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FNIH
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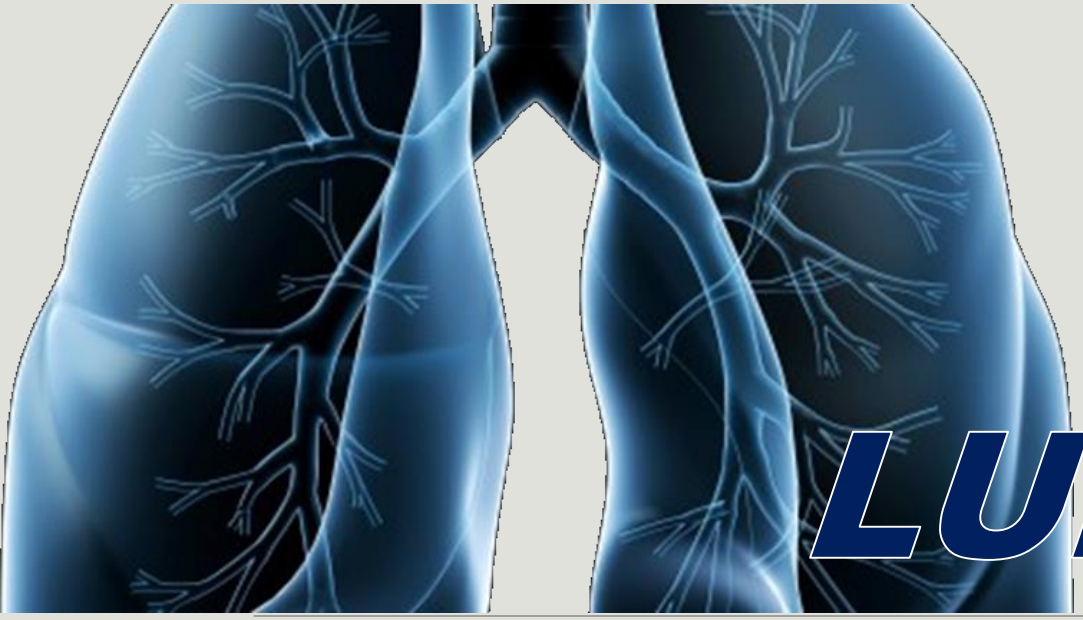
a National Cancer Institute program

