The role of local therapies in advanced molecular-driven NSCLC

J. Vansteenkiste

Respiratory Oncology Unit
Dept. Pulmonology
Univ. Hospital KU Leuven
Leuven Lung Cancer Group

Oligometastatic NSCLC
> theoretical definition

- **1995 : proposal of new clinical concept “Oligometastases”**
  - **Intermediate biologic state of restricted metastatic capacity**
  - **Transitional state to dissemination**
  - **Limited number and organ sites of metastases**

Weichselbaum & Hellman, J Clin Oncol 13:8-10, 1995
Weichselbaum & Hellman, Nat Rev Clin Oncol 8:378, 2011

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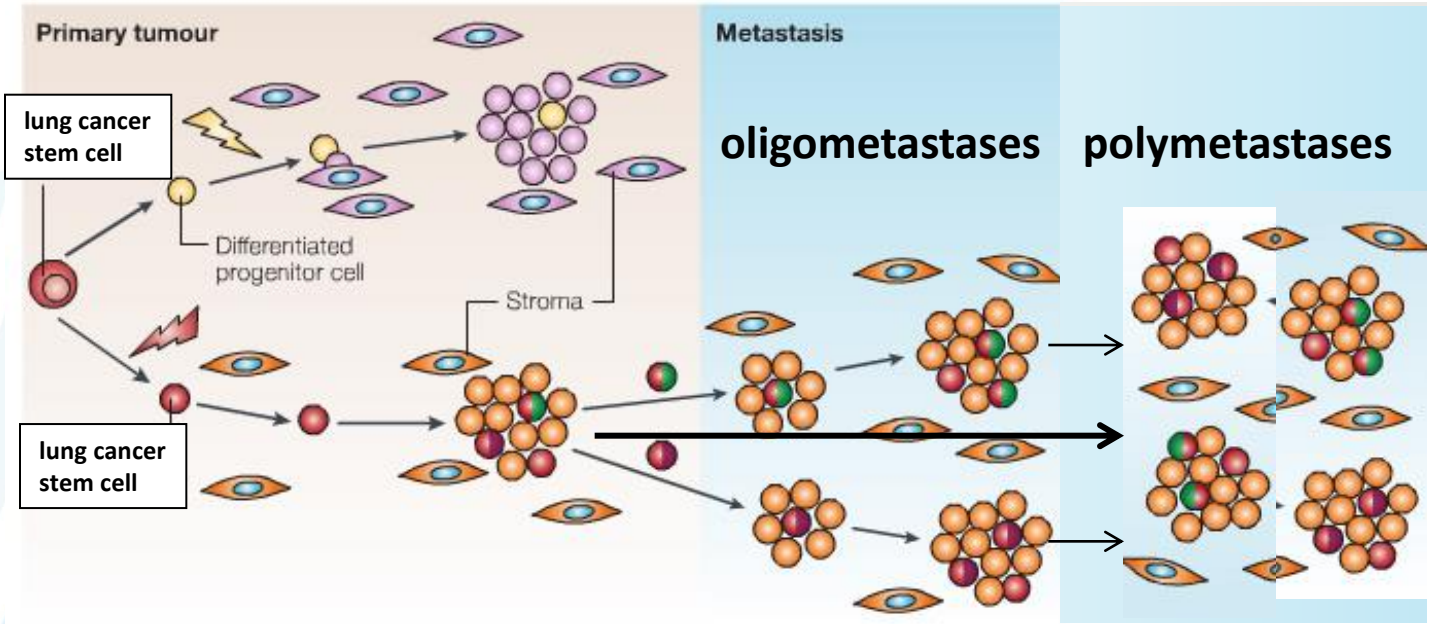
Oligometastatic NSCLC
> theoretical definition

- **Spectrum model for oligometastases :**



Adapted from: Weichselbaum & Hellman, Nat Rev Clin Oncol 8:378, 2011
Weichselbaum & Hellman, J Clin Oncol 13:8-10, 1995

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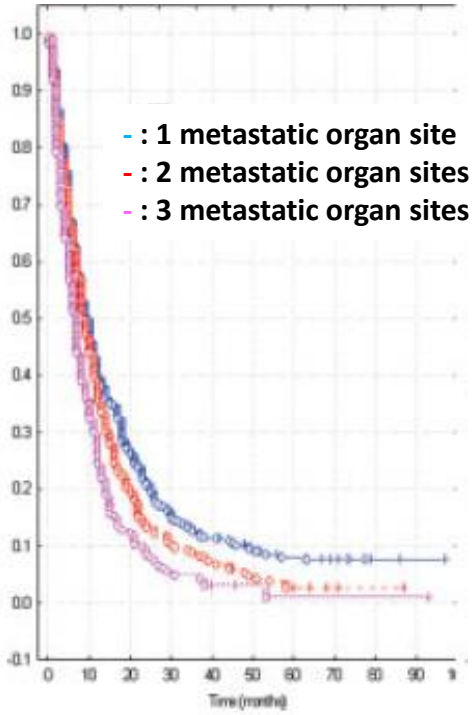
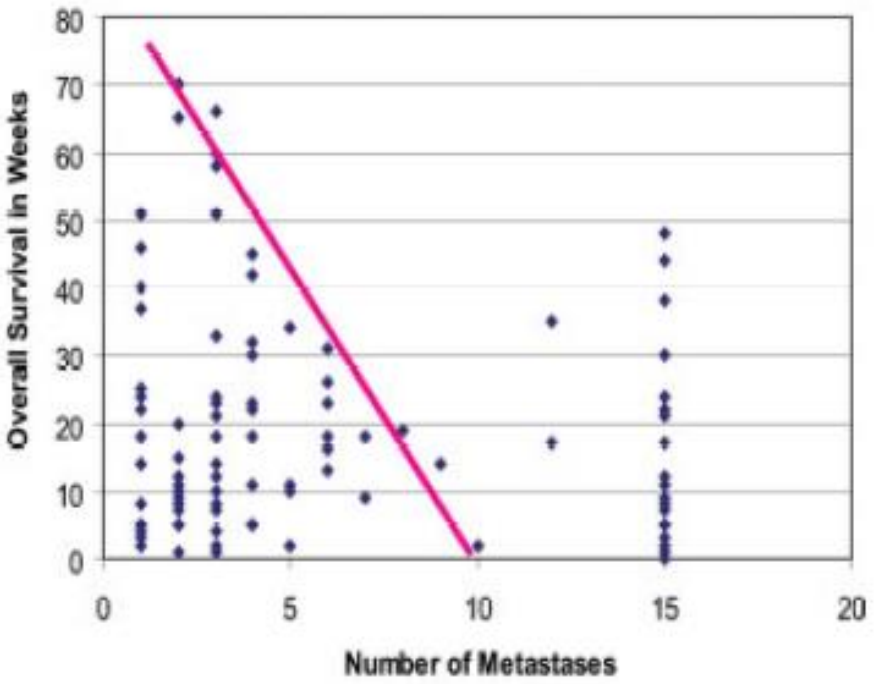
Oligometastatic NSCLC
> prognosis





