Immune-Related Response Criteria: Variations in I-O Response Patterns and Implications for Treatment

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7.14.15
12 – 1 pm, EST

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Objectives

By the end of this e-course, participants will be able to:

- **Understand why RECIST criteria have been adapted in assessing tumor response to immuno-oncologic agents**
- **Understand the differences between RECIST and Immune-related Response Criteria (irRC)**
- **Understand irRC use in evaluating tumor response to immuno-oncologic agents**
- **Understand the diversity of potential tumor responses to IO agents and the direction of treatment planning in the practice setting**

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History of RECIST (Response Evaluation Criteria in Solid Tumors

1960s	• Early attempts to standardize tumor response to oncologic agents
1979	• World Health Organization (WHO) standardized criteria for response assessment; published in 1981
Mid-1990s	• International Working Party simplified response criteria
1999-2000	• New criteria was presented at the American Society for Clinical Oncology meeting; RECIST 1.0 criteria published in 2000
2009	• RECIST updated, latest version - RECIST 1.1, was published

RECIST allows clinicians to determine whether a patient responds to therapy, whether they are stable, or whether their disease has progressed

RECIST 1.1 - Response Criteria

Target Lesions - includes all measurable lesions*; max 2 per organ, 5 lesions total

Evaluation of Target Lesions	RECIST Guideline
CR	Disappearance of all target lesions; confirmed at ≥ 4 weeks
PR	≥ 30% decrease of SoD from baseline, confirmed at ≥ 4 weeks
PD	≥ 20% increase from smallest sum of diameters recorded and 5 mm absolute increase over lowest sum
SD	Neither PR or PD

Non-Target Lesions – all other lesions not classified as a target lesion or sites of disease

Evaluation of non-target lesions	RECIST Guideline
CR	Disappearance of all non-target lesions; normalization of tumor markers
PD	Appearance of ≥ 1 new lesions and/or progression of existing non-target lesions
SD	Persistence of ≥ 1 non-target lesion; tumor marker level above normal

CR (Complete Response); PR (Partial Response); PD (Progressive Disease); SD (Stable Disease)

*measurable lesion = ≥ 10 mm in longest diameter by CT Scan; ≥ 20 mm in longest diameter by x-ray

sources: Eisenhauer et al., 2009; Nishino et al, 2010; and RECIST, Applying the Rules, National Cancer Institute,

RECIST 1.1 – Time Point Response

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

- ***Tumor evaluation should occur every 6-8 weeks where the benefit of the therapy is not known***
  - ***Repetitive tumor evaluations depend on whether the trial has a goal of response rate or the time to an event (e.g. Progression-Free Survival (PFS))***

source: Eisenhauer et al., 2009

RECIST for determining tumor response is applicable to cytotoxic agents

- Cytotoxic agents directly kill a tumor cell or prevent tumor cells from dividing (e.g. chemotherapy); therefore, response of cytotoxic agents can be easily measured from the start of therapy

- Early increase in tumor burden and/or an early increase in tumor size signifies progressive disease
  - Once progression is detected, drug cessation is recommended

Response after initial treatment of a cytotoxic agent can often predict remission and survival

Immuno-oncology agents differ from cytotoxic agents in that they stimulate an innate immune response against the tumor

- *Vaccines*: trigger the immune system to initiate an anti-tumor response against an existing cancer
- *Monoclonal Antibodies*: antibodies directed against tumor cells; they can block signaling pathways needed for tumor growth and trigger an immune-mediated cytotoxic response
- *Checkpoint inhibitors*: tumors escape detection by the immune system through expression of “checkpoint” proteins on their cell surface. CTLA-4 and PD-1 receptors are examples of “checkpoint” receptors; targeted inhibition towards these receptors enhances T cell response towards the tumor
- *Cytokines*: stimulates a broad-based immune response (e.g. interleukin-2 and interferon-α)

Source:
http://www.fightcancerwithimmunotherapy.com/immunotherapyandcancer/typesofcancerimmunotherapy.aspx

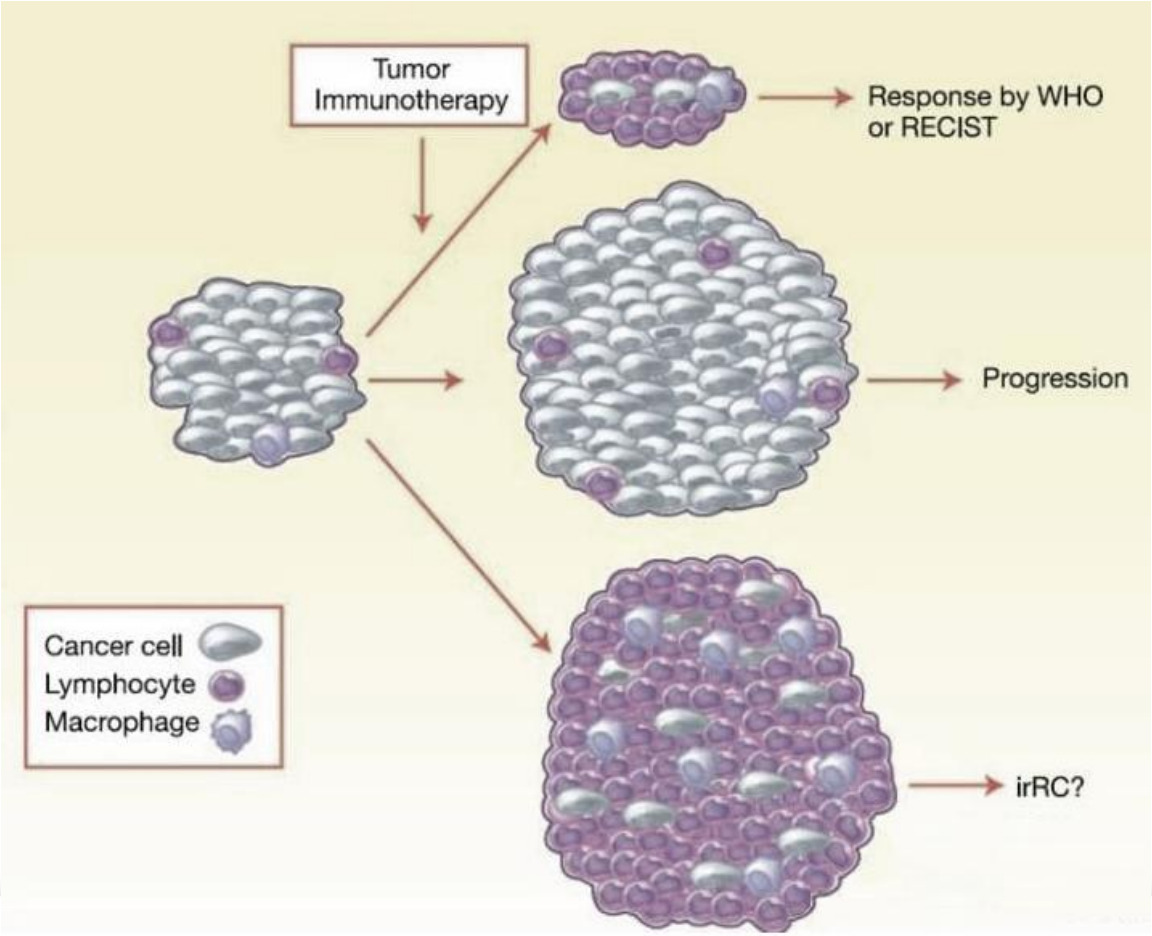
The unique mechanism of action of immuno-oncology agents requires modified tumor response criteria

RECIST may not provide a complete assessment of immunotherapeutics:

- Anti-tumor response to immunotherapy may take longer compared to cytotoxic agent response
- Clinical response to immune therapies can manifest after conventional progressive disease (PD) – "pseudoprogression"
- Discontinuation of immune therapy may not be appropriate in some cases, unless PD is confirmed
- Allowance for "clinically insignificant" PD (e.g., small new lesions in the presence of other responsive lesions) is recommended
- Durable stable disease may represent antitumor activity

source: Wolchock et al., 2009

Differing mechanism of immunotherapy



Ipilimumab – clinical observations and evaluation of a novel set of response criteria

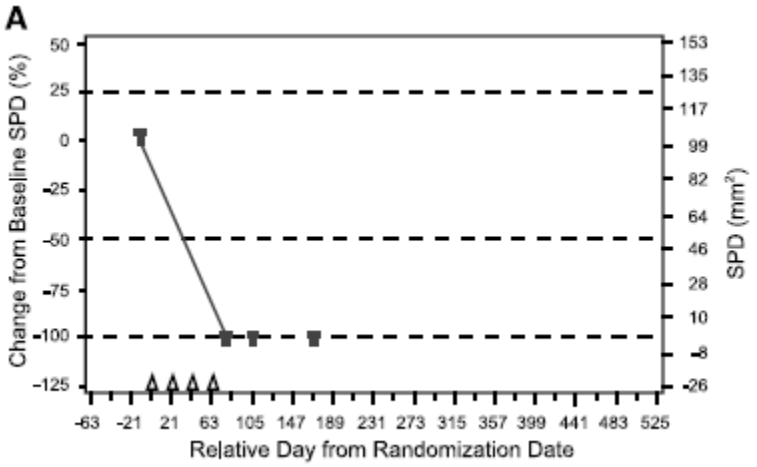
- Ipilimumab: human, monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T cells. Blocking CTLA-4 from interacting with its ligands augments a T cell immune response to tumor cells
- Ipilimumab is indicated for the treatment of unresectable or metastatic melanoma
- Ipilimumab was studied in three multicenter phase II trials evaluating 487 patients with unresectable stage III or IV melanoma
- Activity was categorized using a novel set of criteria
  - Tumor assessments carried out at week 12 following the end of the induction dosing period (ipilimumab 10 mg/kg every three weeks times x4)

source: Wolchock et al., 2009

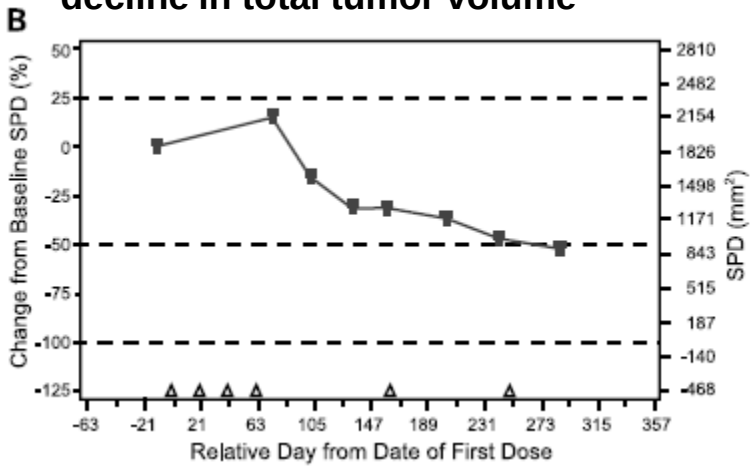
Four patterns of response were observed in patients treated with ipilimumab

- Overall, ~30% of patients had disease control (CR, PR, or SD)
- Of the 4 patterns of response observed two met conventional criteria for tumor response:

Response in baseline lesions



"stable disease" with slow, steady decline in total tumor volume

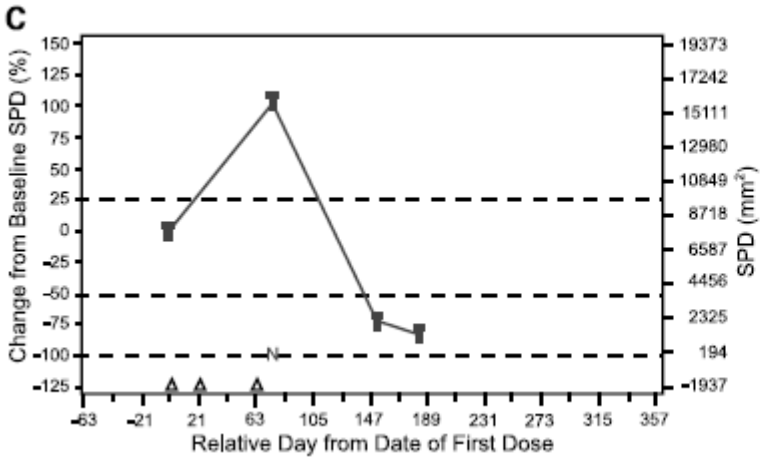


SPD = sum of the product of perpendicular diameters
Triangles = ipilimumab dosing time points

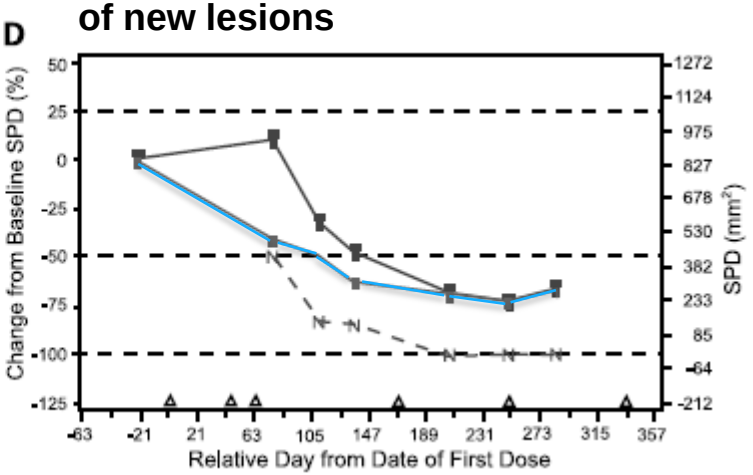
source: Wolchock et al., 2009

The other two response patterns observed go against the standard criteria for tumor response

Responses after an initial increase in total tumor burden



Reduction in total tumor burden during or after the appearance of new lesions



top line, total tumor burden; middle line, tumor burden of baseline lesions; bottom line, tumor burden of new lesions.

SPD = sum of the product of perpendicular diameters (used in WHO criteria)
Triangles = ipilimumab dosing time points
N=tumor burden of new lesions

source: Wolchock et al., 2009

A number of ipilimumab treated patients initially characterized as PD, are considered PR or SD using the irRC Guideline

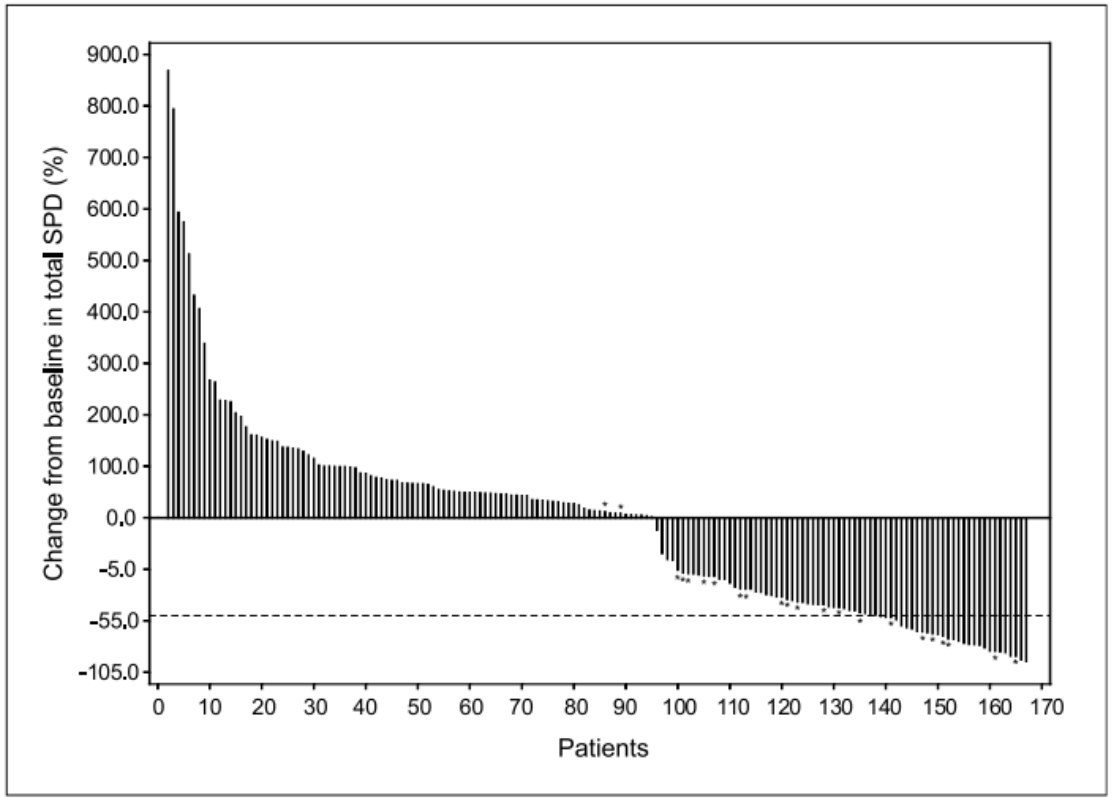
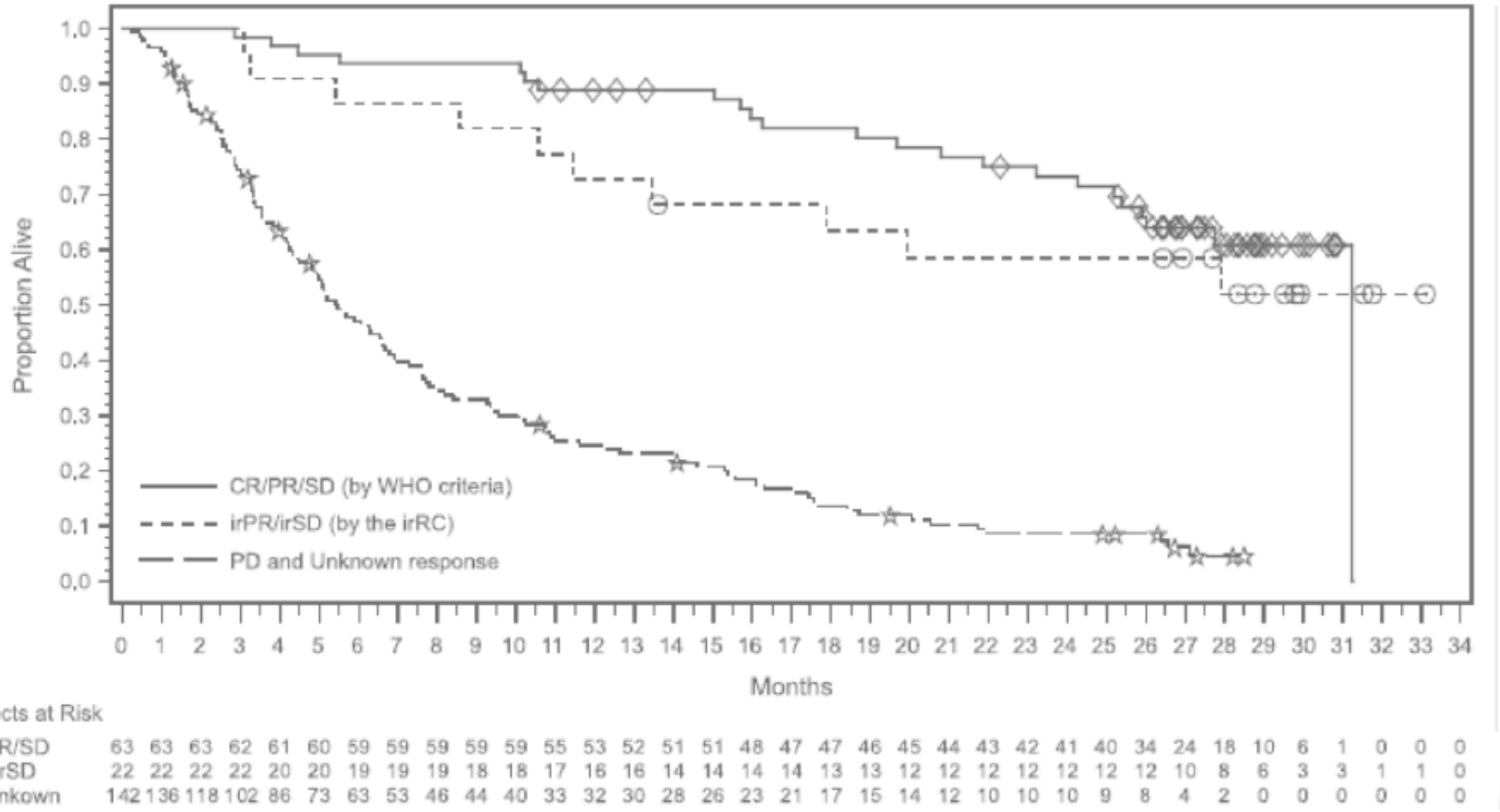


Fig. 2. Waterfall plot of maximum percentage reduction from baseline in total tumor burden. Included are advanced melanoma patients treated with, or randomized to, ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies; the tumor responses of 167 evaluable patients were assessed using the irRC. Twenty-two patients were characterized as irPR ($n = 5$) or irSD ($n = 17$), who otherwise would have been labeled "PD" by conventional WHO criteria. These patients are indicated by an asterisk. In addition, one patient characterized as SD by WHO criteria was evaluated as irPR (patient #148).

source: Wolchock et al., 2009

Association of response with survival



Clinical trials utilizing both irRC and RECIST 1.1 to measure tumor response

Evaluation of immune-related response criteria (irRC) in patients (pts) with advanced melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475.

Citation:
J Clin Oncol 32:5s, 2014 (suppl; abstr 3006^)

- 411 pts, 192 were on MK-3475 (pembrolizumab) ≥ 28 weeks
- 215 patients had either a CR, PR, or SD by RECIST and irRC
- 51 patients had PD by RECIST, but had either a CR, PR, or SD by irRC

Authors concluded:

"conventional criteria such as RECIST may underestimate the benefit of MK-3475 in approximately 10% of treated pts."