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

FRIENDS of CANCER RESEARCH



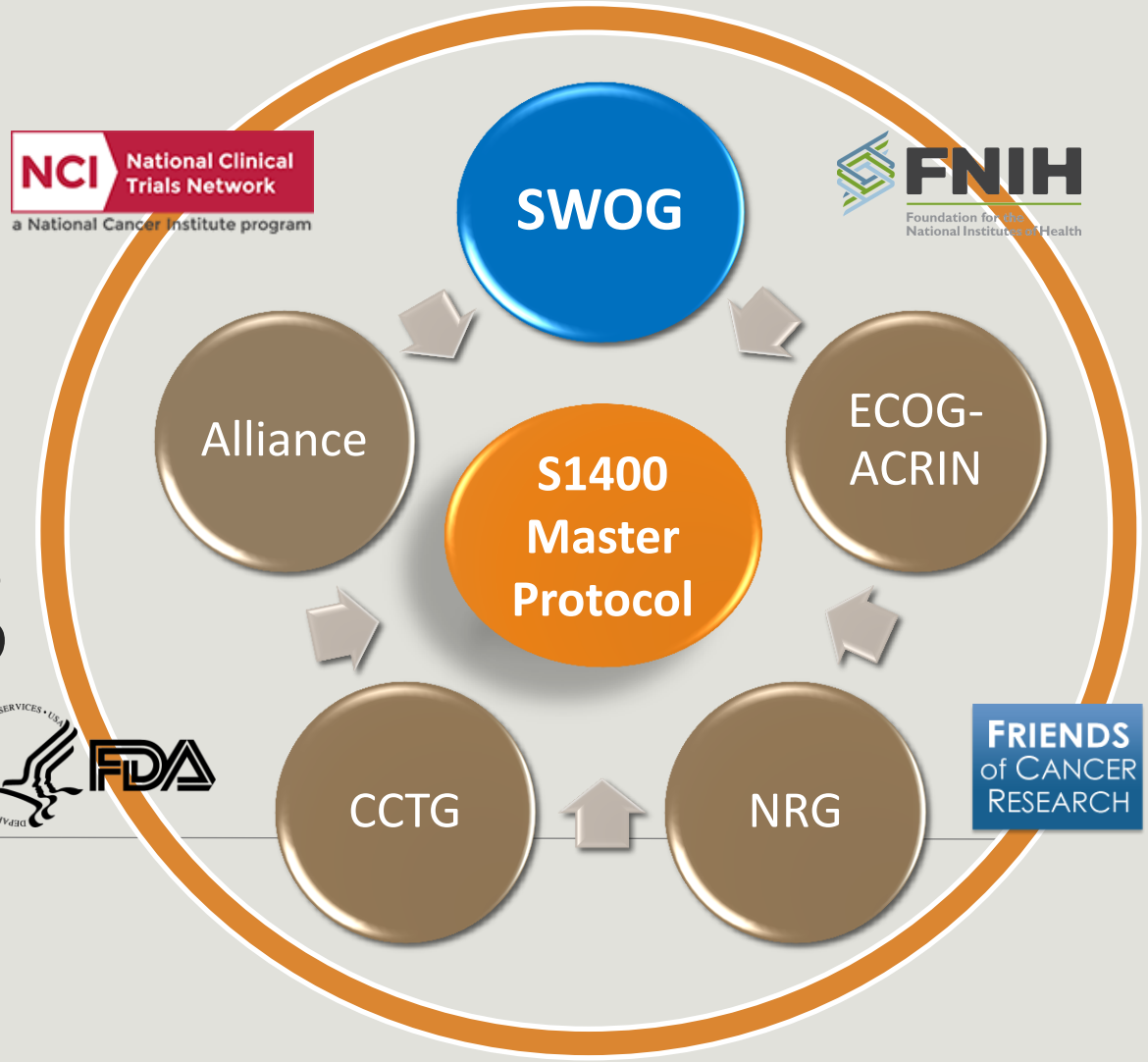
LUNG-MAP

S1400 LUNG MASTER PROTOCOL

SUMMER UPDATE WEBINAR

JUNE 23, 2017

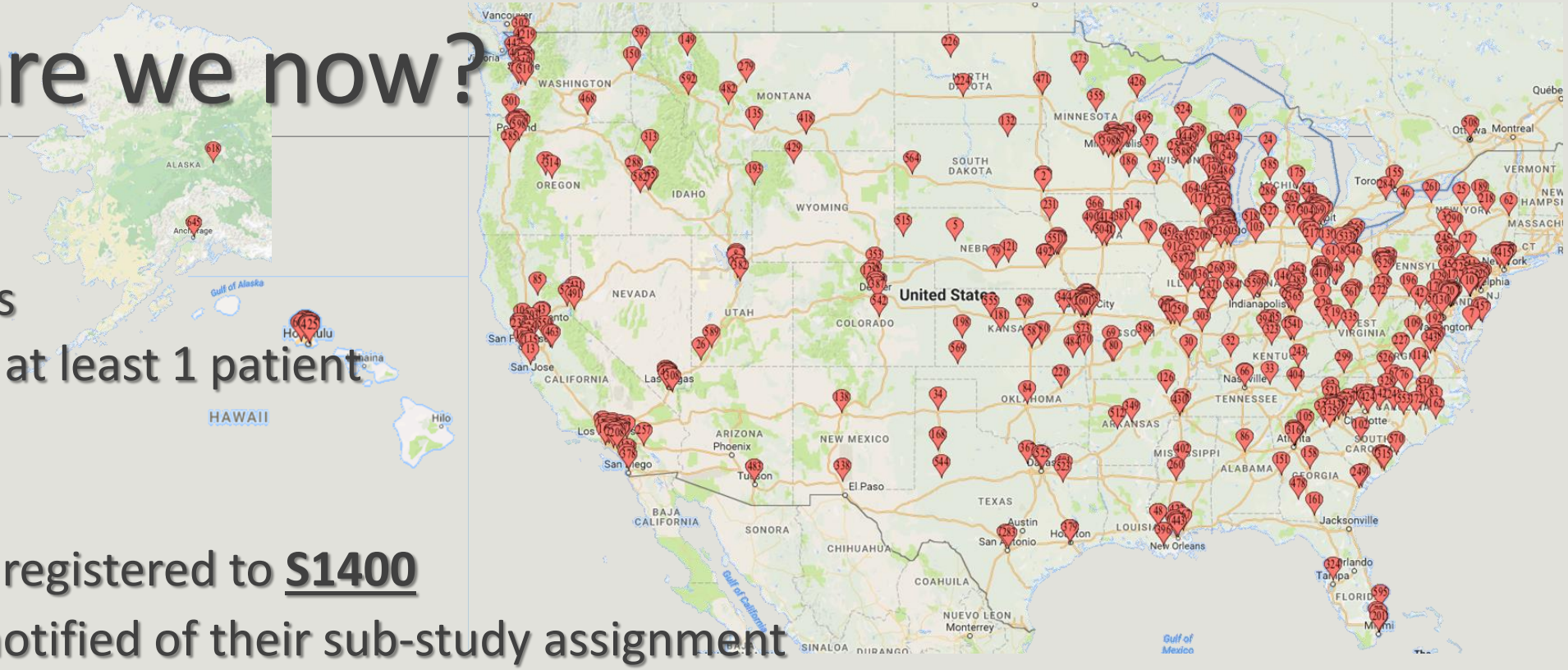
Welcome & Study Updates



VASSILIKI PAPADIMITRAKOPOULOU, MD

STUDY CHAIR, MEDICAL ONCOLOGY

Where are we now?



- IRB Approvals:
  - Up to 740 sites
  - 372 sites with at least 1 patient accrued
- Accruals:
  - 1293 patients registered to **S1400**
  - 996 patients notified of their sub-study assignment
  - 484 patients registered to a sub-study

S1400G: 17

S1400I: 204

Closed Sub-studies/treatment: 263

SWOG STATISTICAL CENTER and CTSU
AS OF 6/13/17

Current Status of Sub-Studies

- **S1400A [MEDI4736]**
  - Completed 12/18/2015
- **S1400B [GDC-0032]**
  - Completed 12/12/2016
- **S1400C [Palbociclib]**
  - Completed 9/1/2016
- **S1400D [AZD4745]**
  - Completed 10/31/16
- **S1400E [Rilotumumab]**
  - Closed 11/25/14
- **S1400F [MEDI4736/Tremelimumab]**
  - Preparing to open Q3 2017
- **S1400G [Talazoparib]**
  - Actively accruing
- **S1400I [Nivolumab/Ipilimumab]**
  - Actively accruing

Study Design Updates

S1400G - PARP Inhibitor

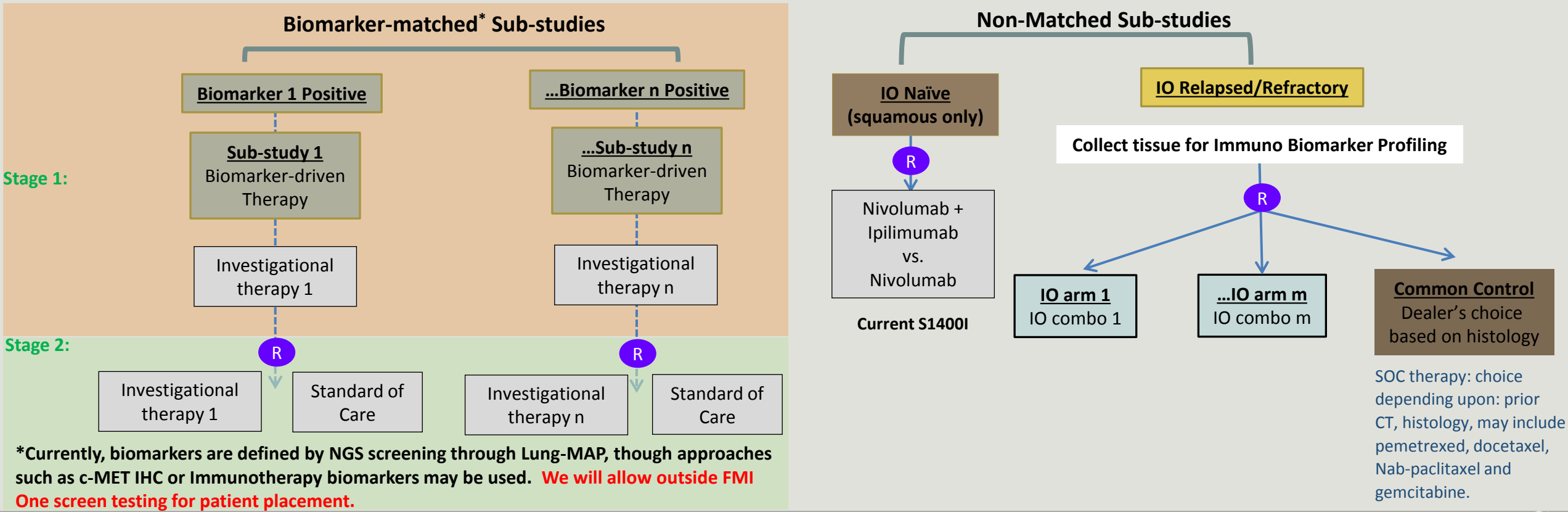
- Patients with homologous recombination DNA repair deficiency (HRRD) may be particularly receptive to treatment with **PARP inhibitors**.
- Sub-study G (**S1400G**) of Lung-MAP seeks to **evaluate the efficacy of talazoparib**, a potent PARP inhibitor, in such patients.
- **S1400G** includes patients with alterations in **BRCA1/2, ATM, CHEK1 and other HRRD genes**.

Study Design Updates

- **Revision #9 (Expected Q3 2017)**
  - **New Sub-Study, S1400F:** A non-match study with previously treated anti-PD-1/PD-L1 inhibitor resistant disease
  - The eligibility criterion regarding patients screened at progression on prior treatment or pre-screened prior to progression has been **opened to include checkpoint inhibitor therapy as a line of therapy.**
- Upcoming Revision:
  - **New Sub-Study, S1400K:** A biomarker-driven study of ABBV-399 in c-MET positive patients
    - Concept approved by CTEP – Protocol in Development

Proposed Trial Redesign Structure

Previously-treated Stage IV or Recurrent
Non-Small Cell Lung Cancer
(all histology)
Immunotherapy or Chemotherapy Relapsed/Refractory Patients



*Currently, biomarkers are defined by NGS screening through Lung-MAP, though approaches such as c-MET IHC or Immunotherapy biomarkers may be used. We will allow outside FMI One screen testing for patient placement.

SOC therapy: choice depending upon: prior CT, histology, may include pemetrexed, docetaxel, Nab-paclitaxel and gemcitabine.

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Prior Treatments Allowed for IO-combination Platform

Group 1:

Plat-based Chemotherapy for Stage I-III* → IO as 1st-line therapy for Recurrent disease (Stage IV)

Group 2:

Plat-based Chemotherapy as 1st –line therapy for Stage IV → IO as 2nd-line therapy for Stage IV

Group 3:

IO as 1st-line therapy for Stage IV → Plat-based chemo as 2nd-line therapy for Stage IV

Group 4:

IO and Plat-Based Chemotherapy as 1st-line therapy for Stage IV

Note: Intervening therapy is allowed

*disease progression on platinum-based chemotherapy must have occurred within one year from the last date that patient received that therapy

Closed Sub-Study Results

	Date of Closure	Number of Patients			Adverse Events Attributable to Treatment N (%)		
		Total	Investigational Arm	Eligible and Evaluable	Grade 3	Grade 4	Grade 5
S1400A (MEDI4736)	12/18/15	116	78	68	18 (26%)	4 (6%)	1 (1%)
S1400B (taselisib)	12/12/16	39	31	26	11 (42%)	1 (4%)	2 (8%)
S1400C (palbociclib)	09/01/16	54	37	32	13 (41%)	5 (16%)	0 (0%)
S1400D (AZD4547)	10/31/16	45	35	27	6 (22%)	1 (4%)	0 (0%)
Combined Docetaxel	05/26/15 (A) 12/18/15 (B/C/D)	73	-	56	24 (43%)	16 (29%)	1 (2%)

