Fall 2020 SWOG GASTROINTESTINAL COMMITTEE Meeting – Virtual

SUMMARY

Date: Thursday, September 24, 2020
Time: 1:30 – 4:00 pm CT

Agenda:

I. Introduction: Philip A. Philip, MD & Cathy Eng, MD

II. SWOG Clinical Trials Management Initiative: Cathy Eng, MD

III. Patient Advocate Update: Carole Seigel, MBA & Florence Kurttila, MS

IV. Updates from the Subcommittees:

- a. Gastroesophageal: Syma Iqbal, MD & Zev A. Wainberg, MD
- b. Hepatobiliary
- c. Pancreatic
- d. Colon
- e. Anorectal
- f. Neuroendocrine

V. Concluding remarks/Adjourn

Introduction

0:00:00

Chair Philip Philip opened the meeting.

0:00:18

Philip welcomed group to open GI meeting.

- Hoped that next year's meetings would be face-to-face again

0:01:04

Philip introduced committee leadership.

- Dr. Mary Kay Washington was recently added to committee to help with pathology
- Dr. Daniel Catenacci also recently joined
- Philip also introduced Jane Rogers, Heinz-Josef Lenz, Christopher Lieu, Lisa Kachnic, Anthony Shields, and Syed Ahmad

0:01:40
Philip acknowledged those who over the past year have served as liaisons and provided advice.

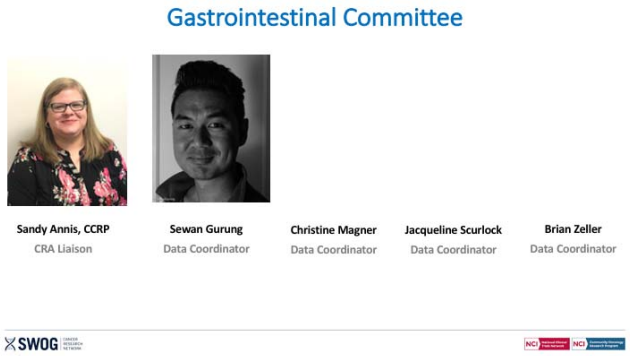
- Jason Zell, Afsaneh Barzi, Gary Buchschacher, Mohamed Salem, Heloisa Soares, Flavio Rocha, and Jeremiah Lee Deneve

0:02:14
Philip recognized the committee's staff.

- Katherine Guthrie, Mai Duong, and Danae Campos

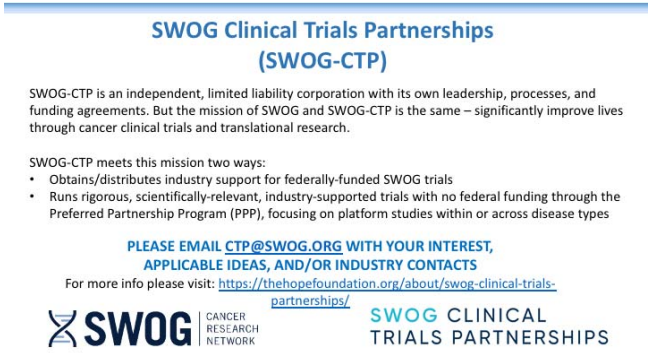
0:02:47
Philip acknowledged data coordination and management staff.

- Sandy Annis, Sewan Gurung, Christine Magner, Jacqueline Scurlock, and Brian Zeller



0:03:09
Philip presented briefly on SWOG initiative to partner with other entities on trials.

- Noted the emphasis was on pharma
- Wanted committee to know this is ongoing opportunity for establishing contacts with industry for trials
- Especially for companies to provide a pipeline that can be a collaboration with SWOG



SWOG Clinical Trials Management Initiative

0:03:59
Philip introduced Cathy Eng to present on SWOG-CTI.

- Said she had been instrumental in an initiative that started in the early days of COVID
- Pressure of COVID triggered a project to do trials in better ways
- Goal is to combine efficiency and simplicity but to ensure SWOG is doing the right thing

Eng thanked group for chance to present.

0:04:53
Eng opened with the rationale for SWOG's post-COVID Clinical Trials Management Initiative.

- Trials in the US have been hampered by
  - Financial constraints
  - Longer activation times
  - Reduced patient enrollment
  - Limited access for general patient population
- Goal is to take pandemic lessons learned to innovate all trials to
  - Improve accessibility for patients

- Increase patient enrollment
- Revise the method of oversight
- Reduce costs
- Improve outreach

- Keep SWOG trials competitive vs. pharma trials
- Keep US competitive for pharma trials vs. Europe and Asia

0:05:54

Eng said a working group was created. Listed examples of ideas suggested.

- First is telehealth, already in use
  - Question was how can SWOG make this standard practice
    - Not only in academic centers
    - Also how to reach out to community physicians and collaborate
- Include smart phone app for SAEs and PROs
- Standardization of treatment orders
  - Started piloting this in SWOG
  - Eng noted Jane Rogers, committee's PharmD, has been instrumental in this
- Remote procedures such as SIVs and audits
- Eng said many of these ideas can reduce trial costs

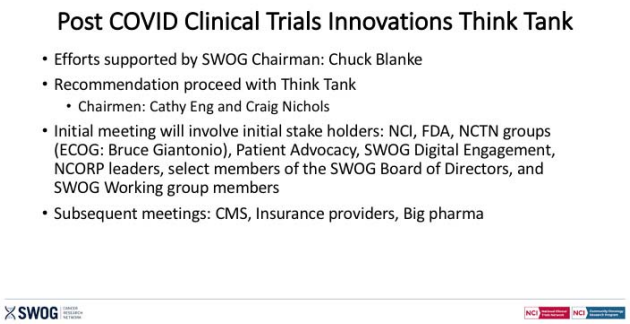
0:06:54

Eng displayed list of working group members.

- Created a white paper
  - Slide lists coauthors
  - Paper under review
  - Provides more information on topics just discussed

0:07:16

- Eng noted SWOG group chair Chuck Blanke has been extremely supportive of effort
- Originally thought of conducting this as pilot through GI group
- Been supported in including initiative across all of SWOG and including other members
- Will conduct a think tank
    - Chaired by Eng and Craig Nichols
    - Initial meeting will involve set of stakeholders
        - Working group members
        - NCI
        - FDA
        - NCTN
        - Digital Engagement Committee
        - NCORP
        - SWOG BoG
    - Eventually will incorporate other stakeholders such as CMS, insurance providers, and pharma
        - Eng noted she had started conversations with some companies
        - Definitely interested



Philip said this was an important initiative and hoped it would change way things are done.

- Be more cost effective without losing good practices of clinical research

Philip reminded group they could submit questions via Chat box.

- Invited constructive comments for the initiative

Philip introduced committee's patient advocates.

- Said Carole Seigel was present, but Florence Kurttila was away today

Patient Advocate Update

0:09:24

Seigel reported on some advocacy work she has been involved with through ASCO Advocacy Summit.

- Dovetails into Clinical Trials Management Initiative
- Seigel reminded group that Medicaid patients do not have standard of care covered if they take part in a trial
- 15 states have mandated Medicaid coverage to those on clinical trials
- Seigel said their initiative is to have this federally mandated
- Huge barrier for those on Medicaid to lack coverage
    - Includes supportive coverage
- Said initiative is now in the House but needs to go to the Senate
- Hoped it would pass

Seigel spoke of another initiative asking for continued reimbursement for telehealth.

- Said this would have positive effect on trials

Seigel said these two efforts should increase accrual to trials and diversity.

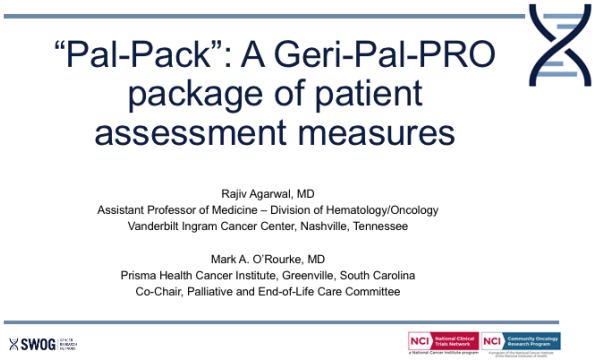
Philip thanked Seigel.

- Noted these were important efforts and asked her to let group know how they could help
- Seigel said all could help by contacting their legislators

0:11:58
Philip introduced Rajiv Agarwal to present on “Pal-Pack”: A Geri-Pal-PRO package of patient assessment measures.

Agarwal introduced himself as a medical oncologist and palliative care physician at Vanderbilt.

- Said he’s been working with Mark O’Rourke, cochair of SWOG’s Palliative and End of Life Care (PELC) Committee, developing this concept
- Concept is package of geriatric palliative care measures and PRO measures to be incorporated into clinical trials



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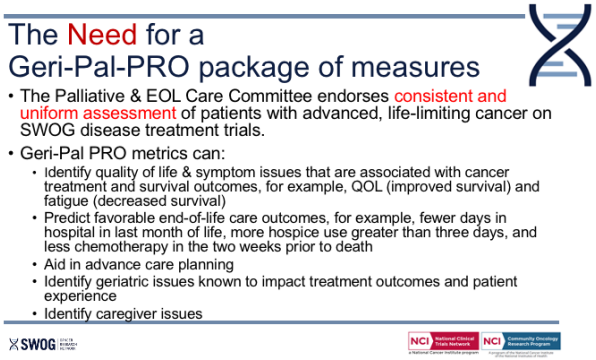
Why is such a package needed?

- Agarwal said that in large trials we want combinations of drugs and modalities that improve not only survival but also QoL and PROs
- Know from meta-analyses of trials, that baseline QoL is prognostic for survival in cancer patients
    - Can be independent predictor of OS and treatment response
- So PELC committee wants to endorse a consistent, uniform assessment for SWOG disease treatment trials
- Idea is to predict outcomes that could be favorable at end of life, if needed
    - E.g., fewer days in hospital
    - More hospice days
    - Less chemo
- … within 2 weeks before death
- Want to aid advanced care planning and identify patients who would benefit from it
- Also identify geriatric and caregiver issues alongside cancer-directed investigational treatment



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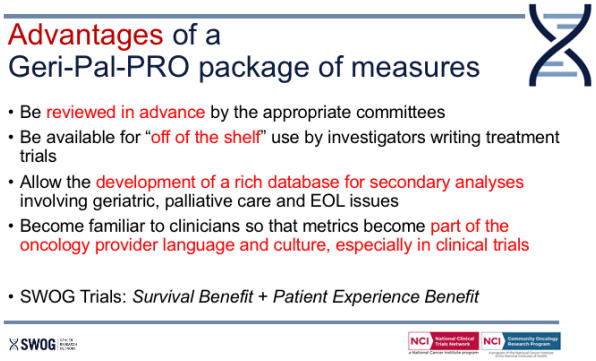
Advantages

- Agarwal identified advantages of such a package:
  - Can be reviewed in advance
  - A menu off the shelf
- PELC committee will develop list of metrics that GI committee investigators can pull from menu and incorporate in treatment trials
- Allows development of rich database of secondary analyses
- Agarwal suggested it would shift the culture such that SWOG can be leader in developing trials for both
  - Survival benefit
  - Patient experience benefit



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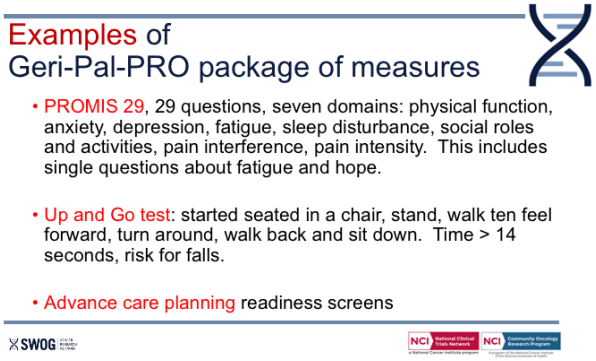
Key features

- Completely voluntary
- Reduces workload for investigators developing treatment trials
- Little or no cost for individual trials for most measures
  - Most survey-based
- With time and experience as they pilot this, they hope to be able to inform disease-specific treatment trials
  - E.g., for borderline performance status patients
  - Or patients receiving 2nd or 3rd line systemic therapy for metastatic disease

0:15:01

Examples of measures

- PROMIS 29
  - List of 29 questions on key care domains
  - Also measures fatigue and hope
  - Well-validated metric
- Up and go test
  - Quick test in geriatric studies
  - Assesses functionality
- Advance care planning readiness screens
  - As patients enroll on trials
    - Meet criteria for 2nd or 3rd lines
    - Or borderline performance status
  - Important to also make sure patients are prepared for their future



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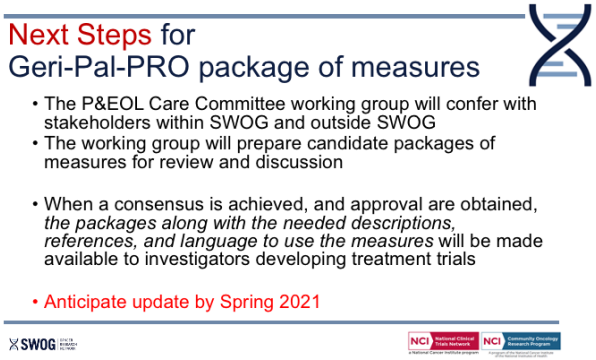
Next steps

- PELC committee working with key stakeholders outside SWOG to develop list of key packages
- Will then prepare these packages for review and discussion
- These packages will include
  - Language to be used in treatment trials
  - Also references and descriptions
- Make it easy to pull off menu and Pal-Pack and include in a trial
- Agarwal said they anticipate an update to this by spring 2021
- Presenting to this committee first
  - Most patients have significant palliative care needs
  - Prime disease group for testing incorporating such a Pal-Pack

Philip said this would be very important for GI.

- Would Agarwal come back at spring meeting with more information?
- Agarwal said yes



- Because he works on both PELC and GI committees, goal is to develop pilot package by spring and present it then

Eng applauded the work and said she would like to see this incorporated into all GI trials

- Know their cancers are challenging, especially in advanced setting
- Philip said he saw lots of opportunities for using this
- Eng referred to treatment algorithm uniformity group is moving forward with
    - Said there was a need to do the same with this

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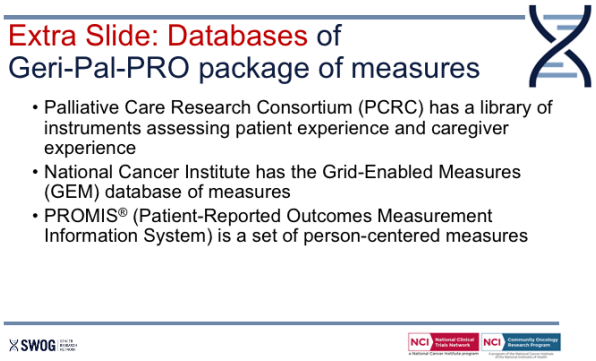

Updates from the Subcommittees

Gastroesophageal

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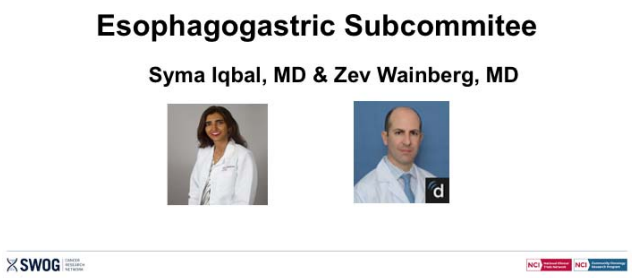
Philip introduced Syma Iqbal and Zev Wainberg.

Wainberg presented.