Oh et al, Cancer 115:2930, 2009

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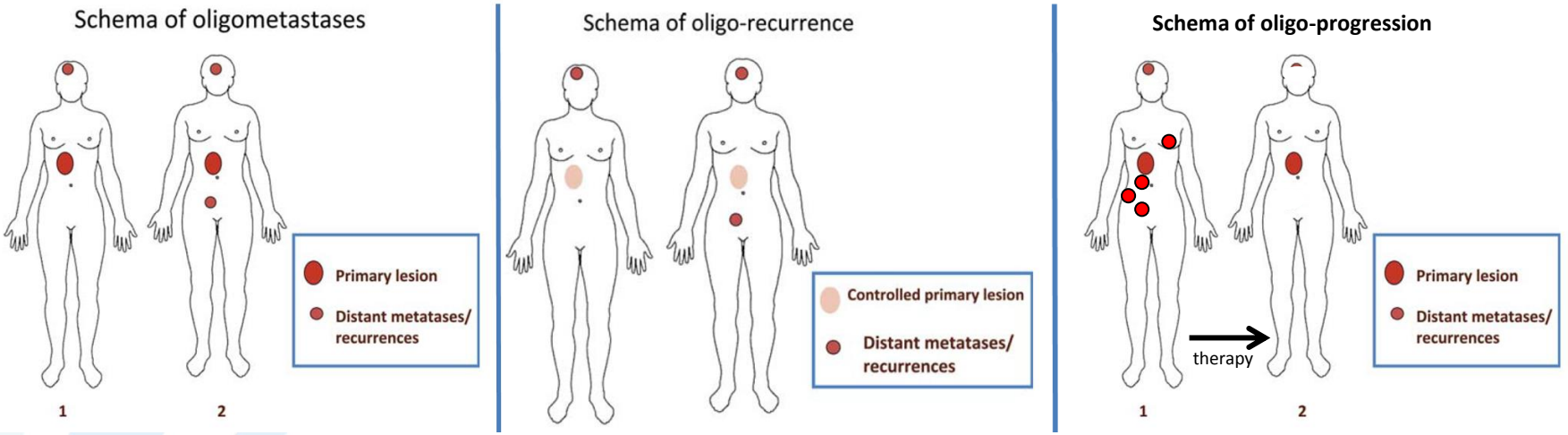
Oligometastatic NSCLC
> distinct cohorts

- **‘oligometastases’ = diagnosed with oligometastatic disease**
- **‘oligorecurrence’ = relapsed oligometastatic disease**
- **‘oligoprogression’ = status after cytoreductive therapy**

  → cohorts probably have different prognoses



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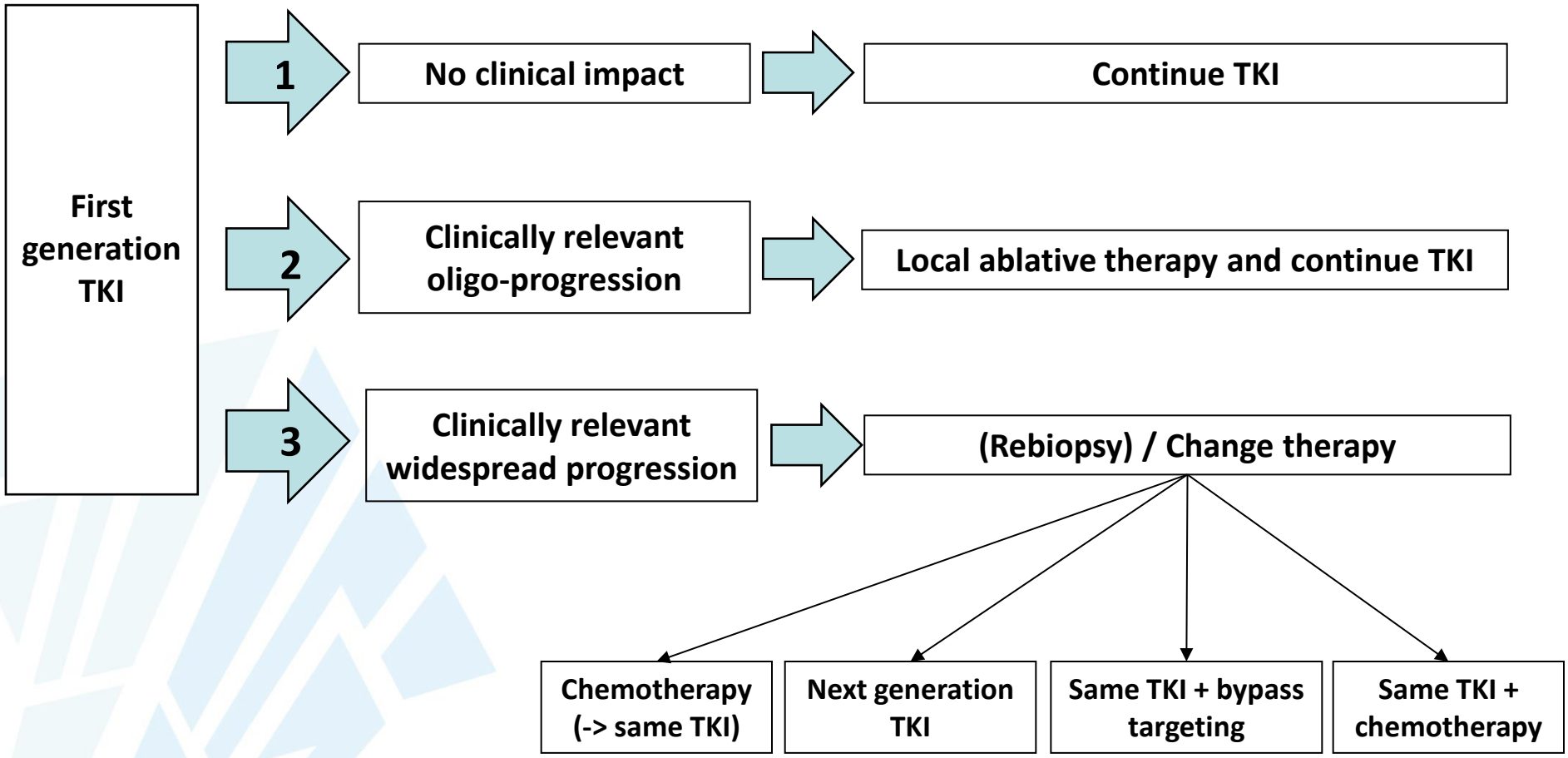
Advanced NSCLC personalized treatment

