



**Multidisciplinary Approaches to Cancer Symposium**

# Role of Radiation Therapy in Oligometastatic and Oligoprogressive Disease

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# Disclosures

- Consultant for AstraZeneca
- Grant/Research Support from Genentech, RefleXion, Regeneron & Varian

*This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.*

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

*This presentation has been peer-reviewed and no conflicts were noted.*

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

## STATE LAW:

The California legislature has passed [Assembly Bill \(AB\) 1195](#), which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed [AB 241](#), which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

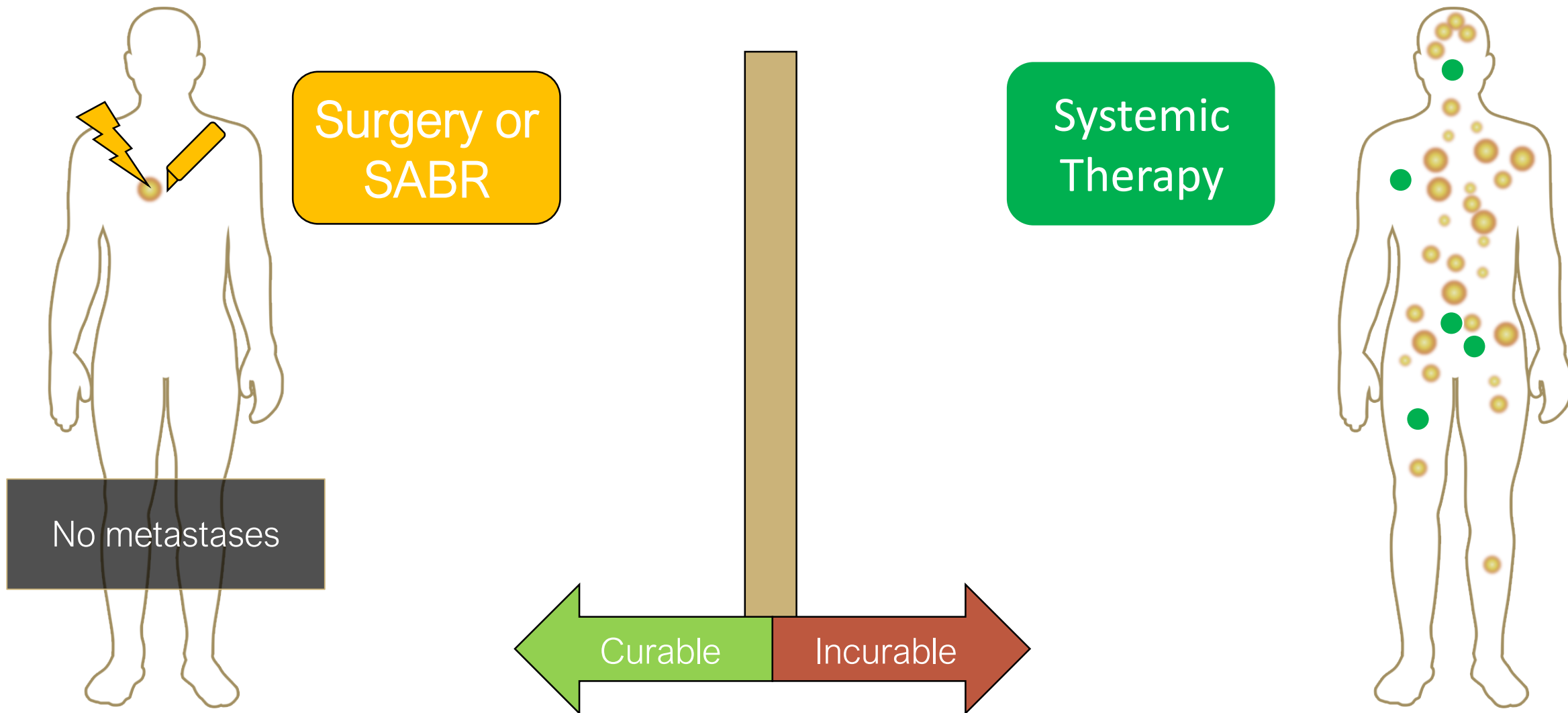
## EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

## ***The following CLC & IB components will be addressed in this presentation:***

- *Will include data representative of diverse populations/ethnicities.*
- *Will address disparities in receiving radiation treatment based on socioeconomic factors and how to improve on this.*

# All or Nothing??

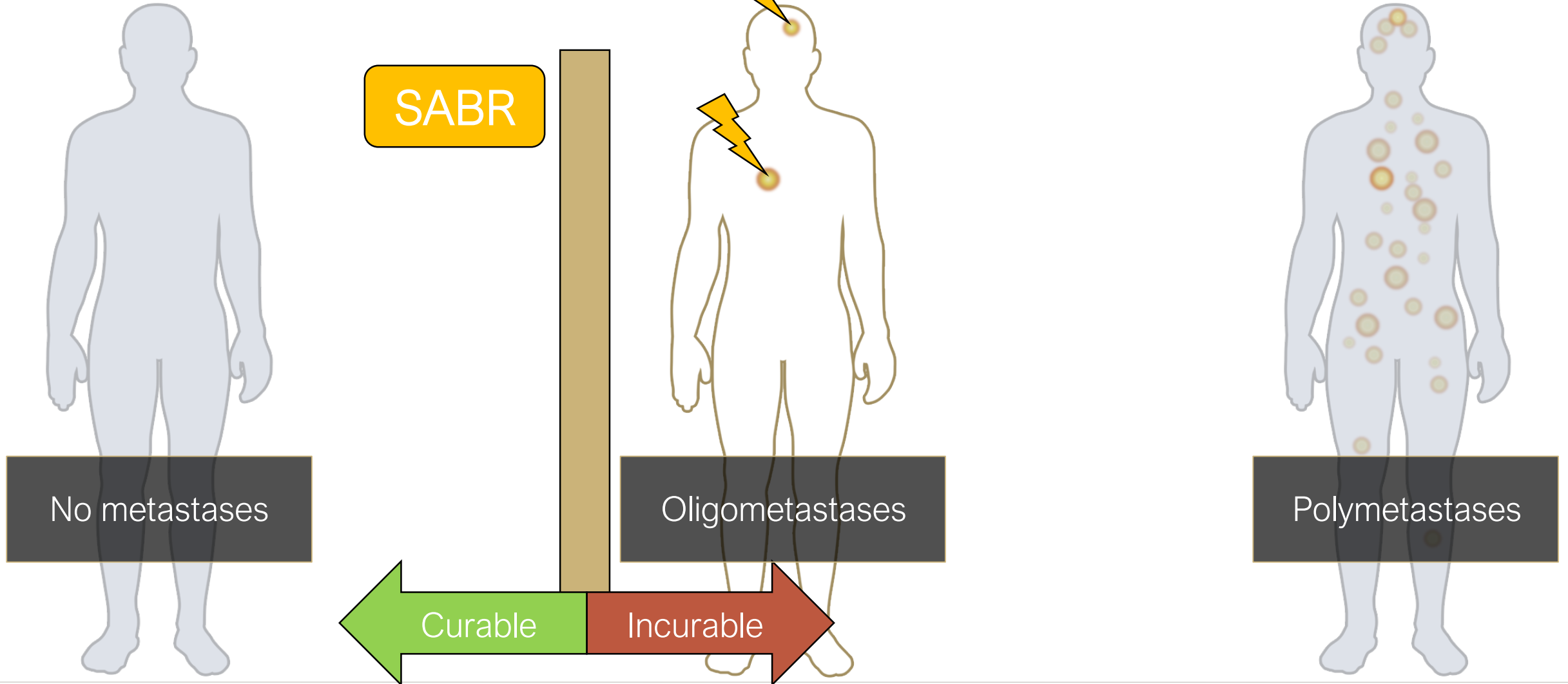


“Tumors early in the chain of progression may have **metastases limited in number and location** because the facility for metastatic growth has not been fully developed and the site for such growth is restricted...”

“An attractive consequence of the presence of a clinically significant **oligometastatic state** is that **some patients so affected should be amenable to a curative therapeutic strategy**”

– Hellman and Weichselbaum, JCO 1995

# A Spectrum?

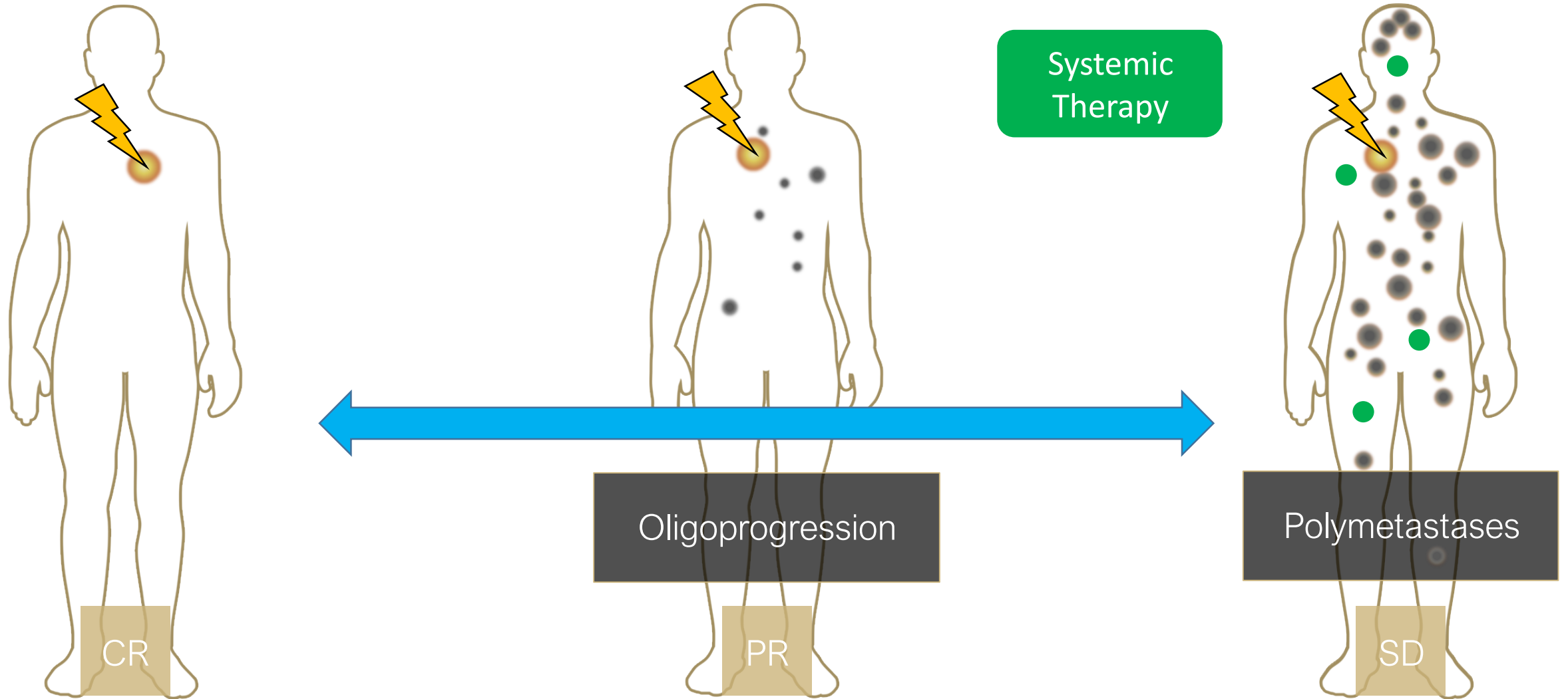


# A Spectrum?

“As effective chemotherapy becomes more widely applicable, there should be another group of patients with oligometastases...patients who had widespread metastases that were mostly eradicated by systemic agents, the chemotherapy having failed to destroy those remaining because of the number of tumor cells, the presence of drug resistant cells, or the tumor foci being located in some pharmacologically privileged site...effective chemotherapy may fail to be curative because of only a few metastases.”