- Said he and Iqbal would present plan for esophagogastric subcommittee, including some recent data that changes things considerably



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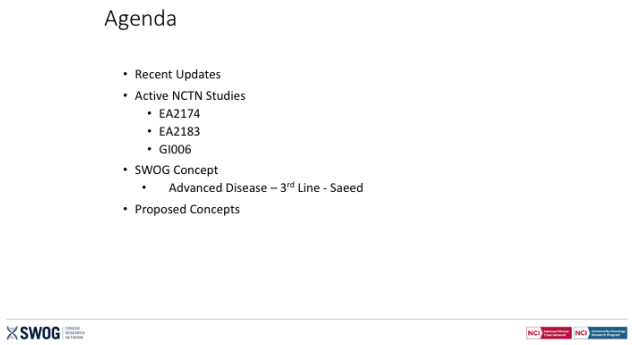
Agenda

- Recent updates in field
- Active studies
- Ongoing concepts that have been approved
- New concepts proposed



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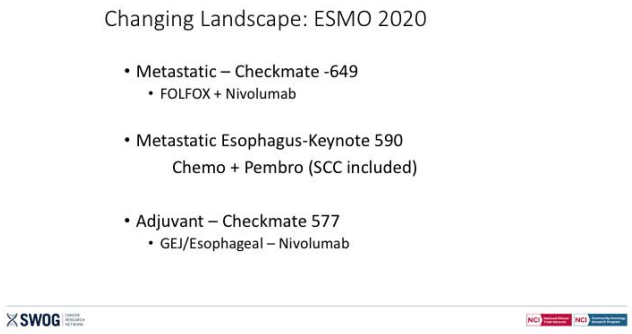
ESMO 2020

- Wainberg said this work was just released in last week at ESMO
- 3 positive studies (said there are more) in esophagogastric cancer that have begun to change the landscape
- Will have important implications for designing new studies and modifying existing studies
- Said he would review 3 of the big findings



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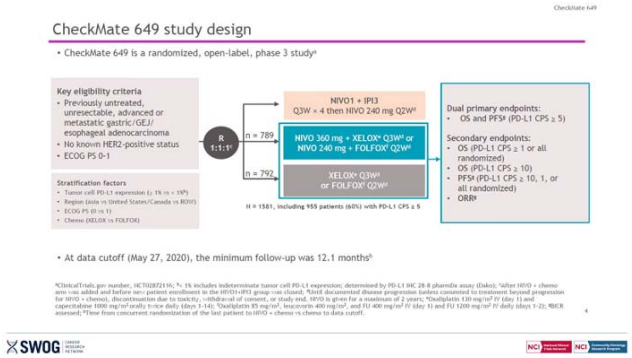
CheckMate 649

- Long-awaited findings
- Largest study to date on metastatic gastric cancer
    - Included GE junction adenocarcinoma
- Randomized patients to
    - Chemo alone: CAPOX or FOLFOX
    - CAPOX or FOLFOX plus nivolumab
    - Third nivo/ipi arm (not presented)
        - Dropped, primarily for toxicities
- Primary endpoint analysis of over 800 patients in each arm was dual OS and PFS



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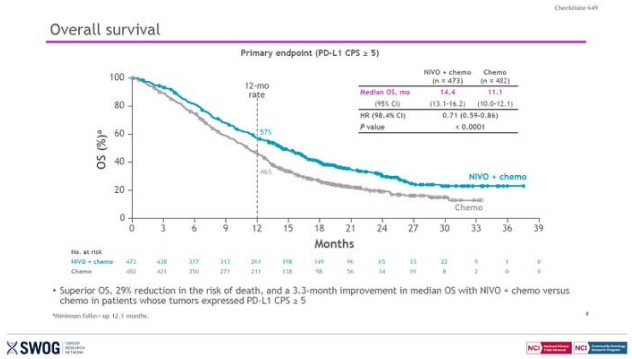
Take home points:

- Most emphasis was on PD-L1 CPS $\geq$ 5
    - Could have separate discussion about this
- Kaplan-Meier curves significant
    - Spread apart early and stay consistently spread
- Survival improvement of >3 months
    - Impressive hazard ratio of 0.71
- In CPS $\geq$5 group, thought this would become new standard of care for patients with metastatic gastric and GE junction adenocarcinoma



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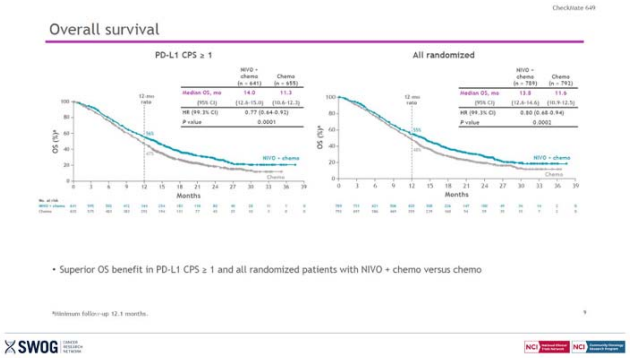
- Wainberg said it was less clear what happened with other patients
- In CPS1, which included CPS5, curves not quite as good
- In group of all randomized patients at far right
    - Included CPS-low patients, here about 20% of population
- Median OS also not as good
    - Although still met some statistical endpoints
- Open debate begins as to who are optimal patients for front-line CAPOX/nivo or FOLFOX/nivo
- But based on data and FDA label, expectation is it will be standard of care for virtually all patients with adenocarcinoma of stomach and GE junction



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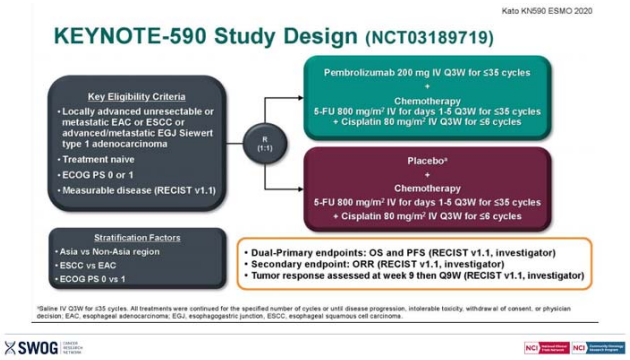
Wainberg said ESMO also included esophageal cancer trial results.

- A pembro plus chemo study
- Chemo was 5-FU/cis
    - Because a heavily Asian study
- Randomized to 5-FU/cis alone or with pembro
- 75% of patients had squamous cell



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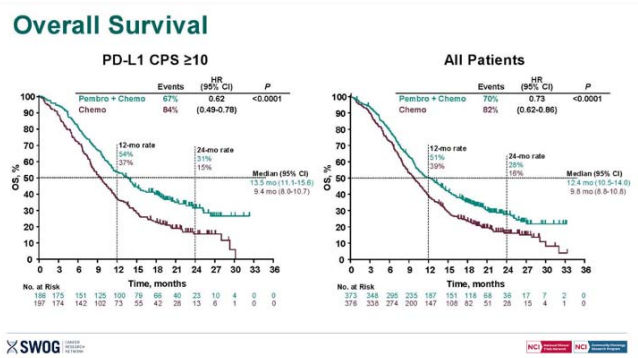
- Results in slide, with all patients on the right
- And in CPS10
- Met primary endpoints in both regards
- Nice HRs, particularly in CPS10 patients
- Met endpoints in both adeno and squamous
    - But most benefit was in squamous
    - Was still benefit in adeno
- May also change our expectation, as label may include both squamous and adeno in newly diagnosed patients with esophageal cancer



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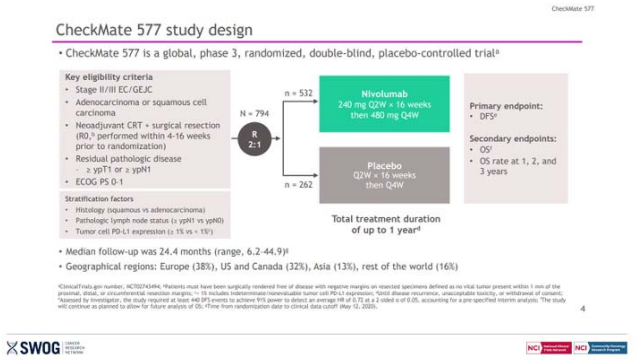
CheckMate 577

- Third big practice-changing trial at ESMO
- Adjuvant study in GE junction adenocarcinoma or squamous after neoadjuvant chemoradiation with cross-regimen
- Patients randomized after surgery to nivo or placebo



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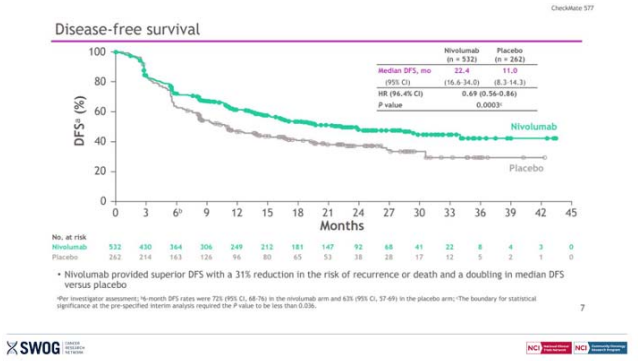
- Slide shows disease free survival was statistically significantly doubled in patients who got nivo over placebo after surgery
- OS won't be out for a while
- Clearly an impressive result
- HR of 0.69
- Expectation is this may also change practice



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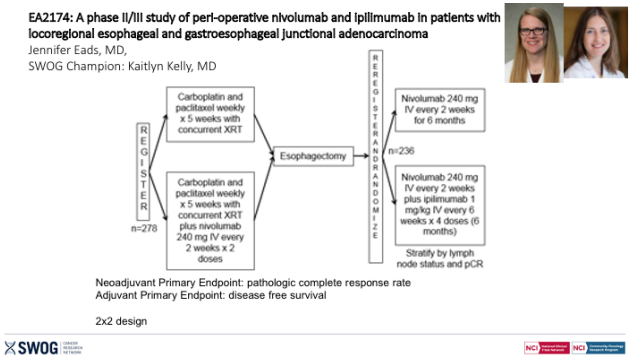
Wainberg summarized:

- Haven't seen session like last week's ESMO in many years
- Lots or positive practice-changing data
- Great thing overall
- But presents challenges in how to design clever and practice-changing studies for SWOG
- Obviously disrupts many ongoing studies in the field, including some of SWOG's

Iqbal presented on ongoing studies.

- Iqbal started with EA2174.
- Phase 2 study of perioperative nivolumab and ipilimumab in patients with locoregional esophageal and GE junction adenocarcinoma
- Kaitlyn Kelly SWOG champion
- Iqbal said given CheckMate 577 results just presented, this study is even more important, as now have data adjuvant nivolumab benefits these patients
- Randomization between carbo taxol radiation vs carbo taxol radiation plus nivolumab
- Then esophagectomy
- Then second randomization to nivolumab with/without ipilimumab
- Safety run-in for study has been completed
- Study will not open broadly
- Is now even more important to accrue to this, given CheckMate 577



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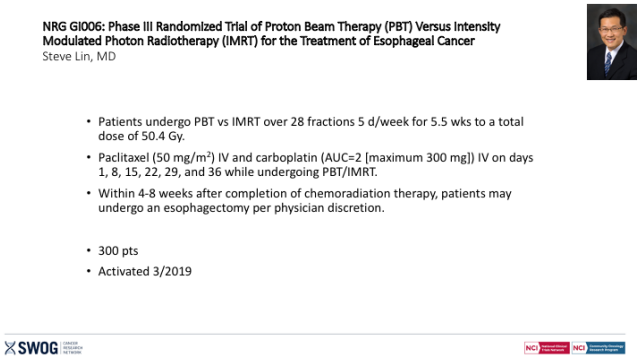
NRG GI006

- Ongoing study evaluating proton beam vs photon radiotherapy in patients with esophageal cancer
- Uses cross regimen and randomizes patients to radiation modality



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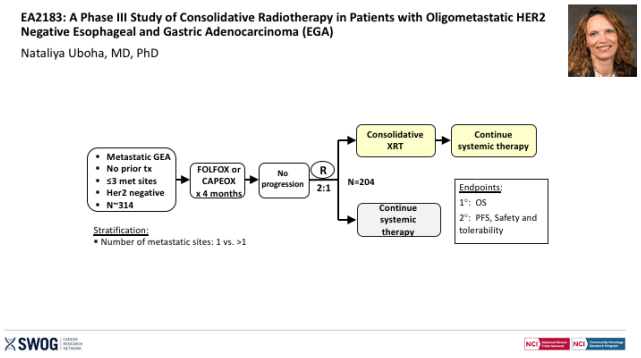
EA2183

- Phase 3 study of consolidated radiotherapy in patients with oligometastatic HER2- esophageal and gastric adenocarcinoma
- Probably will need to be revisited given front-line data from CheckMate 649
- For patients who have <=3 metastatic sites
- Induction chemo with CAPOX or FOLFOX for 4 months
- If remain stable disease or response, randomized 2:1
    - Consolidated radiation follow-up of residual site and continued systemic therapy
    - Continuation of systemic therapy alone
- Iqbal noted when study was first designed, IO therapy was part of induction
    - Negative KEYNOTE data resulted in removal of that
- Might be coming full circle
- New data will affect many ongoing trials and concepts



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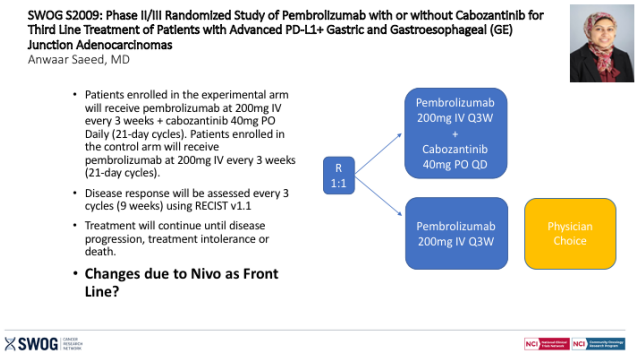
SWOG S2009

- Iqbal said Anwaar Saeed had concept to present

Saeed presented on S2009.

- Phase 2/3 randomized trial of pembro with/without cabozantinib for 3rd-line treatment of patients with PD-L1 positive gastric or gastroesophageal junction adenocarcinoma
- Proposed this concept long ago, before ESMO data, based on pembro monotherapy approval in 3rd-line setting
- Idea is to combine PD-1 inhibitor with VEGF kinase inhibitor will lead to synergy and improved efficacy versus pembro alone
- Based on ESMO data trying to amend the trial
  - Amend control arm to investigator or physician choice chemo
  - Open to everyone regardless of PD-L1
- Primary endpoint of PFS, mainly for phase 2
- If PFS endpoint is met, will open as phase 3 with OS as primary endpoint



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Iqbal presented on future concepts

- Perioperative concept they're revising
  - Looking at either total neoadjuvant therapy with ctDNA
  - Still being discussed
- Maintenance therapy concept
  - More to come

Philip asked presenters for thoughts on changing standard of care.

- Wainberg said he thought standard of care would change
- Would have to wait to see changes to label
- Will change for many patients for upfront therapy
- Noted that as committee designs concepts it will have to be more nimble
- Many other studies ongoing, industry-sponsored

- Becoming harder
- Many unknown questions about CPS and biomarkers

Philip asked about a European trial of cross vs. FLOT

- Wainberg said there is a big trial ongoing for GE junction adenocarcinoma looking at that question
- Philip asked if it had completed
- Iqbal and Wainberg thought it was still ongoing

Wainberg noted several immunotherapy trials ongoing in neoadjuvant space with FLOT.

Iqbal said there were several perioperative trials ongoing in Europe

  - Ramucirumab
  - IO
  - FLOT vs cross
- Thought bulk of perioperative trials were European

Wainberg noted they had not touched on HER2.