Differences between WHO classification and irRC

	WHO	irRC
New Measurable lesions (> 5 x 5 mm)	Always represent PD	Incorporated into total tumor burden
New non-measurable lesions (<5 x 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining best overall response	Contribute to defining ir CR

Using the irRC

- irCR: Complete disappearance of all lesions (whether measurable or not, and no new lesions, and confirmation by a repeat consecutive assessment no less than 4 weeks from date first documented
- irPR: decrease in tumor burden ≥50% relative to baseline confirmed by repeat consecutive assessment at least 4 weeks later
- irSD: not meeting criteria for irCR or irPR in absence of ir PD
- irPD: increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmed by repeat consecutive assessment at least 4 weeks later

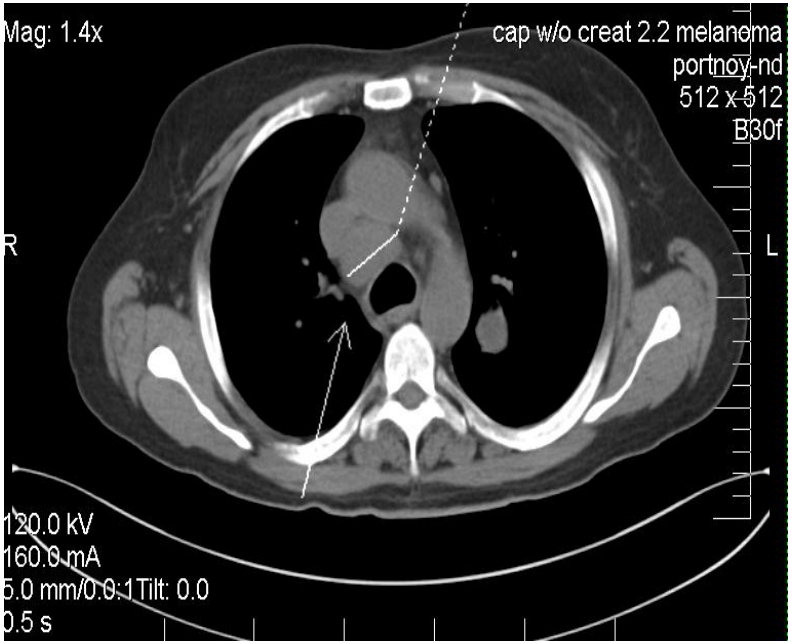
Real World Case Examples: Case Study 1

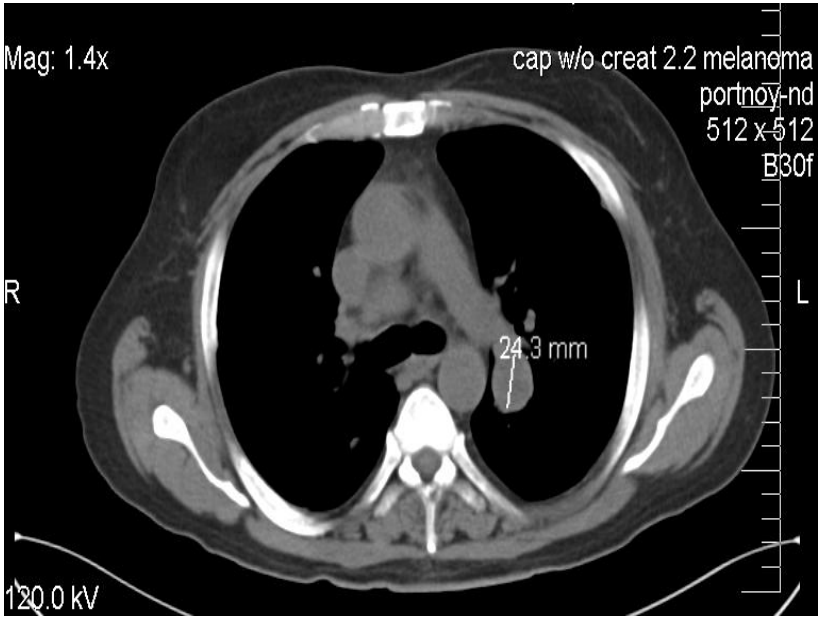
- 52 yo male
- Thyroid nodule: low grade papillary cancer
- Referred to Dr. Portnoy, West Clinic
- CT neck: extensive lymphadenopathy and multiple pulmonary nodules
- PET/CT: 2.5 cm left upper lobe mass, multiple nodules in lungs, subcutaneous met in inferior R axilla, L adrenal mass, 5 cm mass in the gluteus maximus, bony lesions in L iliac bone and R hip
- Pain in R hip, weight loss, fatigue
- Jehovah's Witness
- Anemia with Hemoglobin 7 gm/dl; Creatinine 2.2

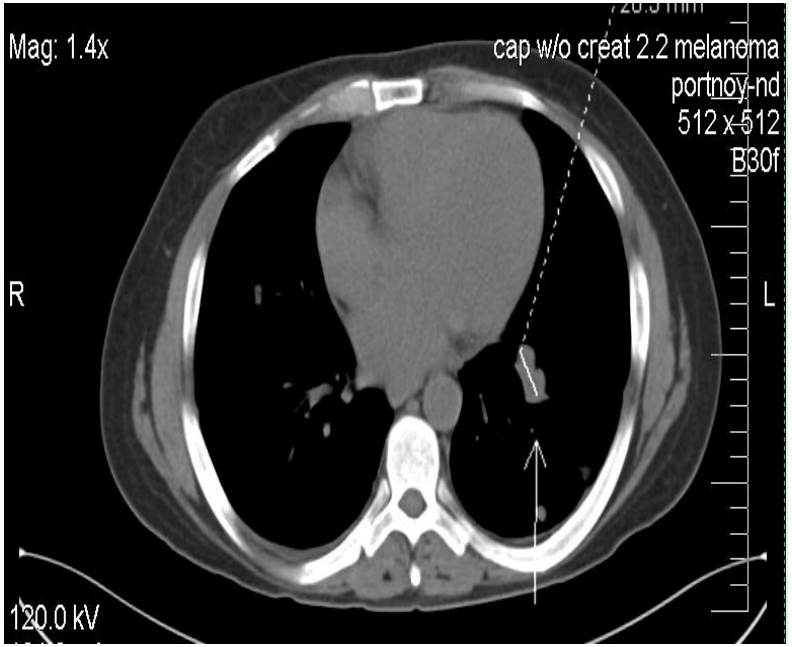
Real World Case Examples: Case Study 1

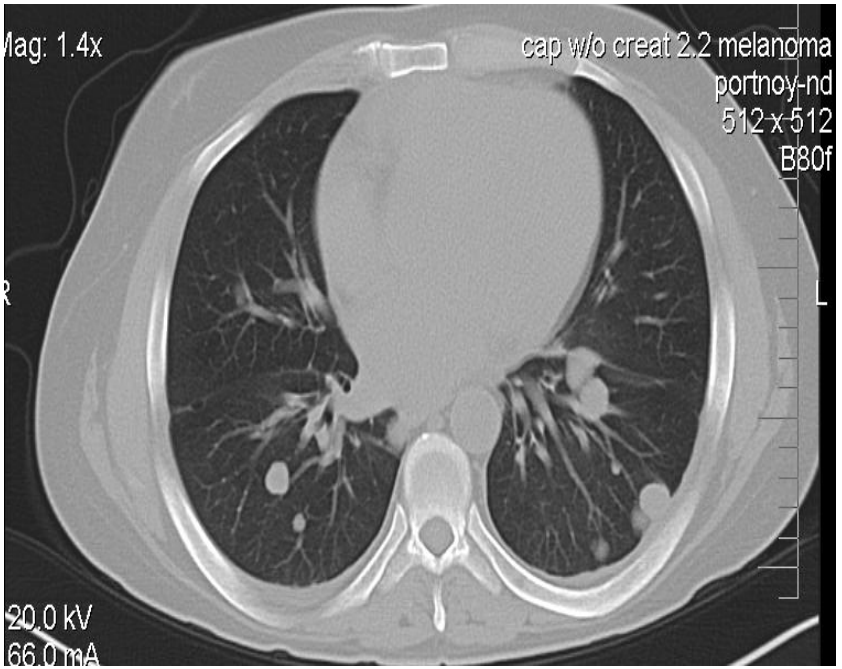
- L superclavicular biopsy
  - Metastatic melanoma
  - BRAF, KIT, HER2 WT
- Received Ferraheme, Procrit, RT to R hip
- CT scan 3/8/13: Progression from 1/13
- Started ipilumumab IV x 4