Efficacy Outcomes

	Best Objective Response		Response N (%)	PFS Median (95% CI)	OS Median (95% CI)
S1400A (MEDI4736)	1 CR 7 PR 3 UPR	26 SD 30 PD 1 NASS	11 (16%)	2.9 (1.8, 4.1)	11.6 (10.1, 15.4)
S1400B (taselisib)	1 PR	17 SD 6 PD 2 NASS	1 (4%)	2.8 (1.7, 4.0)	5.9 (4.1, 11.5)
S1400C (palbociclib)	2 PR	12 SD 16 PD 1 SYMP DET 1 NASS	2 (6%)	1.8 (1.6, 2.9)	7.2 (4.0, 14.6)
S1400D (AZD4547)	1 PR 1 UPR	13 SD 10 PD 1 SYMP DET 1 NASS	2 (7%)	2.7 (1.4, 4.5)	7.5 (3.6, 9.3)
Combined Docetaxel	2 PR 1 UPR	29 SD 13 PD 5 SYMP DET 6 NASS	3 (5%)	2.7 (1.9, 2.9)	7.7 (6.7, 9.2)

S1400I Patient Reported Outcomes

MARY REDMAN, PHD

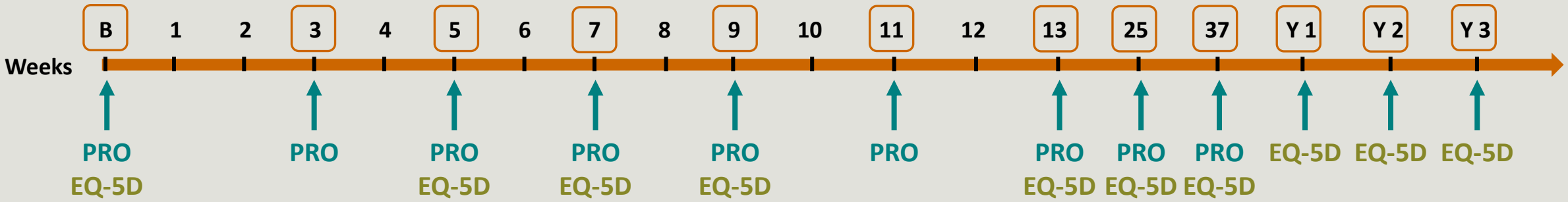
STUDY LEAD BIOSTATISTICIAN

S1400I PRO Overview

- **The Patient Reported Outcomes (PRO) Study will look at capturing the complex symptom profile experienced by patients, which may result from the disease, the therapy, or both. The study will consist of PRO and EQ-5D Questionnaires.**
- **The S1400I trial structure provides an ideal setting for evaluating the information provided by PRO measures and assessing how well PRO measures track with disease symptoms and other clinical outcomes.**
- **The purpose of the EQ-5D is to obtain preliminary survivorship status for this group of patients at the three yearly follow-up assessments for clinical status.**

Assessment Schedule

- **PRO assessment schedule built on existing clinical assessments:**



S1400I Clinical Assessment Schedule

S1400I PRO Sub-study Assessment Schedule

S1400I EQ-5D Questionnaire Assessment Schedule

PRO Data Submission

- **Data Submission Requirements**
  - Data must be submitted according to the protocol requirements for patients registered to **S1400I** after 9/1/2016 and participating in the **S1400I** PRO study (refer to **S1400I** Section 14.4)
- **Master Forms**
  - Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and CTSU website (www.ctsu.org)
- **Data Submission Procedures**
  - In addition to completing electronic forms, upload the patient-completed questionnaires via the Source Documentation: PRO form in Medidata Rave®. https://login.imedidata.com/selectlogin

PRO Training and Contacts

- Staff involved in the collection of quality of life/PRO data in SWOG trials should review the Patient Reported Outcome Training narrated slide program available on the SWOG website (www.swog.org, CRA Training, Tools of the Trade).
- **Nurse PRO/QOL Study Coordinator**