> the TKI progression dilemma



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EGFR case 1

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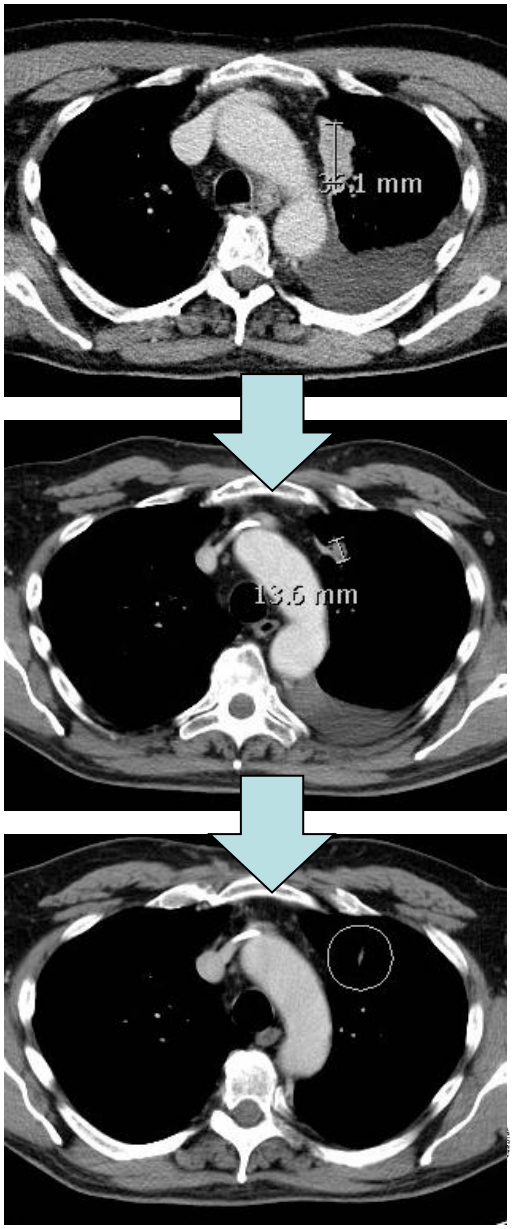
Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **10/2013: 70-year old male, 15 packyears, cough and left thoracic pain**
  - **NSCLC-NOS, cT3N3M1a (based on pleural cytology +)**
  - **4 cycles Cisplatin-Pemetrexed -> partial response but moderate tolerance**
- **01/2014: referral to our center: „give maintenance?“**
  - **Additional biopsy: adenocarcinoma, EGFR L858R mut**
  - **Started on Gefitinib, FU every 3 months**



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Advanced NSCLC personalized treatment

> the TKI progression dilemma

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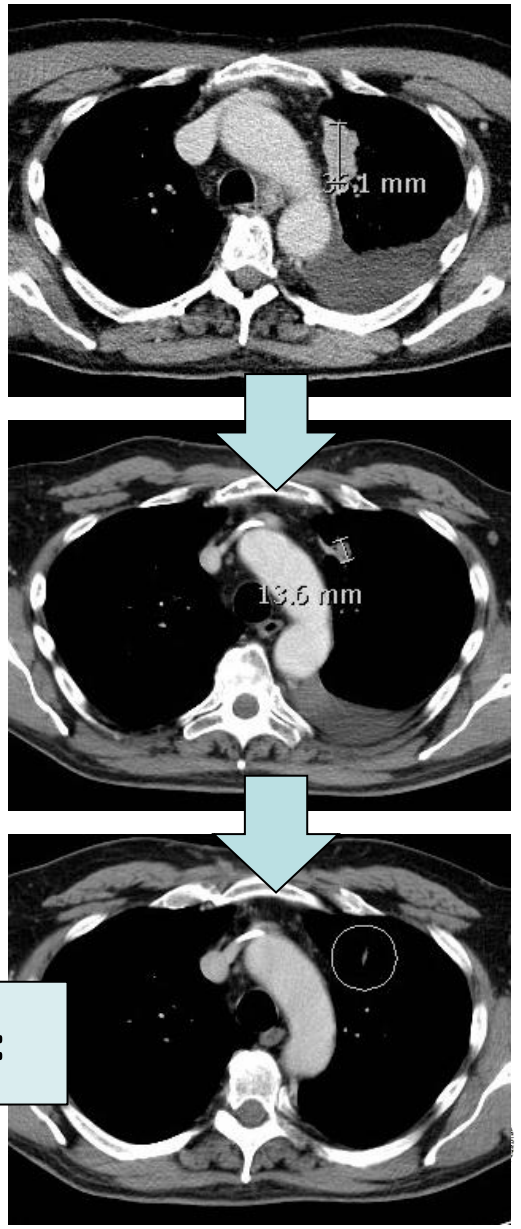
  - Additional biopsy: adenocarcinoma, EGFR L858R mut
  - Started on Gefitinib, FU every 3 months
- 03/2016: change in CT after long-lasting PR



Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **What now?**

1. **Continue Gefitinib**
2. **Continue Gefitinib with closer FU**
3. **Change to Pemetrexed single agent**
4. **Rebiopsy lesion (technically demanding)**
5. **Change to Osimertinib (3rd gen TKI)**

