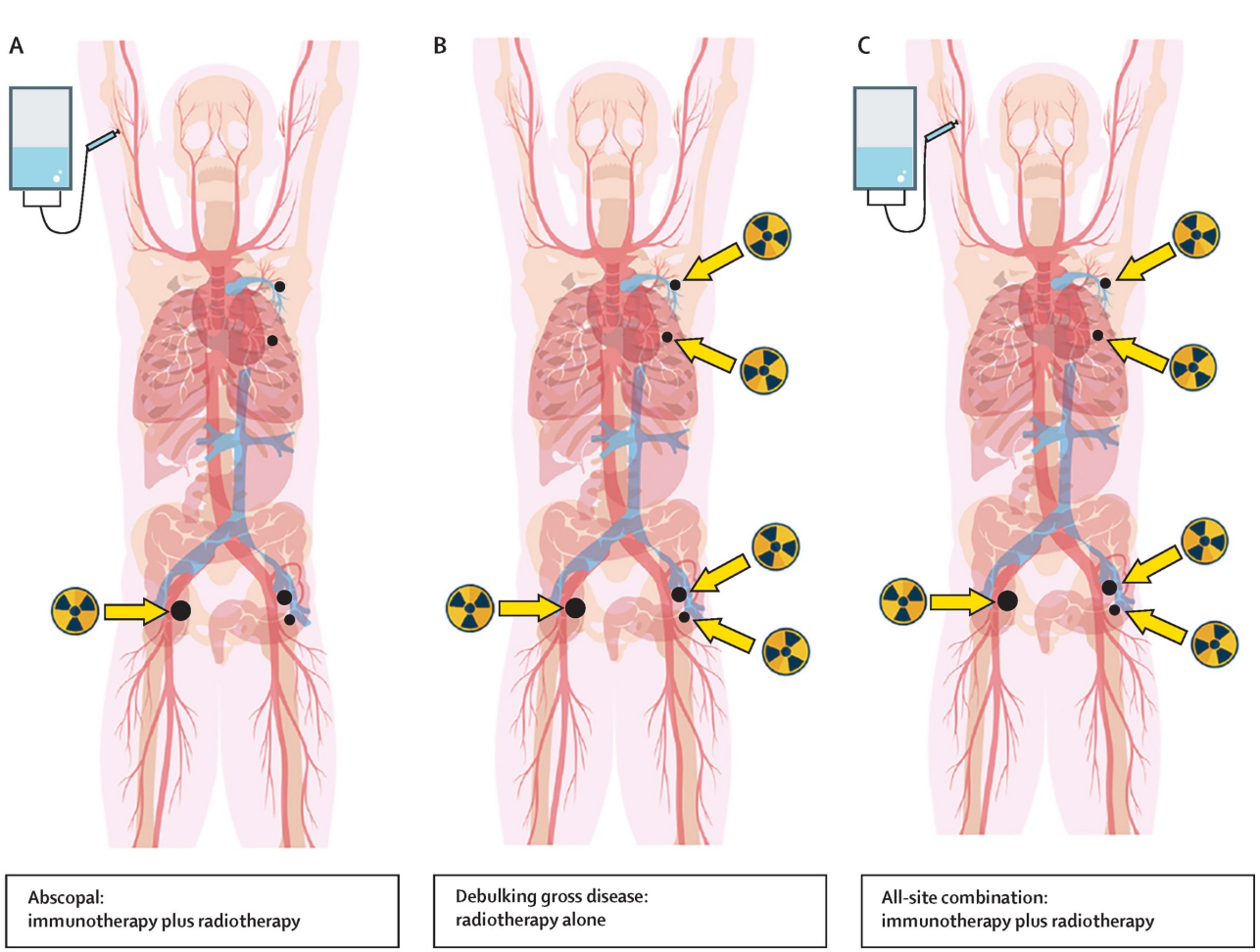
SBRT in oligoprogressive disease for pts with confirmed actionable mutations