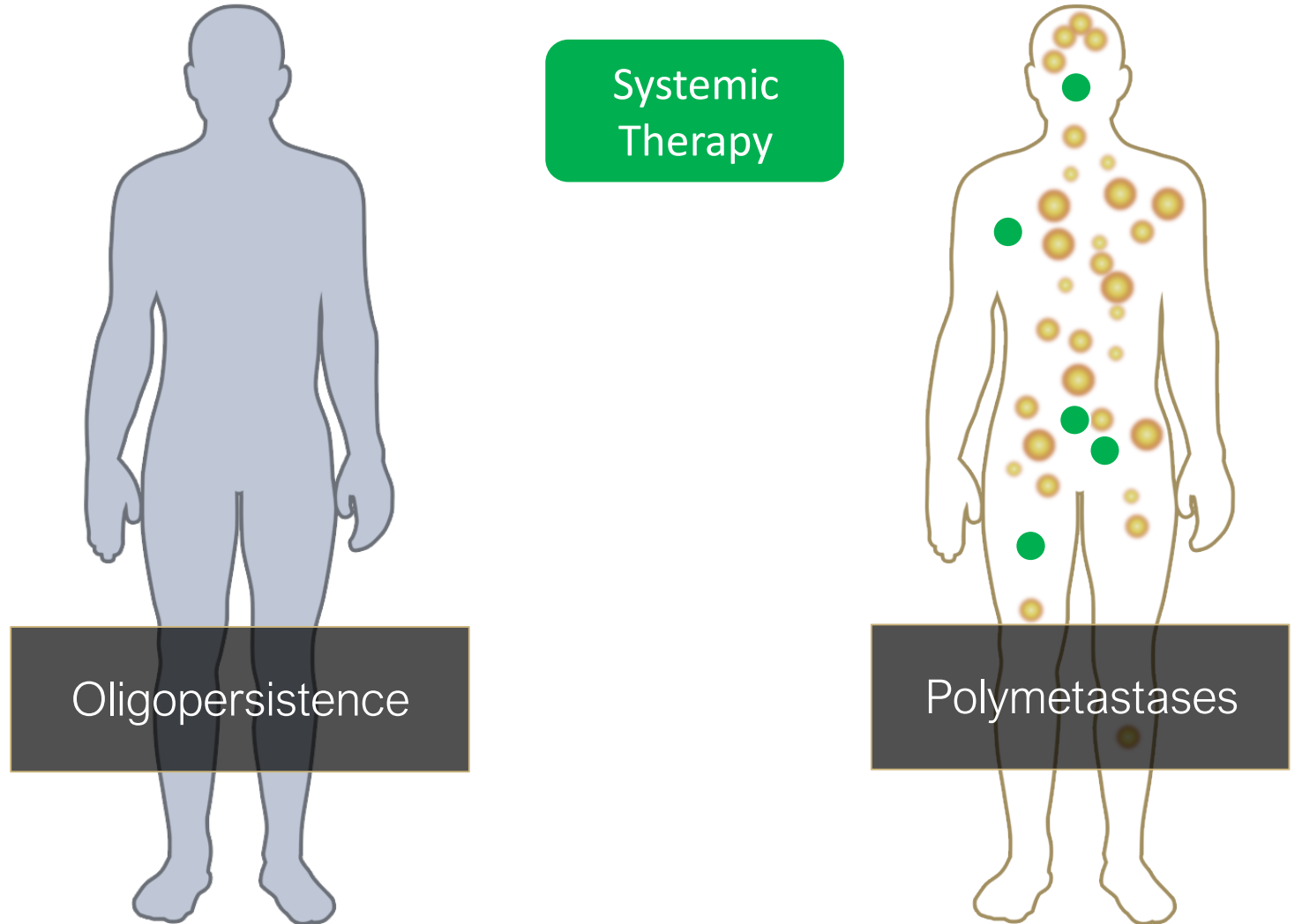
– Hellman and Weichselbaum, JCO 1995

# A Spectrum?

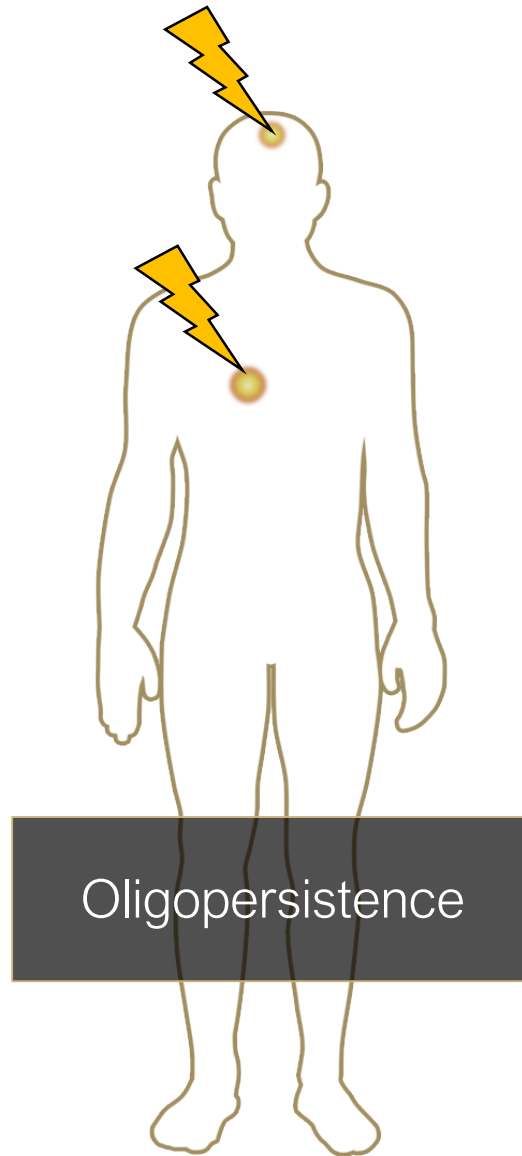




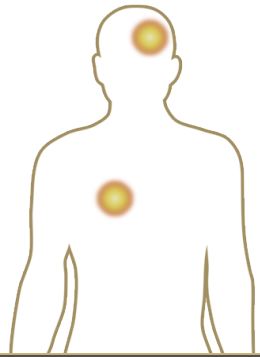
# A Spectrum?



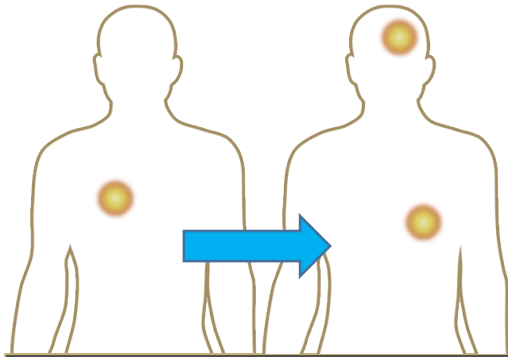
# A Spectrum?



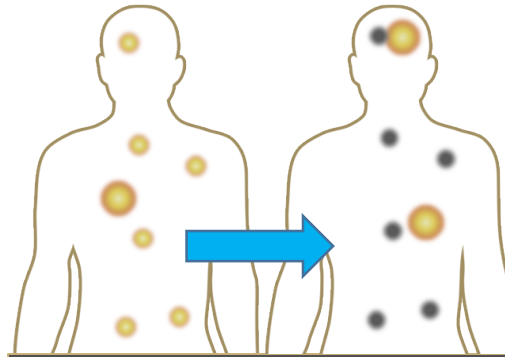
# Oligo-States



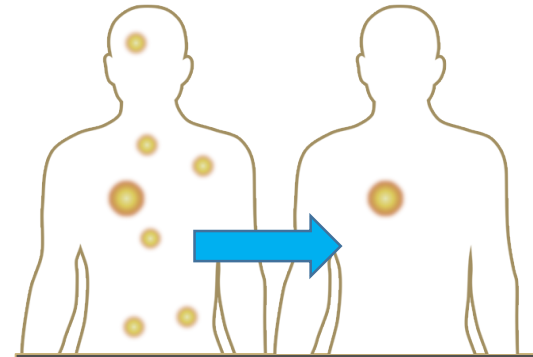
Synchronous  
oligometastatic  
“De novo”



Metachronous  
oligometastatic  
“Oligorecurrent”



Oligoprogession



Oligopersistence

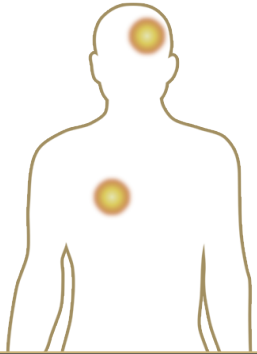
# Definition of Oligo?