3/8/2013 CT Pt #1



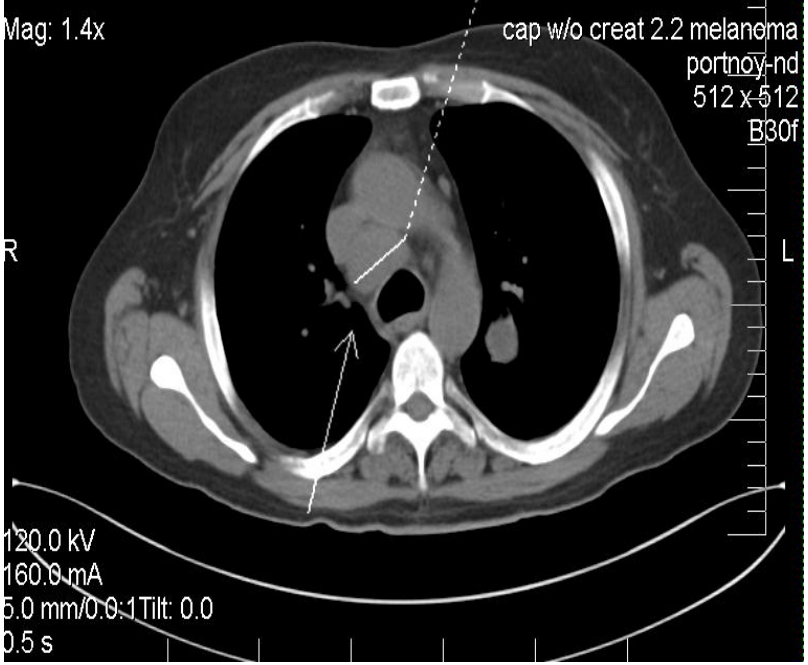






Real World Case Examples: Case Study 1

- Received 4 cycles at 3 weeks interval
- Pruritis and intermittent RUQ pain, mild diarrhea
- 5/24/13 Office visit
  - “Feels best he has in 6 months”
  - Pain much improved, decreased fatigue
  - No change in the palpable disease
  - Hb 11.3 g/dl
- 6/21/13: Repeat CT scans
  - Progression of disease in pleura, L hilar LN and adrenal tumor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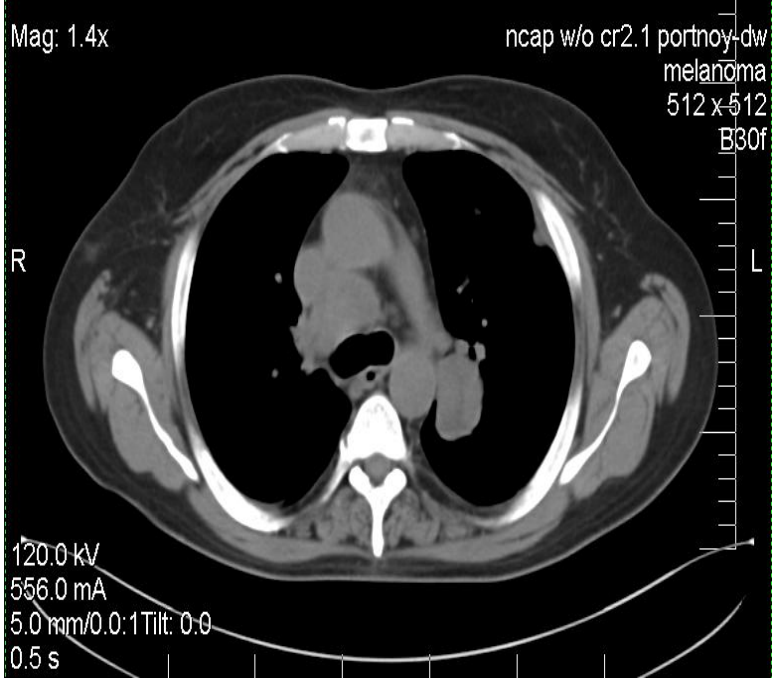
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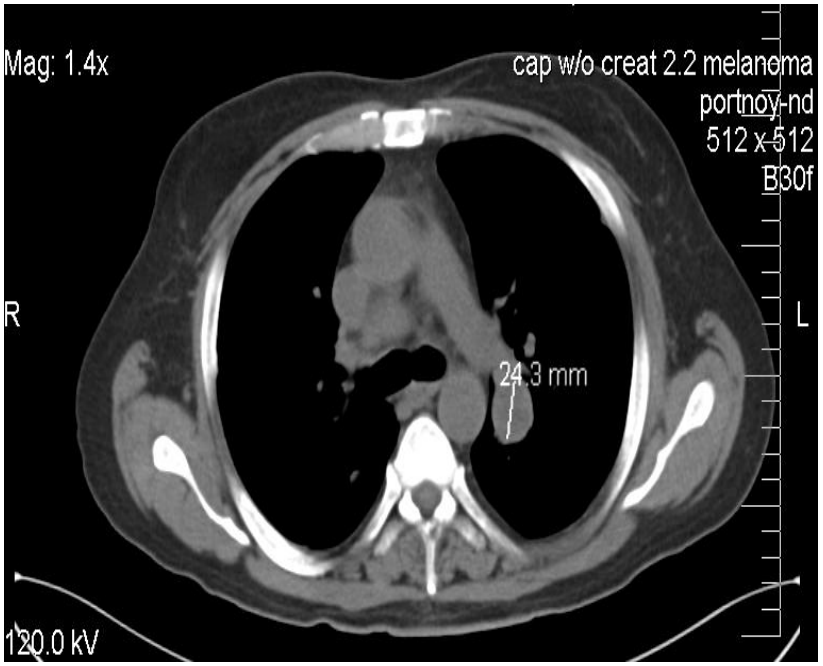
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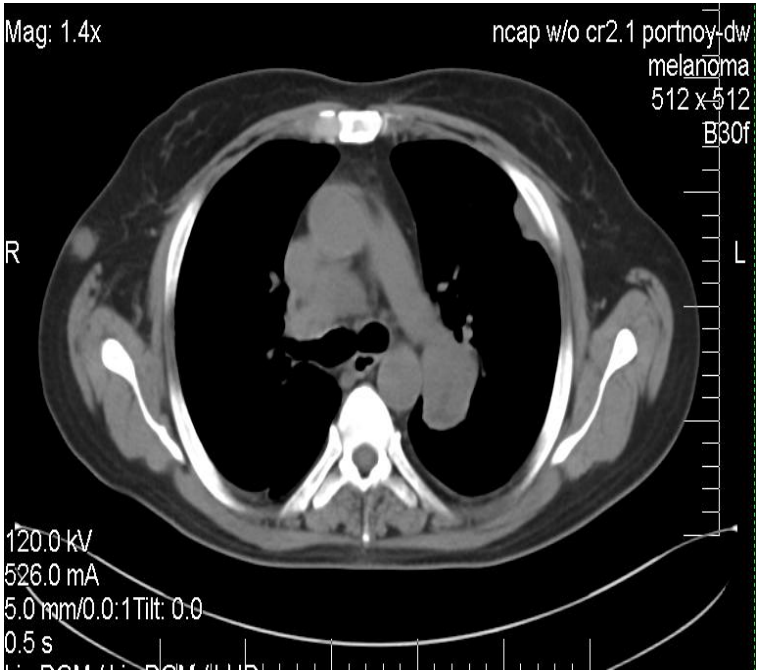
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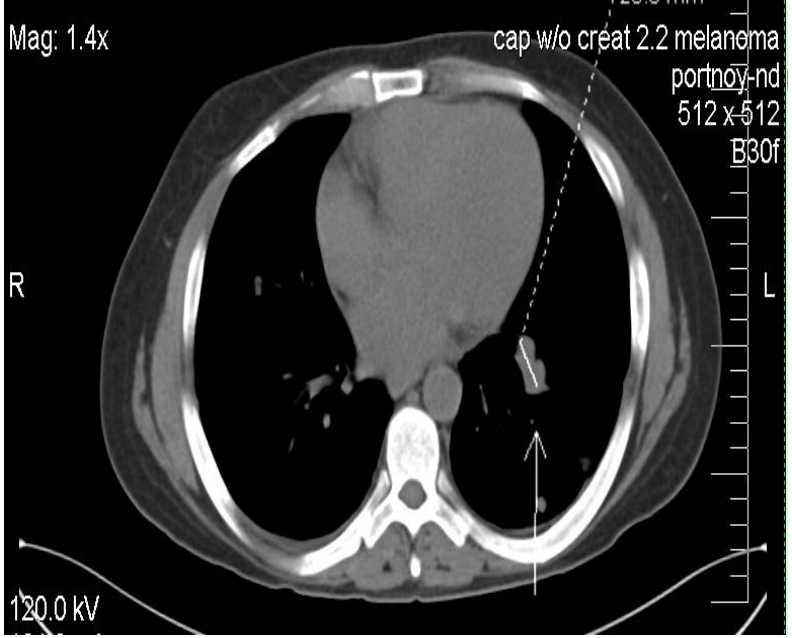
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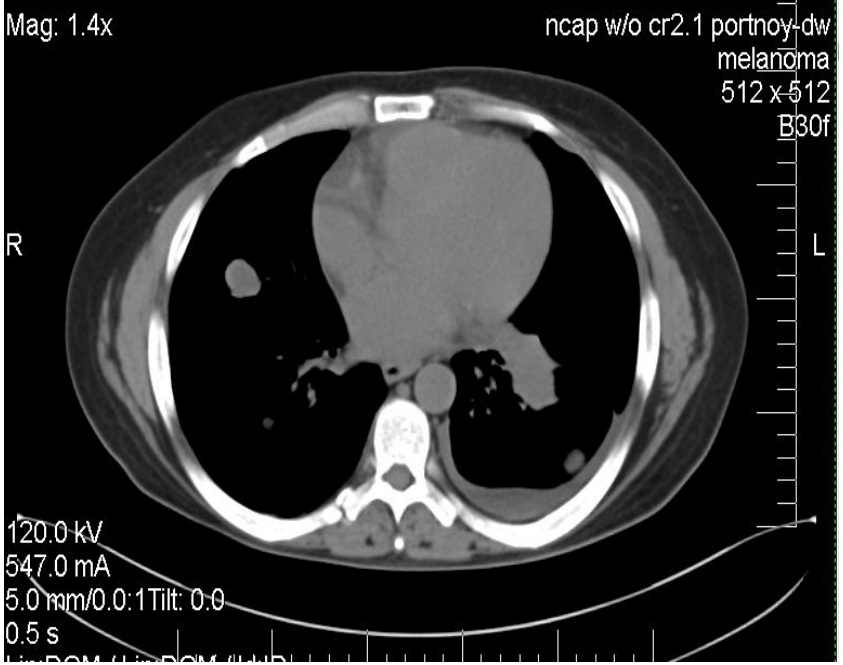
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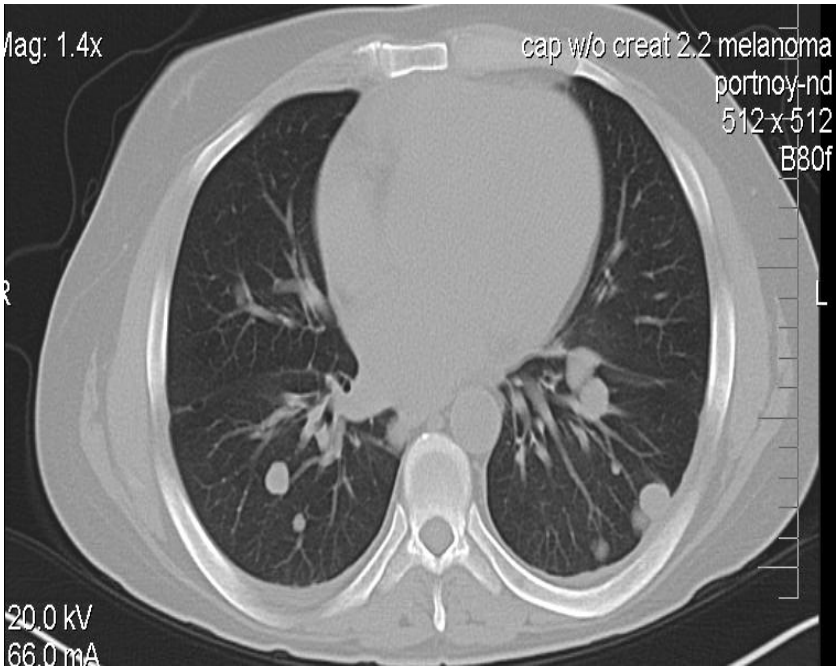
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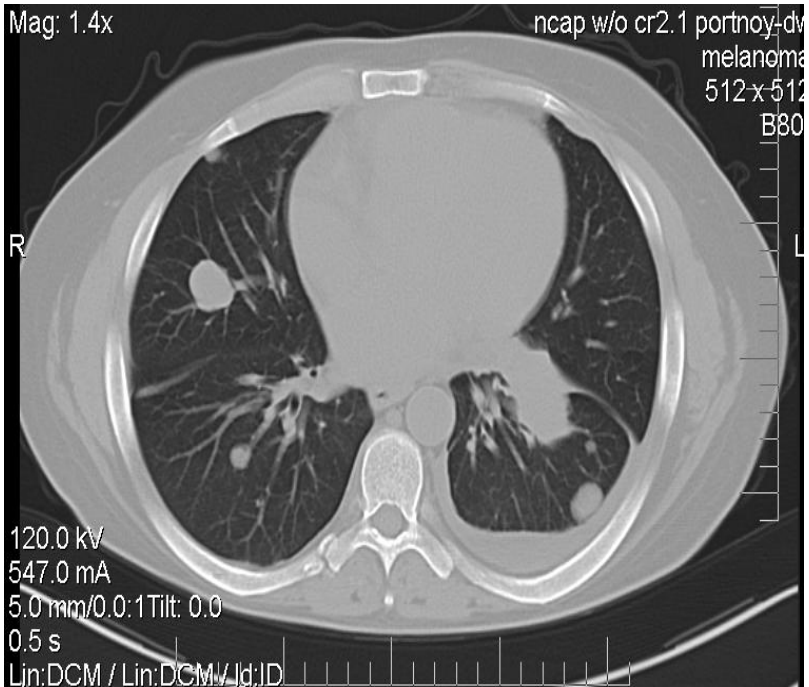
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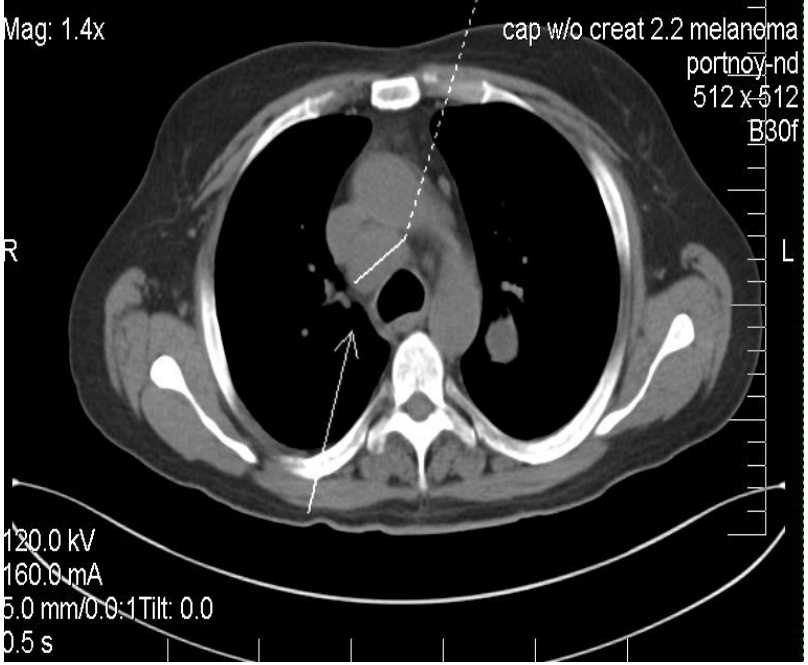
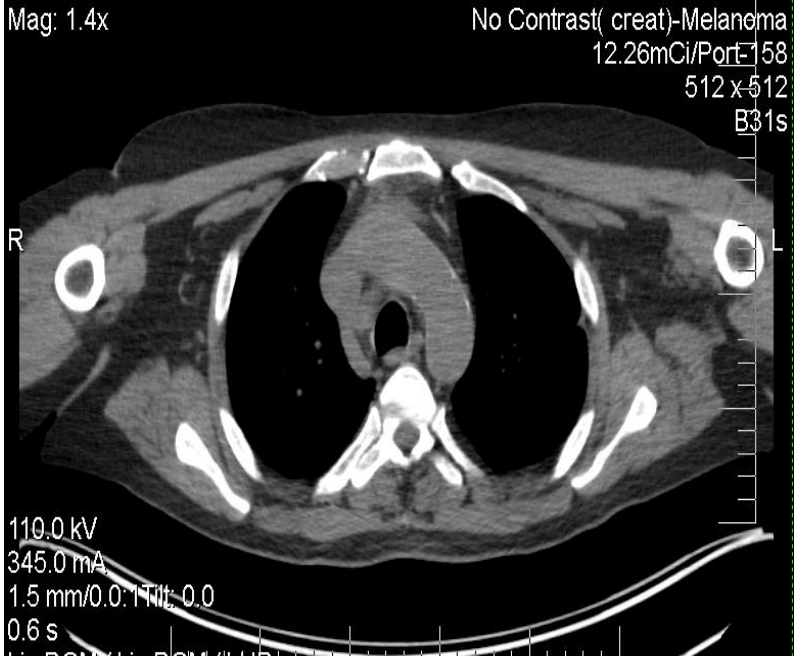
Real World Case Examples: Case Study 1