  Susan S. Tavernier, PhD, APRN-CNS, AOCN

  Assistant Professor

  Accelerated Nursing Program Coordinator

  Idaho State University School of Nursing

  Phone: 208/373-1783

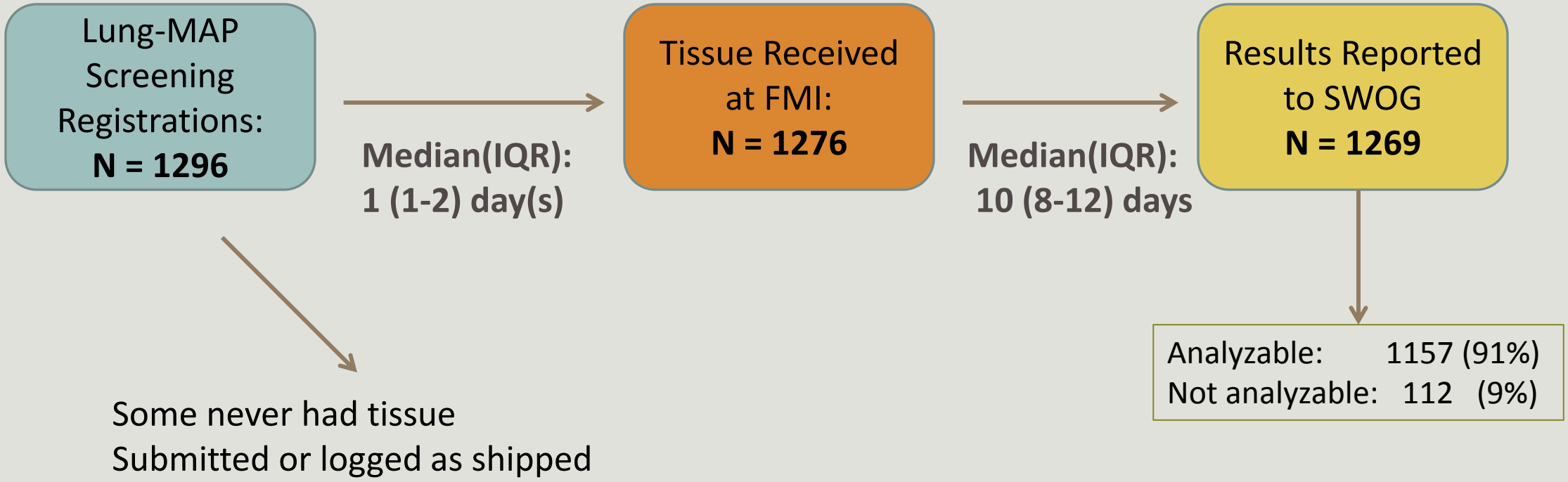
  tavesusa@isu.edu

Tissue Submissions

PHILIP MACK, PHD

STUDY CO-CHAIR, TRANSLATIONAL MEDICINE

Tissue Submission



Go to: http://www.swogstat.org/accrual/lungmap.pdf for current status

As of Jun 14, 2017

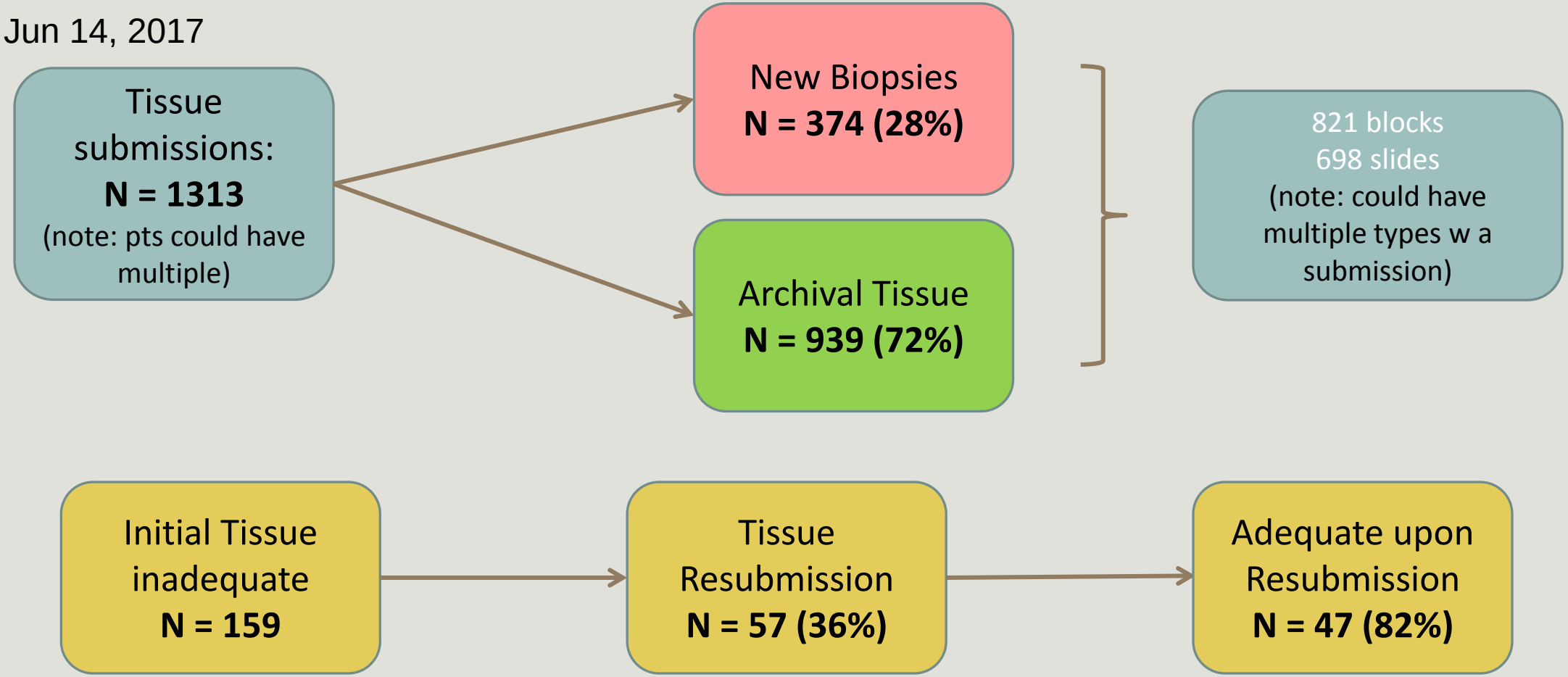
Lung-MAP Biomarker Results

Total Screening/Pre-screening registrations:	N=1296
• Pre-screened prior to PD	459 (35%)
• Screened at PD	837 (65%)
Biomarker testing results:	N=1157
Pi3K+ (S1400B biomarker)	93 (8%)
CCGA+ (S1400C biomarker)	217 (19%)
FGFR+ (S1400D biomarker)	181 (16%)
HRRD+ (S1400G biomarker)	182 (16%)
Multiple Biomarkers	130 (11%)
Others (non-eligible biomarkers):	
EGFR	7 (1%)
ALK	1 (<1%)

As of Jun 14, 2017

New Biopsies vs. Archival

As of Jun 14, 2017



The Tissue is the Issue

~ 14% of tissue submissions are inadequate

Reasons for inadequacy:

- **47%** **Insufficient amount of tissue** →
  - **67%** Insufficient tumor cells only
  - **22%** Insufficient tumor size only
  - **11%** Both insufficient tumor cells & insufficient tumor size
- **34%** **Insufficient DNA**
- **13%** **Failed Sequencing**
- **6%** **Other Reasons**

When tissue resubmissions are accounted for, 10% of patients had inadequate tissue

As of Jun 14, 2017

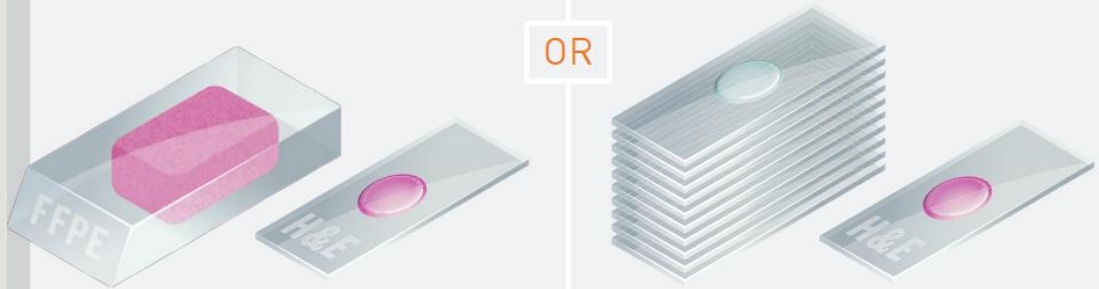
S1400 Specimen Guidelines for FOUNDATIONONE® testing

SAMPLE SIZE

When feasible, please send the block + 1 original (not recut) H&E slide.

OR

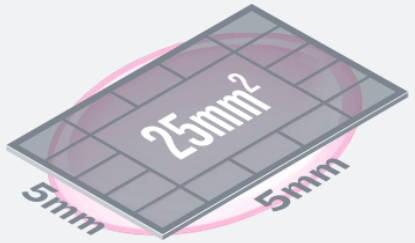
12-20 unstained slides (positively charged and unbaked at 4-5 microns thick) + 1 original (not recut) H&E Slide.



SAMPLE SIZE SURFACE AREA

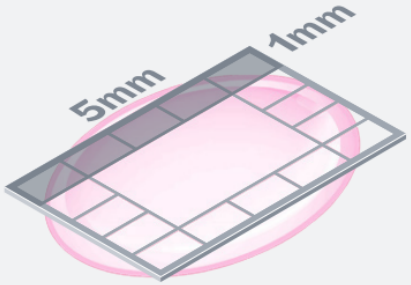
Optimal: 25 mm²

If sending slides, provide **12-20** unstained slides cut at 4-5 microns thick.



Minimal: 5 mm²

For small (<25mm²) or impure samples, additional unstained slides may be needed to extract sufficient DNA for testing.



TUMOR NUCLEI PERCENTAGE

Optimal: 30% Minimal: 20%

Percent tumor nuclei = number of tumor cells divided by total number of all cells with nuclei (Liver specimens may require additional tumor)

LUNG-MAP

SWOG

Quality Assurance and Monitoring

ELAINE ARMSTRONG, MS

SWOG QUALITY ASSURANCE MANAGER

QA/Monitoring Common Problems

- **Regulatory:**
  - **For sites using the CIRB: New 30-day requirement to implement protocol changes**
  - **A delay beyond the 30 days will be considered a deficiency**
  - **< 2 week delay is a lesser deficiency**
  - **> 2 week delay is a major deficiency**
- **Patient Case Review: Eligibility**
  - **S1400**: Failure to confirm ≥ 15% tumor cells by local pathologist

QA/Monitoring Common Problems

- **Consent forms**
  - Mixing up the screening consent and the prescreening consent
  - Failure to inform patients by the next visit of new or increased risks
  - New policy is to provide a consent addendum to facilitate the process of informing patients
- **Patient Case Review: Eligibility**
  - Failure to meet Inc/Exc Criteria
- **Patient Case Review: TRIAD**
  - Delay in submission of scans
- **Patient Case Review: Adverse Events**
  - Failure to report lab values that are considered not clinically significant
  - Failure to report all grade 1 – 5 adverse events

Data Entry Guidelines

- The **S1400** Data Entry Guidelines are now live on the ORP Manual under Chapter 16e: General Forms and Guidelines-S1400 & Sub-Studies.

https://crawb.crab.org/txwb/CRA_MANUAL/Vol1/chapter%2016e_Data_Entry_Guidelines_S1400_1.30.17.pdf

Site Coordinators Committee (SCC)

LAVINIA DOBREA RN, MS, OCN

SITE COORDINATOR COMMITTEE CO-CHAIR

SCC Mission

To represent study site staff at the nursing, CRA, data management, and regulatory levels by providing feedback to and from the study leadership to enhance accrual and improve study management.

SCC Activities:

- **Review & recommend accrual materials and strategies**
- **Review changes to study procedures and updates to data collection forms**
- **Provide content for the Lung-MAP newsletter**
- **Participate in Update meetings**
- **Assist in promoting the study and encouraging accrual**
- **Assist with planning, development, and implementation of staff training tools, such as:**
  - **Patient AE Log**
  - **RECIST Tracker**
  - **CT Reminder**
  - **Progress Notes for Pre-Screening, Screening, Progression, Sub-studies**

NOW available on the **S1400** Abstract Page under **S1400** Resources on the SWOG website (https://swog.org/Visitors/S1400/S1400SampleDocs.asp).

Questions?

- **Have a concern or question?**
- **Do you have an accrual strategy or materials you would like to share?**
- **Do you have tracking forms or procedures to help you manage Lung-MAP at your site?**

Send us the information or materials and include your name, study site, and contact info.

Contact us at LungmapSCC@crab.org

irAE Management

LYUDMILA BAZHENOVA, M.D.

S1400I CO-CHAIR, MEDICAL ONCOLOGY

Unique Toxicities of Immunotherapy

Lyudmila Bazhenova, MD
Clinical Professor of Medicine
Lung Cancer Unit Leader
Associate Director of Hematology Oncology Fellowship
UC San Diego Moores Cancer center

Where discoveries are delivered.℠

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Objectives

- Review the spectrum of immune related toxicities
- Review management of immune related toxicities.