- Most trials: 5 or less sites of disease

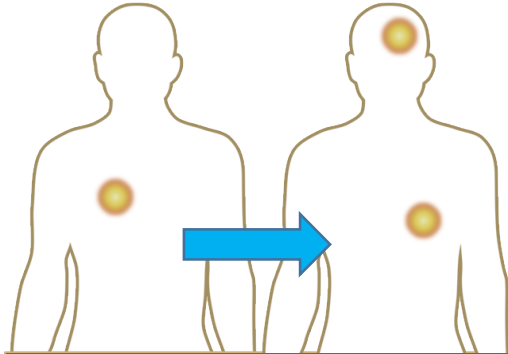
Integration of definitive local therapy if technically feasible and clinically safe to all disease sites, defined as 5 or fewer sites

–ESTRO-ASTRO consensus 2023

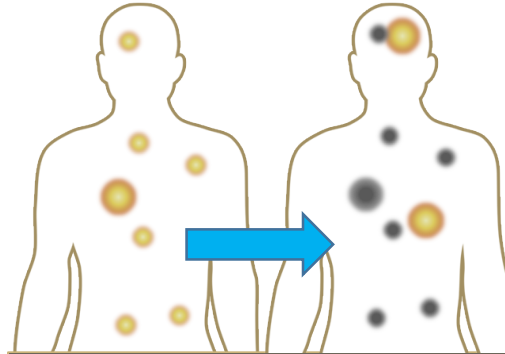
# Trials



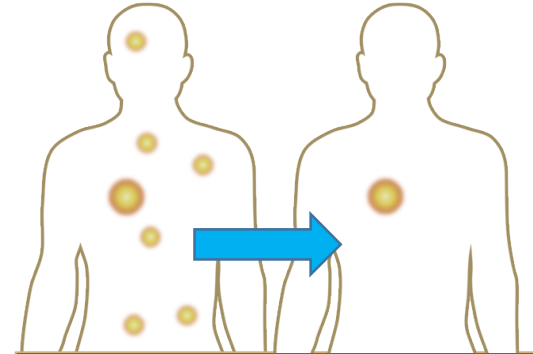
Synchronous oligometastatic  
“De novo”



Metachronous oligometastatic  
“Oligorecurrent”



Oligopropagation



Oligopersistence

## Trials

- Gomez
- Iyengar
- SINDAS
- SABR-COMET

## Trials

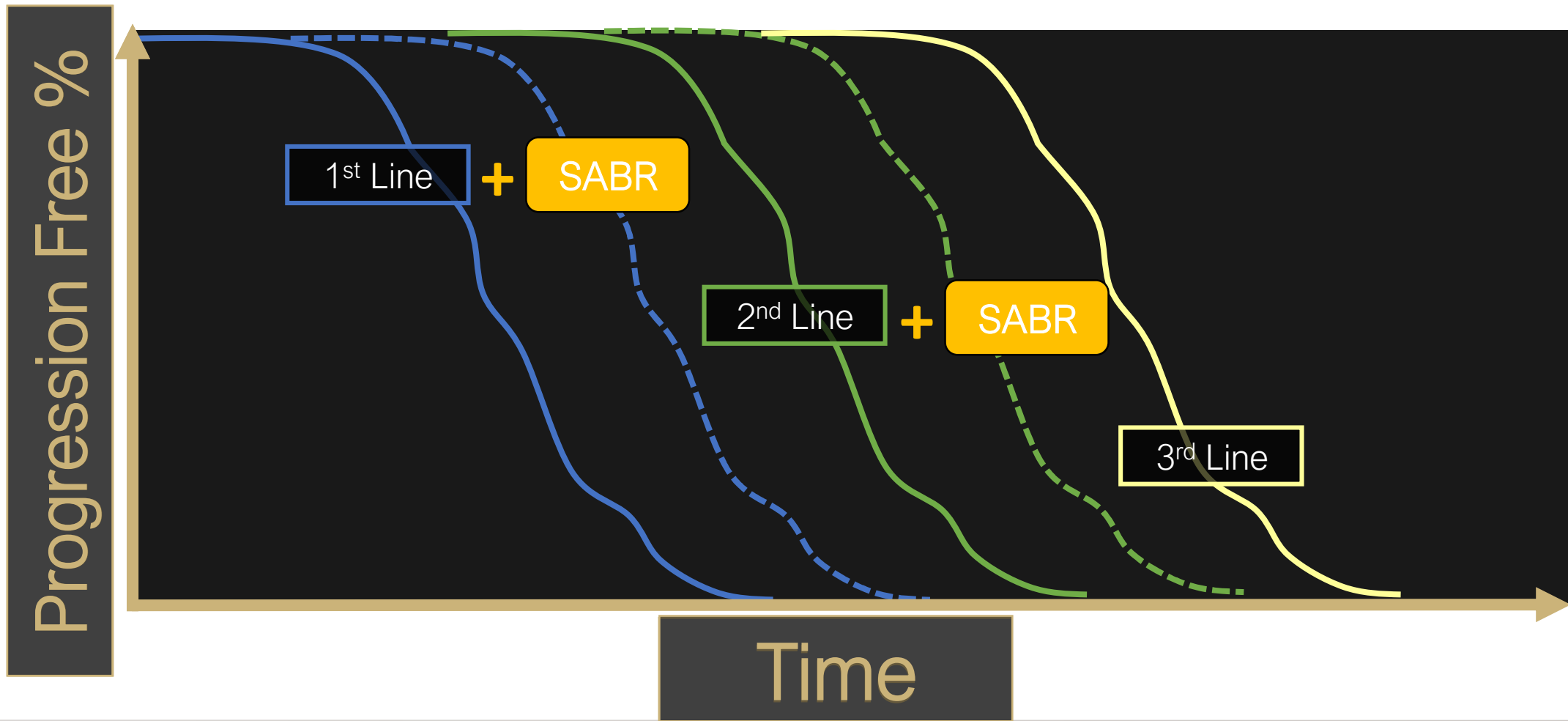
- Gomez
- Iyengar
- SINDAS

## Trials

- MSKCC CURB
- CCTG-BR38

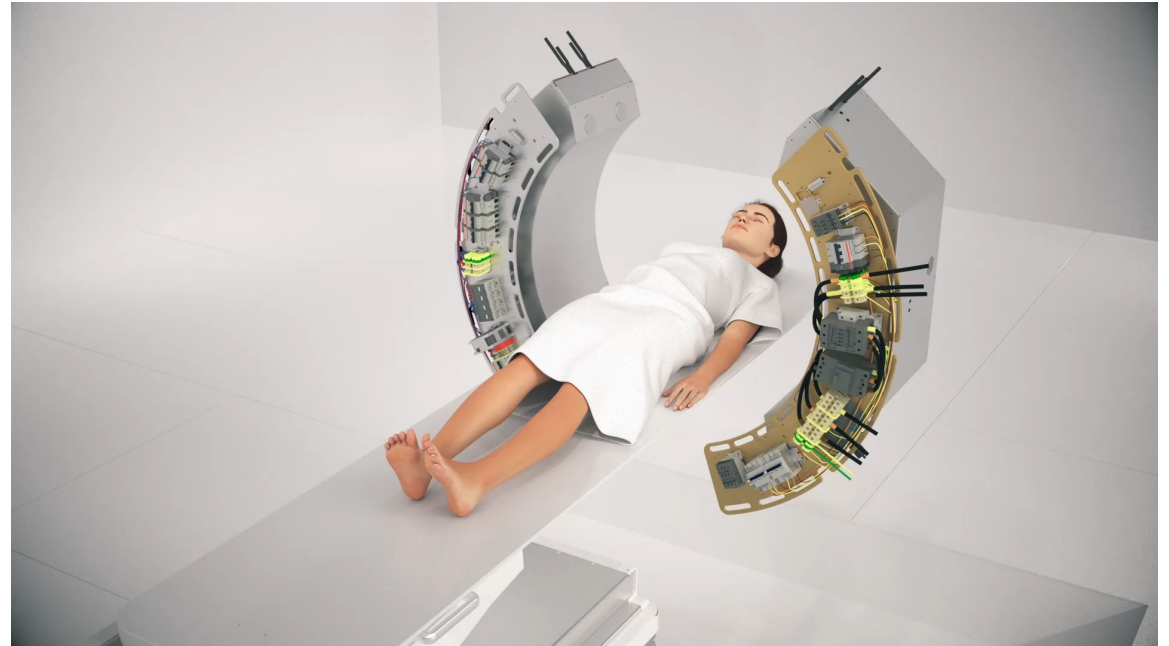
# Why Ablate Metastases

- Reduce burden of treatment-resistant cells
- Potentiate effects of systemic therapy
- Prevent growth of distant micrometastatic disease



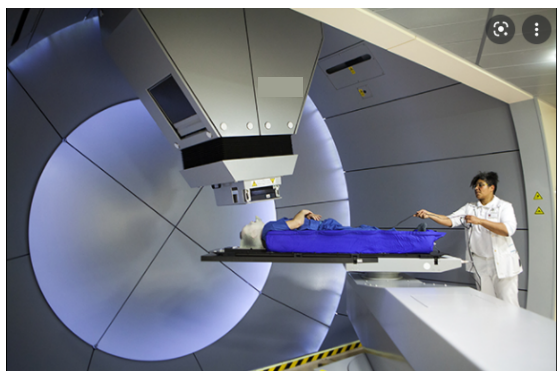
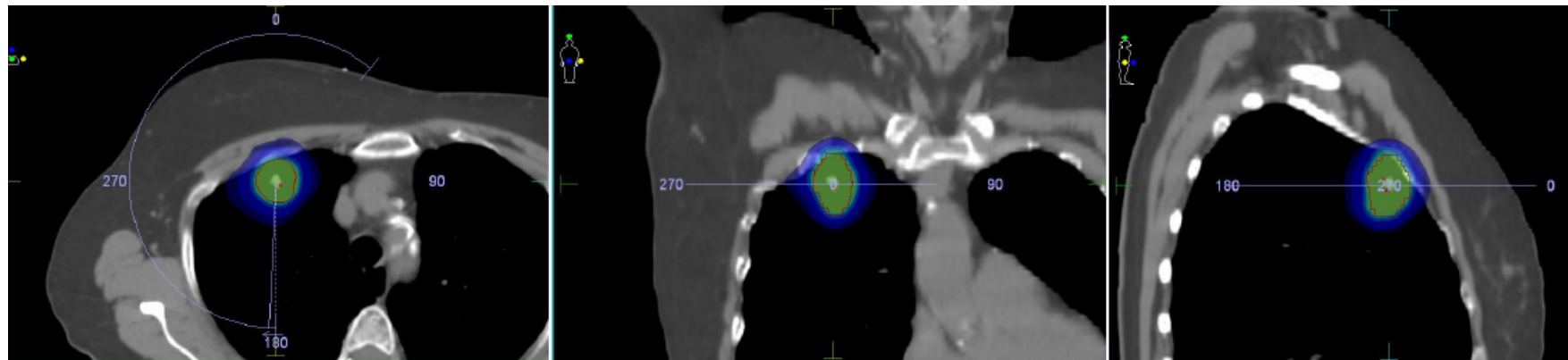
# Why Radiation?