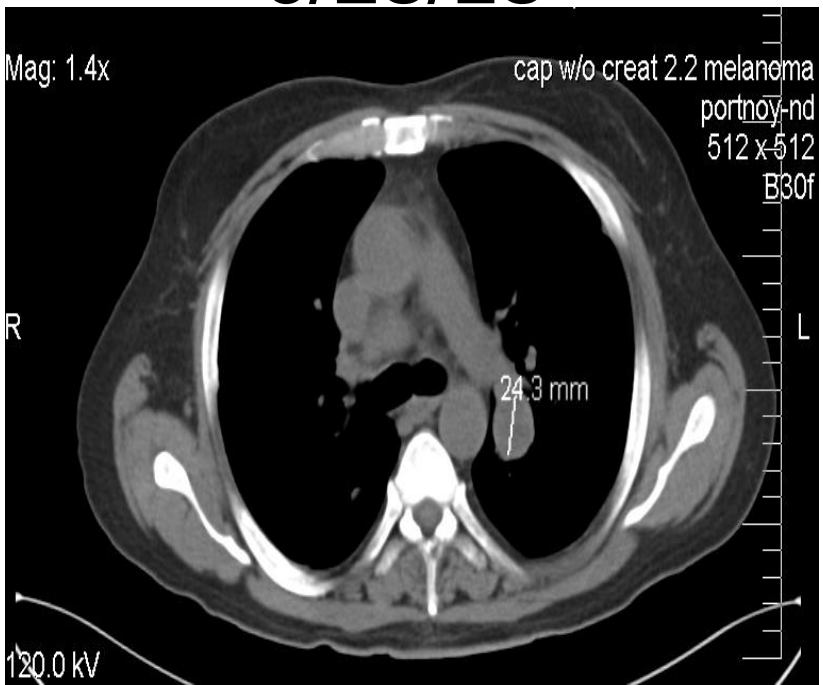
- Prescribed temodar
  - Took two days dose
- Admitted to the local hospital with “pneumonia”
- Seen 7/29/13 for followup at West Clinic
  - Improved R axillary adenopathy
  - ? Delayed response to Yervoy
  - Clinically improved over next two months
- PET/CT 10/4/13: Much improved