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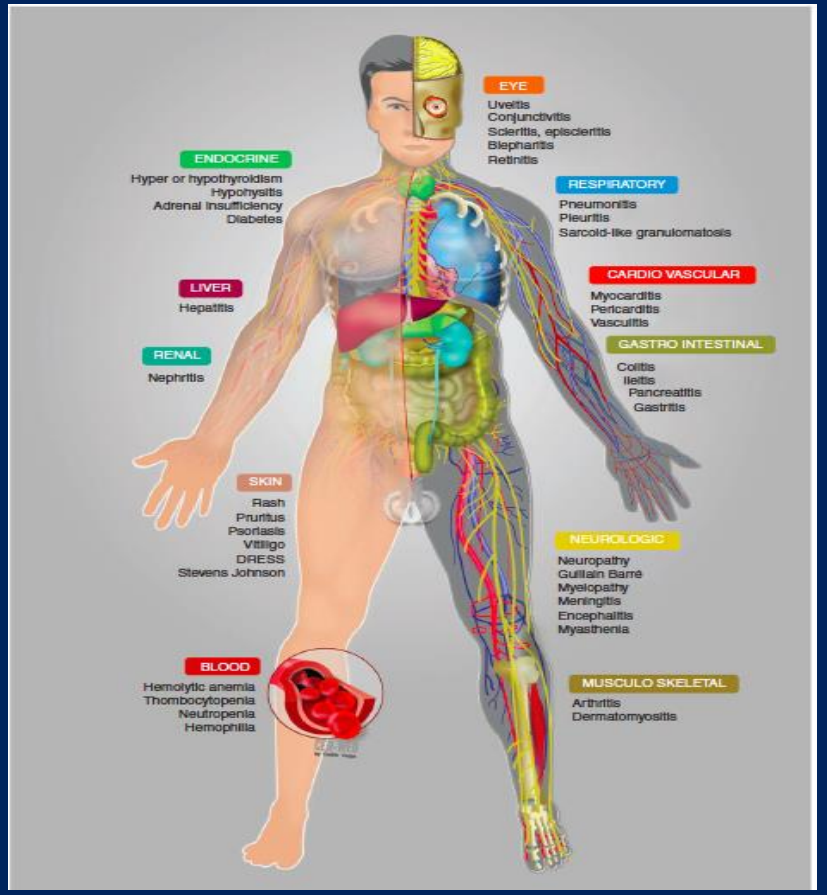
Unique side effect profile consistent with unique mechanism of action

- Checkpoint inhibition results in T cell activation
  - Balance tips towards autoimmunity
  - Immune related adverse events (irAE)

- IrAE have unique characteristics
  - Reversible if treated promptly
  - If left untreated will progress to more severe state
  - If treated early, severity and duration decreases.
  - Any organ can be affected
  - Average 6-12 weeks after initiation of therapy
  - Can occur
    - within days of the first dose
    - after several months of therapy
    - after discontinuation of therapy



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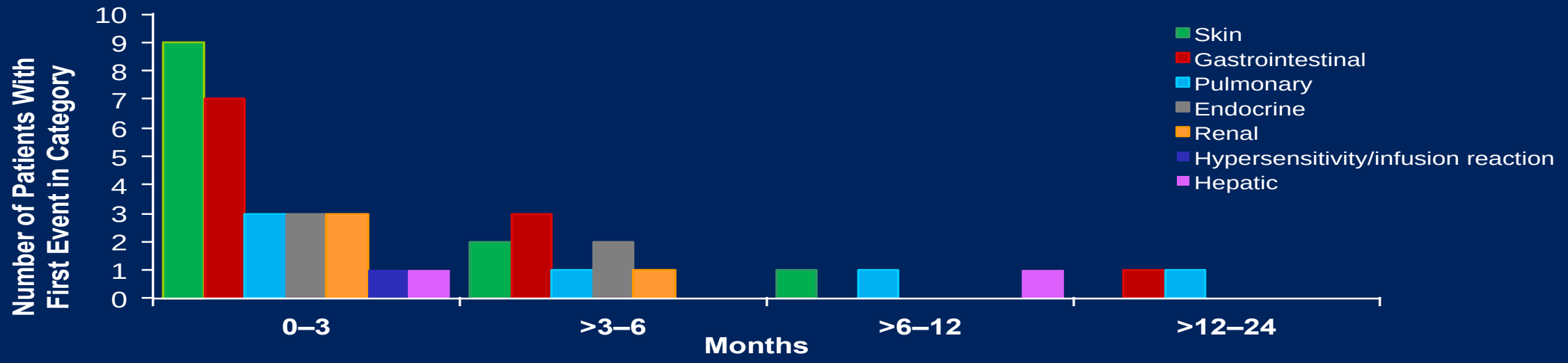
Champiat S, Ann Oncol, April 2016, Weber JS JCO 2012, 2015

Time to Onset of First Treatment-related Select AE With Nivolumab by Category (Any Grade)



Pts still on study, n	131	112	85	52
Pts still on treatment, n	131	73	51	25
Total pts with first event,[a] n	24	6	2	1

- The majority of patients who experienced treatment-related select AEs with nivolumab experienced their first event within the first 3 months of treatment

Select AEs: AEs with potential immunologic etiology that require frequent monitoring/intervention.
Based on December 2014 DBL. Includes events reported between first dose and 30 days after last dose of study therapy.
Within each time interval, patients with ≥1 event were counted only once in each category but could be classified into more than one category

Reckamp K ORAL02.01, Wolrld Lung, 2015

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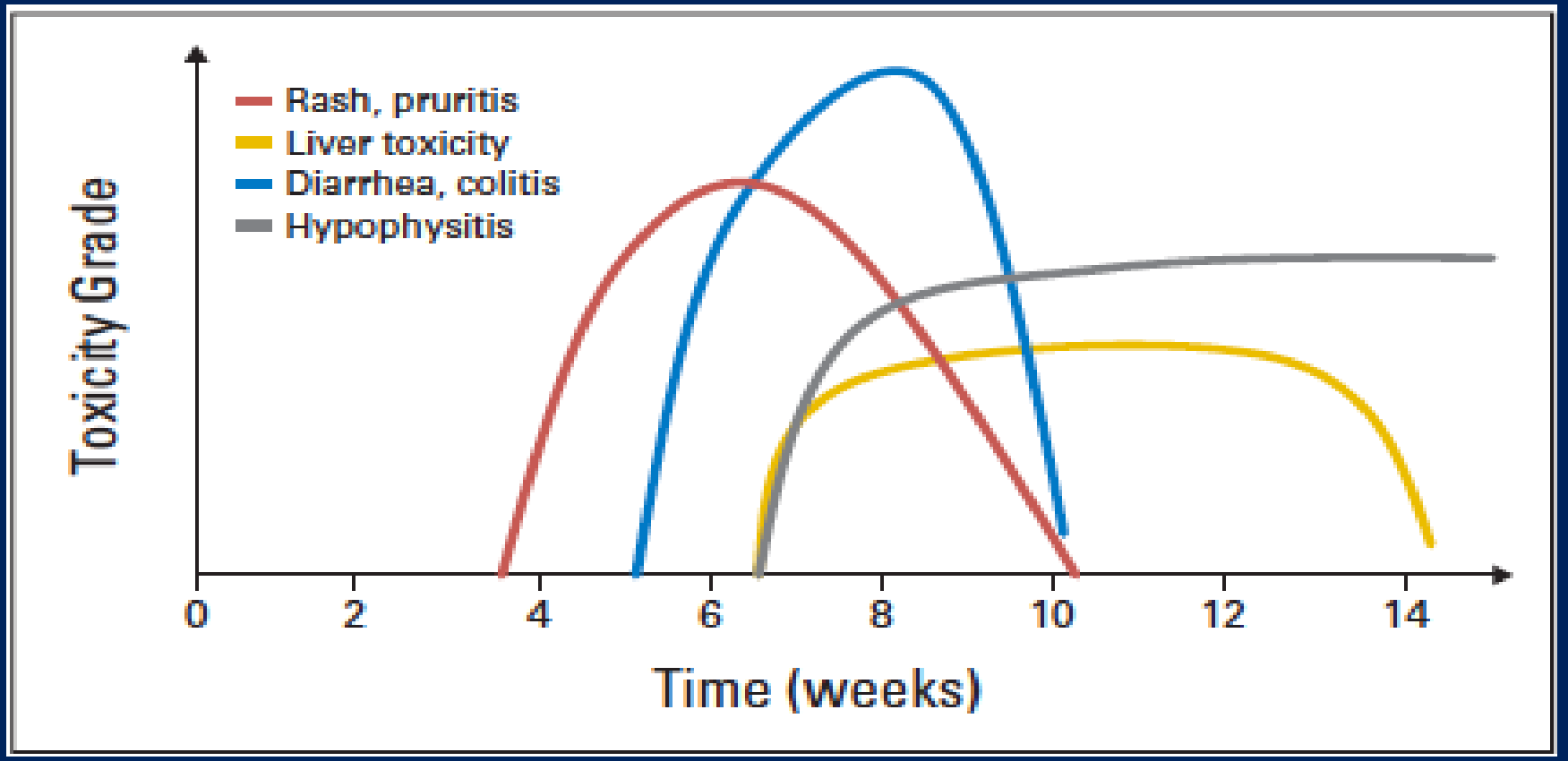
Kinetics of ir AE with CTLA4 Ab