- Non-invasive
- Well-tolerated
- Short courses
- Suitable for multiple sites
- Repeatable for subsequent progression
- Minimal disruption to systemic therapy
- Synergy with systemic therapy?



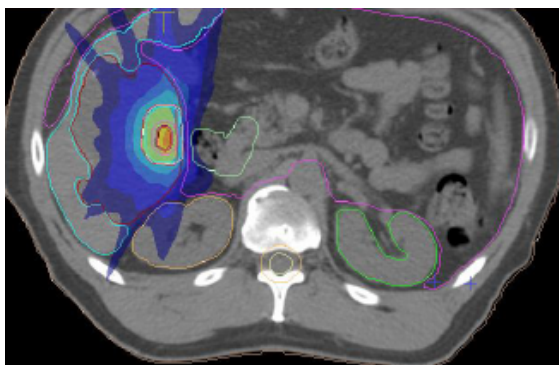
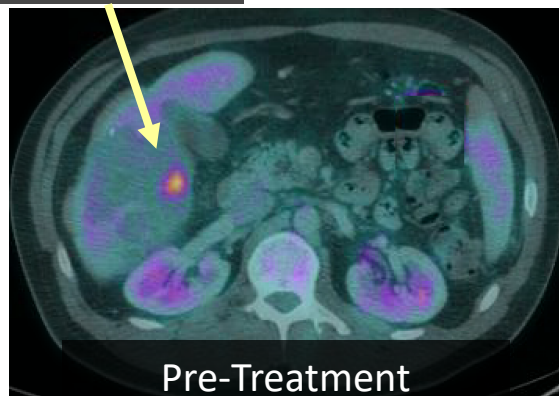
# SBRT/SABR

- High dose, short course
- Good for small targets
- Early-stage NSCLC, metastatic disease

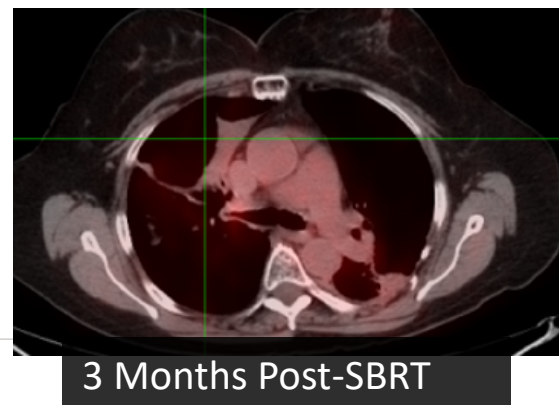
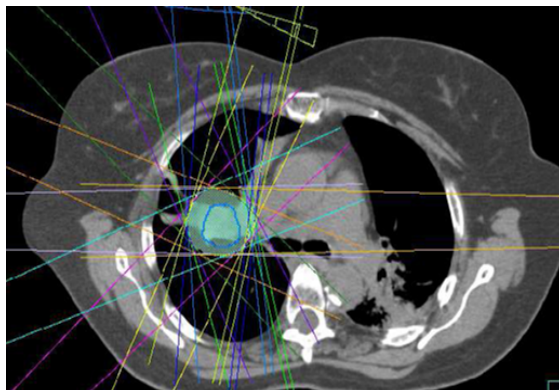
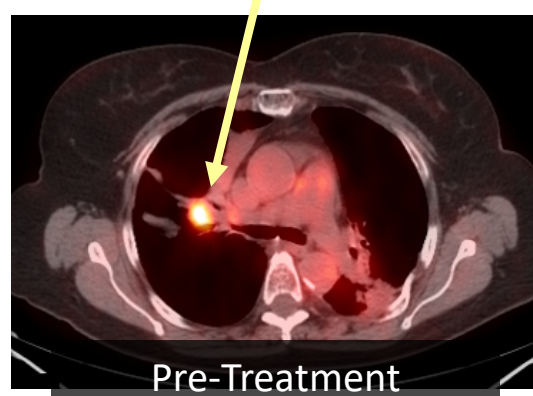




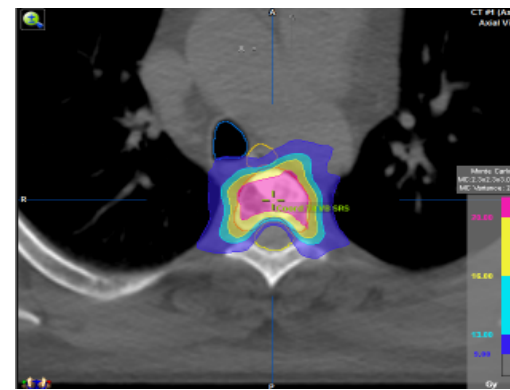
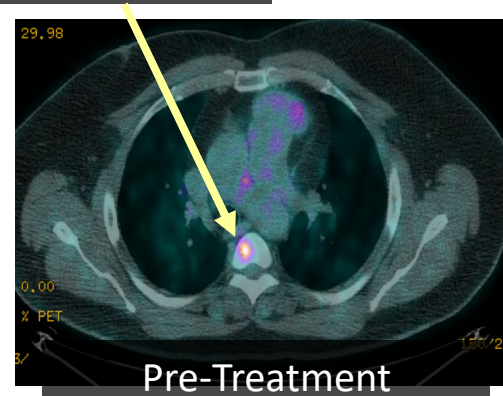
# Liver



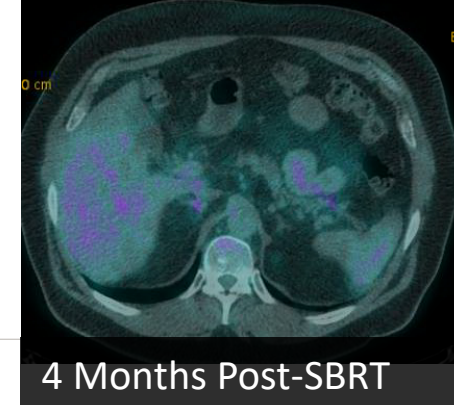
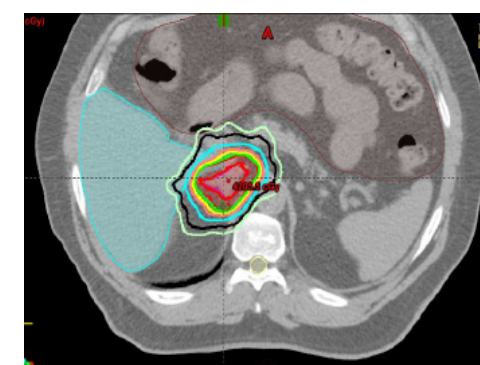
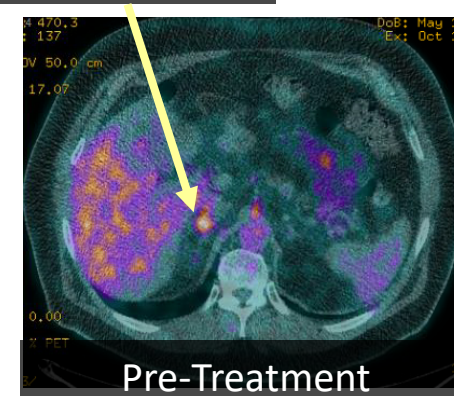
# Hilar Lymph Node