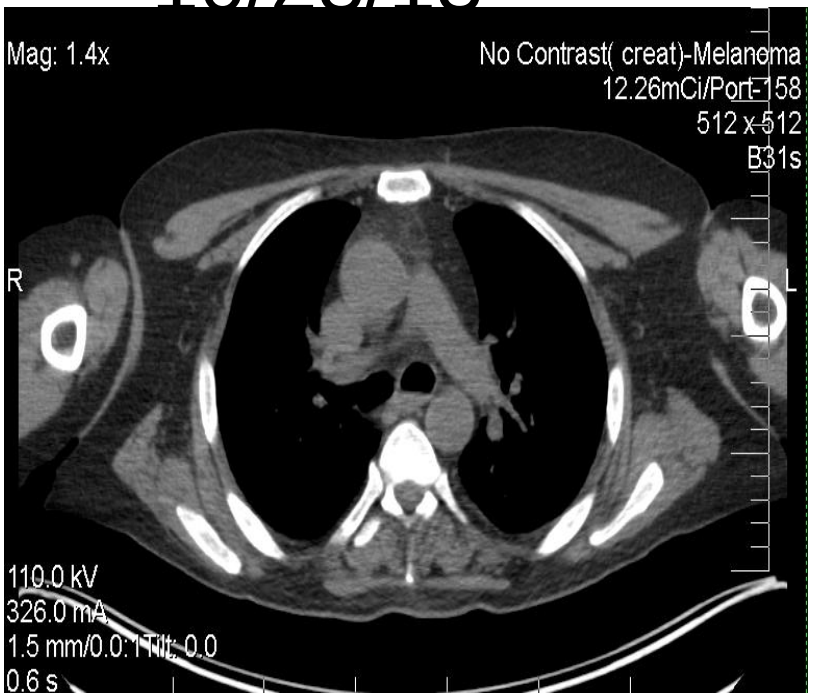


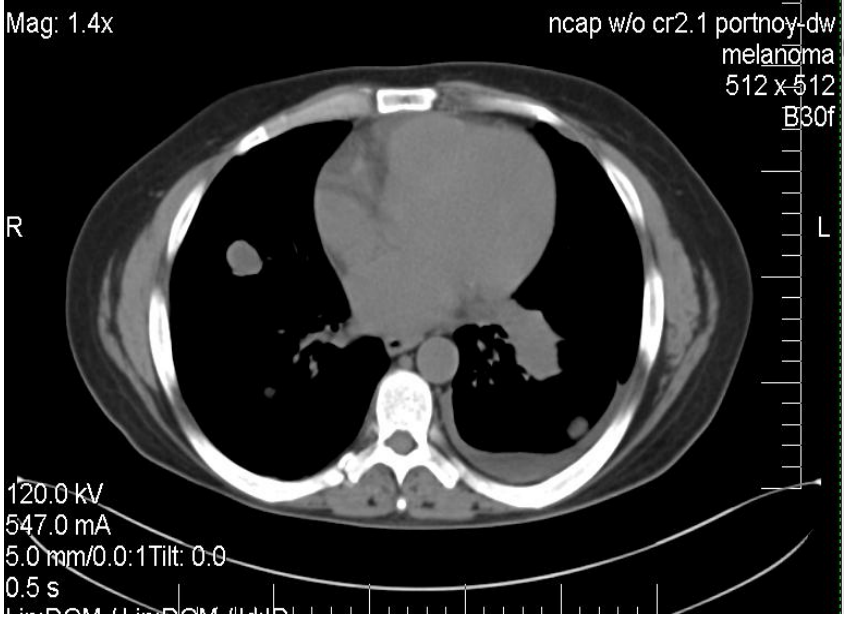


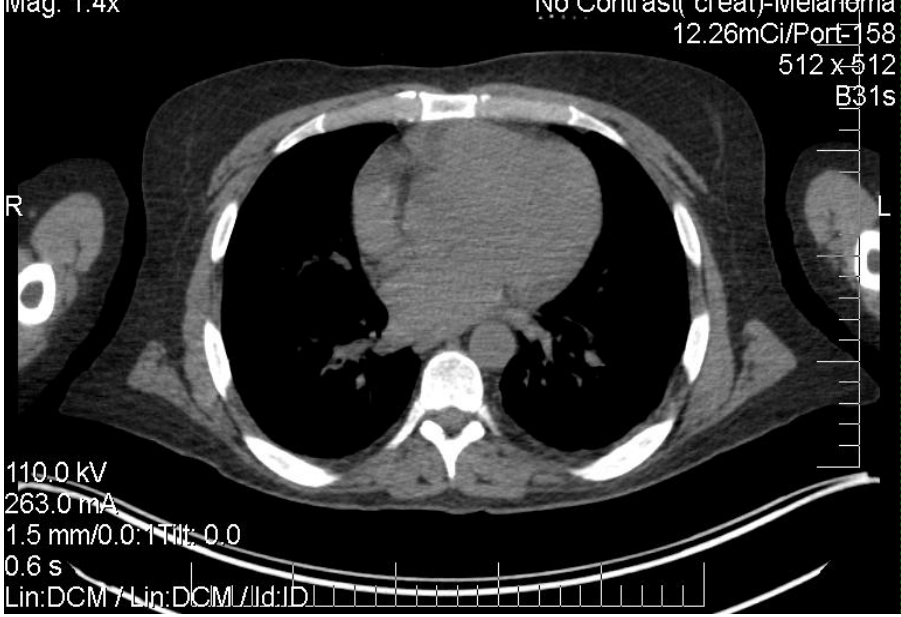
6/23/13

10/23/13









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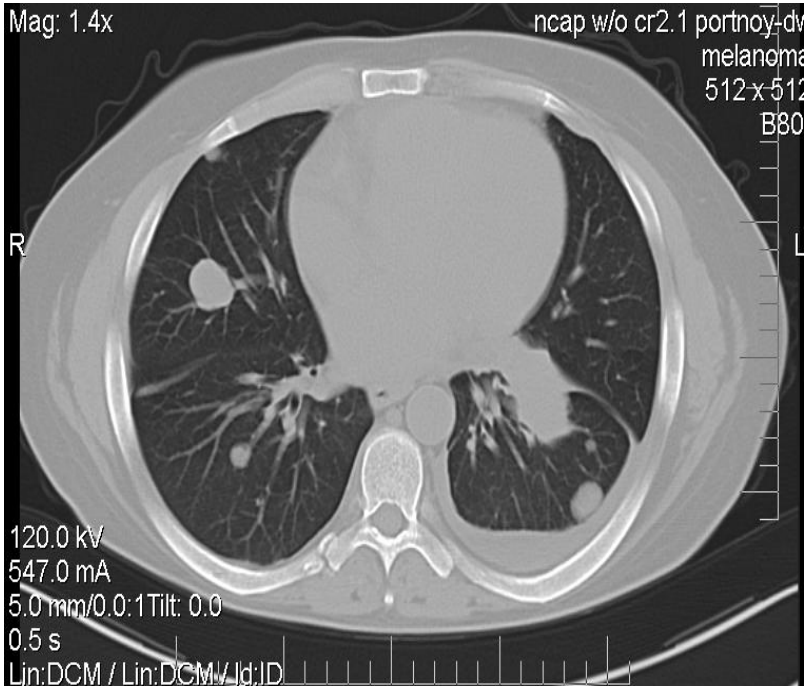
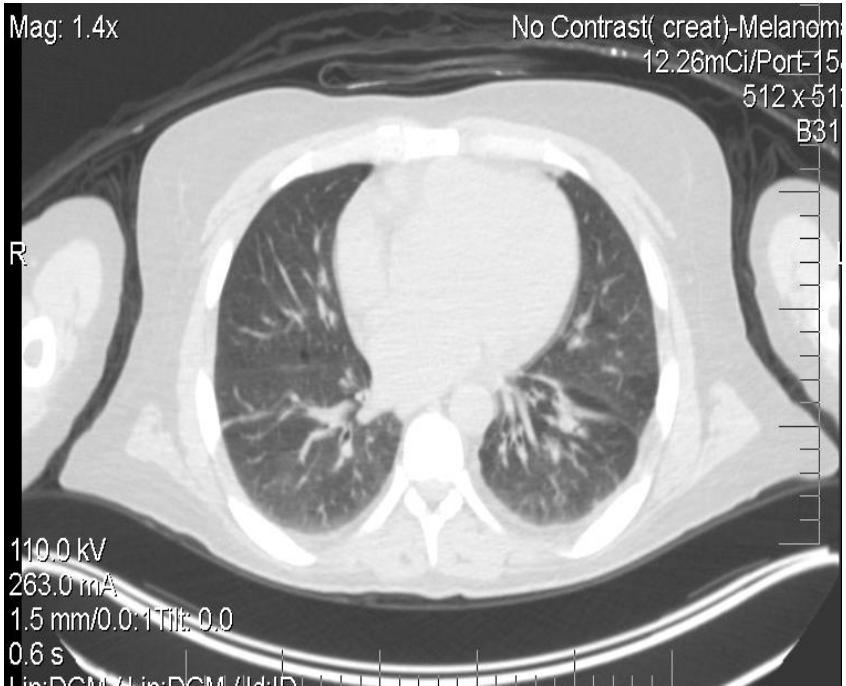




Real World Case Examples: Case Study 1

- 4/13/14: CT scan
  - No pulmonary nodules
  - Sclerotic bone metastases
  - No adrenal metastases
- 4/14/15: CT scan
  - No evidence of disease

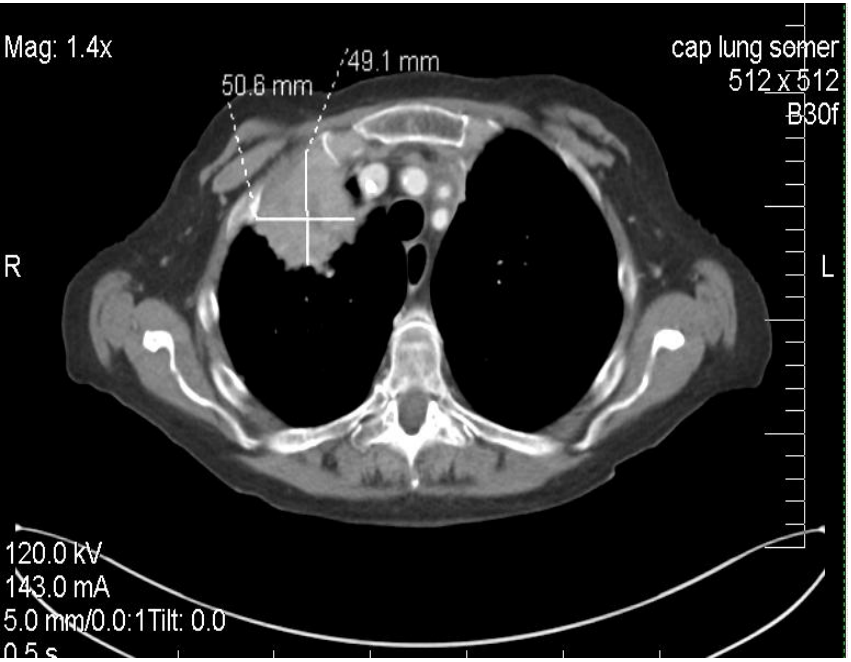
Real World Case Examples: Case Study 2

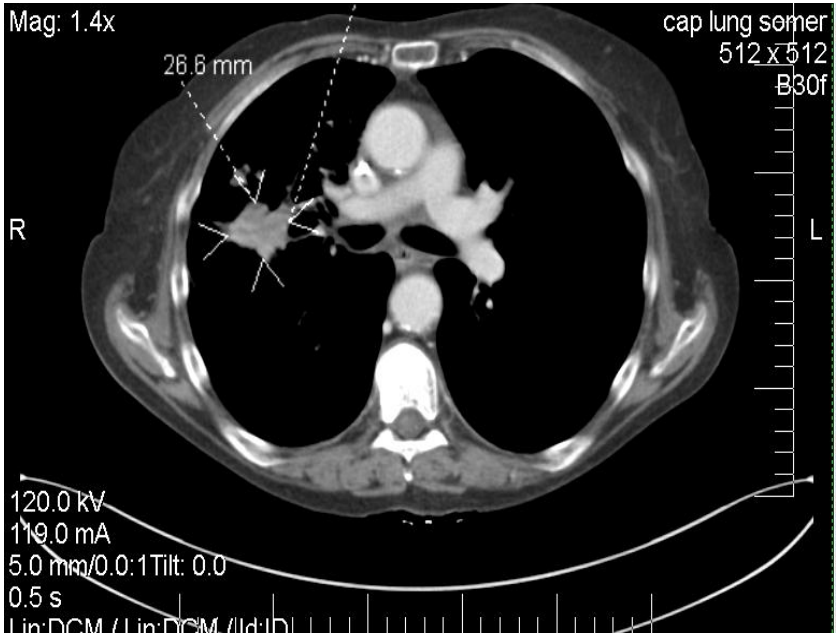
- 66 year old female
- Nausea, cough, weight loss of 40 lbs
- Referred to Dr. Somer, West Clinic
- CT 5/23/13: RUL mass, multiple nodules in both lungs, bilateral hilar and mediastinal lymph nodes, ground glass opacities, confirmed by PET/CT
- CT guided biopsy R lung:
  - moderately differentiated adenocarcinoma
  - Molecular profiling: EGFR WT, ROS and ALK without rearrangement

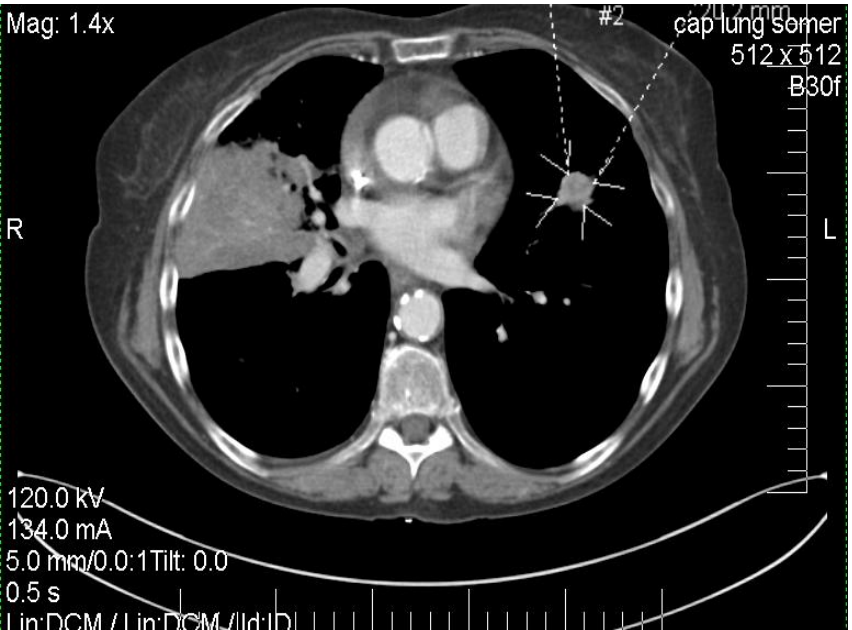
Real World Case Examples: Case Study 2

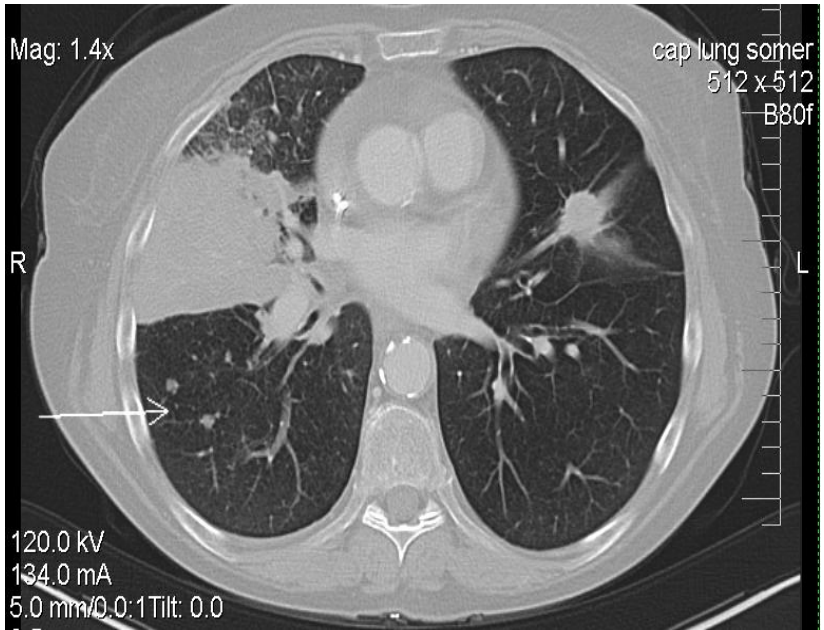
- Started treatment with Carboplatin/pemetrexed
- Received 4 cycles
- CT 8/13: Good response to therapy
- Stable PR 12/13
- CT 5/14:
  - POD with new consolidation/mass RML, multiple bilateral nodules, large RUL nodule
  - Symptomatically worse, on chronic O2
  - Started 2nd line erlotinib, after Veristrat good molecular signature
- 11/6/14: CT showed POD in lungs