Weber, JCO 2012

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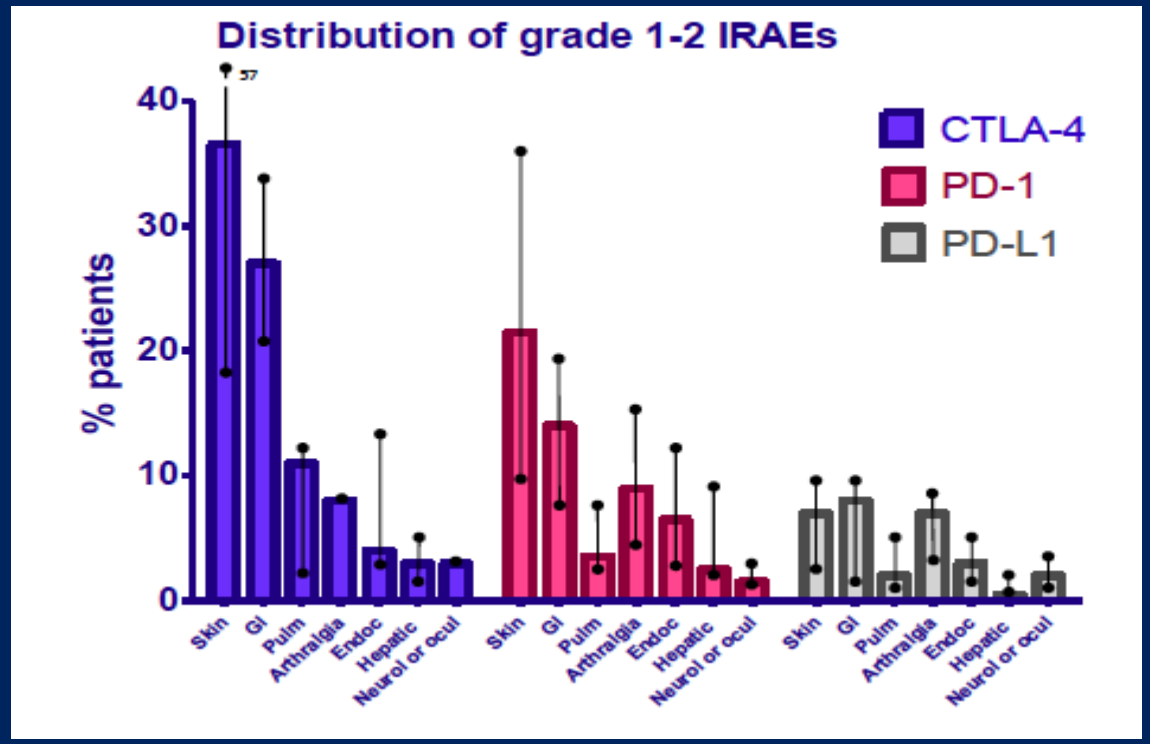
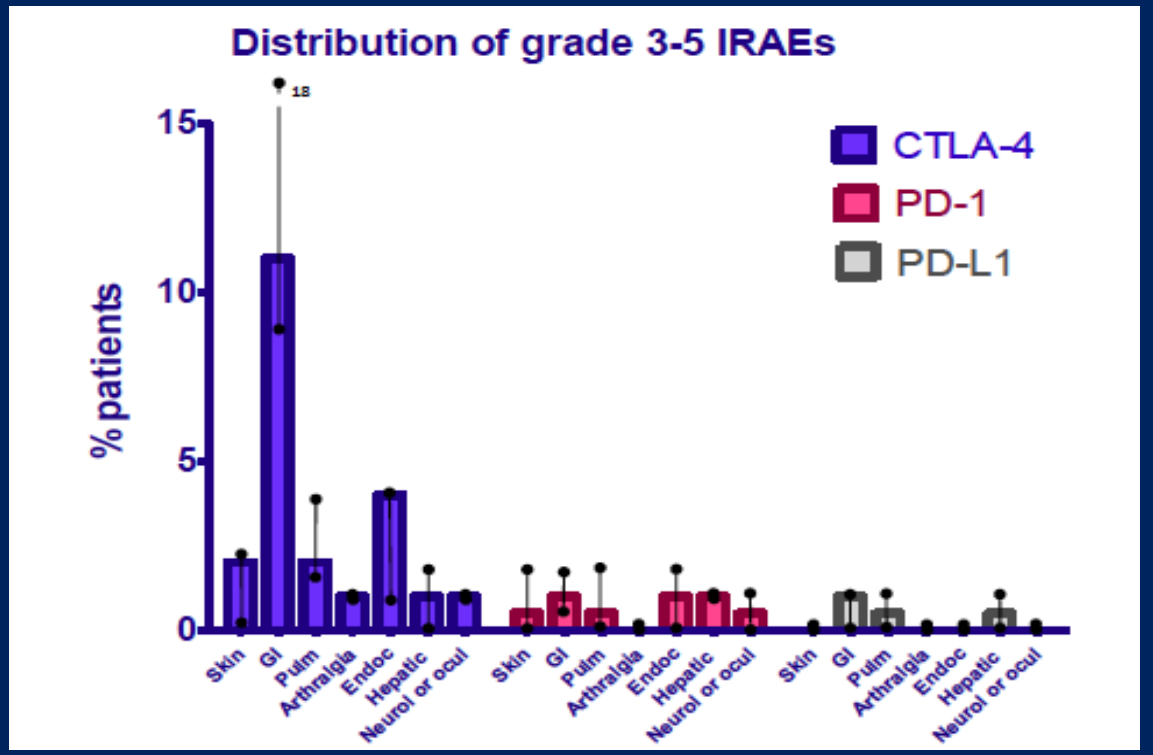
Differences between immunotherapy agents (all cancers)





Michot, European J of Cancer, 2016

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Starting immunotherapy

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Key to safe administration of immunotherapy

- Education
  - Nurses, mid levels providers
  - Emergency room physicians, hospitalists
  - Patients

Understanding the risk or developing immunotoxicity

- Personal and family history of autoimmune diseases
- Remember less common autoimmune conditions.
  - Psoriasis
  - Diabetes
  - Sarcoidosis
  - Idiopathic pancreatitis
  - CHF

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Is it safe to prescribe immunotherapy in patients with autoimmune disorders?

- Retrospective study looking at 119 patients with melanoma treated with PD-1 inhibitors.
- 52 patients with a preexisting autoimmune disorder
  - 20 patients (38%) had a flair of autoimmune disorder requiring immunosuppression
    - 60% chance of flair if clinically active disease at the time of immunotherapy initiation
    - 20% if autoimmune disease was not active
  - 2 patients required discontinuation of PD-1 inhibitor

Menzies, Ann Oncol 2016

Patients must not have an active, known, or suspected autoimmune disease.
Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

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Management of immune related AE

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Management of grade 1 irAE (mild)

- Supportive treatment (antidiarrheal medications, skin creams, hydration, electrolytes)
- Increase monitoring of symptoms
- Exclude infection
- Patient education

Management of grade 2 irAE (moderate)

- As per grade 1 AND
- Hold the drug till symptoms resolve to grade 1
- if symptoms do not improve within 5-7 days initiate corticosteroids.
  - Consider prednisone 0.5 mg/kg/day
- Re challenge allowed if symptoms have resolved.