- HER2 also undergoing changes
- HER2+ gastric cancer crowded right now
  - Seeing new data on multiple new drugs
  - Probably also change standard of care
- Said he thought group's focus should be on HER- disease and subsets

Danae Campos read out questions from Q&A box:

- Any thoughts on immunotherapy with HER2 disease?
  - Wainberg noted there are industry-sponsored studies looking at PD-1 therapy with HER2 disease
  - Conflicting evidence about HER2 in adjuvant setting
    - Saw this at ASCO with RTOG study
  - Thinks they need to wait a little longer before designing studies of HER2+ disease because landscape is changing quickly

- For EA2174, will there be thoughts about allowing FOLFOX in addition to carboplatin/paclitaxel with radiation in the future?
    - Iqbal said backbone of trial is cross regimen with carbo taxol
    - Will not be with 5-FU

Hepatobiliary

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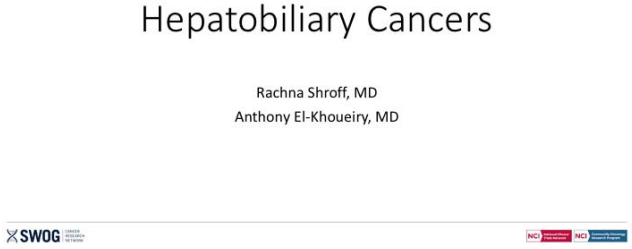
Philip introduce Rachna Shroff and Anthony El-Khoueiry for the Hepatobiliary Subcommittee.

El-Khoueiry noted they would start with biliary, presented by Shroff.



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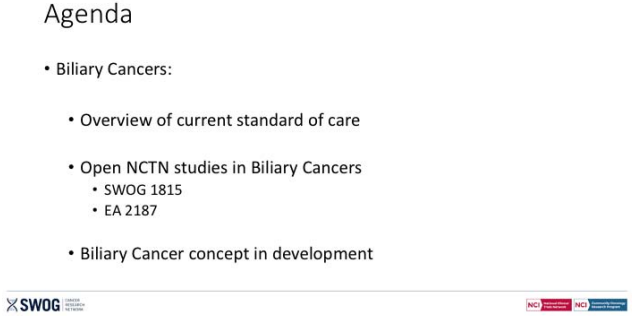
Shroff presented the agenda.



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Shroff said to provide context, she and El-Khoueiry would briefly touch on where they stand with current treatment paradigms, staring with biliary cancers.

- Noted slide said “still” because same couple of slides been showing for years

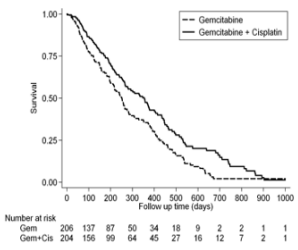
Biliary Cancers

Where we are (still)

0:37:22

- For advanced biliary tract malignancies, including cholangiocarcinoma and gall bladder cancers, since 2010 standard of care in unresectable and metastatic setting has been combo of gemcitabine and cisplatin
    - Based on pivotal ABC-02 study
    - Combo median survival still <1 year
    - Is based on data from 2010

ABC-02: Survival Data (ITT)[1]



	Gem	Gem + Cis
Patients, n	206	204
Deaths, n (%)	141 (68.5)	122 (59.8)
Median survival, mo	8.3	11.7
Log rank *P*	.002	
Hazard ratio (95% CI)	0.70 (0.54, 0.89)	

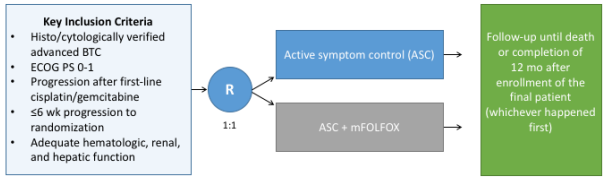
1. Valle J et al. *N Engl J Med*. 2010;362:1273-1281.

0:37:53

For those who progress on combo of gemcitabine and cisplatin:

- ABC-06 looked at second-line therapy in advanced biliary tract malignancies
- Data presented at ASCO in 2019
- Patients had progressed on gem/cis
- Randomized to
    - Active symptom control
    - Active symptom control with modified FOLFOX
- As in ABC-02 study, total of 6 months therapy
- Primary endpoint of OS
- Was a positive study

Phase 3 ABC-06 Trial: mFOLFOX vs Active Symptom Control in Advanced Biliary Cancers[1]



- Stratification: platinum sensitivity, serum albumin, stage
- Primary endpoint: OS

1. Lamarca A et al. *J Clin Oncol*. 2019;37(15 suppl):4003.

- Absolute difference in OS was small, but statistically significant P value
- Technically the standard of care for 2nd line

0:38:48

Shroff displayed set of ongoing studies looking to change 1st and 2nd line settings.

- Hoped that in the next few years might be a shift in approach to these biliary tract malignancies
- First study listed here is SWOG study
- Number of other studies building on gem/cis

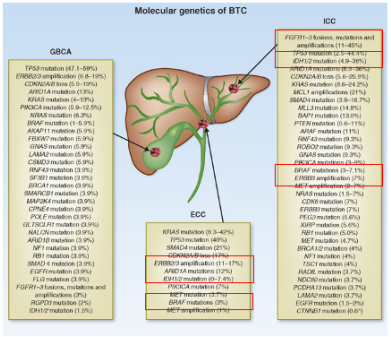
Other Ongoing Trials
With Chemotherapy Platforms[1]

Drug	Phase	Treatment setting	NCT
Gemcitabine/cisplatin + nab-paclitaxel	3	First-line	NCT03768414
NUC-1031 + gemcitabine/cisplatin (NuTide:121)	3	First-line	NCT04163900
Nab-paclitaxel + gemcitabine/cisplatin (AX-CSARC)	2	First-line	NCT02632305
Telotristat ethyl + first-line chemotherapy (TELE-ABC)	2	First-line	NCT03790111
Nan-irinotecan + fluorouracil + leucovorin (NAPOLI-2)	2	Second-line	NCT04005339
Trifluridine/Tipiracil + irinotecan	2	Second-line	NCT04072445

1. clinicaltrials.gov. Accessed January 13, 2020.

0:39:26

- Shroff said world of biliary tract malignancy research has shifted to targeted therapy space
- Based on better understanding of molecular profiles
- Quite distinct between intrahepatic and extrahepatic cholangiocarcinoma
- Also between gall bladder cancers
- Now thinking that instead of lumping, should be splitting
- Should be looking at patients based on their molecular profile
- Many studies in refractory setting looking at this
- SWOG has particular interest in this in perioperative space



Valle, et al, Cancer Discov. 2017

0:40:38

Shroff shifted to active studies.

- S1815
- Randomized phase 3 study comparing gem/cis/nab-paclitaxel vs standard of care gem/cis in newly diagnosed advanced biliary tract cancers
- Open across NCTN

SWOG 1815: : A Phase III Randomized Control Trial of Gemcitabine, Cisplatin, and Nab-Paclitaxel Versus Gemcitabine and Cisplatin in Newly Diagnosed, Advanced Biliary Tract Cancers

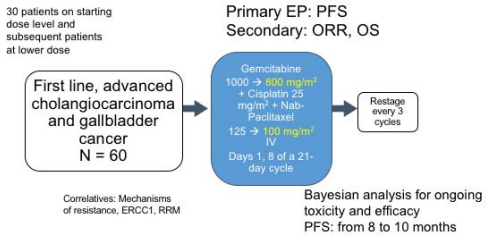
PI: RACHNA T. SHROFF, MD, MS
STUDY CO-CHAIR: AARON J. SCOTT, MD
ALLIANCE CHAMPION: Mitesh Borad, MD
ECOG-ACRIN CHAMPION: Laura Goff, MD
NRG CHAMPION: Khalid Matin, MD

0:41:10

Background

- This was phase 2 study—called regimen GAP—of GAP in 60 patients
- Single arm
- Primary endpoint PFS
- Done at MD Anderson and Mayo Arizona

Background: GAP Study Schema



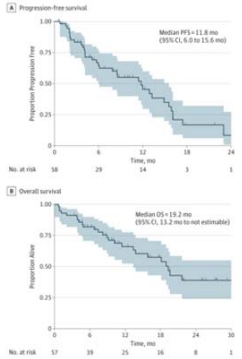
0:41:36

- Shroff said slide showed the data that led them to pursue current phase 3 study
- Primary endpoint median PFS of 11.8 months
- Historical control with gem/cis is 8 months
- Median OS was 19.2 months compared to historical control of 11.7 months
- ORR also more profound than typically seen with gem/cis
- Also interesting signal in patients converted from unresectable to resectable
- 20% of patients were taken for curative resection
- Some pathCRs also seen

GAP PFS and OS: ITT

- mPFS in 58 patients – 11.8 months
- mOS in 57 patients – 19.2 months
- ORR in 50 evaluable patients – 45%
- 12 of 60 (20%) patients converted from unresectable to resectable disease and taken for curative surgery
  - 2 of 12 with pCR

Shroff RT, et al. JAMA Oncol 2019.



- Prompted a multicenter study headed by Flavio Rocha and researcher from ECOG/ACRIN looking at neoadjuvant gap in high-risk cholangiocarcinoma

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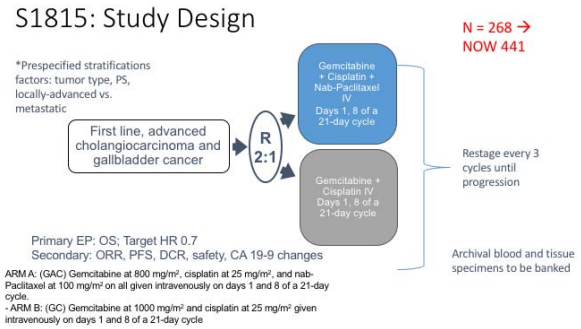
0:42:31
S1815

- Front -line study for all comers, cholangiocarcinoma and gall bladder cancer
- Randomized 2:1 to
  - Triplet arm using doses found well-tolerated in phase 2
  - Gem/cis
- Primary endpoint is OS
- Stratifying for tumor type, PS, and locally advanced vs metastatic
- Collecting and banking archival tissue and blood serially
- Target HR now 0.7 and target N now 441



0:43:25
Criteria

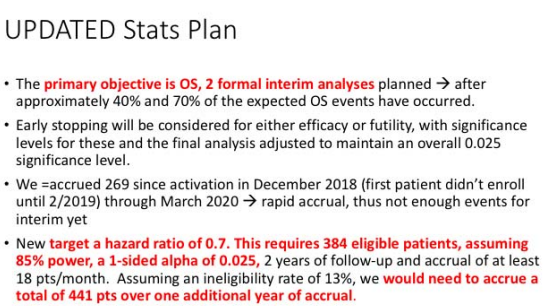
- All intra- and extrahepatic cholangiocarcinoma and gall bladder
- Metastatic or unresectable disease
- Measurable by RECIST
- No prior therapy except prior adjuvant therapy >6 months prior
- Patients with good performance status and adequate organ function

KEY INCLUSION CRITERIA:

- Patient must have histologically or cytologically confirmed intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer. Ampullary excluded.
- Metastatic or unresectable disease documented on diagnostic imaging studies with measurable disease per RECIST version 1.1.
- May not have received prior systemic chemotherapy for advanced biliary cancer. If patient has received prior adjuvant therapy, must be > 6 months from treatment.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1
- Adequate organ function

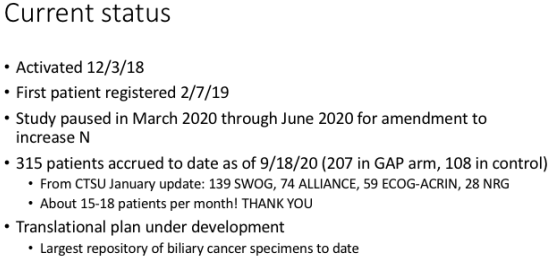
0:43:52
Updated stats

- Primary endpoint always OS
- Always 2 interim analyses planned: 40% and 70% of expected OS events
- Activated December 2018
- First patient Feb 2019
- Within 1 year accrued 269 patients
- Rapid accrual but not enough events for interim analysis
- Went back to NCI
    - Proved it can accrue rapidly
    - Can we adjust for higher N
    - Also more reasonable HR
- Target HR now is 0.7
    - 384 patients, 85% power, 1-sided alpha of 0.025
    - Looking for 441 patients



0:45:00
Current status

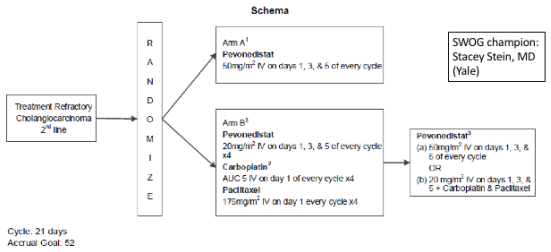
- Paused study March 2020
- Reactivated with amendment and increased N in June 2020
- Now at 321 patients
- 207 in GAP arm, 108 in control arm
- Breakdown by group shown in slide
- 15–18 patients per month
- Now closer to 20–25 patients per month
    - Close to pre-COVID rate
- Thanked attendees
- Proving can get job done in biliary
    - Important message for NCI
- Largest repository of biliary cancer specimens
    - Working on TM plan



0:46:13
EA2187

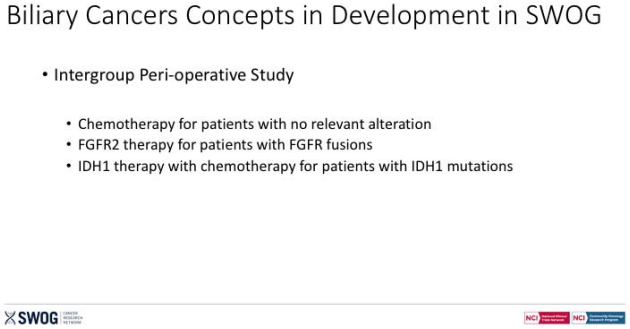
- Only other active study they need to talk about in biliary cancer is EA2187
- Now have SWOG champion, Stacy Stein
- Looking at pevonedistat combined with carboplatin and paclitaxel in advanced intrahepatic cholangiocarcinoma
- Randomized phase 2
- Drug affects neddylation pathway within ubiquitin pathway
- Preclinical data in models of these cancers indicate upregulation of neddylation seems to be prognostic
- Interest in modulating this pathway with this drug
- Works through both NF-kB signaling and autophagy
- Safety data when combined with carboplatin and paclitaxel
- Second-line study
    - Patients must have progressed on gem/cis-based therapy
- Randomized to
    - Carbo/taxol with pevonedistat
    - Drug alone
- In arm B (3-drug), after 4 cycles continue on pevonedistat
- Accrual goal is 52 patients
- Primary endpoint is OS
- Simon 2-stage design
    - Enroll 16 patients on each arm, then pause
    - 2 responses out of 16 to move to next stage
- Goal of 30% ORR to be considered positive

EA2187: A phase 2 study of Pevonedistat in combination with Carboplatin and Paclitaxel in Advanced Intrahepatic Cholangiocarcinoma



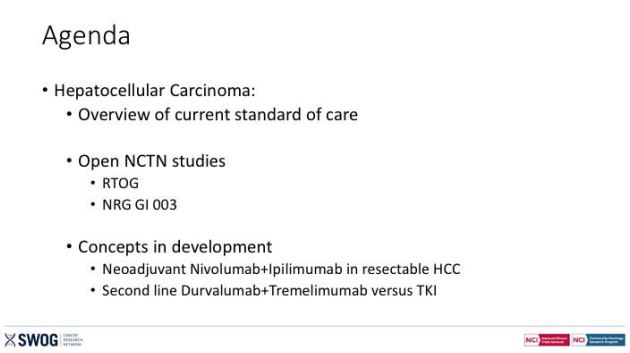
0:48:16
Concepts in development

- Intergroup perioperative study Shroff mentioned earlier
- Lot of interest in this space in refractory biliary cancers
  - FGFR2 fusions
  - IDH-1 mutations
- Interested in looking at targeted approaches perioperatively
  - Neoadjuvant
  - Adjuvant
  - Peri-op
- Ongoing concept in development led by El-Khoueiry
  - Perioperative study with options for FGFR2 therapy for patients with FGFR fusions
  - IDH-1 therapy, possibly with chemo, for patients with IDH1 mutations
  - Chemotherapy option for patients with no relevant alterations
  - Raw concept being worked on
  - Group will hear more about this