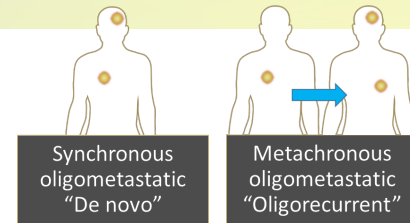
# Spine



# Adrenal

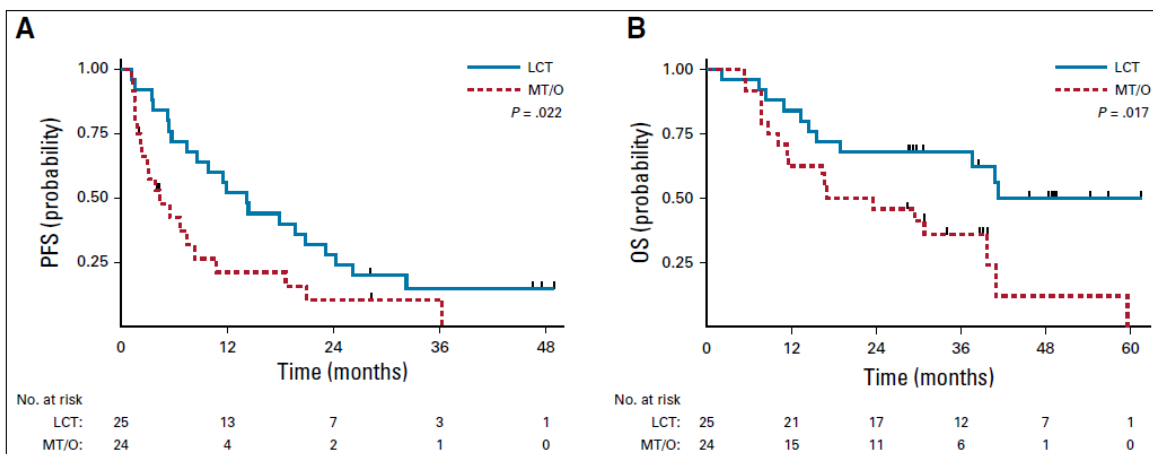


# SBRT in Oligometastatic NSCLC

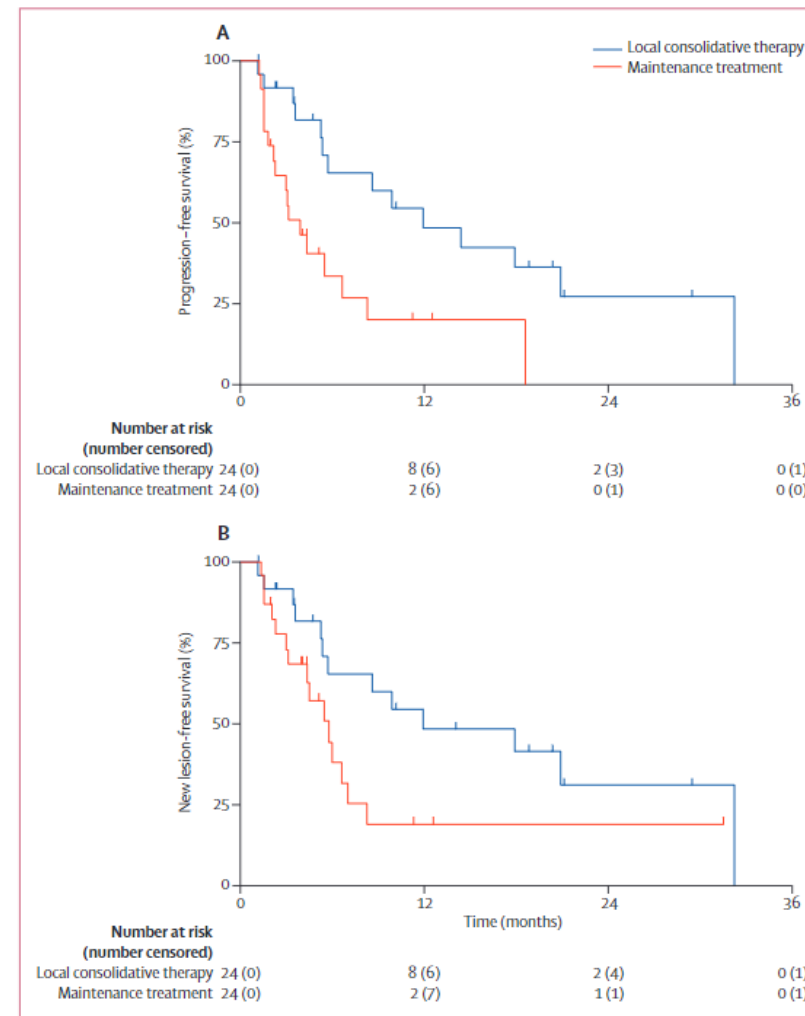


**Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study**

*Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinando Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher\*, John V Heymach\**



**FIG 1.** (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non-small-cell lung cancer.



**Figure 2:** Progression-free survival (A) and time to appearance of disease at a new site (B)

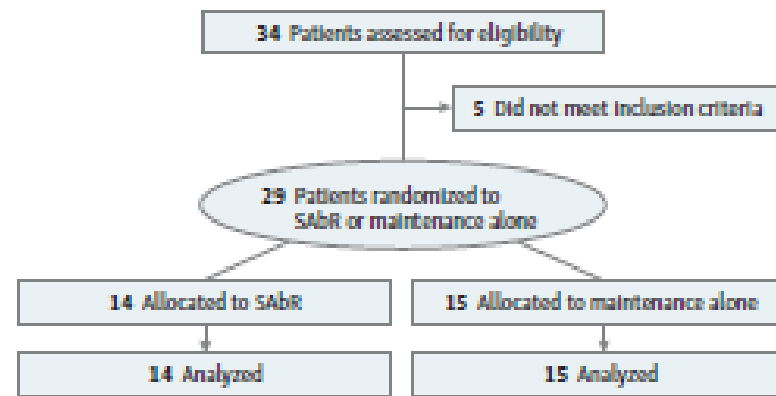
# SBRT in Oligometastatic NSCLC

JAMA Oncology | Original Investigation

## Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer A Phase 2 Randomized Clinical Trial

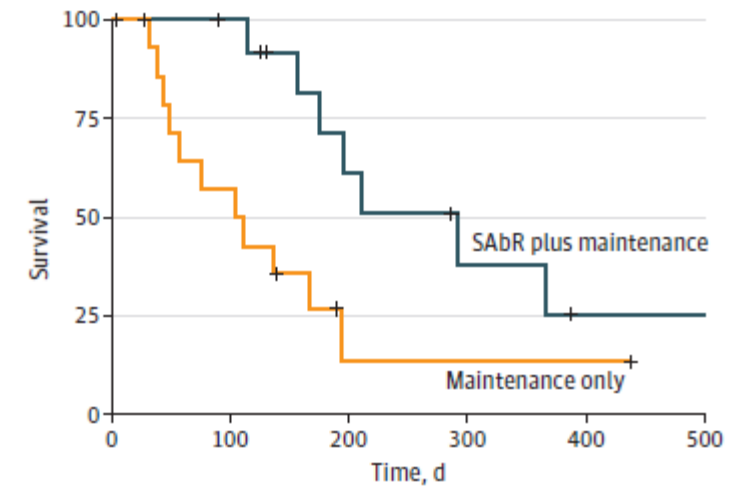
Puneeth Iyengar, MD, PhD; Zabi Wardak, MD; David E. Gerber, MD; Vasu Tumati, MD; Chul Ahn, PhD; Randall S. Hughes, MD; Jonathan E. Dowell, MD; Naga Cheedella, MD; Luden Nedzi, MD; Kenneth D. Westover, MD, PhD; Suprabha Pullipparacharuvil, PhD; Hak Choy, MD; Robert D. Timmerman, MD

Figure 1. CONSORT Diagram



SABR indicates stereotactic ablative radiotherapy.

Figure 2. Analysis of Progression-Free Survival



No. at risk	0	100	200	300	400	500
SABR plus maintenance	14	12	6	3	1	
Maintenance only	15	8	1	1	1	

Log-rank testing reveals a statistically significant benefit in progression-free survival for SABR-plus-maintenance chemotherapy (hazard ratio, 0.304; 95% CI, 0.113-0.815;  $P = .01$ ). SABR indicates stereotactic ablative radiotherapy.



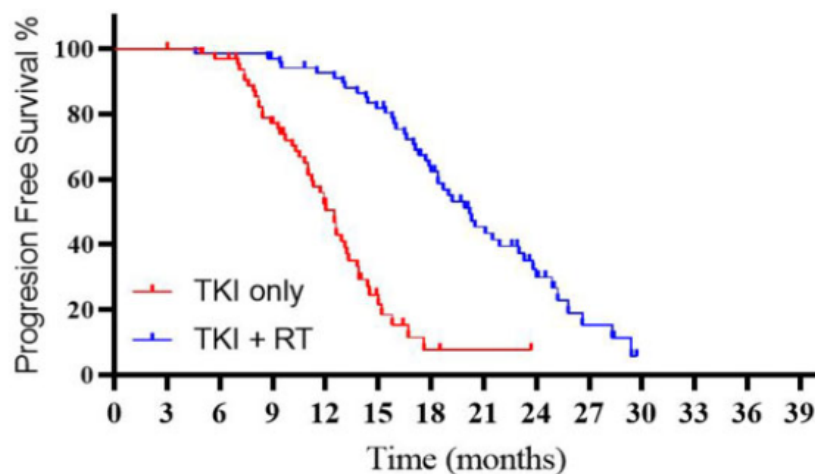


# SBRT in Oligometastatic Oncogenic Driver NSCLC

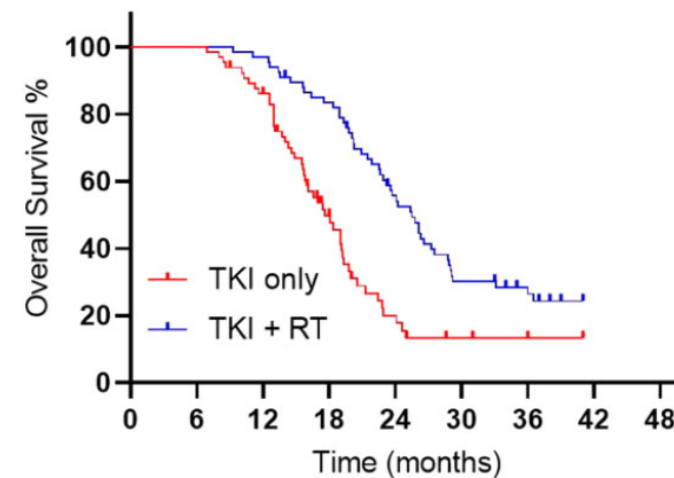
## Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic EGFR-Mutated Non-Small Cell Lung Cancer

Xiao-Shan Wang, MD,<sup>1\*</sup> Yi-Feng Bai, MD,<sup>1\*</sup> Vivek Verma, MD,<sup>2</sup> Rui-Lian Yu, MD,<sup>1</sup> Wei Tian, MS,<sup>1</sup> Rui Ao, MD,<sup>1</sup> Ying Deng, MD,<sup>1</sup> Xue-Qiang Zhu, MD,<sup>1</sup> Hao Liu, MD,<sup>1</sup> Hai-Xia Pan, MD,<sup>1</sup> Lan Yang, MD,<sup>1</sup> Han-Song Bai, MD,<sup>3</sup> Xing Luo, MD,<sup>3</sup> Yan Guo, MS,<sup>3</sup> Ming-Xiu Zhou, MD,<sup>3</sup> Yue-Mei Sun, MD,<sup>4</sup> Zi-Can Zhang, MD,<sup>4</sup> Si-Min Li, MD,<sup>3,5</sup> Xue Cheng, MD,<sup>3</sup> Bang-Xian Tan, MD,<sup>3</sup> Liang-Fu Han, MD,<sup>6</sup> Ying-Yi Liu, MD,<sup>7</sup> Kai Zhang, MD,<sup>8</sup> Fan-Xin Zeng, PD,<sup>9</sup> Lin Jia, MD,<sup>10</sup> Xin-Bao Hao, MD,<sup>11</sup> You-Yu Wang, MD,<sup>1</sup> Gang Feng, MD,<sup>1</sup> Ke Xie, MD,<sup>1</sup> You Lu, MD,<sup>12</sup> Ming Zeng, MD, PhD<sup>1,\*</sup>

- Randomized trial comparing upfront RT to no RT for oligometastatic (1-5) EGFRm NSCLC
- Median PFS 12.5 mo vs 20.2 mo (HR 0.22, p<0.001)
- Median OS 17.6 mo vs 25.5 mo (HR 0.44, p <0.001)