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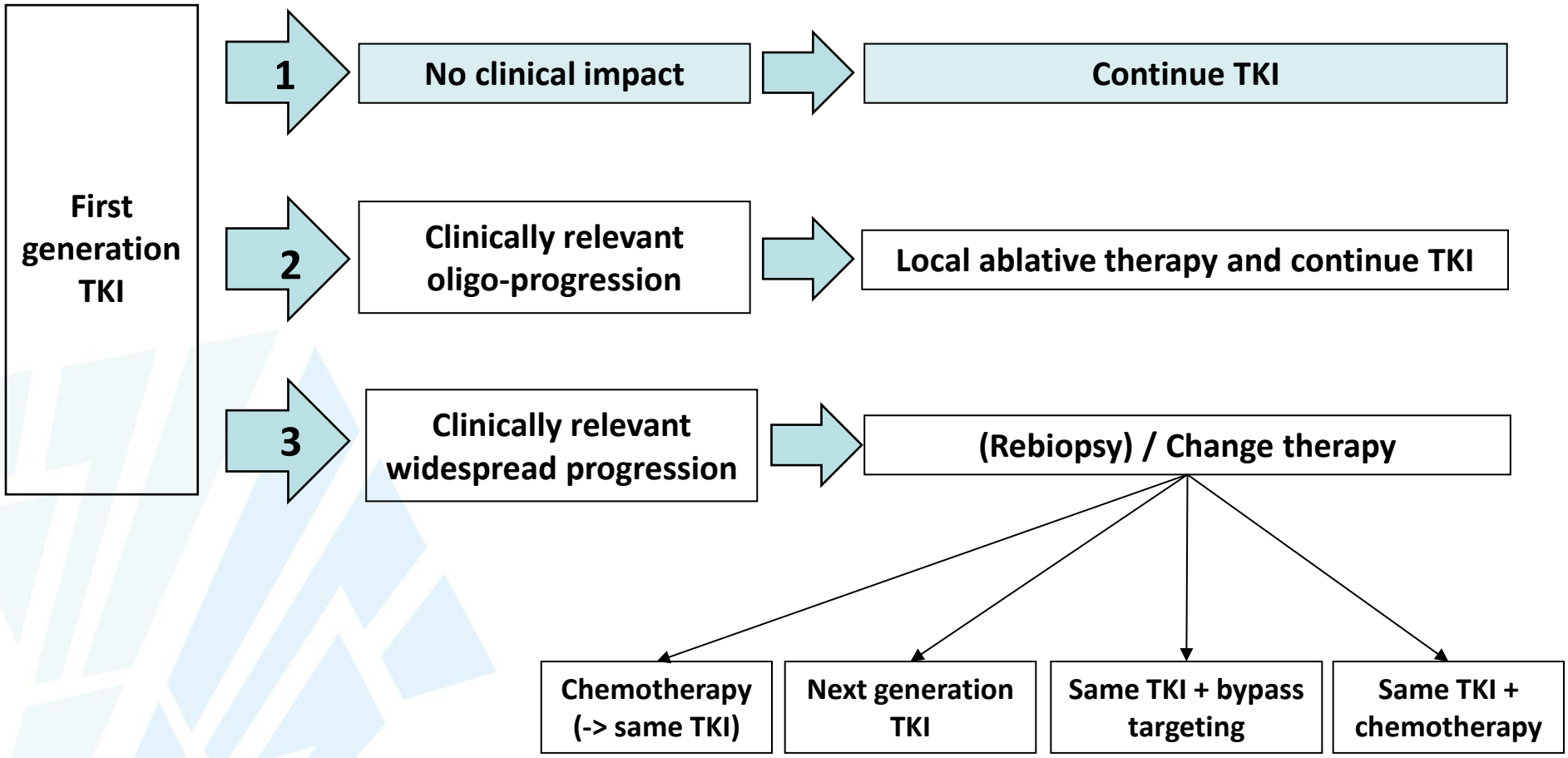
Advanced NSCLC personalized treatment

> the TKI progression dilemma



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EGFR case 2

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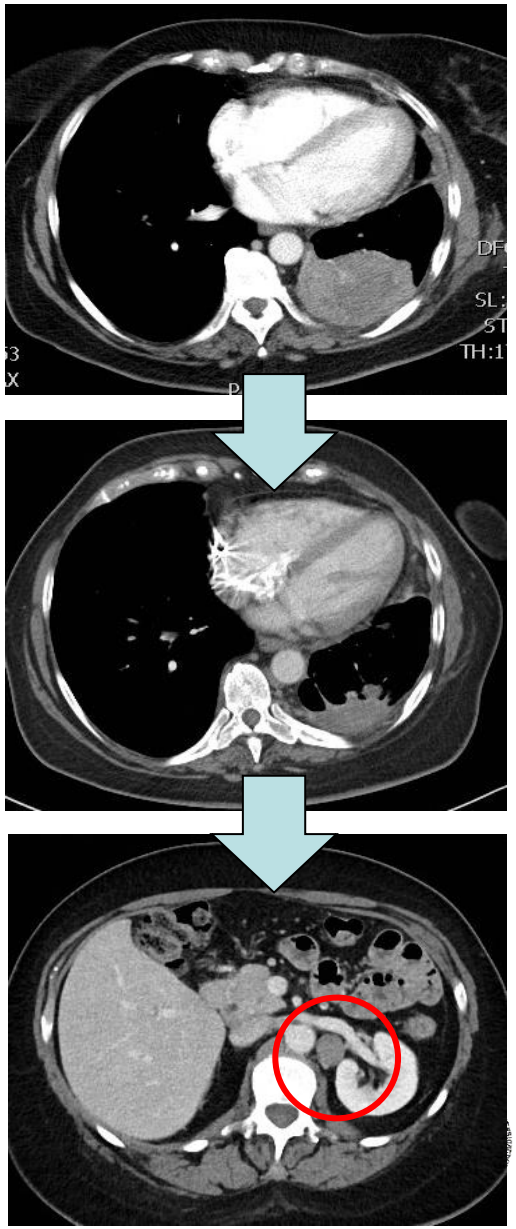
Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **10/2014: 55-year old female, 30 packyears, dyspnea and left thoracic pain**
  - **NSCLC-adenocarcinoma, cT3N1M1a (based on pleuro-scopy with biopsy and talk poudrage)**
  - **EGFR del 19 mut: started on Gefitinib**
  - **Durable remission, free of symptoms**

- **03/2016:**
  - **New onset major pulmonary osteoarthropathy (Pierre Marie Bamberger syndrome)**
  - **Progressive disease: stable thoracic findings, but new infradiaphragmatic lesion**
  - **Fine needle aspiration: adenocarcinoma, EGFR del 19 and T790M mutation**



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Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **What now?**

1. **Continue Gefitinib**
2. **Change to Cisplatin-Pemetrexed**
3. **Surgical removal of new lesion**
4. **(Stereotactic) radiotherapy to new lesion**
5. **Change to Osimertinib (3rd gen TKI)**