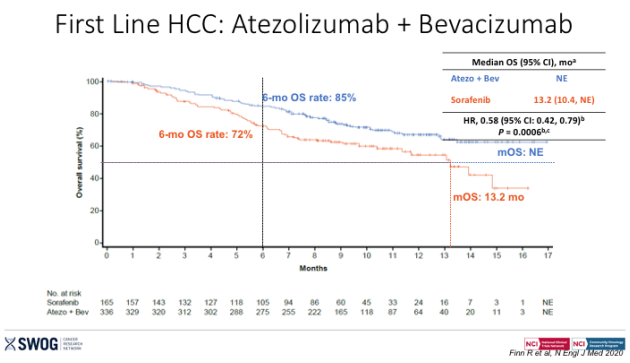
0:49:27
El-Khoueiry reviewed agenda for his presentation on hepatocellular carcinoma

- Current standard of care for HCC
- NCTN studies
- Concepts in development



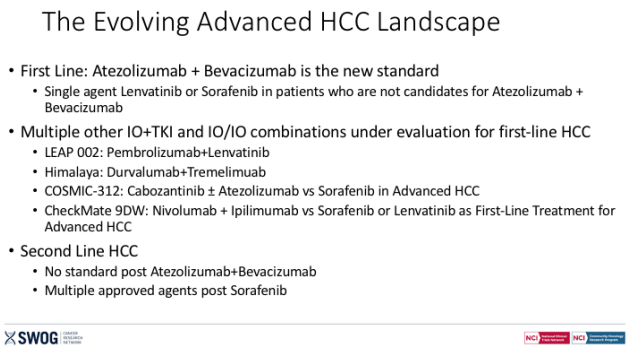
0:49:51
First line HCC

- First line treatment of HCC radically changed by data from IMbrave150 study
- Showed superiority of atezo/bev to sorafenib
- HR of 0.58
- Median OS for atezo/bev not yet reached; 13 months for sorafenib
- Median PFS endpoint also positive
- Study had coprimary endpoints
- Response rate to this combination was 27%
- Study has changed landscape and moved checkpoint therapy to first-line space
- One of the challenges of study is that patients must qualify for treatment with both atezo and bev
- All patients required to have endoscopy within 6 months of starting treatment and have their varices treated
- Words of caution re use of this therapy
- Also limited to Child Pugh A



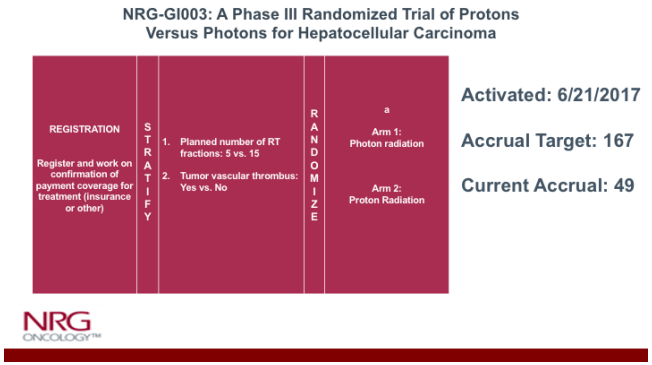
0:50:55
Advanced HCC

- El-Khoueiry said single-agent lenvatinib and sorafenib have been relegated to use only with patients who are not candidates for atezo/bev
- Many combinations being evaluated for first line
    - I/O TKI combos
    - IO/IO combos
        - PD-1/CTLA4
    - Slide shows all phase 3 trials ongoing or for which results are pending
- Field is moving to combo therapy for first line
- Advent of atezo/bev had significant impact on 2nd line treatment and beyond
    - Currently no standard
    - All approved agents have post-sorafenib data
    - Post-atezo/bev space is wide open for studies



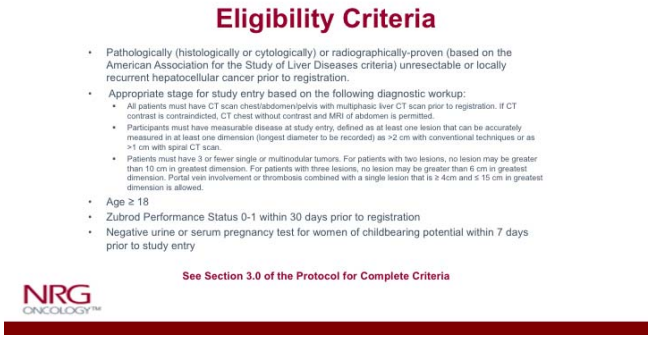
0:51:58
Ongoing NCTN studies
NRG-GI003

- Randomized phase 3 study of radiation
- Protons vs photons
- Based on some smaller studies showing great promise from photon therapy
- Limited to patients with liver-limited disease
    - But allowed to have vascular thrombosis
    - Stratification factor
- Randomized 1:1
- Accrual target 167
- Accrued 49 patients over about 3 years, so relatively slow
- El-Khoueiry said patients with vascular thrombosis will probably no longer be going on this study because they're BCLCC patients and are likely to be going on atezo/bev
- Several participating SWOG sites



0:53:17
Eligibility

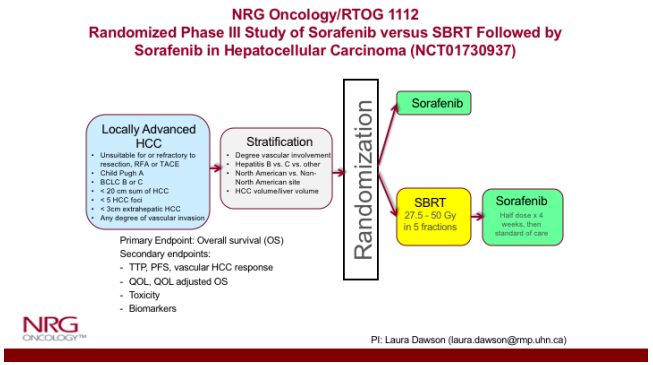
- Already covered



0:53:26

NRG/RTOG 1112

- Study is answering important question about role of SBRT in addition to systemic therapy in patients with either higher tumor burden in liver or tumor vascular invasion in portal vein
- Eligibility criteria on left in slide
    - Maximum tumor burden 20 cm
    - No tumor focus >10
    - Cannot be more than 5 HCC foci
    - Extrahepatic disease limited to 1 site <3 cm
- Multiple stratification factors
- Primary endpoint OS
    - Arm A: sorafenib
    - Arm B: SBRT followed by sorafenib
- El-Khoueiry said standard of care has changed in first line
    - Correct, but study is still accruing a bit in the US
    - Mostly outside the US
    - Even though systemic therapy has changed, role of SBRT remains in question
    - Some promising data from single-site studies about value of SBRT
        - Especially for patients with vascular invasion
- Answering this question is important
- And there are patients not candidates for atezo/bev for whom this may be a good option
- El-Khoueiry encouraged those who had it open to continue to support it



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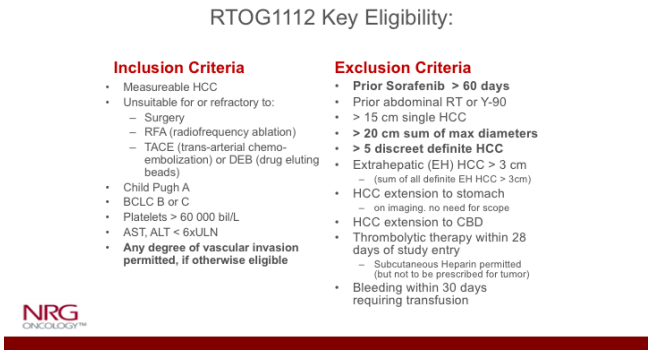
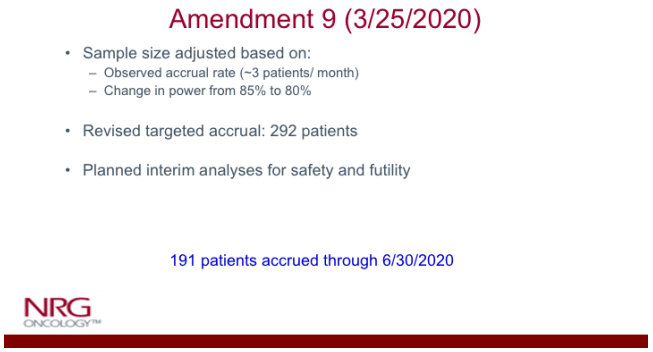


0:55:09

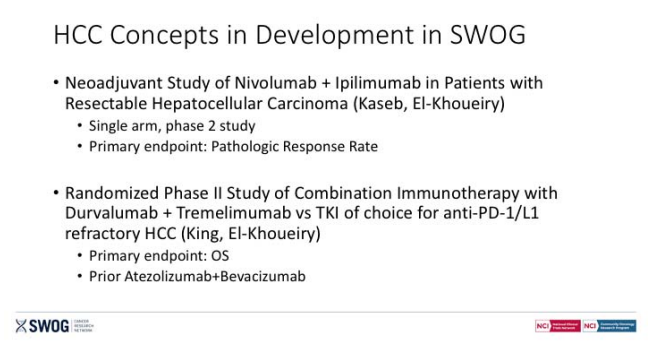
- Sample size adjusted
  - Accruing about 3 patients/month
- Power of study has been decreased
- Revised accrual target is 292
- At 191 at end of June



0:55:34

HCC concepts in development

- 1) Neoadjuvant study of nivo and ipi in patients with resectable HCC
  - Single arm phase 2 design
  - Primary endpoint of pathologic response rate
  - This builds on promising data Dr. Kaseb from MD Anderson has presented couple of times
    - Showing a promising pathologic response rate with nivo and nivo/ipi combo
  - Study moving through SWOG review process
  - Hope to move forward; endorsed by task force



- 2) Very early concept for second-line study
    - Randomized phase 2
    - Durvalumab + tremelimumab vs TKI of choice
    - After atezo/bev
    - Primary endpoint of OS
    - Durva/treme regimen
        - Treme 300 1 dose as priming dose
        - Then durvalumab alone
    - TKI physician choice
    - Still working on details
    - Will go through SWOG review if fully endorsed by GI Committee

Philip asked Shroff about GAP.

- Has reasonable chance to become standard of care if positive
- Asked Shroff to comment on side effects she is seeing
- Asked what side effects are compared to GC
- Shroff acknowledged this is an important question
- Said she likens GAP to experience of moving FOLFIRINOX to pancreatic cancer
- Probably best reserved for good PS patients
- Primary toxicities in phase 2 and now are myelosuppression
- Day 1 and 8 of 21-day cycle
- Typically see neutropenia
    - Interesting because it presents at start of next cycle
        - Able to get dose and when they come for cycle 2 day 1 is when they're neutropenic
    - Mitigated with hematopoietic growth factor support
- Shroff said when she puts patients on the study she gives them Neulasta on day 8 to mitigate these issues
- Said they do also see some thrombocytopenia
- Said surprisingly neuropathy has not been a major issue
- Nonhematologic toxicities not a major issue

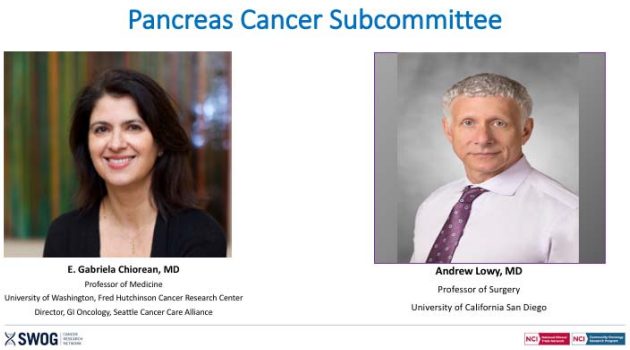
Question from Q&A:

- Any updates on progress on immunotherapy TKI/VEGF inhibitors for patients with cholangiocarcinoma?
- Shroff said progress is not there
- Lots of work studying gem/cis + IO right now
    - Primarily company sponsored
- Some provocative data at ASCO on durvalumab and tremelimumab with gem/cis
- Some data with nivo/ipi
- So far data has been underwhelming, but lots of I/O–chemo trials
- As for TKI/VEGF, was early data on bevacizumab and erlotinib
- ABC group had some VEGF data with gem/cis
- Lots of other TKI/VEGF studies
    - Single-agent study of ramucirumab
    - Nothing positive per se
- Philip noted the person who asked the question meant combination of I/O and TKI
- Shroff said in biliary there is not positive data yet
- Some ongoing studies of TKI + pembro and TKI + nivo
    - No data yet

Pancreatic

1:01:45

Gabriela Chiorean and Andrew Lowy presented for the pancreatic subcommittee.



1:02:02
Chiorean reviewed the agenda.

- Active studies
- Near active studies
- Concepts in development
- Chiorean said she had not seen much data from ESMO in terms of pancreatic cancer

Agenda

- Active NCTN studies
  EA2186 (GIANT): 1st line metastatic PDA older adults Gem/nab-P vs nal-Iri/5-FU
  A021806: resectable PDA perioperative vs adjuvant FOLFIRINOX
- Near Active SWOG/NCTN
  S2001: maintenance 1st line g*BRCA1/2*+ metastatic PDA olaparib +/- pembrolizumab
  EA2192: g/s *BRCA1/2/PALB2*+ resectable PDA adjuvant rucaparib vs placebo maintenance
- Concepts In Development

1:02:22
Chiorean asked David Zhen to present EA2186.

Zhen presented the GIANT study comparing gem/abraxane and 5FU-nal-IRI in older patients.

- Dedicated study for older patients with metastatic pancreatic cancer

EA2186 – GIANT: A Randomized Phase II Study of Gemcitabine and Nab-Paclitaxel Compared with 5-Fluorouracil and Liposomal Irinotecan in Older Patients with Treatment Naïve Metastatic Pancreatic Cancer

Study Chair:
Efrat Dotan, MD
Fox Chase Cancer Center

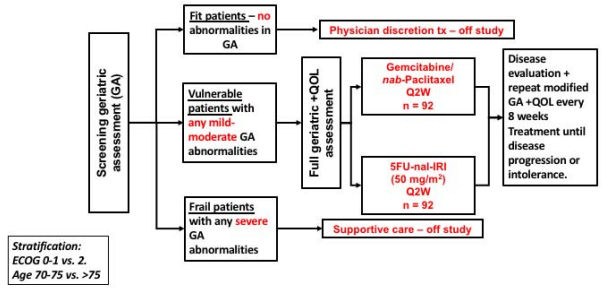
SWOG Study Champion:
David B. Zhen, MD
University of Washington/
Fred Hutchinson Cancer Research Center

Activated 06/18/2020
Accrual 1/184

1:02:51
Schema

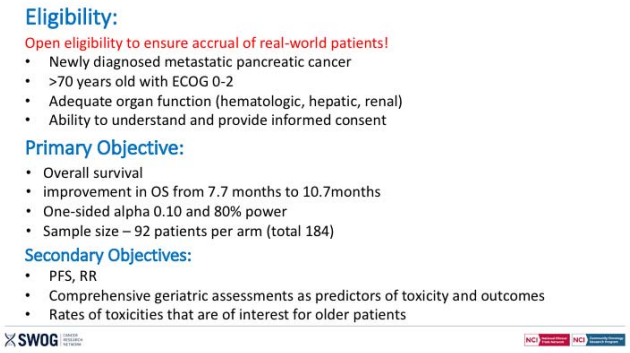
- Zhen noted many contemporary studies for both gem/abraxane and FOLFIRINOX exclude patients >70 years old
  - Also the same group of patients they see in clinic
- Purpose of this study is to see how they can better treat these patients
- Vulnerable population
  - Assessed by routine screening geriatric assessments
- Looking for vulnerable patients in the middle with mild or moderate abnormalities
- Full assessment

EA2186 - Study Design



- Randomized to
    - Gem/abraxane every 2 weeks
    - 5FU and nal-IRI every 2 weeks
- Primary endpoint is OS
- Activated June 2020
- 1 patient enrolled now out of 184 planned

1:04:26

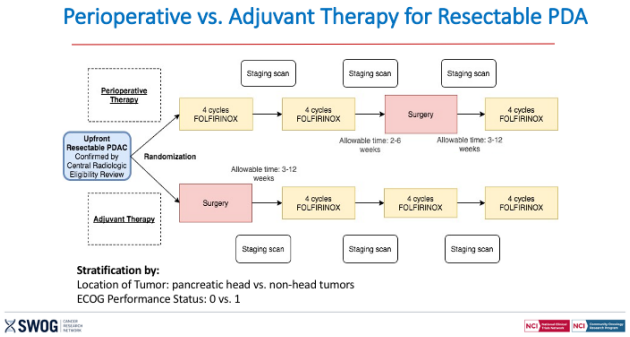


1:04:24
Lowy discussed A021806.