November 6, 2014, Pt # 2



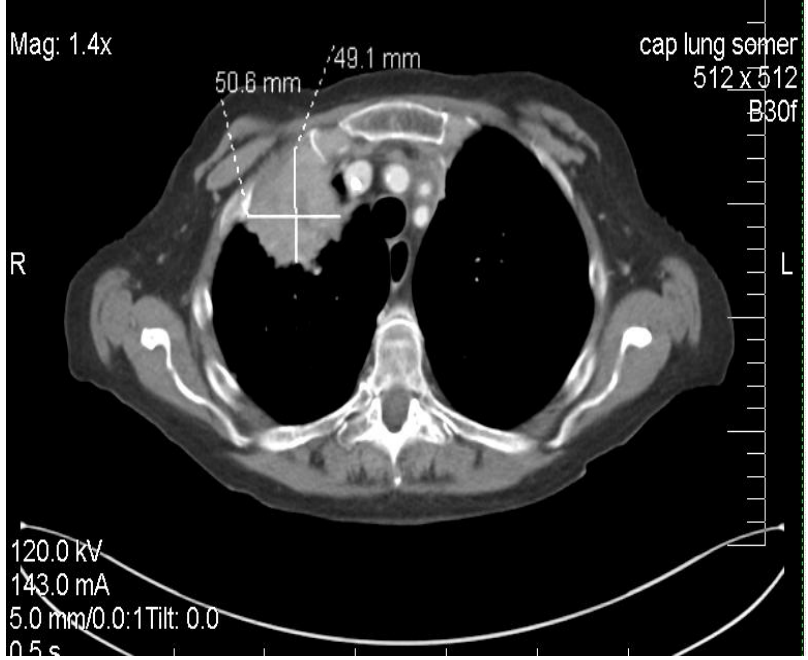




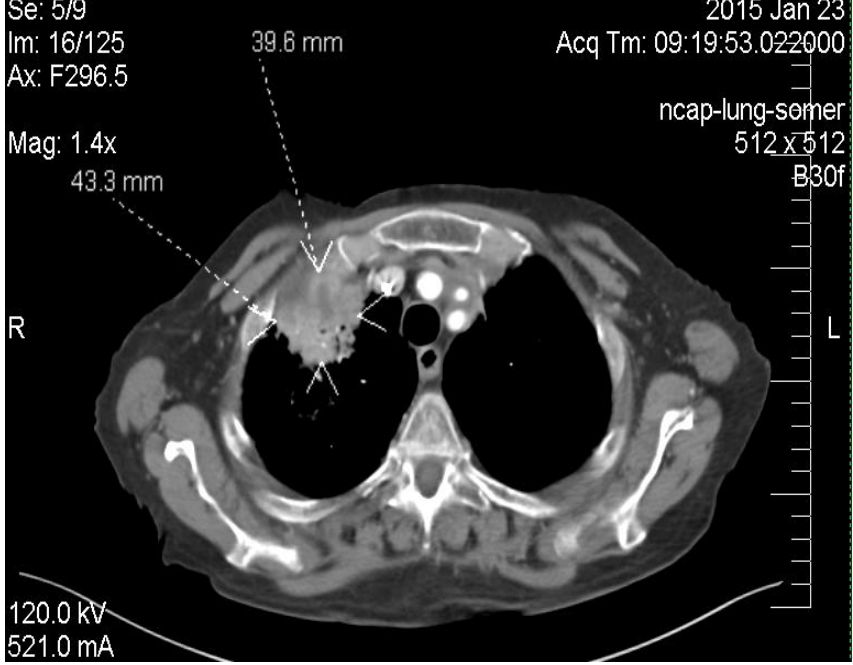


Real World Case Examples: Case Study 2

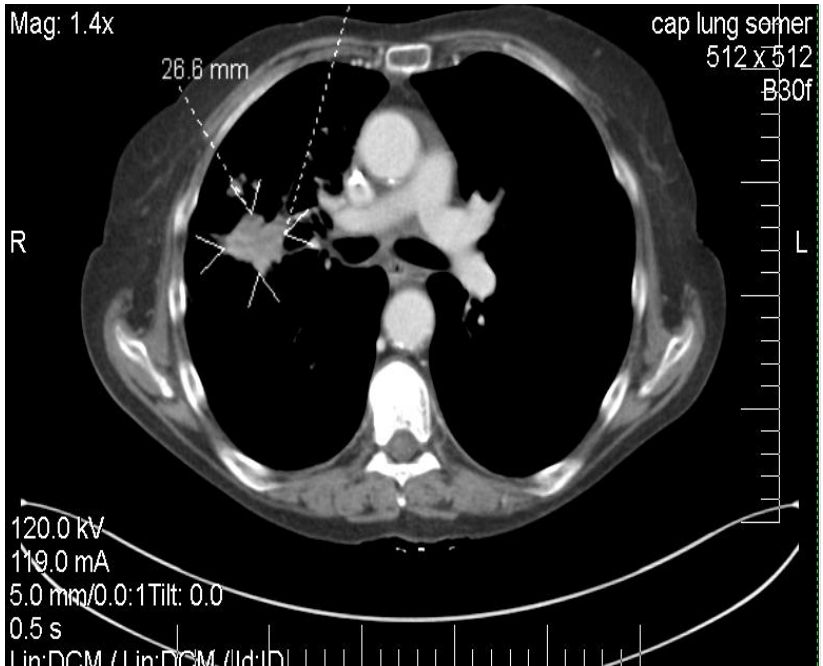
- Evaluated for Nivolumab trial
- Initiated 11/21/14
- One week later, admitted to hospital with increased SOB, nausea and diarrhea
- Treated with aggressive pulmonary measures, O2, and antibiotics for VRE in urine
- Improved symptomatically and was able to resume nivolumab
- Re-evaluated 1/3/15 with CT

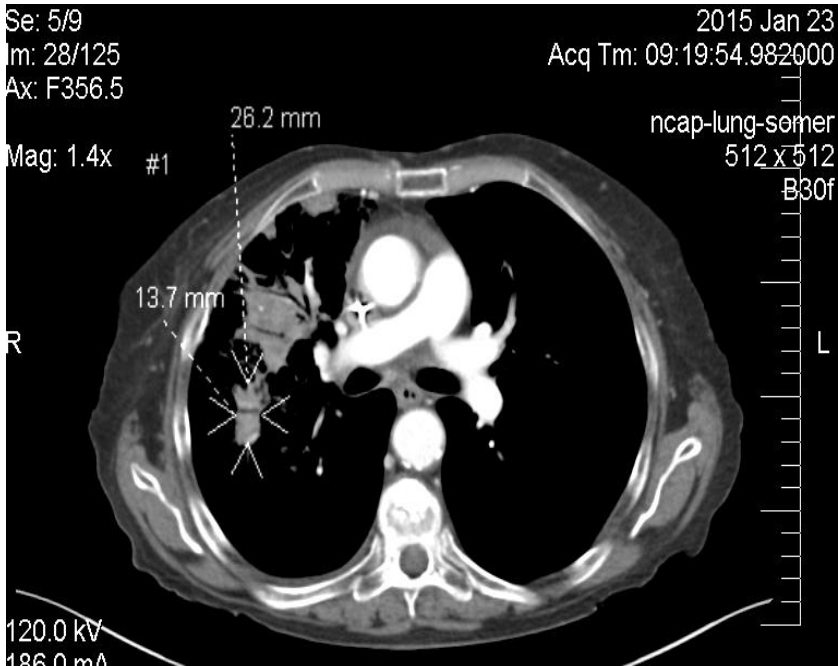

Mag: 1.4x
50.6 mm
49.1 mm
cap lung somer
512 x 512
B30f
R
L
120.0 kV
143.0 mA
5.0 mm/0.0:1Tilt: 0.0

11/6/14


Se: 5/9
Im: 16/125
Ax: F296.5
39.6 mm
2015 Jan 23
Acq Tm: 09:19:53.022000
Mag: 1.4x
43.3 mm
ncap-lung-somer
512 x 512
B30f
R
L
120.0 kV
521.0 mA

1/3/15


Mag: 1.4x
26.6 mm
cap lung somer
512 x 512
B30f
R
L
120.0 kV
119.0 mA
5.0 mm/0.0:1Tilt: 0.0
0.5 s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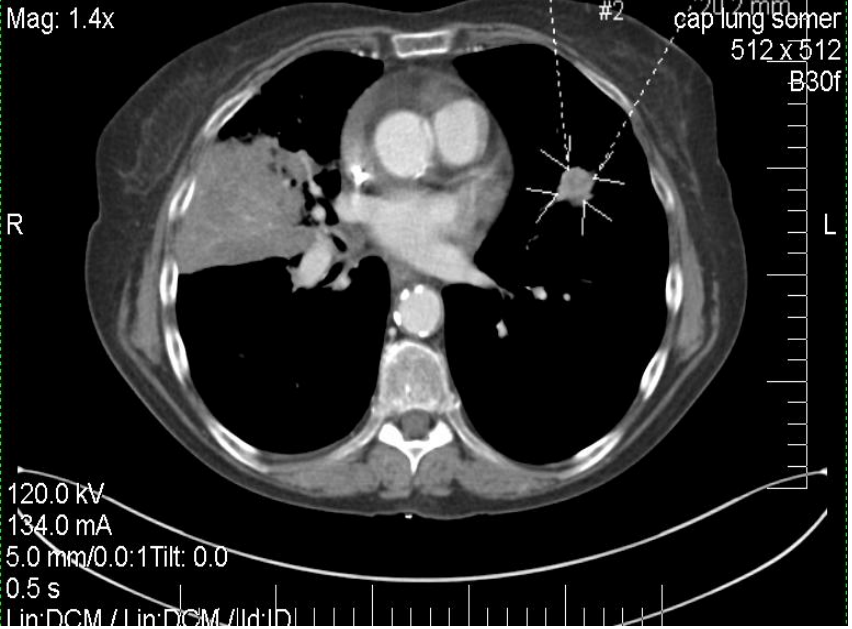
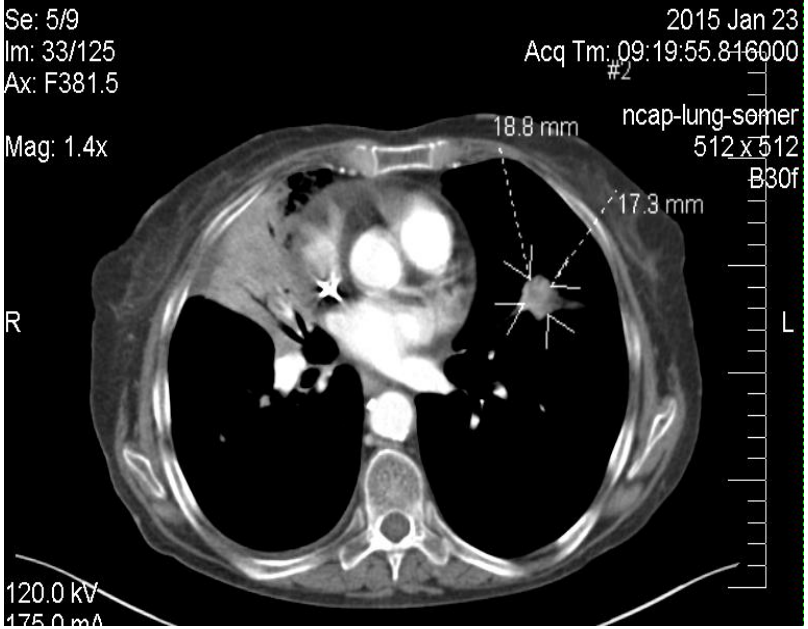
26.2 mm
Mag: 1.4x
#1
ncap-lung-somer
512 x 512
B30f
13.7 mm
R
L
120.0 kV