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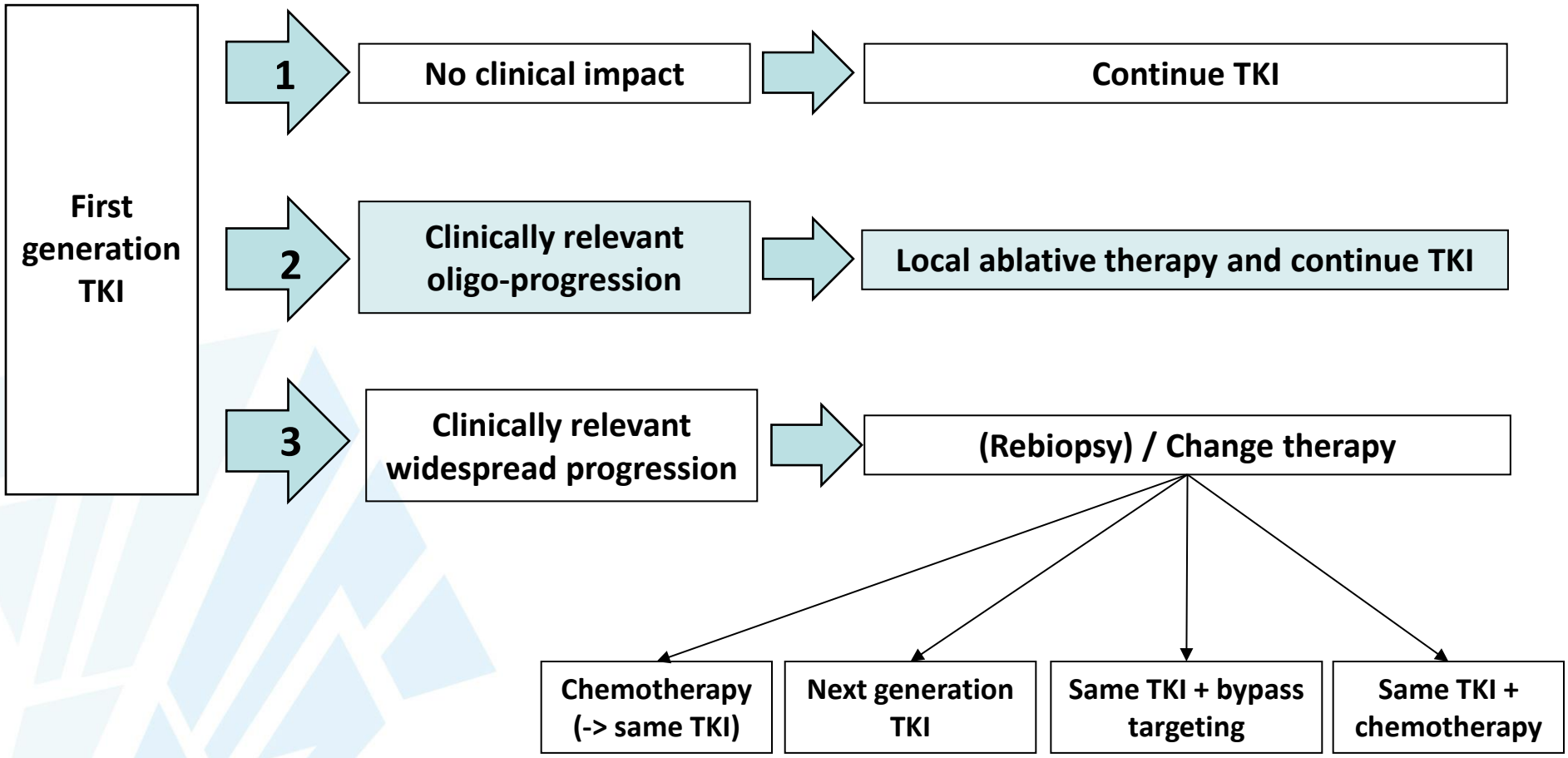
Advanced NSCLC personalized treatment

> the TKI progression dilemma



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ALK

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Advanced NSCLC personalized treatment
> ALK+: brain metastases

- ***ALK*+ NSCLC has a propensity for early brain dissemination (40% to 70% in PROFILE Crizotinib data)**
- **Poor blood-brain barrier penetration of Crizotinib: CSF-to-plasma ratio of 0.0026 ***
- **This low CSF-to-plasma ratio may explain the often encountered persistent systemic disease control with Crizotinib in patients relapsing in the brain**

*Costa et al, J Clin Oncol 29:e443-e445, 2011

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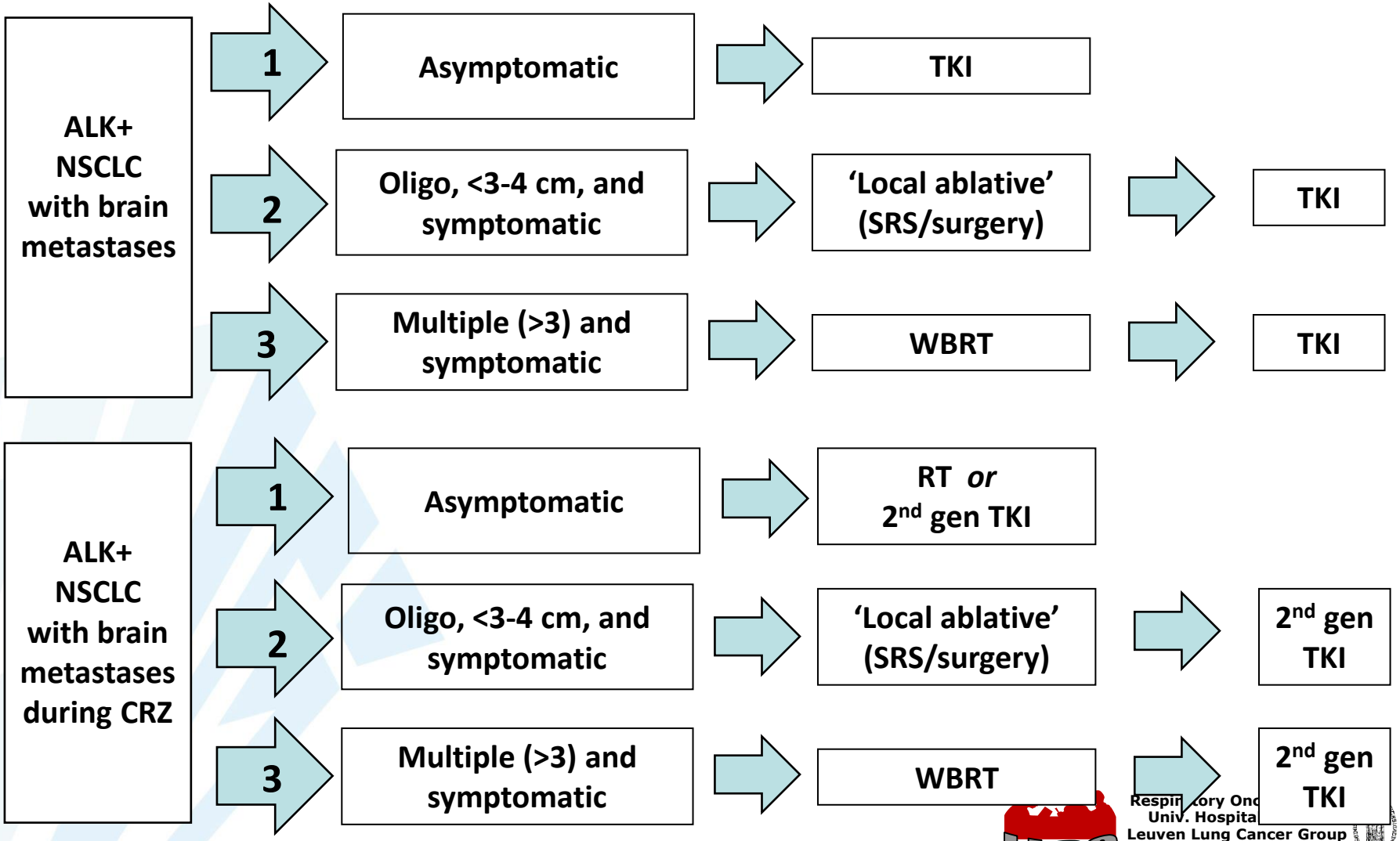
Advanced NSCLC personalized treatment