- Phase 3 study to examine perioperative FOLFIRINOX vs adjuvant FOLFIRINOX

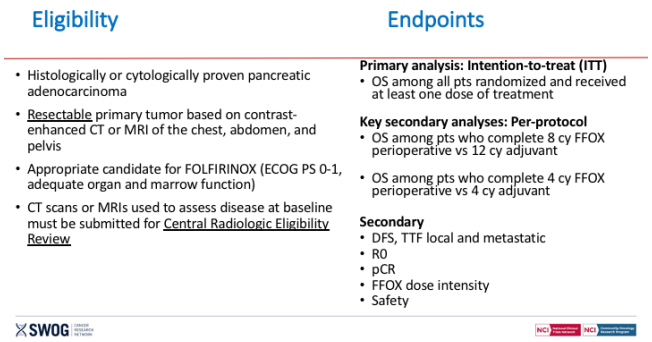
1:05:02
Schema

- 8 cycles preoperative FOLFIRINOX on experimental arm
  - Plan for 4 cycles postoperative



1:05:21

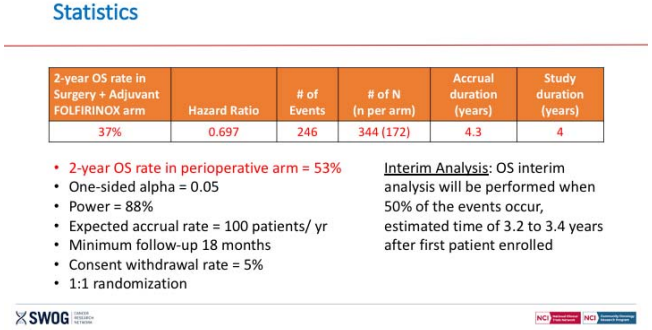
- Resectable; not borderline or locally advanced
- Primary endpoint is intention-to-treat OS
- Multiple secondary endpoints listed in slide
- Lowy said given move to neoadjuvant therapy, this is an important study
  - First to compare neoadjuvant or perioperative approach with more traditional adjuvant therapy approach



1:05:58
Lowy said there was no need to go through statistics.

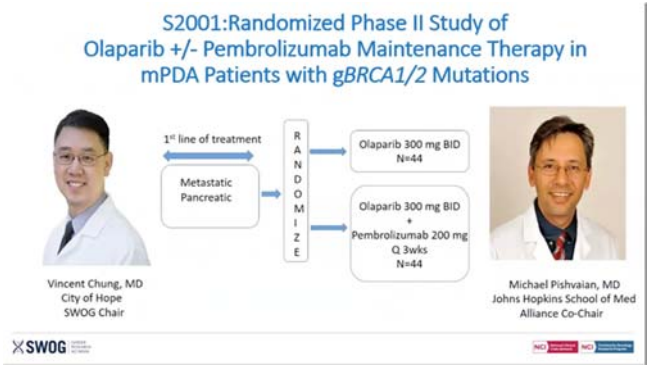
Lowy said strategy at SWOG has been to pursue neoadjuvant strategy.

- Said they are skating to where the puck is going
- If this study is positive, it will reinforce move to preoperative therapy
- Thought that is what most people are doing in practice



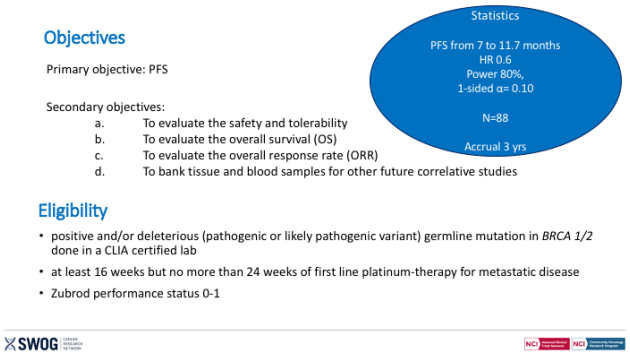
1:06:06
Vincent Chung presented S2001.

- Randomized phase 2 study of olaparib + pembro vs olaparib alone in patients with germ line gBRCA1 and 2 mutated pancreatic cancer
- Chung said POLO trial showed olaparib maintenance therapy improved PFS to just over 7 months
- Have seen with BRCA mutations and treatment with PARP inhibitors is increased genomic instability, increased PD-L1 expression, and less stimulation of the STING pathway
    - Makes combination with checkpoint inhibitor logical choice
- Preclinical data from genetically engineered mouse model shows combination is synergistic
- First line metastatic maintenance trial
- Patients on platinum-based chemo will have germline testing done as part of standard of care
    - Per 2019 NCCN guidelines, germline testing is recommended for all patients with pancreatic cancer
    - So it's known if patients are BRCA-mutated
- If restaging scan done between 4 and 6 months of therapy does not show progression, patients randomized
    - Olaparib alone
    - Olaparib with pembro
- Chung expressed excitement about trial
- Presented at CIRB previous week
    - Just got their conditions back
    - Respond to those this week
- Study should open soon



1:08:39

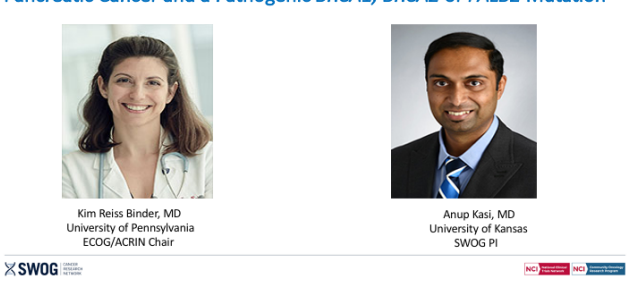
- Chung said they wanted to accrue 88 patients over 3 years
- Looking for HR of 0.6
- Looking to improve PFS from 7 months to 11.7 months



1:09:27

Chiorean introduced Anup Kasi to present EA2192.

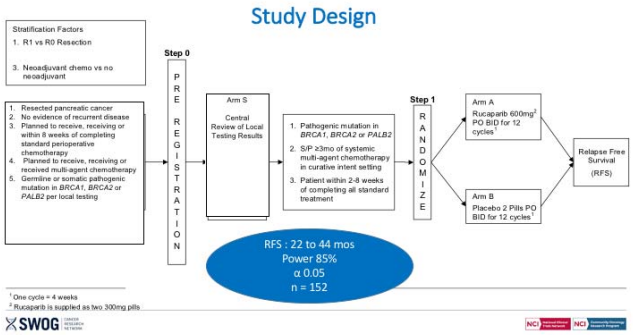
- Kasi said study idea is to move PARP inhibition in adjuvant maintenance setting for resected pancreatic cancer
- Phase 2 randomized blinded study
- Kasi said although slide says rucaparib, they discussed very recently with task force, and it will instead be olaparib vs placebo following adjuvant/perioperative therapy
- Looking at cancers that harbor either somatic or germline pathogenic mutation in BRCA1, 2, or PALB2



1:10:22

Design

- Resected patients
- No evidence of recurrent disease
- If they've received at least 3 months of systemic chemo
  - Had initially planned to limit to platinum-based chemo
  - Now also allowing non-platinum-based
- Then patients randomized
  - Maintenance PARP inhibitor (olaparib) for 12 months
  - Placebo for 12 months



- Primary objective RFS
- Goal is to improve RFS from median of 22 months to 44 months
- Power of 85%
- Requires 152 enrolled in 38 months
- Patients stratified based on
    - R1 vs R0 resection
    - Neoadjuvant chemo vs no neoadjuvant chemo
    - Platinum vs no platinum
- Allow radiation in neoadjuvant or adjuvant setting

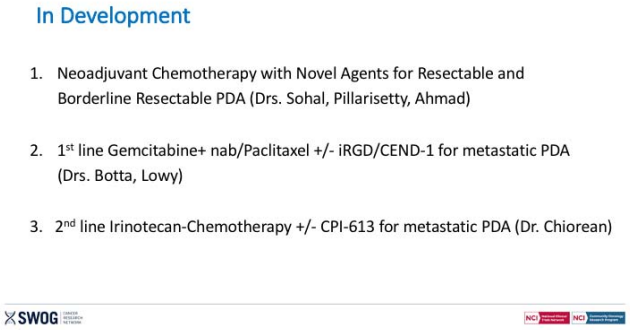
Chiorean noted study would start soon, but given change from rucaparib to olaparib, sounds like will open in 2021

- Kasi confirmed it may take a few months

1:12:24

Chiorean presented studies in development.

- Drs. Sohal and Pillarisetty have a neoadjuvant platform study combining chemo with novel agents for resectable and borderline resectable pancreas cancer
    - Chiorean said they're hoping to have a CXCR4 PD-1 inhibitor arm
    - Also potentially CPI-613
    - Said they will know more about these drugs toward the end of 2020 as more results are available
- Drs. Botta and Lowy have proposed first-line metastatic pancreas cancer with gemcitabine nab-paclitaxel with and without CEND-1
    - CEND-1 is an iRGD receptor modulator which allows penetration of chemotherapeutics and potentially immunotherapeutics into a tumor
    - Preliminary phase 1 data presented at ESMO with CEND-1 and gem-nal-paclitaxel showing response rates of 58% and disease control rate at 16 weeks of about 80% for pancreas cancer
    - Chiorean said this was very encouraging data
    - Study well received by pancreas task force
    - Now waiting for stats



- Finally is a 2nd-line irinotecan-based trial with CPI-613 for metastatic pancreas cancer
    - Could even be combined with gemcitabine/nab-paclitaxel
    - Won't know more until Q1 2021

Philip asked Dr. Lowy his view about preop radiation treatment Alliance trial.

- Asked what Lowy thought we should be doing in terms of standard of care and in terms of trials
- Lowy said we haven't seen data yet but should be soon; will be helpful
- His bias based on his own experience is he believes that preop radiotherapy for patients with borderline resectable and locally advanced disease does improve margin-negative resection
    - Unequivocal
- Difficult question because until there's systemic therapy that's effective enough to make local control matter, hard to elicit survival advantage
- Lowy said he'd had discussion with leadership of NRG about lack of clear agreement on endpoints or on radiotherapy technical details and dose and schedule
    - Has hamstrung progress
- Said he knows they're having discussions and have a working group
- Should await their outcome
- Lowy said they use it in preop setting in those circumstances and use it in postop setting in R1 resection

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Colon

1:16:50

Philip introduced Wells Messersmith and Philip Gold for colon subcommittee.

1:17:03

Messersmith presented an update on the field.

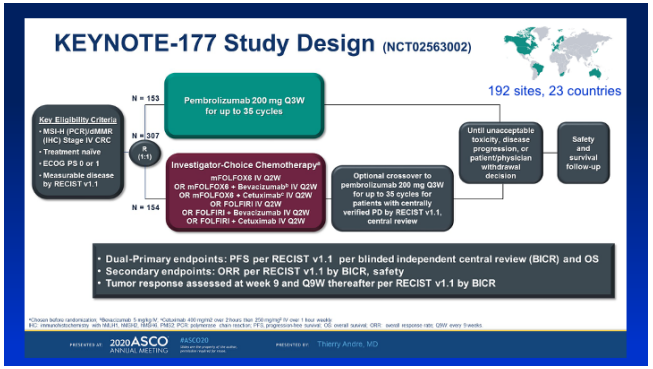
1:17:07

KEYNOTE 177

- Presented at ASCO
- QoL results presented at ESMO

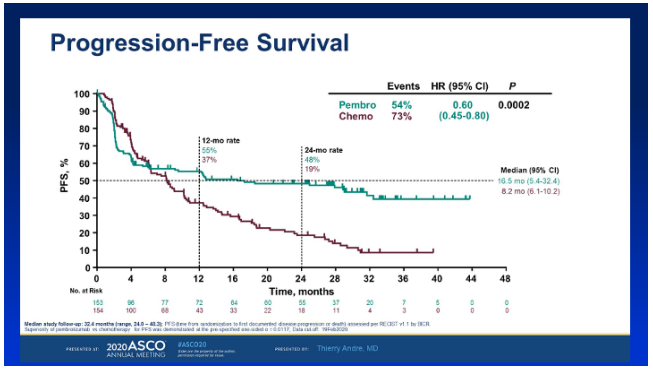
1:17:24

- For microsatellite high deficient mismatch repair colorectal cancer
- Good PS
- 300 patients
- Randomized to
    - Pembrolizumab or
    - Investigator's choice chemo
    - Optional crossover
- Many sites and countries involved
- Dual primary endpoints
    - PFS per RECIST
    - PFS per
- Survival tracked as well



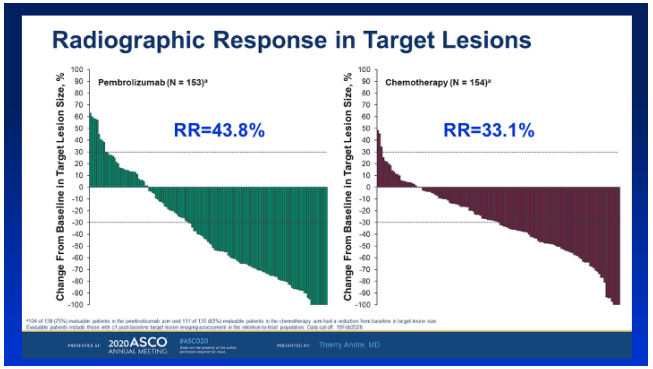
1:17:59

- PFS curves
- Messersmith referred to yin-yang curves crossing
- Advantage to pembro vs chemo
- HR of 0.6



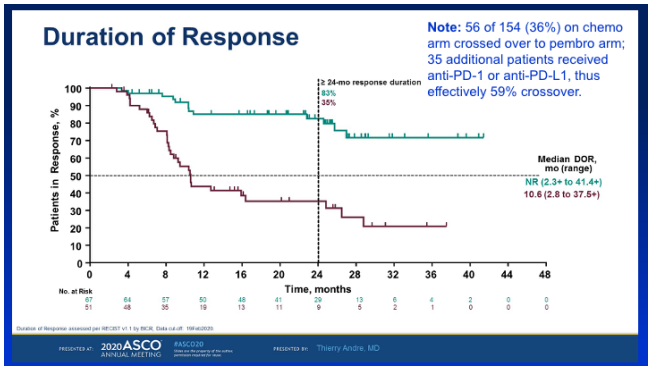
1:18:19
Radiographic response

- Also favored pembro arm by about 10%



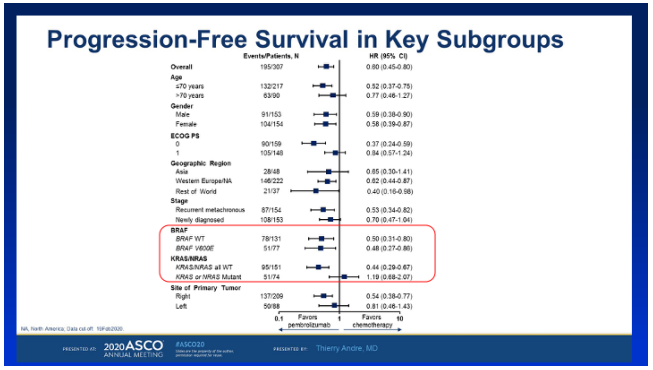
1:18:32
Duration of response

- Messersmith noted this is a big advantage of immunotherapy
  - Once you get a response, can be long-lived
- About 60% crossover
  - Either crossed over formally or received PD-1 subsequently



1:18:53
PFS

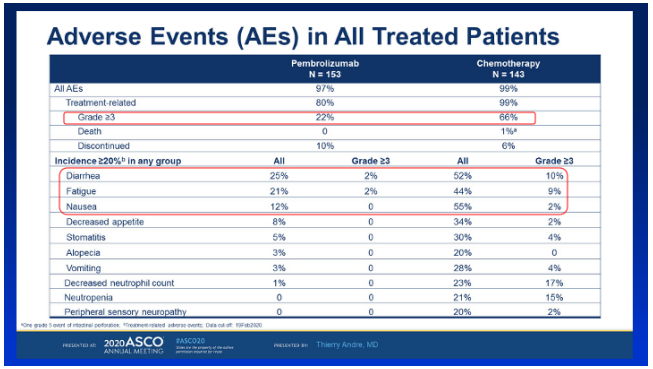
- Messersmith said we think of BRAF as aggressive subtype
- But regardless of BRAF status, patients had good benefit
- Small groups, so hard to say
- Question of RAS mutations



1:19:22

Adverse events

- Pembro much better tolerated
- About 1/3 rate of grade 3 or higher AEs compared to chemo
- Most common ones from chemo as shown in slide
- Multiple chemo regimens



Adverse Events (AEs) in All Treated Patients

	Pembrolizumab N = 153		Chemotherapy N = 143	
All AEs	97%		99%	
Treatment-related	80%		99%	
Grade ≥3	22%		66%	
Death	0		1%[a]	
Discontinued	10%		6%	
Incidence ≥20%[b] in any group	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Diarrhea	25%	2%	52%	10%
Fatigue	21%	2%	44%	9%
Nausea	12%	0	55%	2%
Decreased appetite	8%	0	34%	2%
Stomatitis	5%	0	30%	4%
Alopecia	3%	0	20%	0
Vomiting	3%	0	28%	4%
Decreased neutrophil count	1%	0	23%	17%
Neutropenia	0	0	21%	15%
Peripheral sensory neuropathy	0	0	20%	2%

[a]One grade 5 event of intestinal perforation. [b]Treatment-related adverse events. Data cut-off: 19Feb2020.