Mag: 1.4x
#2
cap lung somer
512 x 512
B30f
R
L
120.0 kV
134.0 mA
5.0 mm/0.0:1Tilt: 0.0
0.5 s

11/6/14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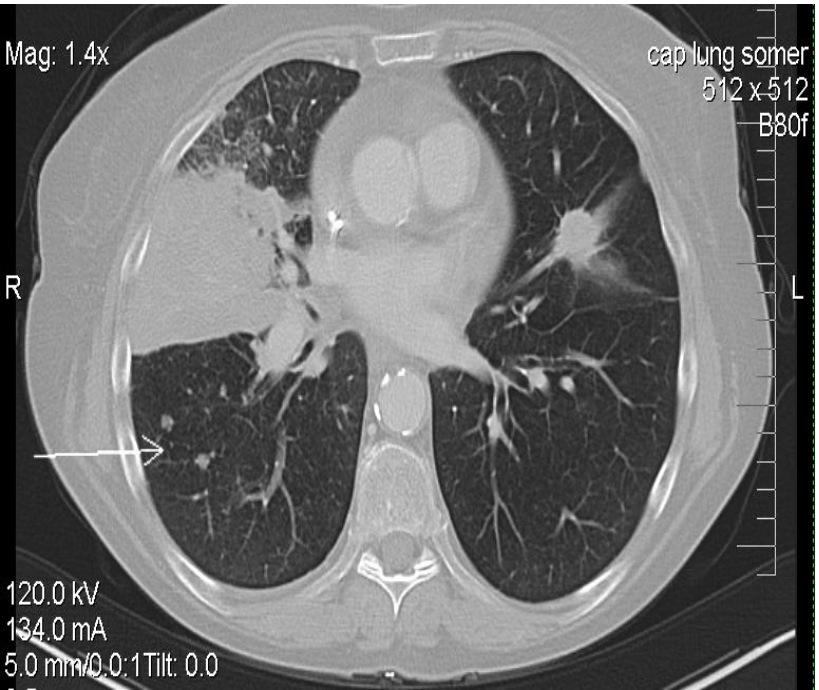
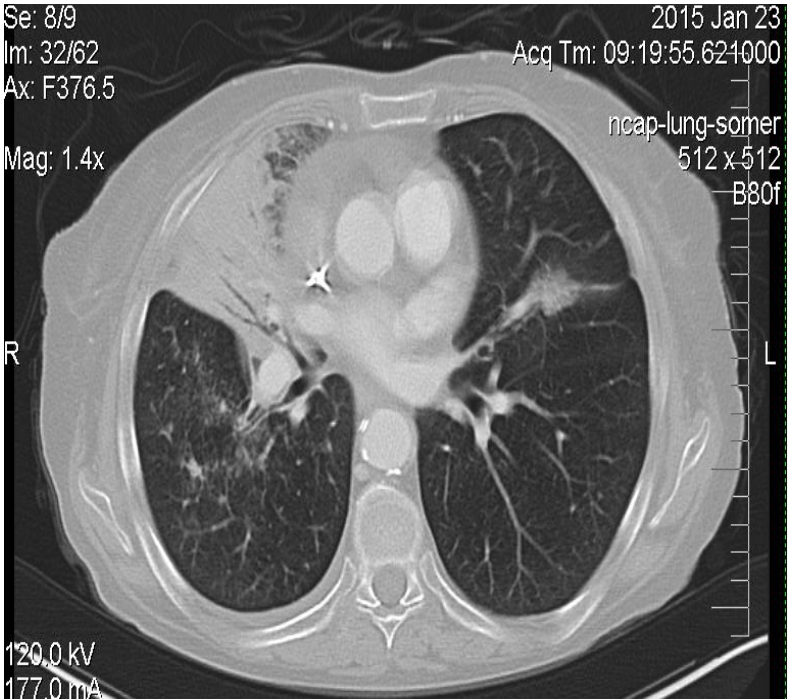
#2
18.8 mm
17.3 mm
ncap-lung-somer
512 x 512
B30f
R
L
120.0 kV

1/3/15


Mag: 1.4x
cap lung somer
512 x 512
B80f
R
L
120.0 kV
134.0 mA
5.0 mm/0.0:1Tilt: 0.0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2015 Jan 23
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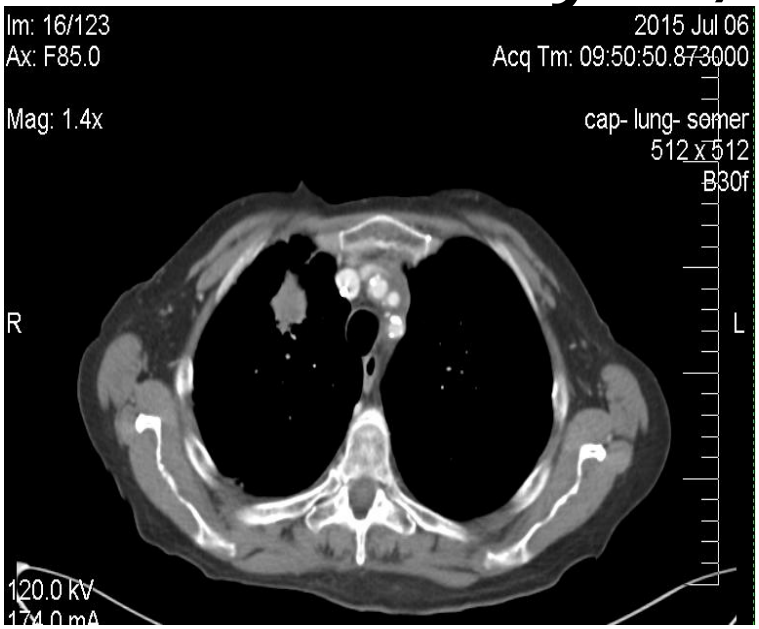
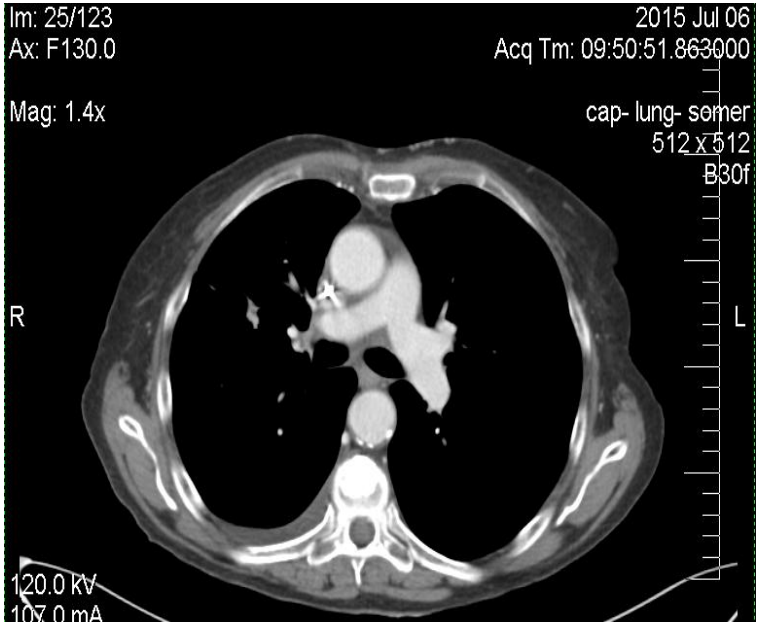
ncap-lung-somer
512 x 512
B80f
R
L
120.0 kV
177.0 mA

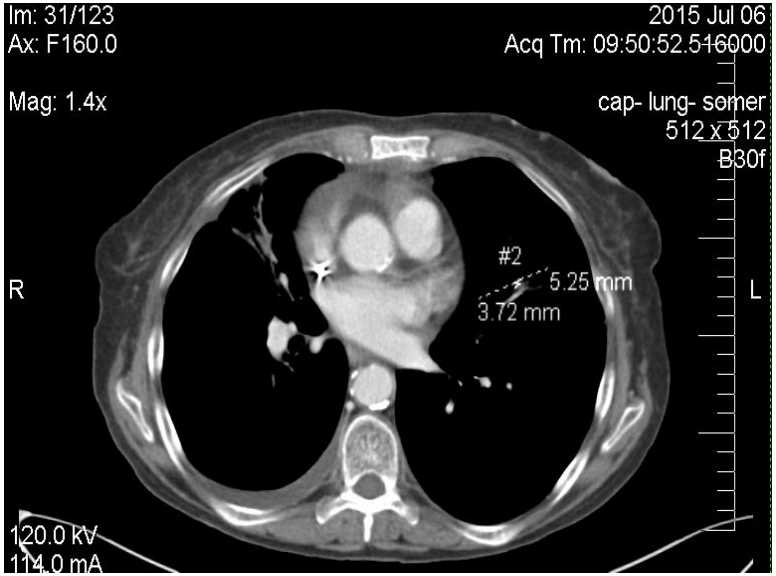
Real World Case Examples: Case Study 2

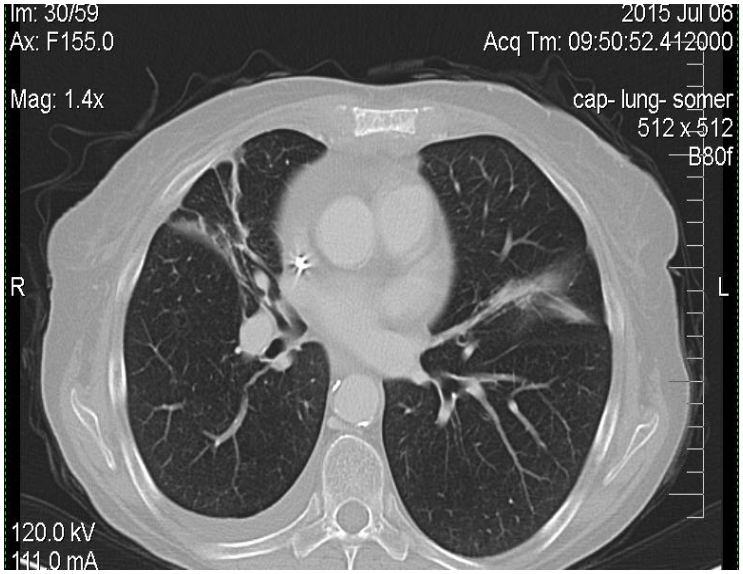
- Continued on Nivolumab Q 2 week
- Symptomatically improved
- Back to work part-time
- 14 cycles of Nivolumab to date
- CT scan 7/6/15: 70% reduction in tumor size

July 6, 2015, Pt #2









Summary

- Immune mediated drugs (such as CTLA-4 inhibitors and PD (L)-1 inhibitors are finding use in many cancer types
- Immuno-oncology drugs work differently than traditional cytotoxics but stimulating the immune system
- With immunotherapy, imaging studies may show initial worsening of lesions in terms of size and even new lesions during initial therapy evaluation
- A new response system, the irRC, was developed and is in use now for patients treated with immuno-oncology agentsd
- In absence of clinical progression, pseudo-progression on scans should be strongly considered and patients re-evaluated carefully

Questions?

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Association of Community Cancer Centers

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RECIST, Applying the Rules, National Cancer Institute

Immunotherapy: Fight Cancer with Immunotherapy