Stratification: stop or no stop of TKIs during SBRT



Radioimmunotherapy and combination of TKI and RT led by genomics and radiomics…

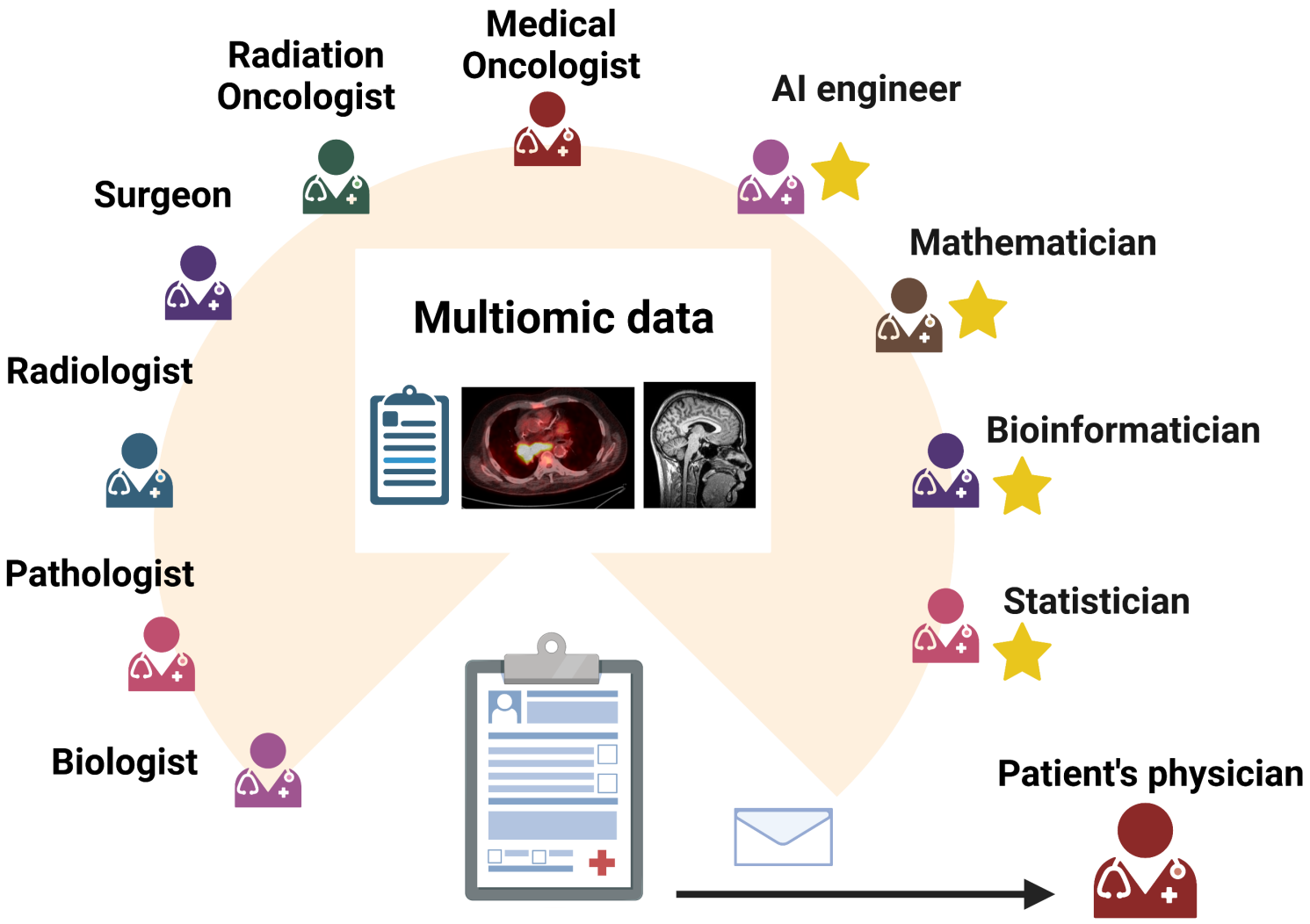




Deutsch *et al.* Lancet Oncol 2019

Courtesy of Dr R Sun Adapted..

“I have a dream, that one day” …



« Next-generation » Tumor Board

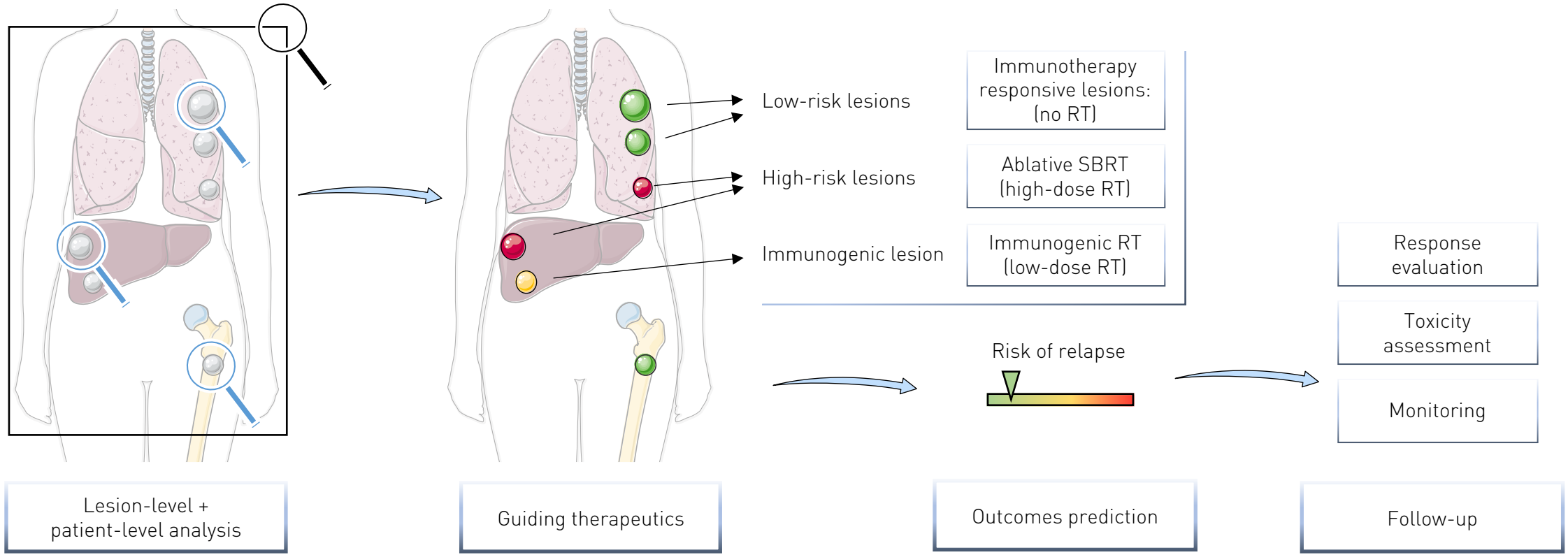
Integration of big data analysis in routine practice

Collaboration is KEY

Courtesy of Dr M Aldea

Toward ultra-precision radioimmunotherapy ?

Imaging-biomarkers guided radiotherapy



Sun R et al JITC 2022

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Thank you!! Grazie per l'invito!

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

UNIVERSITÉ PARIS SUD
FACULTÉ DE MÉDECINE

ÉCOLE DES SCIENCES DU CANCER GUSTAVE ROUSSY

MRO.ART
MODERN RADIATION ONCOLOGY