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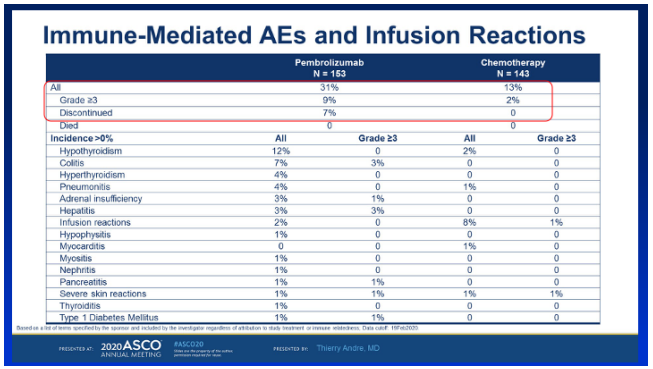
1:19:48

Immune-related AEs

- Consistent with many other PD-1/PD-L1 studies
- Grade 3 AEs fairly rare (<10%)



Immune-Mediated AEs and Infusion Reactions

	Pembrolizumab N = 153		Chemotherapy N = 143	
All	31%		13%	
Grade ≥3	9%		2%	
Discontinued	7%		0	
Died	0		0	
Incidence >0%	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Hypothyroidism	12%	0	2%	0
Colitis	7%	3%	0	0
Hyperthyroidism	4%	0	0	0
Pneumonitis	4%	0	1%	0
Adrenal insufficiency	3%	1%	0	0
Hepatitis	3%	3%	0	0
Infusion reactions	2%	0	8%	1%
Hypophysitis	1%	0	0	0
Myocarditis	0	0	1%	0
Myositis	1%	0	0	0
Nephritis	1%	0	0	0
Pancreatitis	1%	1%	0	0
Severe skin reactions	1%	1%	1%	1%
Thyroiditis	1%	0	0	0
Type 1 Diabetes Mellitus	1%	1%	0	0

Based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness. Data cutoff: 19Feb2020.

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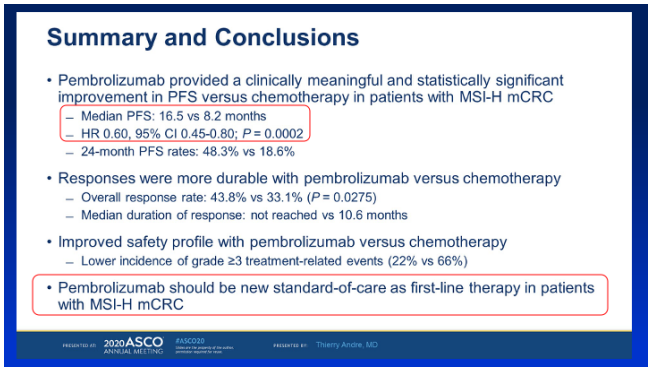
1:20:04

Conclusions

- Provided meaningful and statistically significant benefit in PFS and RR
- Felt to be new standard of care
- Affected design of one of our studies
    - Covered later
- QoL abstract presented at ESMO showing pembro patients had improvement in QoL, whereas chemo patients' QoL scores decreased



Summary and Conclusions

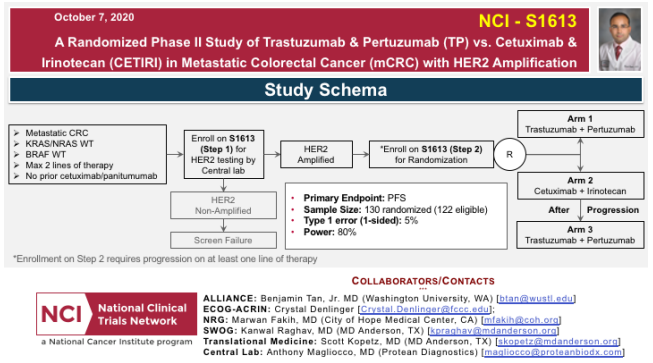
- Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS versus chemotherapy in patients with MSI-H mCRC
  - Median PFS: 16.5 vs 8.2 months
  - HR 0.60, 95% CI 0.45-0.80; $P = 0.0002$
  - 24-month PFS rates: 48.3% vs 18.6%
- Responses were more durable with pembrolizumab versus chemotherapy
  - Overall response rate: 43.8% vs 33.1% ($P = 0.0275$)
  - Median duration of response: not reached vs 10.6 months
- Improved safety profile with pembrolizumab versus chemotherapy
  - Lower incidence of grade ≥3 treatment-related events (22% vs 66%)
- Pembrolizumab should be new standard-of-care as first-line therapy in patients with MSI-H mCRC

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Thierry Andre, MD

1:20:49
Gold presented active SWOG studies.

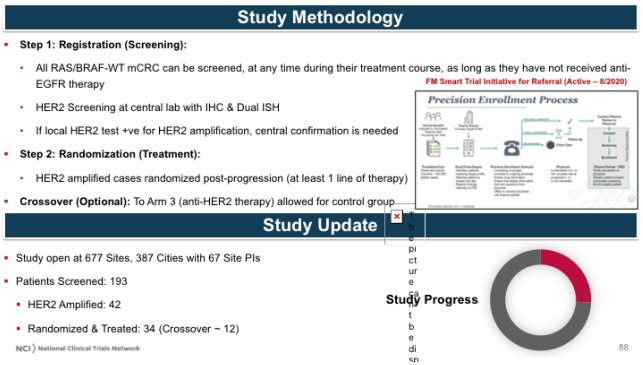
1:21:08
S1316

- HER2-amplified colon cancer trial
- Underway for a bit of time
- Patients randomized to
    - Herceptin and pertuzumab or
    - Cetuximab and irinotecan
    - Crossover
- Trial highlights need for appropriate testing on all metastatic colon cancer patients
- Frequency of HER2 amplification in this cancer is quite low



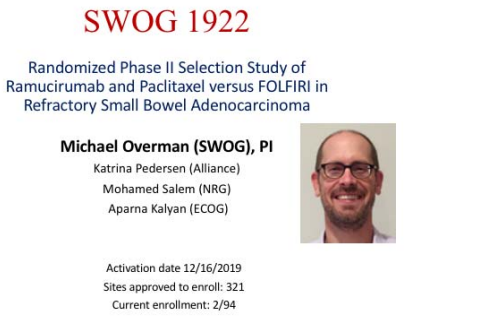
1:21:58

- Screened 193 patients
- 34 treated
- 12 crossed over
- Now participating in a partnership: precision enrollment process
  - Foundation Medicine will notify investigators about HER2 amplification AND potential eligibility for this trial
- Accrual a bit slow
- Have track record in SWOG of doing studies like this in BRAF-mutated patients
  - Frequency of mutations are quite similar
- Gold encouraged all to sequence their patients
  - Also to stain patients when necessary by IHC
  - And enroll them in this trial



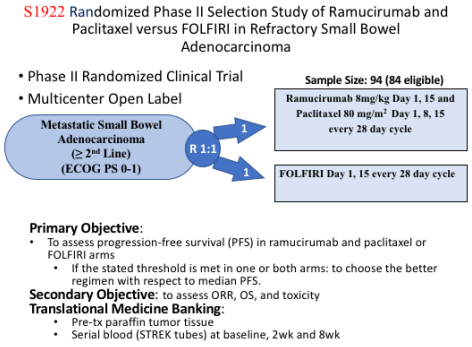
1:22:47
SWOG 1922
Gold presented.

- One of first SWOG trials Gold can remember in small bowel adenocarcinoma
- Randomized phase 2
  - Ramucirumab and paclitaxel
  - FOLFIRI
- Second line treatment of refractory disease



1:23:23

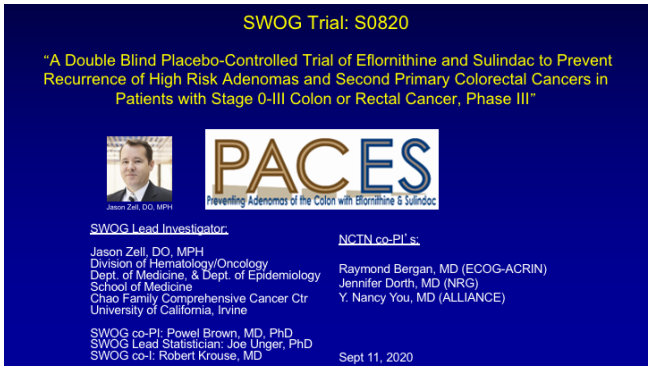
- Study recently activated and has accrued couple of patients
- Patients should have had prior first-line therapy or beyond
- Randomizes them 1:1
- Looking for total sample of 84
- Uncommon malignancy, but Gold asked group to please consider their patients for this trial



1:23:52

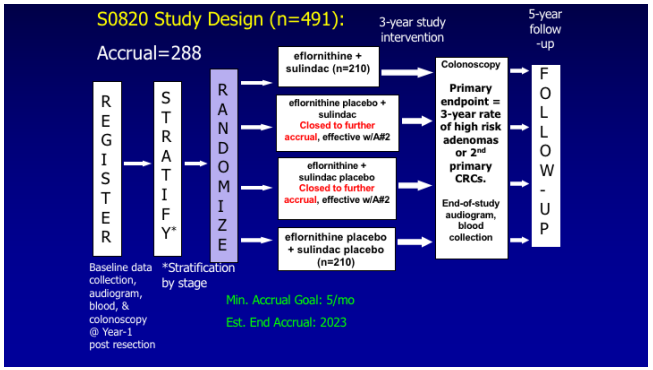
Jason Zell gave update on S0820 PACES.

- Tertiary prevention study among colon and rectal cancer survivors



1:24:05

- CALGB 80702 reported its primary endpoint as negative
  - No benefit of celecoxib vs placebo
  - At recent ASCO
- *NEJM* of 2 weeks ago has article on these 2 agents
  - Eflornithine and sulindac
  - Higher dose of eflornithine
  - Vs. each agent individually in FAP patients
  - 175 patients
  - Overall no difference in combo vs single agent
  - But very interesting effect of combo in FAP patients with intact colons



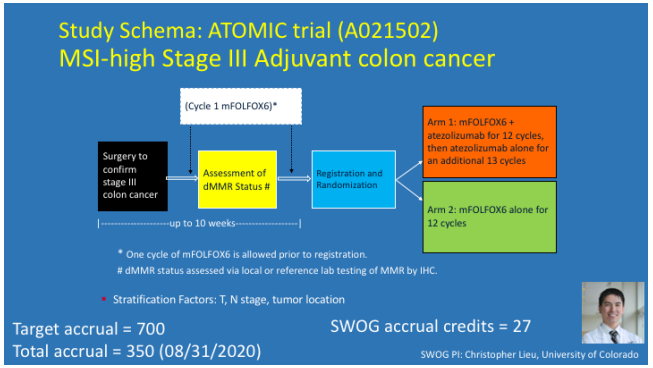
    - Zell encouraged group to look at article
- Provided accrual update: 289 patients of 491
- Recovered from COVID and back at target of 5 per month
- Still slow and steady
- Great sites contributing patients
    - Yale, Virginia Mason, Kaiser, UC Irvine, Hawaii
- Encouraged everyone to continue

Gold noted that Dr. Zell gets the persistence/perseverance award for this trial.

1:25:47
Gold discussed four active NCTN trials in colon.

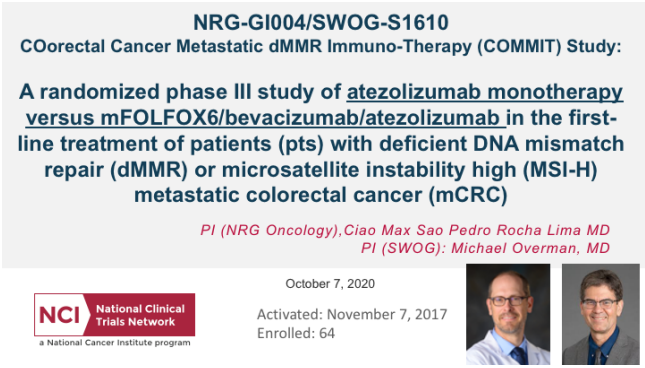
1:25:57
A021502

- ATOMIC trial
- Very important trial
- Patients with stage 3 colon cancer with evidence of mismatch repair
- Randomly assigned to
    - Conventional chemo with FOLFOX
    - FOLFOX with atezolizumab
- Half accrued



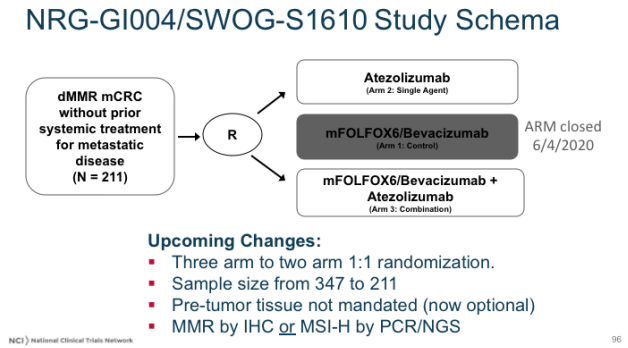
1:26:25
NRG-GI004/SWOG S1610

- Trial of upfront immunotherapy in metastatic colon cancer
- Initially randomized patients to
  - Chemo
  - Chemo + immunotherapy or
  - Immunotherapy alone
- Patients with dMMR



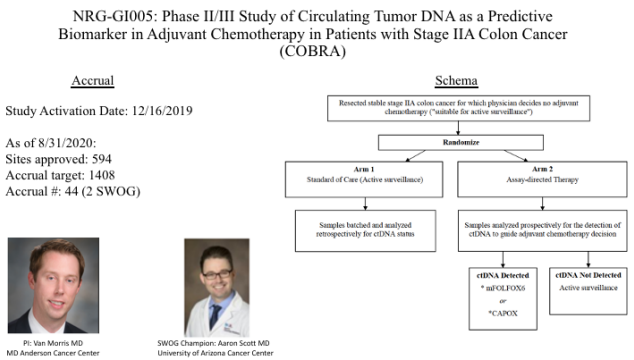
1:27:00

- Originally a 3-arm trial
- With results of KEYNOTE 177, can no longer consider it appropriate to offer chemo and biologic therapy alone in untreated dMMR metastatic cancer
- Now becoming 2-arm trial
  - Single agent atezo
  - Chemo/bio/immunotherapy with FOLFOX, bev, and atezo
- Sample size down to 211 patients
- Gold encouraged all to enroll this trial