Management of grade 3 irAE (severe)

- Supportive therapy
- Hold Immunotherapy
- initiate intravenous steroids (methylprednisolone 1-2 mg/kg/day).
- If symptoms do not resolve in 48 -72 h consider adding other immunosuppressants.
  - Infliximab 5 mg/kg (may repeat two weeks later), mycophenolate
  - Wait till symptoms resolved to grade 1, then slowly taper over 3-6 weeks.
    - Watch for rebound of the symptoms.
    - Do not forget about PCP prophylaxis if patient requires a prolonged taper
  - Re challenge is controversial and needs to be decided on the individual basis.
  - NO role for dose reductions

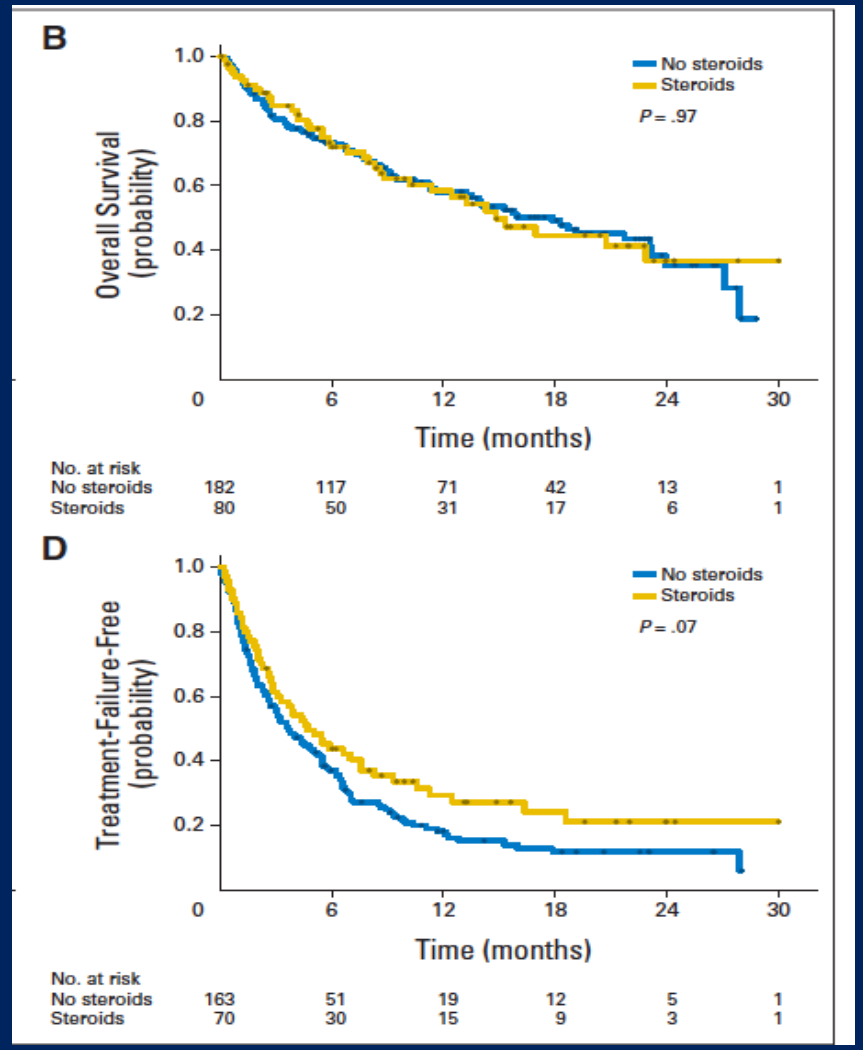
Management of grade 4 irAE

- As in grade 3, but permanently discontinue immunotherapy

Does treatment of irAE impact overall efficacy?

- 294 patient treated with ipilumumab
  - IrAEs were seen in 254 patients (85%)
  - 103 patients (35%) required corticosteroids.
  - Anti TNF therapy was used in 29 cases (10 %)
- There was no outcome differences for patients requiring corticosteroids and those not requiring immunosuppressive therapy.

- 576 patients treated with nivolumab
  - Similar response rates were reported in patients treated with nivolumab +/- Immuno supressive agents



Horvat, JCO 2015, Weber, ASCO 2015 abs 9018

Key toxicity points

Gastrointestinal toxicity key points

- Colitis
  - If patient develops bowel perforation
    - Stop steroids, stop infliximab
    - Manage surgically
- Autoimmune hepatitis
  - Use mycofenolate mofetil (500 mg BID) in addition to steroids if severe hepatic failure
  - Infliximab is relatively contraindicated due to its potential for hepatic toxicity
  - When working up transaminitis on immunotherapy, consider viral reactivation
- Asymptomatic elevations of amylase and lipase.
  - Steroids or drug hold are not indicated

Skin Toxicities

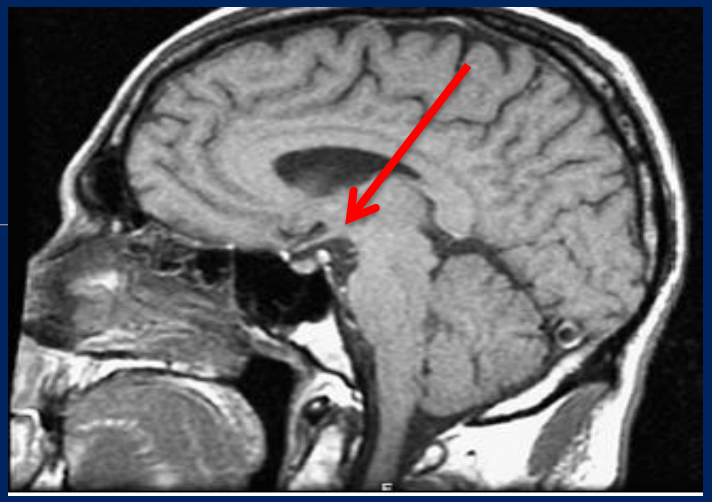
- Rash and pruritis most common
  - grade 3 and 4 are rare
- Exam is important
  - Blistering rash could be a sign of impending TEN or Stevens-Johnson syndrome
  - In case of blistering rash referral to dermatology is warranted.
- Topical steroids and antihistamines for mild rash
- High dose IV steroids for grade 3 and 4 rash

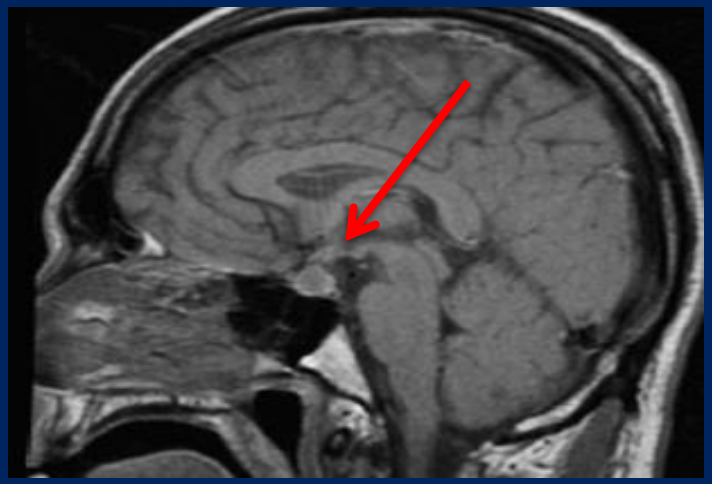
Endocrinopathy

- Hypothyroidism is managed with hormone replacement therapy
- Adrenal insufficiency has been described.