> ALK+ brain metastases possible algorithm



ALK case 1

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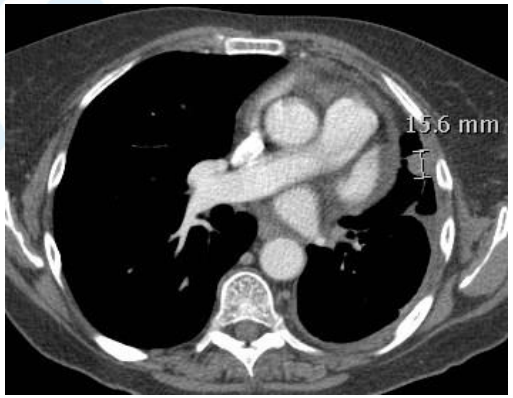
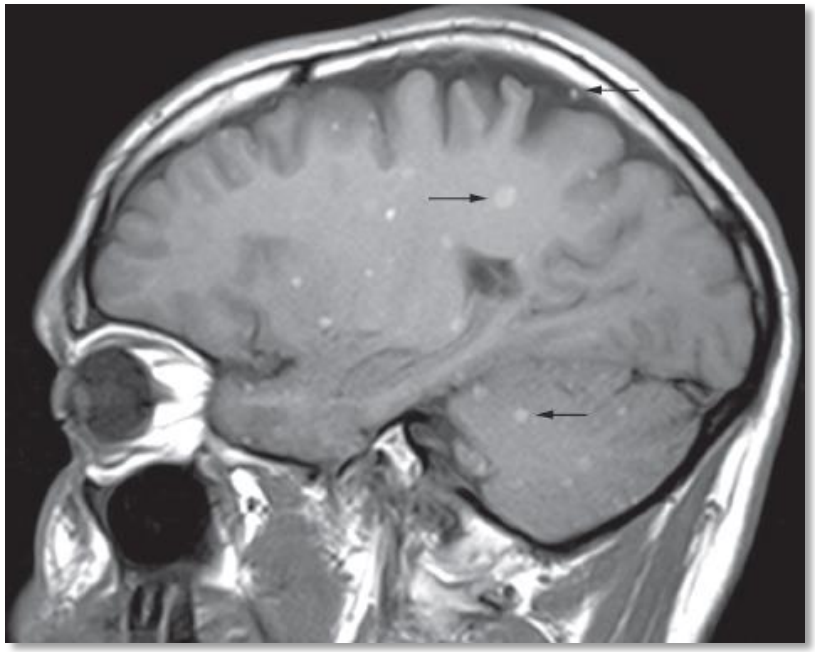
Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **12/2013: 62-year old female, never-smoker**
  - **Other hospital: adenocarcinoma left hilum, stage IV, ALK translocation**
  - **Start Cisplatin-Pemetrexed: PR after 4 cycles, no maintenance therapy**
- **09/2014:**
  - **Progression, start Crizotinib (500 mg/d)**
- **07/2015:**
  - **Referral: fatigue ≈ progressive disease**
  - **Pleural lesions (one measurable)**
  - **Bone metastases and brain metastases**





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Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **What now?**

1. **Continue Crizotinib**
2. **Recommend SRS**
3. **Recommend WBRT**
4. **Switch to Ceritinib**
5. **Go back to Platinum-Pemetrexed**

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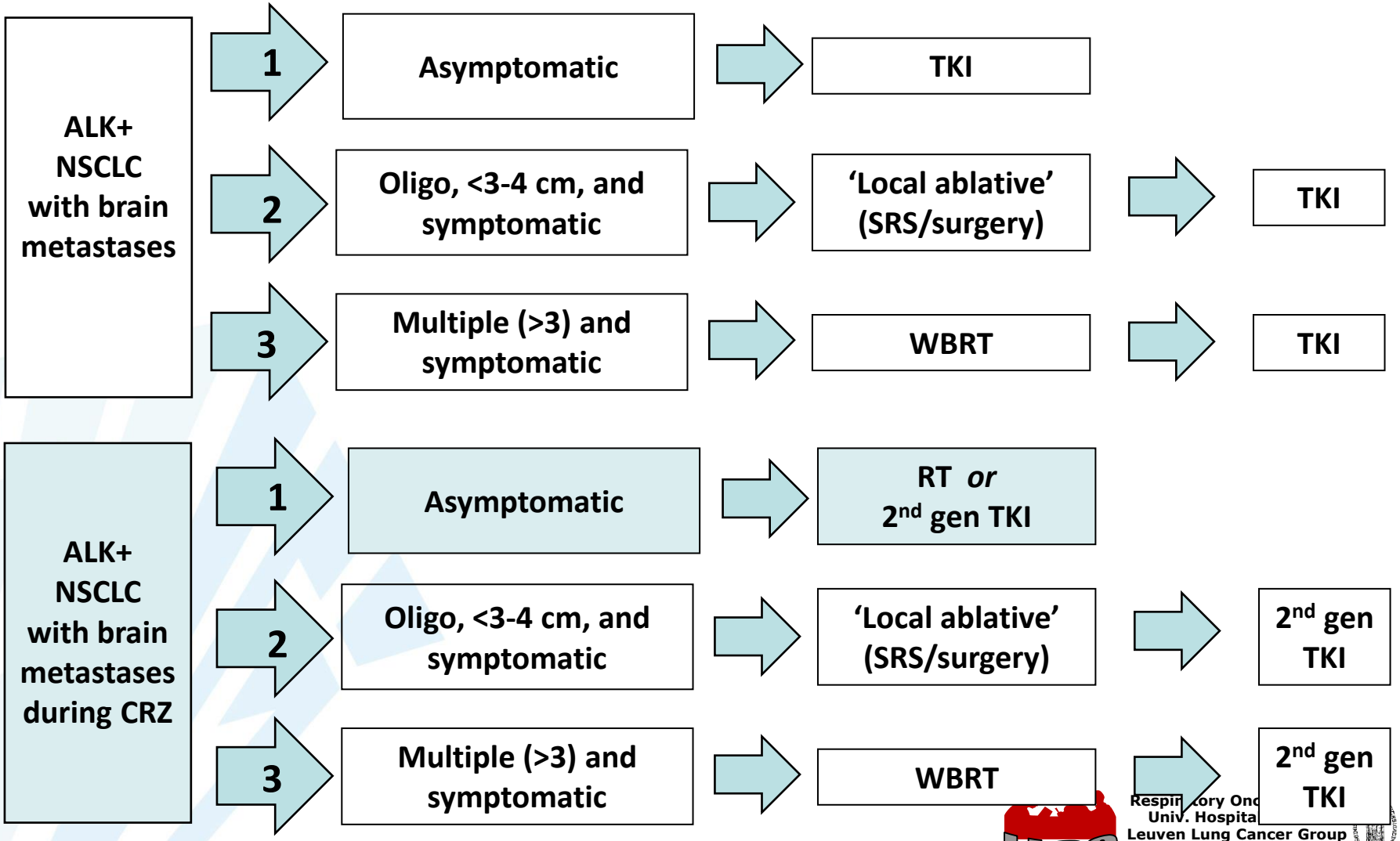
Advanced NSCLC personalized treatment