1:27:50
NRG-GI005

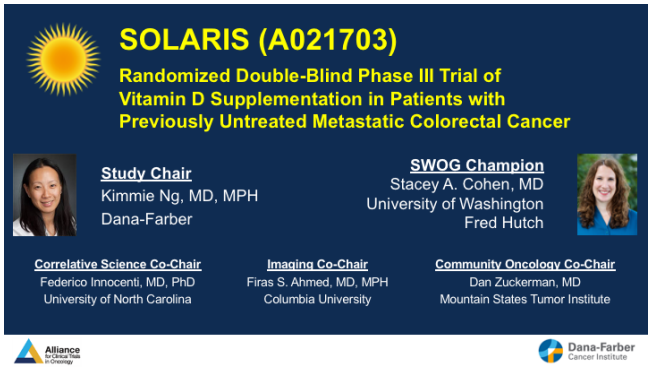
- COBRA trial
- Phase 2/3 trial looking at ctDNA as predictive biomarker
- Study started recently
- 44 patients accrued
- Patients who don't need chemo are randomized to
  - Active surveillance with retrospective review of ctDNA or
  - Assay-direct therapy
    - First time for colon cancer in SWOG
    - Samples analyzed



    - Patients with ctDNA assigned chemo
    - Patients with no ctDNA detected assigned surveillance
- Gold said he had a patient consent today to COBRA
- T3/N0 disease

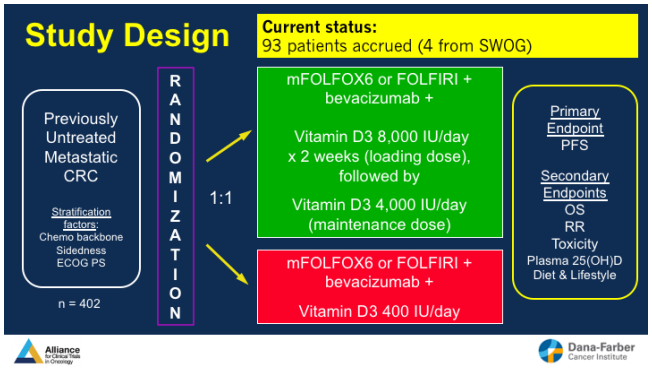
1:29:13
A021703

- SOLARIS trial
- Randomized double-blinded phase 2 trial of vitamin D supplementation in patients with untreated metastatic colon cancer



1:29:31

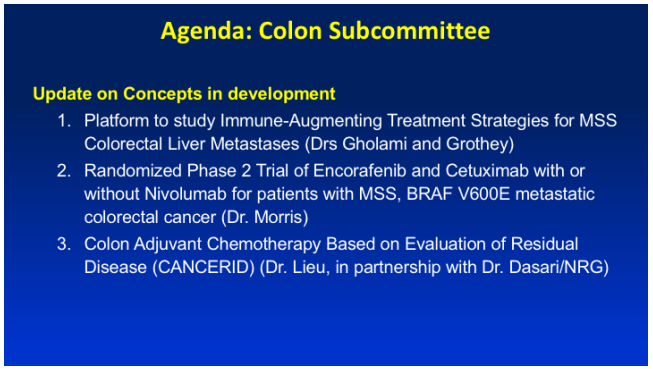
- Randomized 1:1
- Looking for 400 patients; 93 thus far
- All arms same chemo but different doses of vitamin D
- Primary endpoint PFS
- Secondary endpoints OS, toxicity
- Gold said all are aware from previous trials of the importance of vitamin D in colon cancer
- Gold said for those who were going to treat these patients with this standard chemo regimen, no reason not to offer them this protocol



1:30:17
Next agenda item: concepts in development, presented by Gold.

1:30:29

- Platform to study immune-augmenting treatment strategies for microsatellite colorectal cancer liver metastases
    - Essentially in vivo sensitivity testing
        - Patients assigned treatment, then go for liver resection
    - Reviewed at colon task force
    - Platform endorsed
        - But will be reviewing for other potential treatment combos
- Next study is randomized phase 2 trial of encorafenib and cetuximab with or without nivolumab for patients with microsatellite-stable BRAF V600E-mutated colon cancer
    - Builds on PI's previous S1406 results showing importance of BRAF inhibition in patients with V600E mutations
    - Reviewed favorably in colon task force
    - Gold hoped it would now go into capsule summary and soon be approved and activated within next several months
- CANCERID protocol
    - Like COBRA trial, study will assign chemo for more advanced high-risk patients based on ctDNA results
    - To be discussed in upcoming colon cancer translational meeting



Eng encouraged all on call to try to enroll to small bowel trial being led by Mike Overman.

- And the MSI studies mentioned earlier
- Obviously the HER2 study Dr. Raghav is leading

Philip asked Messersmith about the yin-yang survival curves.

- Not every MSI-high patient will get immunotherapy.
- Asked if there were patients for whom he would not use single agent immunotherapy but opt for combination chemo
- Gold responded
- Suggested they might recommend conventional chemo/bio instead of immunotherapy for untreated disease in patients who have autoimmune disease and patients with contraindications to immunotherapy
- Philip said these are well known; apart from these?
- Gold said no: he thought the tide had turned
- Zell said the crossing yin-yang curves represented a violation of the proportionality hazards assumption
    - When curves cross, it's inappropriate to use a hazards ratio
    - Doesn't mean difference doesn't exist, just need different statistical methods
    - But in medicine tend to refer back to HR
    - More of a statistical thing
- Gold suggested one potential scenario in which one might want to do chemo first
    - Patient with very rapidly progressing disease
    - Onset of response to immunotherapy may take a little longer
    - For a rapid response, could envision FOLFOXIRI in patient who is quite ill where you don't have the luxury of time
- Kanwal Raghav suggested that, when looking at those curves, there is a section of population that does dramatically poorly on immunotherapy
    - Large part of benefit is carried by responders
    - Duration of responses much more than for chemo

- Some scope of improvement in finding who among those MSI-high patient are the early responders

Philip referred to question from Tom Semrad:
There is an ongoing phase I/II study of encorafenib, cetuximab and nivolumab in BRAF CRC (NCT04044430). I assume the SWOG study will use this as the phase I data? Why not do the randomized study as a phase II/III?

- Van Morris responded
- Trial mentioned in question is single-site trial at MD Anderson
- Expect enrollment will complete within 6–12 months
- Moving to the randomized trial as a phase 2
- Had discussions with both BMS and Pfizer on vision for this plan
- Discussions he and Gold have had with these pharma leaders they feel most prudent next step would be randomized phase 2
- Must remember in these very rare mutations—only 4% of colon cancer population—keeping sample size down also has merit in terms of time to accrue

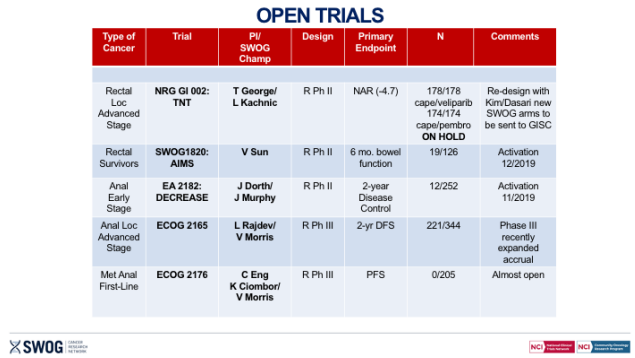
Philip moved to rectal-anal subcommittee.

Anorectal
1:38:16
Kennecke opened.

- Said he and Kachnic would present studies open and pending.
- Not huge number of ESMO updates

1:38:34
Open trials

- Two rectal, three anal trials
- First rectal is NRG-GI002 TNT
    - Kachnic will update
    - Still on hold
- Sun will update on well-accruing S1820 AIMS
- DECREASE study is open
- Two ECOG studies of locally advanced adjuvant and first-line metastatic

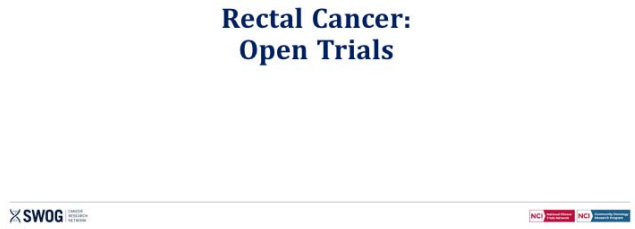


OPEN TRIALS

Type of Cancer	Trial	PI/ SWOG Champ	Design	Primary Endpoint	N	Comments
Rectal Loc Advanced Stage	**NRG GI 002: TNT**	**T George/ L Kachnic**	R Ph II	NAR (-4.7)	178/178 cape/veliparib 174/174 cape/pembro **ON HOLD**	Re-design with Kim/Dasari new SWOG arms to be sent to GISC
Rectal Survivors	**SWOG1820: AIMS**	**V Sun**	R Ph II	6 mo. bowel function	19/126	Activation 12/2019
Anal Early Stage	**EA 2182: DECREASE**	**J Dorth/ J Murphy**	R Ph II	2-year Disease Control	12/252	Activation 11/2019
Anal Loc Advanced Stage	**ECOG 2165**	**L Rajdev/ V Morris**	R Ph III	2-yr DFS	221/344	Phase III recently expanded accrual
Met Anal First-Line	**ECOG 2176**	**C Eng K Ciombor/ V Morris**	R Ph III	PFS	0/205	Almost open

SWOG

1:39:50
Kachnic presented.



Rectal Cancer: Open Trials

SWOG

1:39:54
NRG-GI002

- Some revisions are proposed for TNT trial
- Trial gives chemo up front before chemo and radiation
- Has been for locally advanced cancer

NRG ONCOLOGY
Advancing Research. Improving Lives.

Proposed Revisions to NRG-GI002:

A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer

PI George; SWOG Champion Kachnic

NCT02921256

1:40:16

- Primary objective will be updated
- Amendments going to NCI
- New objective: To test new agents and TNT approaches that maximize tumor downstaging as a surrogate for improved survival
- Kachnic said they have been doing most locally advanced patients
    - Ones that potentially could need an APR up front because distal or bulky

Updated Primary Objective

To test new agents and TNT approaches that maximize tumor downstaging as a surrogate for improved survival

Inform future definitive studies for patients with or without sphincter preservation goals

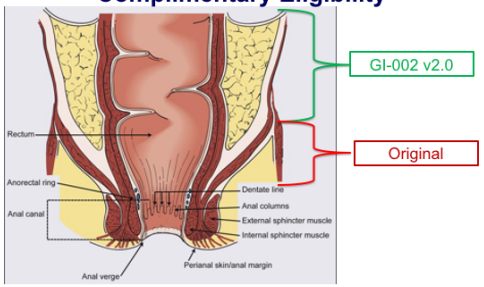
Any experimental arm reaching the pre-specified statistically significant endpoints, in the context of no new safety concerns, would meet criteria for moving forward into a definitive phase III RCT

NRG ONCOLOGY™

1:40:47

- Moving to included disease going up the rectum (not necessarily distal)
- And potentially nonoperative management

Complimentary Eligibility



-Image c/o Karyn A. Goodman, Lisa A. Kachnic and Brian G. Czito

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1:40:59

- Key updated eligibility in red in slide
- Can have tumor higher from distal and verge
- Also candidate for LAR

Key Updated Eligibility

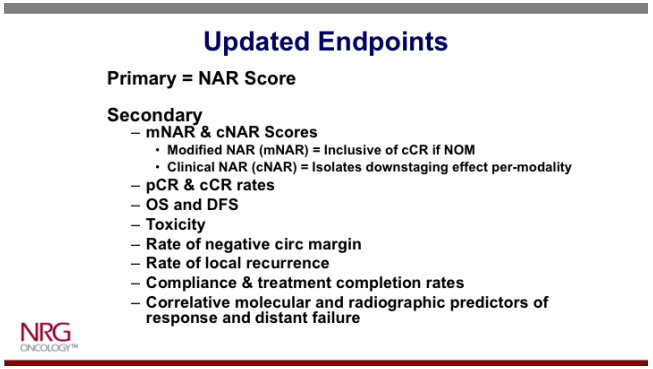
- Biopsy proven rectal adenocarcinoma
- ECOG PS 0-2
- Clinical stage II or III as defined by MRI
- ≥6cm from anal verge and candidate for LAR
- Adequate untreated tumor specimen must be available for mutational profiling

- Adequate marrow, liver, kidney function
- Operative candidate

NRG ONCOLOGY™

1:41:28

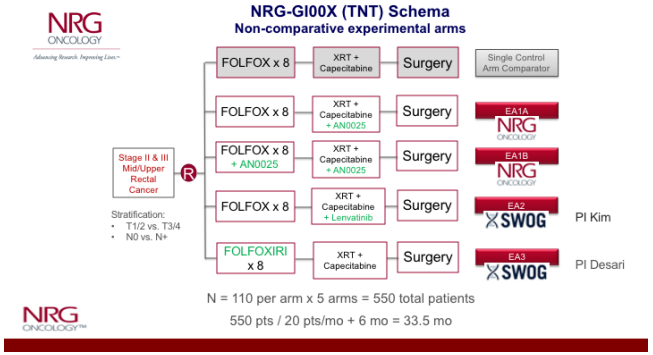
- Updated endpoints
- Because of potential to include nonoperative management, will include an updated secondary endpoint
    - Modified NAR score
        - Differs from PCR
        - Either have PCR or you don't
        - NAR takes into account all pathological downstaging
        - Validated in previous trials of chemoradiation and TNT



1:42:07

NRG-GI00X

- Among potential new arms, SWOG has 2
- One is from Richard Kim
    - Lenvatinib with cape and radiation after FOLFOX
- Second is from Dr. Dasari
    - Looks at FOLFOXIRI before cape and radiation
- Potentially other arms too

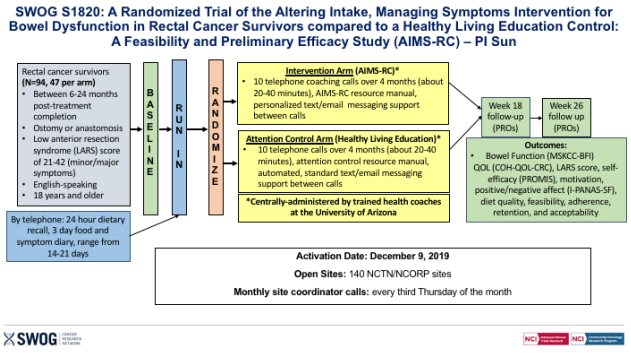


1:42:42

S1820

Virginia Sun presented.