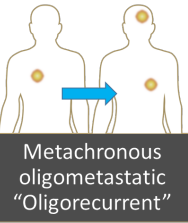


TKI only	65	65	62	48	28	8	3	2	1	0	0
TKI + RT	68	67	67	65	60	51	37	22	12	5	1



TKI only	65	65	55	26	9	5	3	2
TKI + RT	68	68	66	56	36	20	14	9

# SABR-COMET



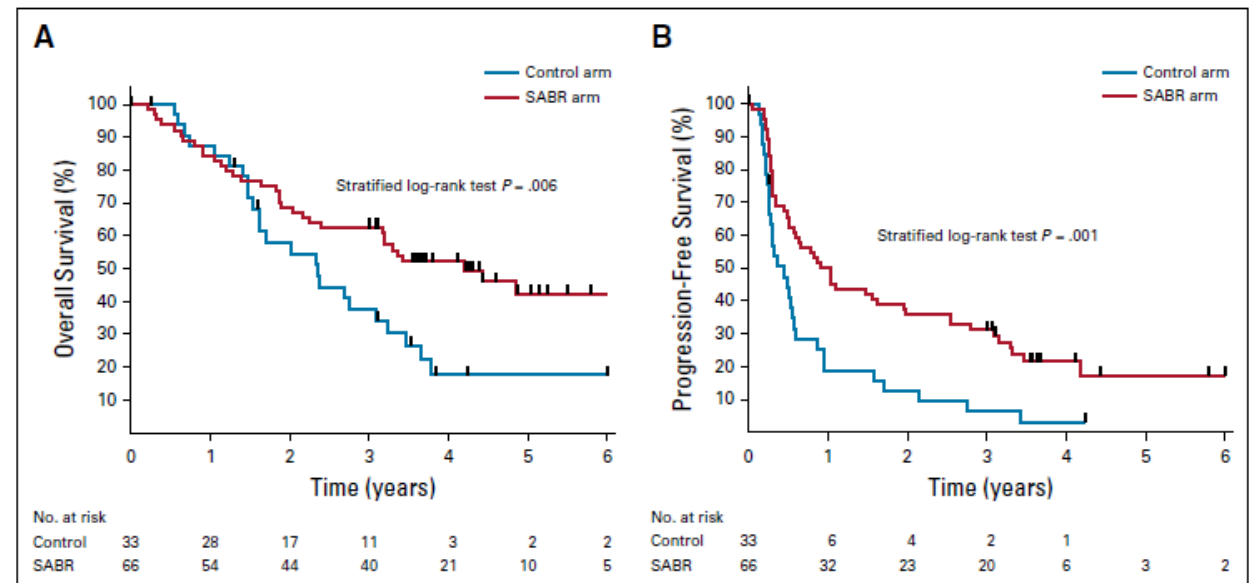
- 10 international sites
- 5-yr OS 17.7% vs 42.3% favoring SABR

TABLE 1. Baseline Characteristics

Characteristic	Arm, No. (%)	
	Control (n = 33)	SABR (n = 66)
Median age, years (IQR)	69 (64-75)	67 (59-74)
Sex		
Male	19 (58)	40 (61)
Female	14 (42)	26 (39)
Site of original primary tumor		
Breast	5 (15)	13 (20)
Colorectal	9 (27)	9 (14)
Lung	6 (18)	12 (18)
Prostate	2 (6)	14 (21)
Other	11 (33)	18 (27)
Median time from diagnosis of primary tumor to random assignment, years (IQR)	2.3 (1.3-4.5)	2.4 (1.6-5.3)
No. of metastases		
1	12 (36)	30 (46)
2	13 (40)	19 (29)
3	6 (18)	12 (18)
4	2 (6)	2 (3)
5	0 (0)	3 (5)
Location of metastases (n = 191 lesions)		
Adrenal	2 (3)	7 (6)
Bone	20 (31)	45 (35)
Liver	3 (5)	16 (13)
Lung	34 (53)	55 (43)
Other <sup>a</sup>	5 (8)	4 (3)

## Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

David A. Palma, MD, PhD<sup>1</sup>; Robert Olson, MD, MSc<sup>2</sup>; Stephen Harrow, MBChB, PhD<sup>3</sup>; Stewart Gaede, PhD<sup>1</sup>; Alexander V. Louie, MD, PhD<sup>4</sup>; Cornelis Haasbeek, MD, PhD<sup>5</sup>; Liam Mulroy, MD<sup>6</sup>; Michael Lock, MD<sup>1</sup>; George B. Rodrigues, MD, PhD<sup>1</sup>; Brian P. Yaremko, MD, PEng<sup>1</sup>; Devin Schellenberg, MD<sup>7</sup>; Belal Ahmad, MD<sup>1</sup>; Sashendra Senthil, MD, PhD<sup>8</sup>; Anand Swaminath, MD<sup>9</sup>; Neil Kopeck, MD<sup>10</sup>; Mitchell Liu, MD<sup>11</sup>; Karen Moore, MSc<sup>3</sup>; Suzanne Currie, MSc<sup>3</sup>; Roel Schlijper, MD<sup>2</sup>; Glenn S. Bauman, MD<sup>1</sup>; Joanna Laba, MD<sup>1</sup>; X. Melody Qu, MD, MPH<sup>1</sup>; Andrew Warner, MSc<sup>1</sup>; and Suresh Senan, MBBS, PhD<sup>5</sup>

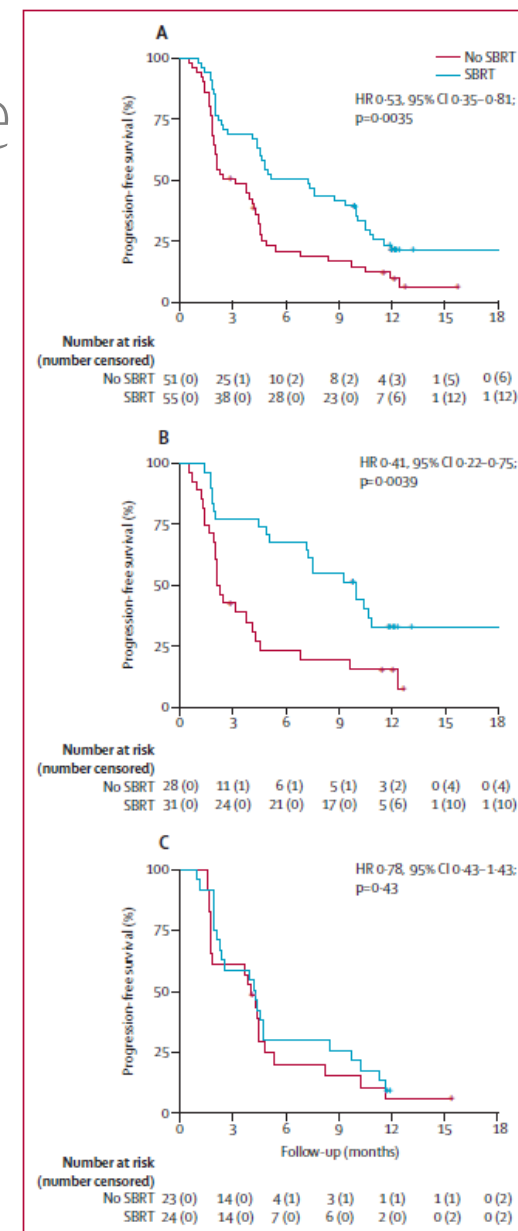
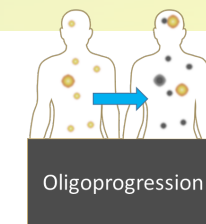


# Studies Suggesting Benefit of SBRT in the Oligoprogressive Setting

**Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study**

*Chiaojung Jillian Tsai, Jonathan T Yang, Narek Shaverdian, Juber Patel, Annemarie F Shepherd, Juliana Eng, David Guttmann, Randy Yeh, Daphna Y Gelblum, Azadeh Namakydoust, Isabel Preeshagul, Shanu Modi, Andrew Seidman, Tiffany Traina, Pamela Drullinsky, Jessica Flynn, Zhigang Zhang, Andreas Rimner, Erin F Gillespie, Daniel R Gomez, Nancy Y Lee, Michael Berger, Mark E Robson, Jorge S Reis-Filho, Nadeem Riaz, Charles M Rudin, Simon N Powell, on behalf of the CURB Study Group\**

- 106 patients
- Median PFS 3.2 vs 7.2 months
  - NSCLC: 10.0 vs 2.2 months
  - Breast: 4.4 vs 4.2 months



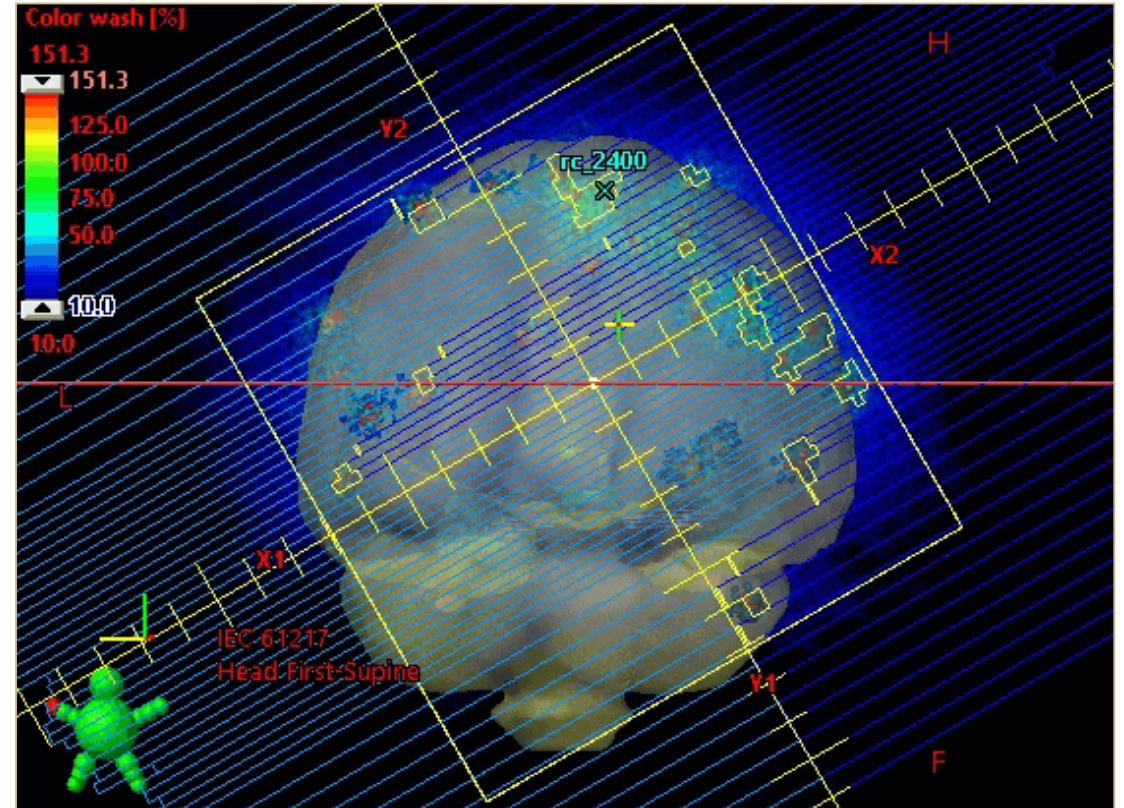
**Figure 2: Progression-free survival**  
Progression-free survival in the entire cohort (A), patients with non-small-cell lung cancer (B), and patients with breast cancer (C). Tick marks indicate censored data. HR=hazard ratio. SBRT=stereotactic body radiotherapy.