> ALK+ brain metastases possible algorithm



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> Ceritinib Ph1 trial [ASCEND 1, NCT01283516]

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Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

Shaw et al, N Engl J Med 370:1189-1197, 2014

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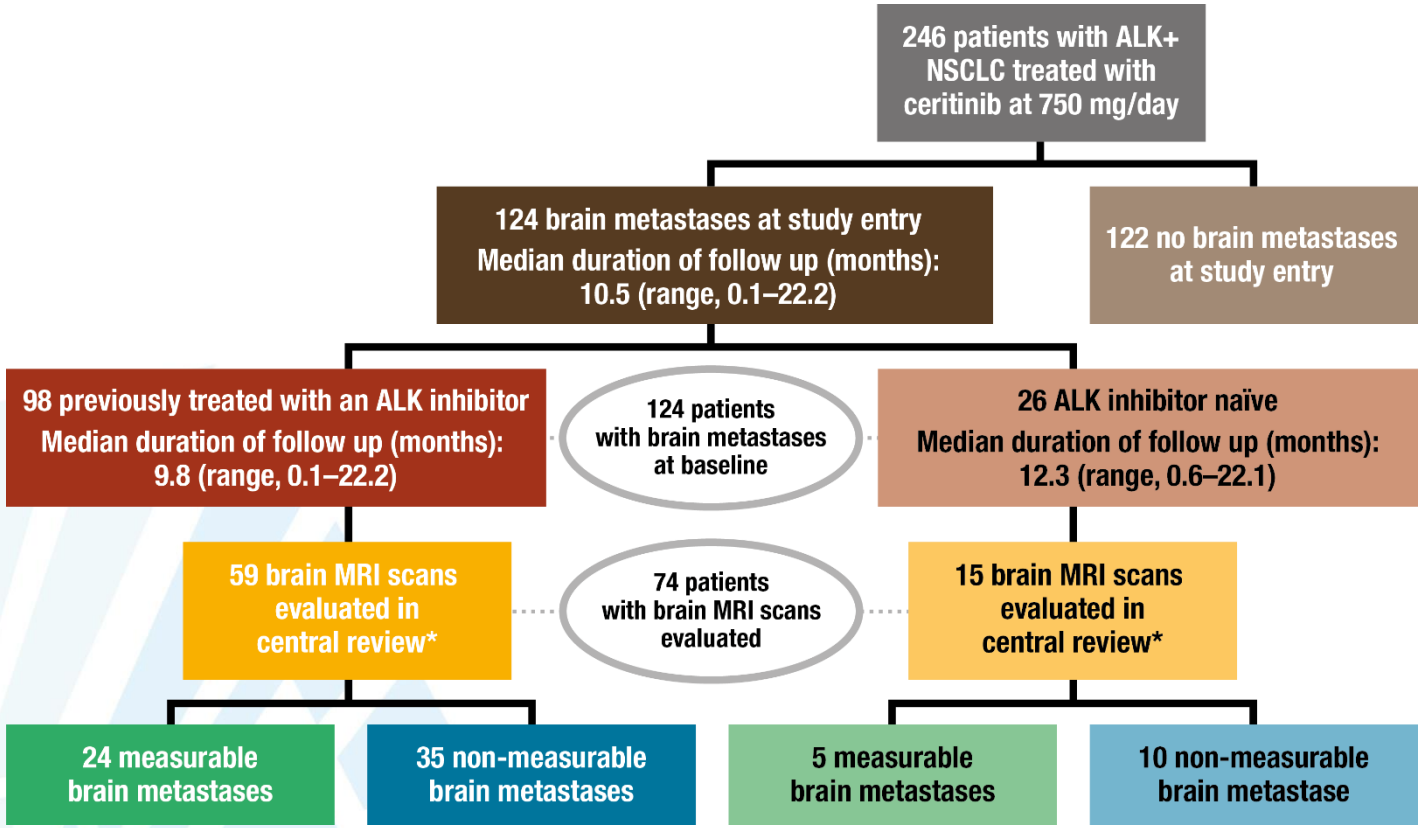
> ASCEND 1: brain metastases



Shaw et al, ESMO 2014

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> ASCEND 1: brain metastases

- **Retrospective review by independent neuroradiologists**

Efficacy Parameter	ALKi-Pretreated	ALKi-Naive
	All patients	
	N = 75	N = 19
CR, n (%)	4 (5.3)	3 (15.8)
PR, n (%)	10 (13.3)	5 (26.3)
SD, n (%)	35 (46.7)	7 (36.8)
PD, n (%)	12 (16.0)	0 (0.0)
Unkn, n (%)	14 (18.7)	4 (21.1)
IDCR, n (%)	49 (65.3)	15 (78.9)

Kim et al, Lancet Oncol 2016 E-pub March 10

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Advanced NSCLC personalized treatment
> ASCEND 1: brain metastases

- **Retrospective review by independent neuroradiologists**

Efficacy Parameter	ALKi-Pretreated	ALKi-Naive	ALKi-Pretreated	ALKi-Naive
	All patients		No previous brain RT	
	N = 75	N = 19	N = 23	N = 8
CR, n (%)	4 (5.3)	3 (15.8)	2	1
PR, n (%)	10 (13.3)	5 (26.3)	3	3
SD, n (%)	35 (46.7)	7 (36.8)	10	3
PD, n (%)	12 (16.0)	0 (0.0)	5	0
Unkn, n (%)	14 (18.7)	4 (21.1)	3	1
IDCR, n (%)	49 (65.3)	15 (78.9)	15 (65.2)	7 (87.5)

Kim et al, Lancet Oncol 2016 E-pub March 10

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ALK case 2

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Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **05/2011: 61-year old male, 15 packyears, cervival lymphadenopathy**
  - **NSCLC-adenocarcinoma, cT3N1M1a (based on cytology of fine-needle biopsy)**
  - **No molecular tests feasible**
  - **Started on Cisplatin-Pemetrexed, PR after 4 cycles, maintenance therapy**
- **03/2012:**
  - **Progression, start Erlotinib**
  - **Stop after 6 weeks: rash grade 3, further progression**
- **06/2012:**
  - **Referral: new biopsy reveals ALK translocation.**
  - **Started in phase 1 ceritinib clinical trial [ASCEND 1]**
  - **Durable partial response**
- **08/2013:**
  - **Headache and vertigo**