Hypophysitis

- Symptoms include: HA, fatigue, weakness, memory loss, impotence, personality changes and visual field impairment
  - Mechanism is pituitary infiltration by lymphocytes
  - Diagnosis is confirmed by MRI and hormonal profile
    - 25% of patients have normal pituitary MRI
  - Check TSH, T4, LH/FSH, prolactin, ACTH, and cortisol levels in patients presenting with profound fatigue
- Physiologic steroid replacement may be sufficient
- Most likely will require endocrinology input in managing hormone replacement
- Usually irreversible requiring long term hormone therapy





Blansfield, J Immunother, 2005

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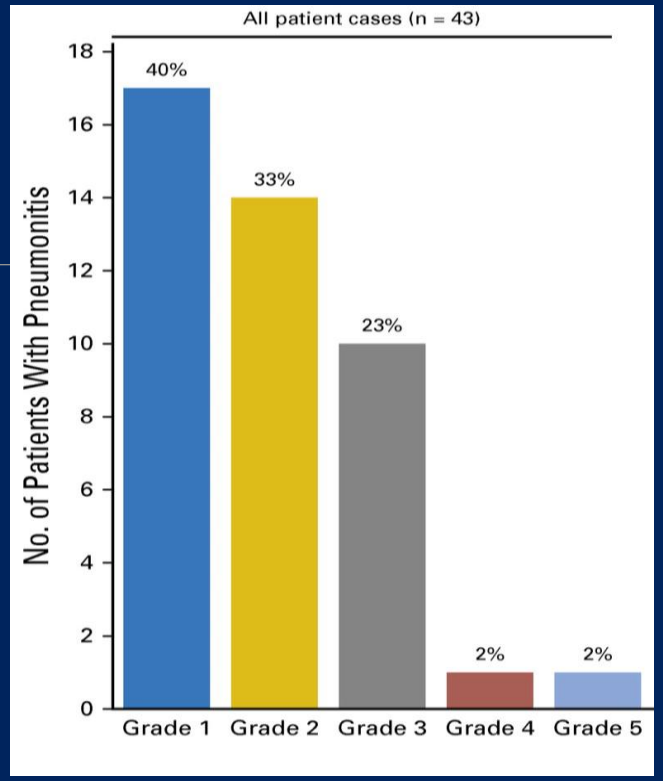
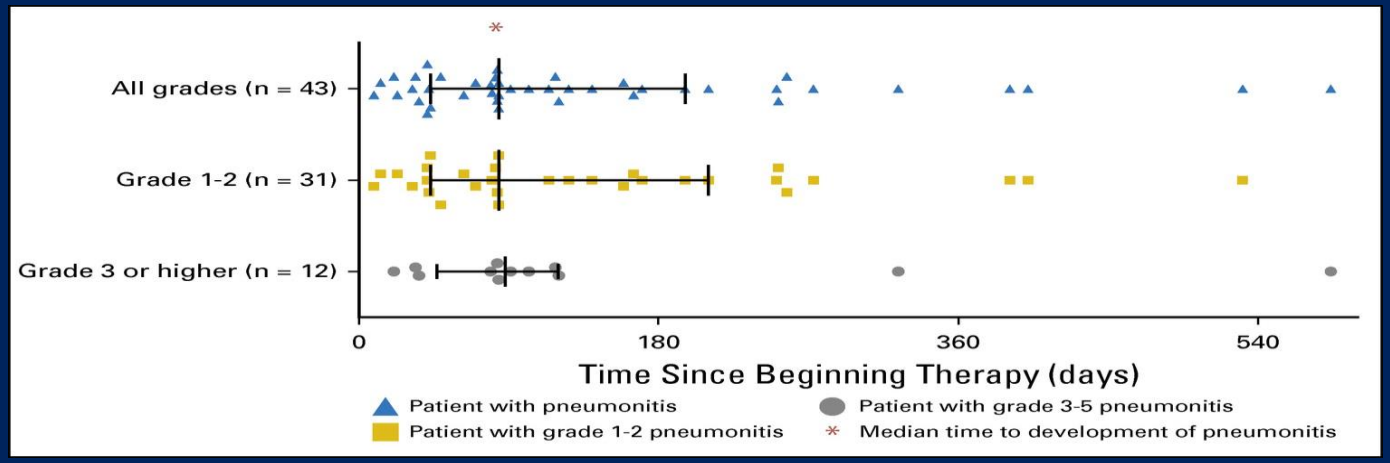
Pneumonitis

- Incidence is 5% with PD-1/PD-L1 monotherapy
  - 10% with combination therapy
- Median time of onset 2.8 months (9 days to 19.2 months)
- 88% of cases resolved
  - Death could be caused by pneumonitis or infections associated with immunosuppression
  - 0.5% death rate
- Patients can be re challenged but with expected recurrence rate of 17%





Naidoo, JCO epub September 30 2016

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Neurologic toxicities

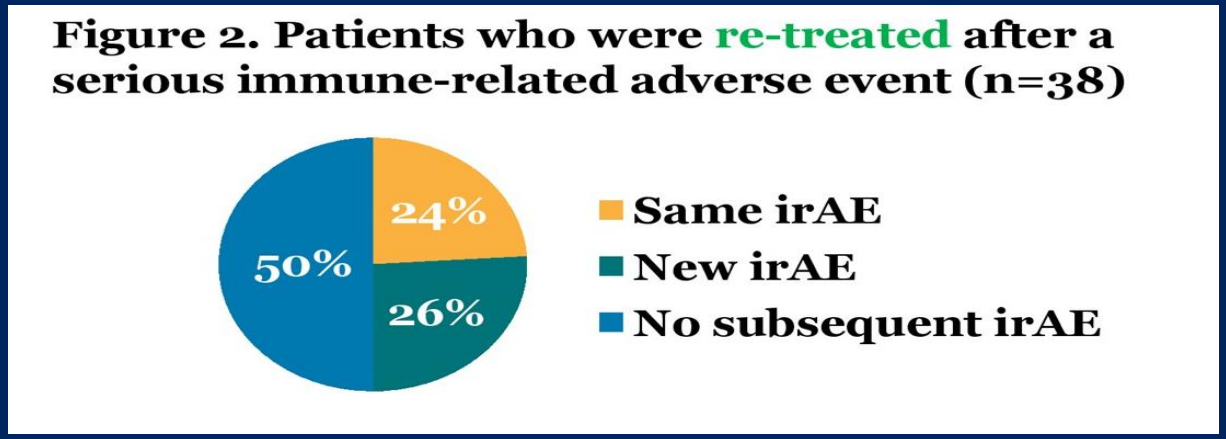
- Transient peripheral neuropathies, both sensory and motor, have been reported in less than 1% of patients.
  - In mild cases they can resolve spontaneously
  - Severe neuropathy can be treated with steroid taper.
- Cases of Guillain-Barre´–type syndrome has been described
- Several cases of a myasthenia gravis–type syndrome have been observed

Less common irAE

- Hematologic (hemolytic anemia, thrombocytopenia, acquired hemophilia A)
- Cardiovascular (myocarditis, pericarditis, vasculitis)
- Ocular (blepharitis, conjunctivitis, iritic, scleritis, uveitis)
- Renal (nephritis)

How safe is rechallenge

- 484 patients single institution study, 38 restarted immonotherapy after hold for irAE.
  - If recurrent irAE developed - 84% resolved and improved.
  - two treatment related death
- Two factors are associated with recurrence of the irAE
  - hospitalizations for irAE management
  - irAE within 3month of initiation of immunotherapy.



Santini, ASO 2017, abs 9012

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Summary

- Immunotherapy compounds have unique toxicity profile
- Providers need to be proactive in anticipation of the irAE
  - Education is key for patients, nurses, mid level providers
- Resources are available

Grade 1	Grade 2	Grade 3	Grade 4
Supportive care Continue therapy	Supportive care Hold therapy If not better after a week of holding, start steroids	Supportive care Hold therapy Start steroids immediately If not better in 3 days consider infliximab	Same as grade 3, and permanently discontinue immunotherapy

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Immune-Related AE (irAE) Forms

KRYSTLE PAGARIGAN

CLINICAL RESEARCH DATA COORDINATOR

Additional Collection of irAE Data

- For sub-studies that utilize immunotherapy treatment:
  - Modified existing Adverse Event forms (MEDI4736 arm of S1400A, S1400I)
  - Developed new immune-related AE-specific forms (S1400I only)
- Forms will not be released until Revision #9, but will ask for retrospective data entry on any irAE's that occurred on S1400I and the MEDI4736 arm of S1400A.

Retrospective Data Entry for AE's

- S1400I Adverse Event form modified to ask for all grades of an AE seen during a cycle to be reported as separate events.
- Can also report CTEP-AERS report ticket number.
- Retrospective entry will only need to be done for S1400I.

Early Release of Draft AE and irAE Forms

- Will be releasing draft paper versions of the modified AE forms and the new irAE form *prior* to Rave version roll-out on Revision #9 release.
  - Can use these draft forms as worksheets to preemptively gather data prior to the Rave release.
- Draft forms will be on CTSU and SWOG websites; a protocol memo will be released to sites when those are available.

Additional Resources

- The Lung-MAP Data Entry Guidelines will be updated to reflect irAE and AE changes.
- If you have any questions about the forms, please email S1400Question@crab.org or call 206-652-2267.
- Site Coordinators Committee is also a great resource, and can be reached at LungMapSCC@crab.org.

Questions?

Thank you for your time.

The slides are available on the SWOG website→ S1400 Protocol Abstract page→ Other Study Materials→ **S1400** Group Meeting Materials link