# Summary of Oligo Trials

Trial	Median PFS	Median OS
Gomez	4.4 mo	17 mo
	14.2 mo	41 mo
Iyengar	3.5 mo	17 mo
	9.7 mo	N.R
SINDAS	12.5 mo	17.4 mo
	20.2 mo	25.5 mo
SABR COMET	5.4 mo	28 mo
	11.6 mo	50 mo
MSKCC CURB	3.2 mo	N.R
	7.2 mo	N.R

# Brain Metastases

- Not typically counted as an “oligo” site
- Management
  - Referral to radiation oncology
  - Consider surgery for larger lesions with edema
  - ? Intracranial penetration of systemic therapy
  - WBRT vs SRS





# Holding Systemic During Radiation

- No clear data and often at discretion of treating oncologists
- Immunotherapies – generally can continue; possible pneumonitis risk
- TKIs – generally can continue but need to consider in certain settings

**Table 1 Summary of suggested approaches**

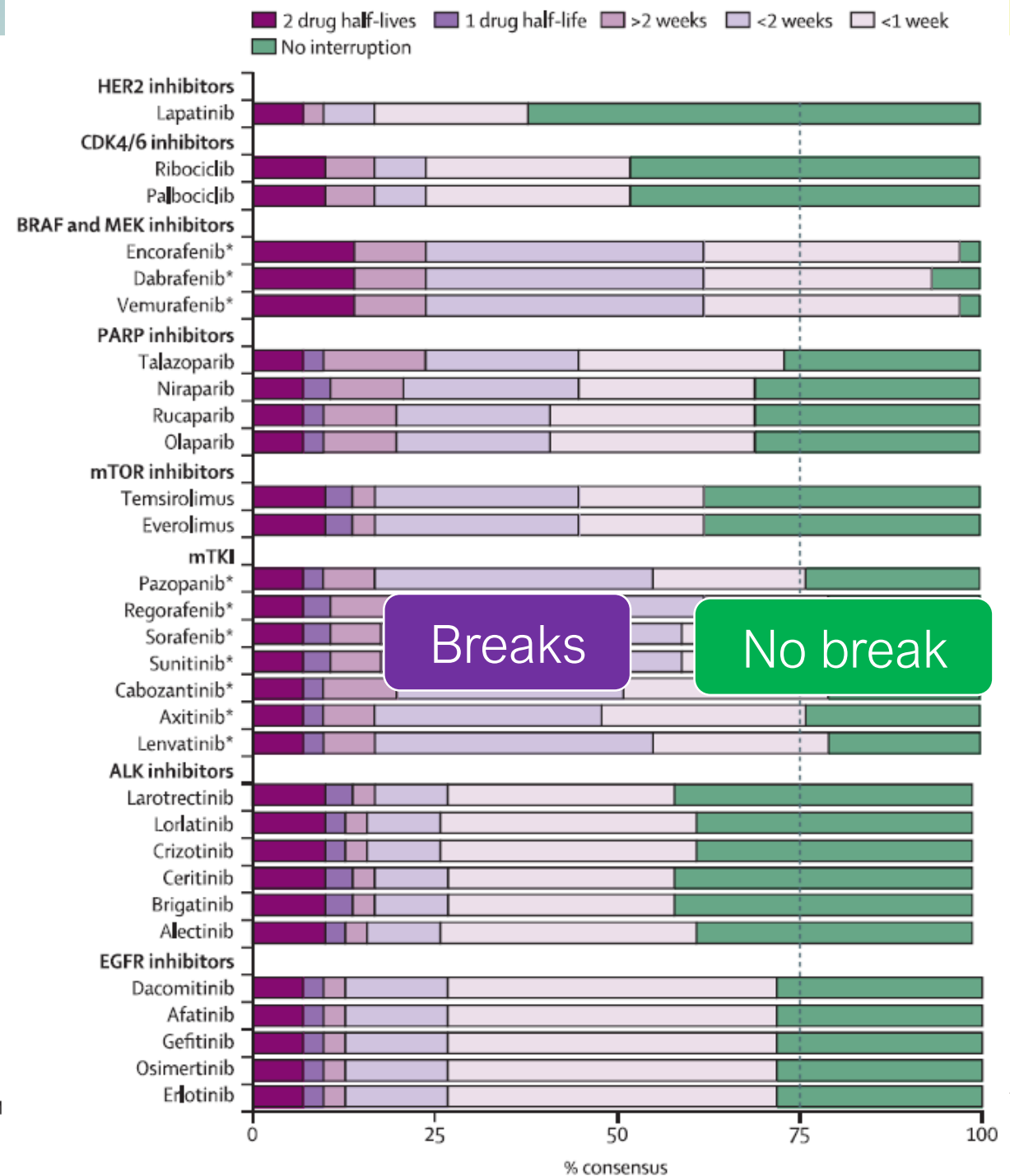
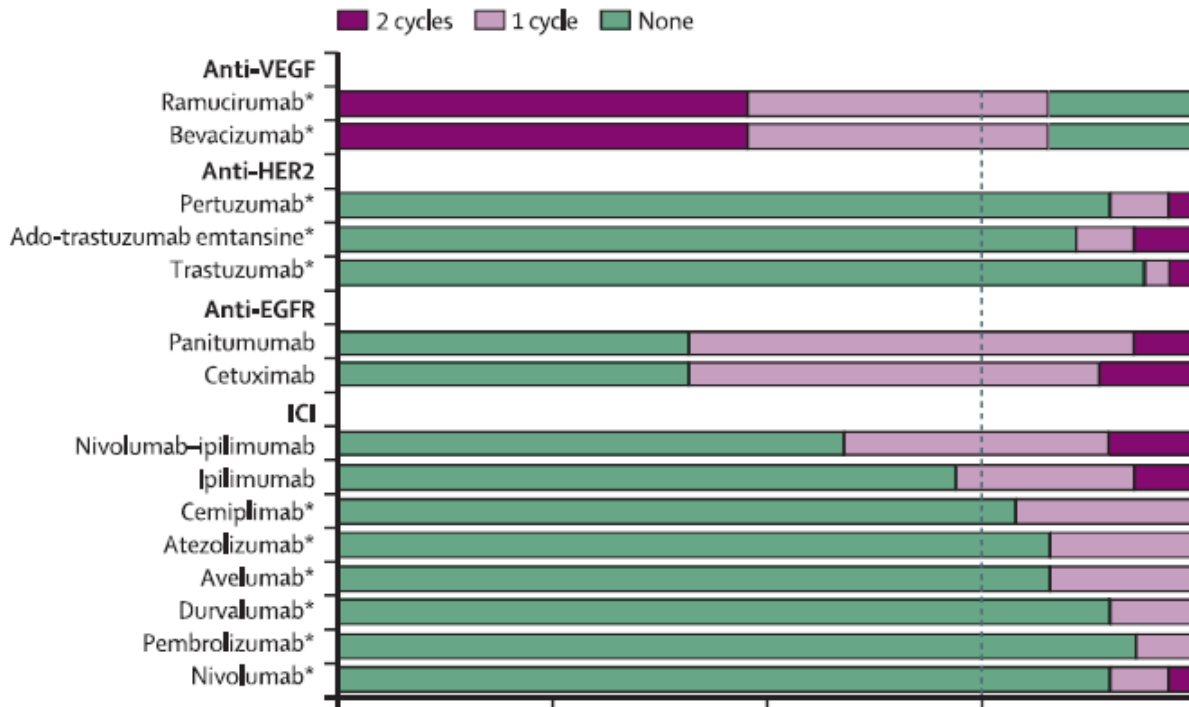
Agents	Drug	Suggestions
BRAF and MEK inhibitor	Vemurafenib and dabrafenib; trametinib	Suspend 3 d before and after RT. Suspend 1-2 d before and after RT.
EGFR and ALK inhibitor	Cetuximab; erlotinib and gefitinib; crizotinib and osimertinib	Suspend the week of radiation if SBRT. Suspend 1-2 d before and after RT. Suspend $\geq 2$ d before and after RT.
VEGF inhibitor	Bevacizumab; sorafenib and sunitinib	Suspend 4 weeks before and after RT. Suspend 5-10 d before and after RT.
Cyclin-dependent kinase (CDK) inhibitors 4-6	Palbociclib and ribociclib	Suspend 3 d before and after RT.
Immunotherapy	Ipilimumab; other	Suspend 2 d before and after RT if 8 Gy in single fraction to bone. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis.
HER2 target therapy	Trastuzumab and pertuzumab; lapatinib; T-DM1	Generally safe to use concomitantly with RT. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis.

*Abbreviations:* ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; RT = radiation therapy; SBRT = stereotactic body RT; VEGF = vascular endothelial growth factor; CDK = cyclin-dependent kinase; TDM1 = trastuzumab emtansine.

# Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC-ESTRO OligoCare consortium



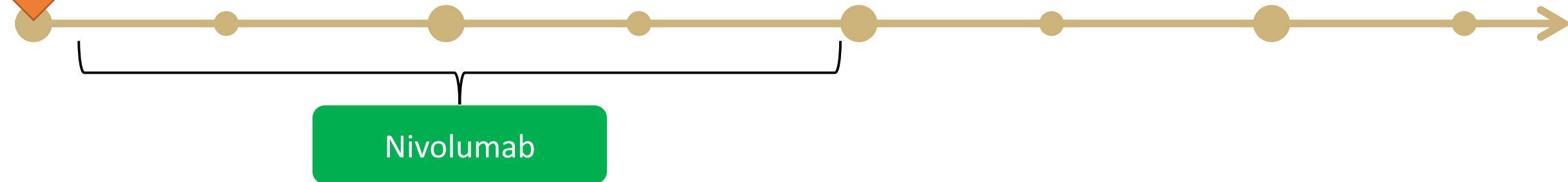
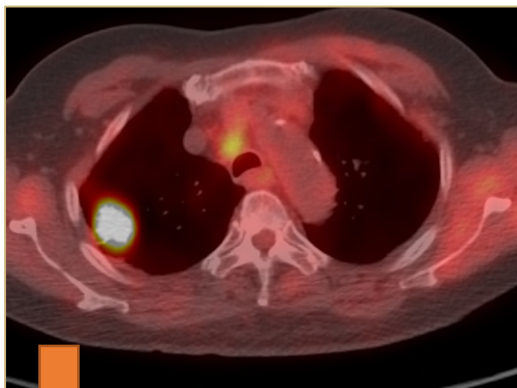
Stephanie G C Kraeze\*, Matea Pavic\*, Karin Stellamans, Yolande Lievens, Carlotta Becherini, Marta Scorsetti, Filippo Alongi, Umberto Ricardi, Barbara Alicja Jereczek-Fossa, Paulien Westhoff, Jasna Bub-Hadzic, Joachim Widder, Xavier Geets, Samuel Brai, Maarten Lambrecht, Charlotte Billiet, Igor Sirak, Sara Ramello, Ivaldi Giovanni Battista, Sergi Benavente, Almudena Zapatera, Fabiola Ramera, Thomas Zilli, Kaouthar Khanfir, Hossein Hemmatzad, Bernardino de Bari, Desiree N Klass, Shaikat Adnan, Heike Peulen, Juan Salinas Ramos, Michiel Strijbos, Sanjay Popat, Piet Ost, Matthias Guckenberger



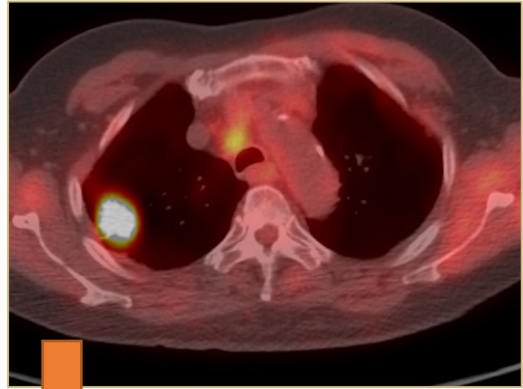
# Case

80 year old female with oligoprogressive SCC of the RUL

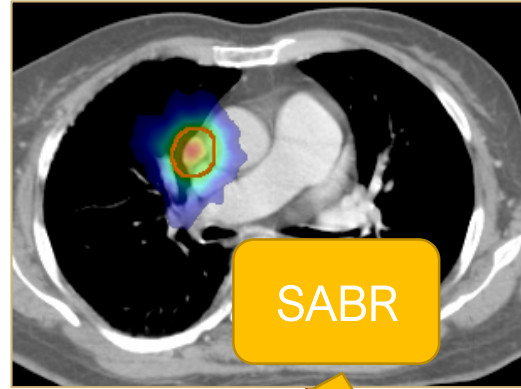
PET avid disease in bilateral lungs and lymph nodes



PET avid disease in bilateral lungs and lymph nodes



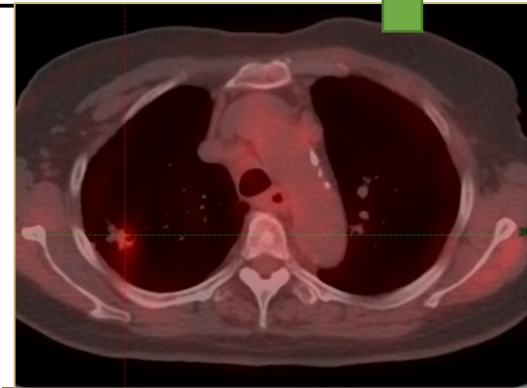
Oligoprogression in lymph node



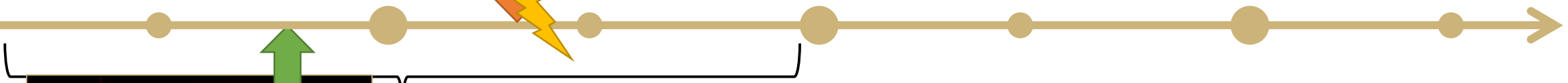
SABR



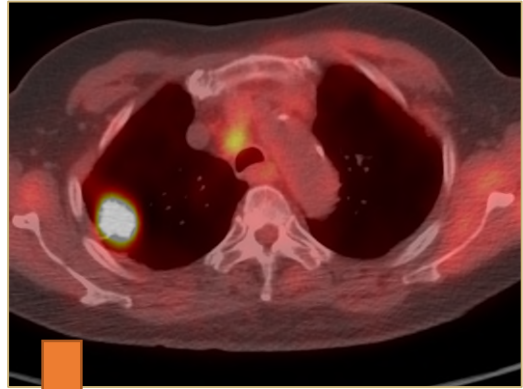
olumab



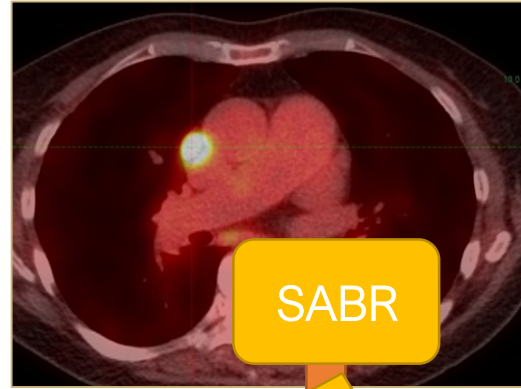
Resolution of avid disease



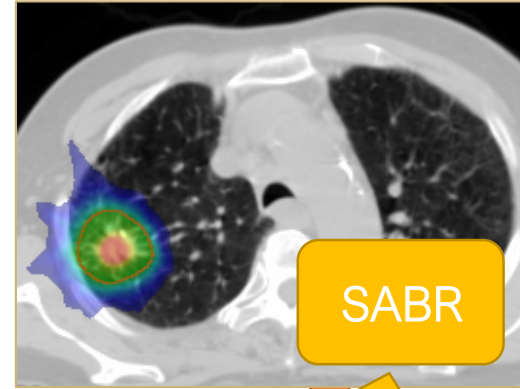
PET avid disease in bilateral lungs and lymph nodes



Oligoprogession in lymph node



Oligoprogession in right lung primary



SABR

SABR



olumab

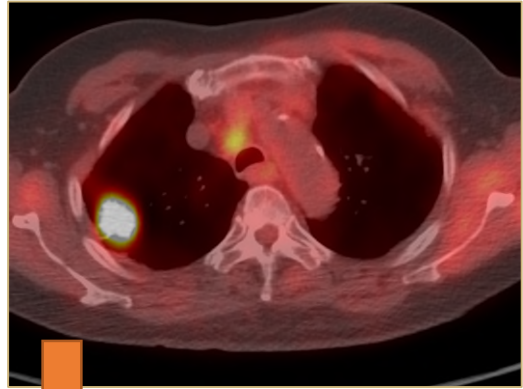
Resolution of avid disease

Resolution of avid disease

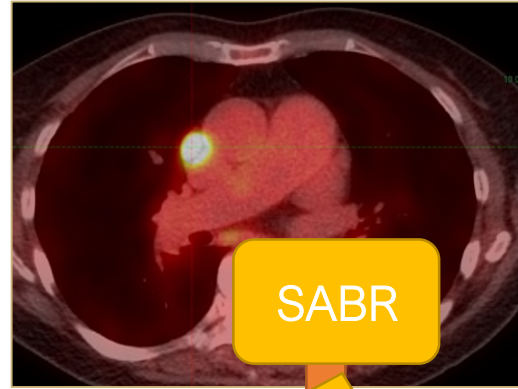




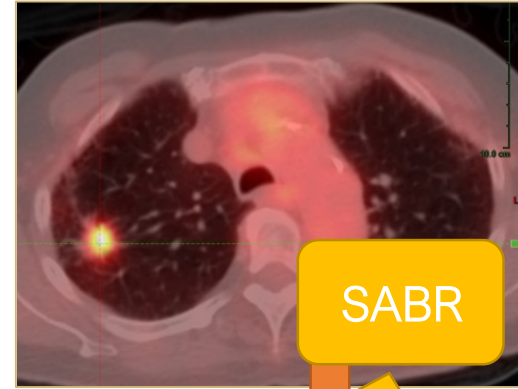
PET avid disease in bilateral lungs and lymph nodes



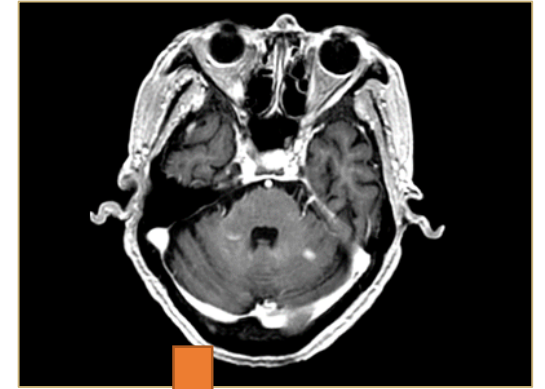
Oligoprogession in lymph node



Oligoprogession in right lung primary



Oligoprogession in brain



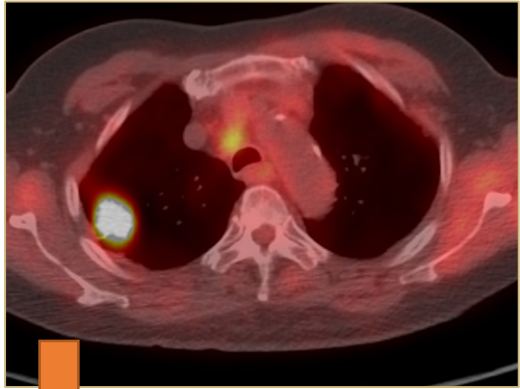
olumab

Resolution of avid disease

Resolution of avid disease

Resolution of avid disease

PET avid disease in bilateral lungs and lymph nodes



Oligoprogression in brain



Nivolumab

SABR



SABR



Passes away 8 months later



# Summary

- Many states of oligometastatic
- Defined as 5 sites or less
- Multidisciplinary discussion is key
  - Med onc, surgery, rad onc, IR, interventional pulm
- Many trials ongoing
- The dream vs reality: can we make stage IV NSCLC curable/chronic?





# Questions?

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