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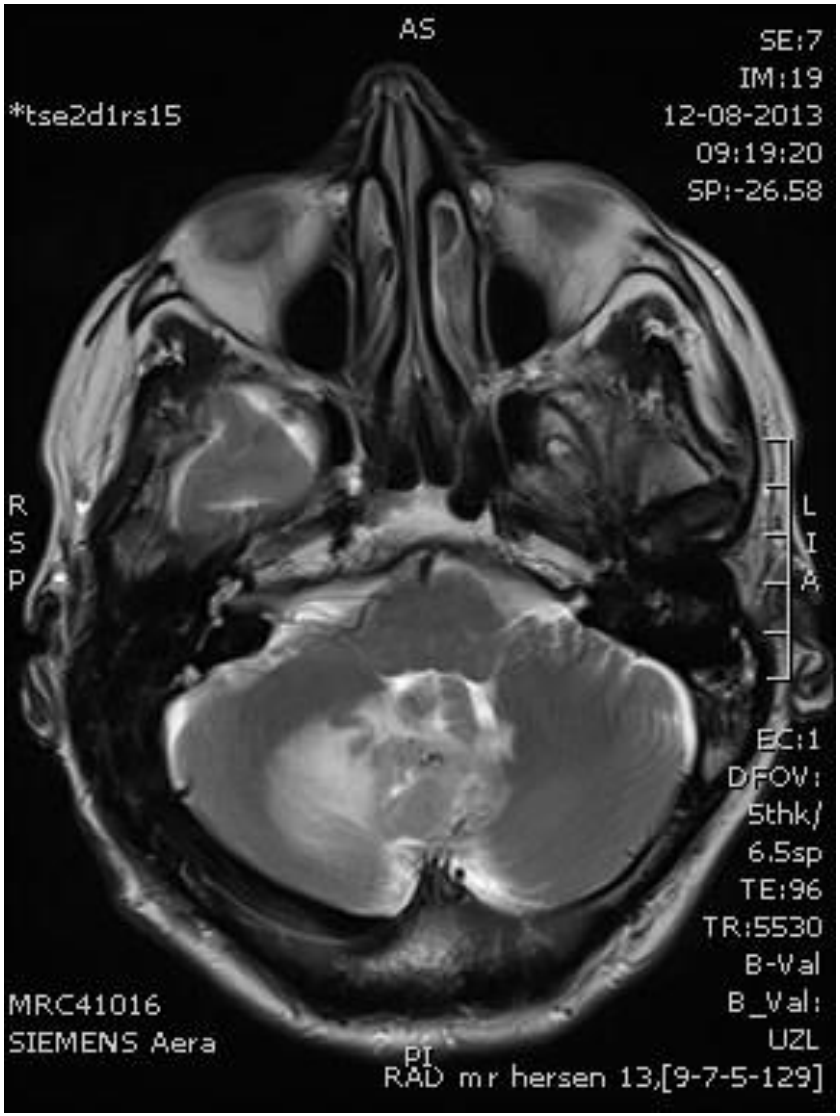
Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **08/2013:**
  - **Headache and vertigo**
  - **Ongoing response in the thorax**
  - **But…**



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Advanced NSCLC personalized treatment
> the TKI progression dilemma

- **What now?**

1. **Continue Ceritinib (2nd gen TKI)**
2. **Recommend SRS**
3. **Recommend neurosurgical resection**
4. **Recommend neurosurgical resection followed by radiotherapy**
5. **Recommend WBRT**

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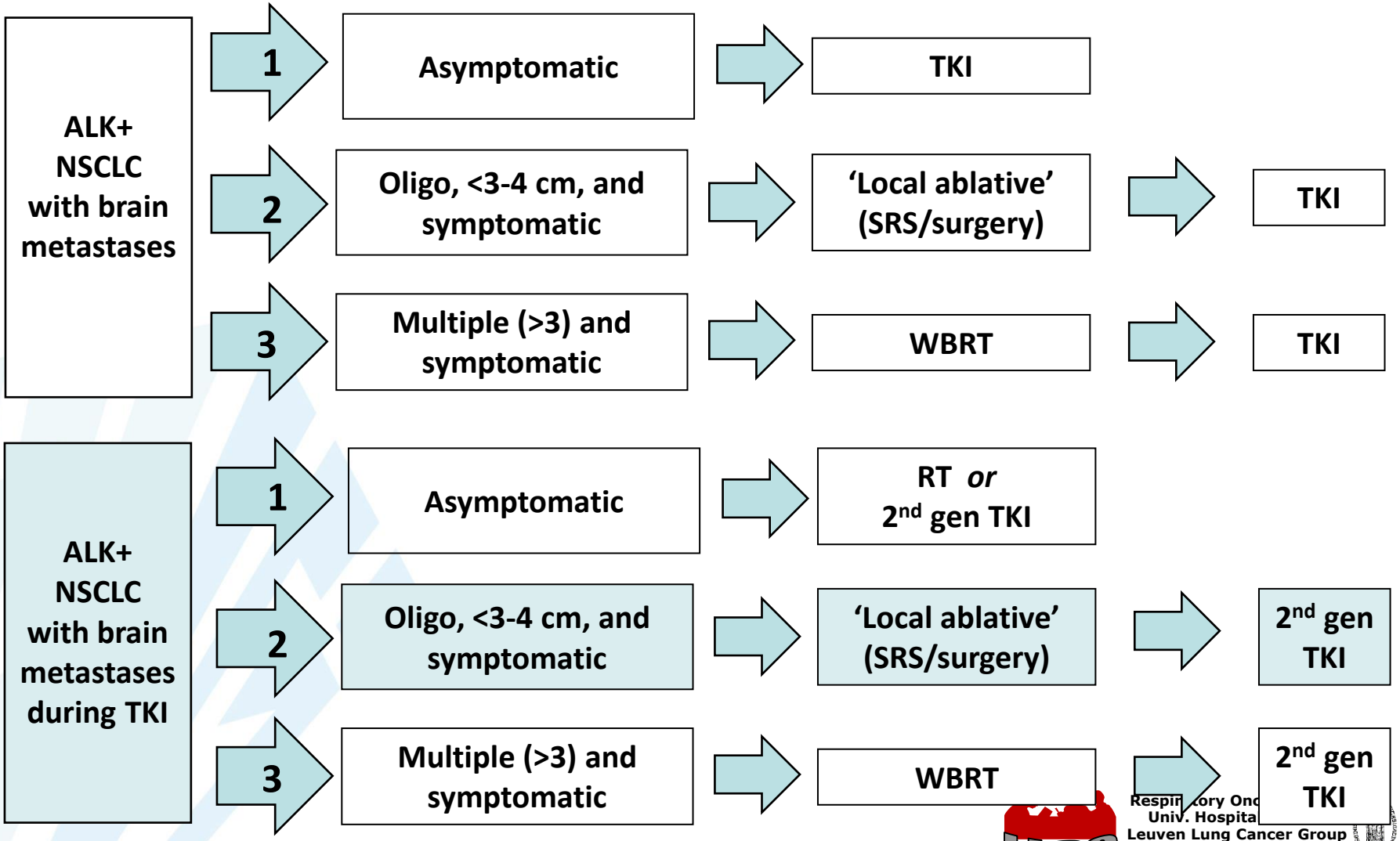
> ALK+ brain metastases possible algorithm



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Thank you for your kind attention

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