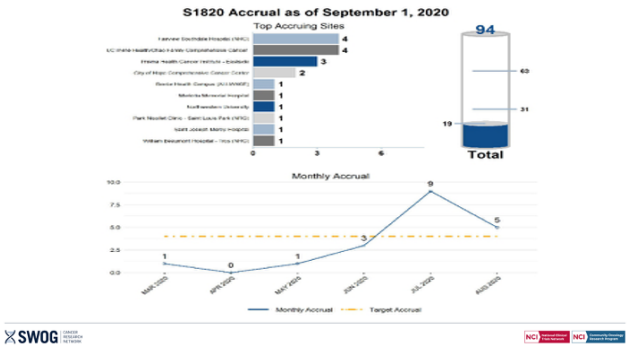
- AIMS trial: Altering Intake Managing Symptoms
- Randomized trial
- Focused on rectal cancer survivors with target sample of 94
- 6–24 months post treatment completion
- Both ostomy and anastomosis
- For patients with anastomosis, screening with LARS score of 21–42
- After baseline questionnaires, begin 14–21 day run-in



    - Done by phone through 24-hour diet recall and 3-day food and symptom diaries
- After run-in, randomized
    - AIMS-RC
        - 10-call coaching over 17 weeks
        - 20–40 minutes per
        - Resource manual to patient with intervention content
        - Personalized texts and emails between calls for motivation support
    - Attention control arm
        - 10 healthy living topics relevant post treatment
        - Given in course of 10 calls as well
        - Resource manual
        - Automated standard texts and emails focused on content
- Grateful study could continue through COVID
- Trained coaches are based at U Arizona
    - Easier for sites
    - Can monitor intervention fidelity
- Follow-ups at weeks 18 and 26
    - Primarily PROs
- Primary endpoint is bowel function at 18 weeks
    - Measured by MSKCC bowel function index
- Secondary include feasibility, adherence, retention, and acceptability
- Activated Dec 2019
- Have about 140 sites
- Engage site coordinators on calls monthly

1:45:57

- Accrual graph sent to investigators and site staff every month
- At 22 now
- Sun expressed appreciation for group's support of trial



1:46:23

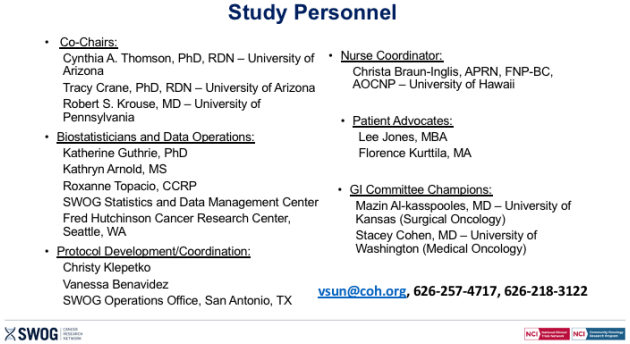
- Sun acknowledged study personnel and GI Committee champions
- Contact info in slide for those with questions

Kennecke noted the study is innovative.

- Just opened at his site
- Accruing quickly
- Virtual intervention
- Innovative care example
- Kennecke asked if anyone had questions

Kachnic wondered whether anyone had identified barriers.

- Zell said study takes some time initially
  - There is some training
- Calculating LARS score also takes time
  - His site put macro in Epic to do this
    - Enter "S1820" and all figures needed to calculate the score appear

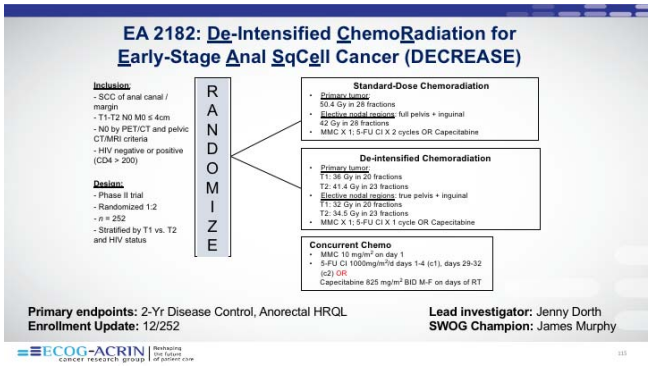


1:48:03

1:48:09
Kachnic introduced James Murphy to present on EA2182 (DECREASE).

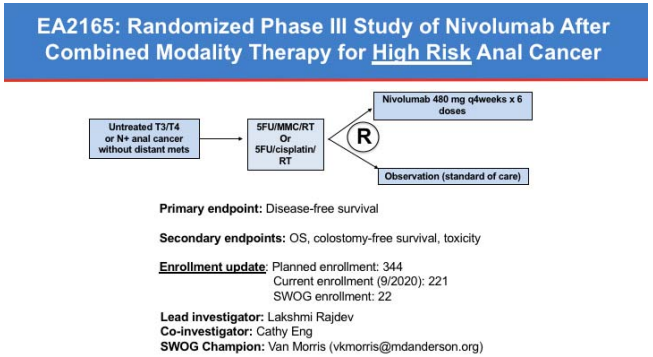
Murphy was not present.
Kachnic presented

- Looking at lowering dose of radiation for early stage anal cancer
- T1 or T2, <=4 cm
- Node-negative tumors
- HIV+ as long as CD4 count >200
- Phase 2 randomization
    - Standard chemo radiation
    - De-intensified
        - Down from 50 Gy to 36 Gy for T1
        - Down to 41 Gy for T2
- Concurrent chemo is standard 5FU CI or capecitabine
- Primary endpoint is 2 year disease control
- Must also have patient-reported anorectal QoL
- Intent for secondary endpoint is to show improve anorectal function with lower radiation doses
- Enrollment early September was 12



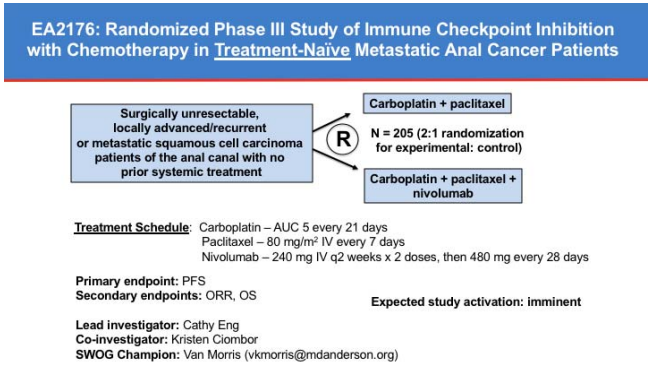
1:50:20
Van Morris presented EA2165.

- Trial builds on success of nivolumab in metastatic setting with NCI9673 trial
- Looks to use nivo with patients with locally advanced disease
    - Defined by T3 or T4 primary tumor or node+ nonmetastatic anal cancer
- Patients get standard of care chemoradiation with 5FU/mitomycin C or 5FU/cisplatin
- Randomized to
    - Standard of care, which is observation
    - Nivolumab for 6 months
- Primary endpoint DFS
- Accruing very well: 221 of 344 patients accrued



1:51:47
Morris also presented EA2176.

- Seeking to activate across US
- Adds PD-1 therapy to front line setting for patients with metastatic anal cancer
- Trial also builds on the INTERACT trial, which defined carbo/taxol as standard of care as front line treatment for metastatic anal cancer
- Patients randomized 2:1
    - Carbo/taxol with nivo
    - Carbo/taxol alone
- Expect it to activate very soon
- Eng noted it was approved by CTEP but she's waiting for coding paperwork



1:52:46

Developing Trials

SWOG

1:52:58
Kennecke referred to 1-slide summary of concepts in development.

First concept: had lively debate about concept at Tuesday GI meeting

- Randomized intervention of 2 types of chemo with ipi/nivo for high-risk anal cancer as potential successor to adjuvant nivo trial
- David Horowitz then presented
    - Randomized noncomparative study comparing short-course chemoimmunotherapy before standard dose-painted IMRT and mitomycin C with 5FU or capecitabine
    - Looks to build on data from head and neck sphere on induction chemoimmunotherapy
    - Putting together for Hope Foundation IMPACT grant application

Kennecke presented 2nd concept.

- NEO-RT study
- Follow-up to NEO trial, a CCTG study that just completed enrollment
- Expect results by end of 2020
- Building a successor
- For stage 1 rectal cancer patients
- Intervention will be either FOLFOX or FOLFOX followed by chemoradiation along with surgical intervention of trans anal endoscopic resection of primary tumor

SWOG Concepts in Development

Type of Cancer	PI	PIs	Design	Primary Endpoint	N	Comments
Anal Locally Advanced	 	D Horowitz/ May Cho	**R Ph II** Cis-5FU Ipi-Nivo vs. Carbo-Taxol Ipi-Nivo	3month cCR		RA-TF Presented Hope Foundation Application
Stage I Rectal **NEO-RT**	 	H Kennecke/ C Brown	**R Ph II** FOLFOX vs. FOLFOX + CRT	2 Year Organ Sparing Survival	200	SWOG CCTG Workinggroups
Stage II/III Rectal **TNT Arm**		Arvind Dasari	**Multiarm RPh II** Multiarm R Ph II FOLFOXIRI + CRT	NAR Score	110	RA-TF Presented GISC submission in development * new study?
Stage II/III Rectal **TNT Arm**		Richard Kim	**Multiarm R Ph II** FOLFOX + RT with Cap Lenvatinib	NAR Score	110	RA-TF Presented GISC Submission in development *new study?
Stage II/III Rectal		S Cohen	RPh II	ctDNA clearance		ctDNA in TNT

SWOG

- Primary endpoint organ-sparing survival
- Update: estimated sample size changed to 200 patients
- Also signing contract to analyze the samples of ctDNA
    - Had been collected at baseline, before excision, and in follow-up for NEO study
    - Will thus have good data about role and prognostic ability of ctDNA assays
    - Can hopefully apply these assays to NEO-RT

Kennecke commented on two TNT arms.

- Have been waiting for quite some time for reopening of TNT study GI002
- It has gone through task force and will be submitted soon
- Chance that because of introduction of new drugs
    - Specifically Lenvatinib
- By adding another experimental therapeutic, could be an entirely new study, which could delay things

Kennecke presented the last concept.

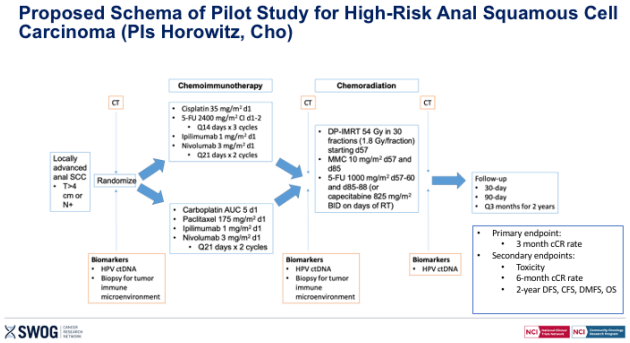
- Been at work on this
- Neoadjuvant chemo looking at role of ctDNA and ctDNA clearance
- Using ctDNA endpoint to make decision about radiation or just bimodality therapy or trimodality therapy
- Early stage concept

Philip asked when TNT would reopen.

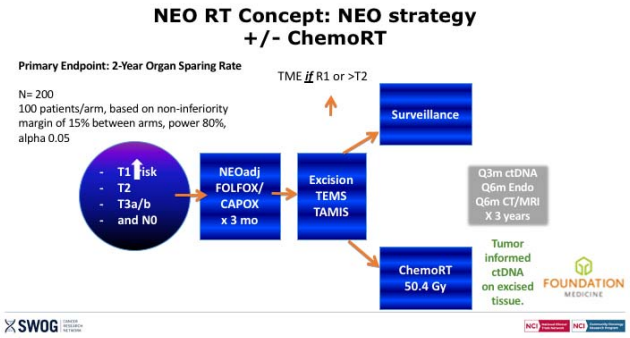
- Kachnic and Kennecke both said 2021

Philip introduced Jonathan Strosberg and Arvind Dasari of the neuroendocrine subcommittee.

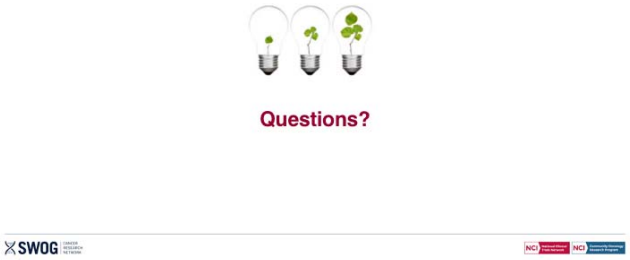
1:58:20



1:58:22



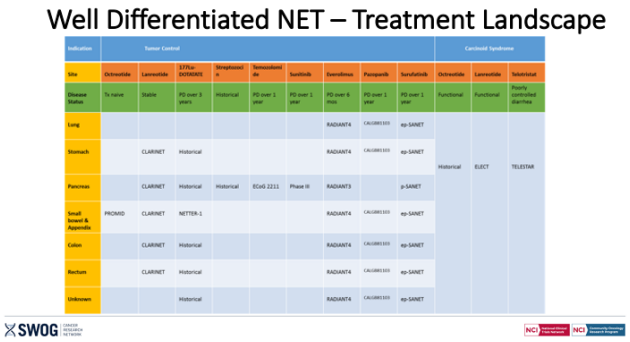
1:58:24



Neuroendocrine
1:58:26
Dasari presented.

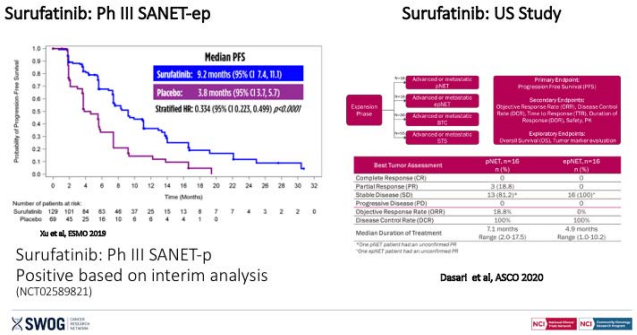
1:58:36
Dasari presented slide with treatment landscape for well-differentiated neuroendocrine tumors (NETs).

- Arranged according to primary site in left column
- Indication on top row
- Agents that are FDA approved or have data from large randomized trials
- For tumor control and carcinoid syndrome control
    - Analogs including octreotide and lanreotide are mainstay of management
    - Pancreatic NETs are unique in responding to cytotoxic therapy including streptozocin and temozolomide
    - Everolimus is FDA-approved for all NETs, regardless of primary site
    - VEGF inhibitors have been approved for pancreatic NETs (sunitinib)
    - Fairly robust hints of activity of VEGF inhibitors in extrapancreatic and carcinoid tumors, but never really large randomized trials until recently
        - CALGB trial showed activity for pazopanib in large phase 2 trial
        - More recently 2 large phase 3 trials from China with surufatinib
    - Only other drug in carcinoid syndrome space is telotristat, a peripheral l-tryptophan hydroxylase inhibitor for poorly controlled diarrhea



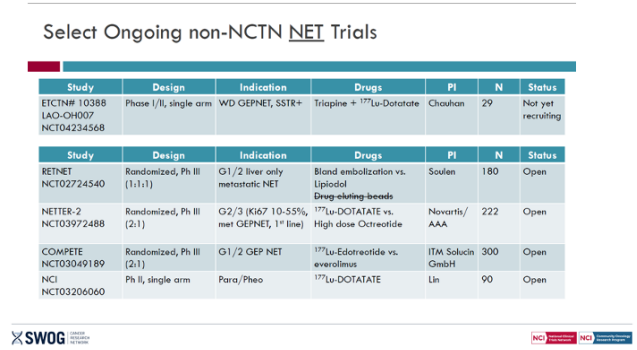
2:00:59
Surufatinib

- Dasari referred to this as new kid on the block
- Two large placebo-controlled phase 3 trials in China
- Both were stopped based on interim analyses
- First trial presented was in extrapancreatic NETs
    - Showed HR for primary endpoint of PFS of 0.33
- Trial for pancreatic NETs just presented at ESMO with HR for primary endpoint of 0.49
- Phase 1b trial in US that confirmed tolerance and MTD to be identical to those found in Chinese trials
- Initial plan was to do a phase 3 trial, but after FDA meeting company is filing for new drug application in both Europe and US using Chinese data and US phase 1 data, which will be filed later this year



2:02:42
Dasari presented slide of ongoing non-NCTN NET trials.

- Many are around PRRT or trying to improve efficacy or move to an area line or extend indication to other tumor types
- COMPETE trial looking at grade1/2 GEPNETs
    - Randomized 2:1 to Lu-edotreotide vs everolimus control arm
    - Patients with progressive disease
- NETTER-2 trial is randomizing GEPNET patients in first line for grade 2/3 tumors, Ki67 10%–55%, to Lu-Dotatate vs high-dose octreotide
- Phase 2 of Lu-Dotatate in gangliogliomas and pheochromocytomas
- Phase 1/2 of adding triapine to Lu-Dotatate in well-differentiated neuroendocrine tumors



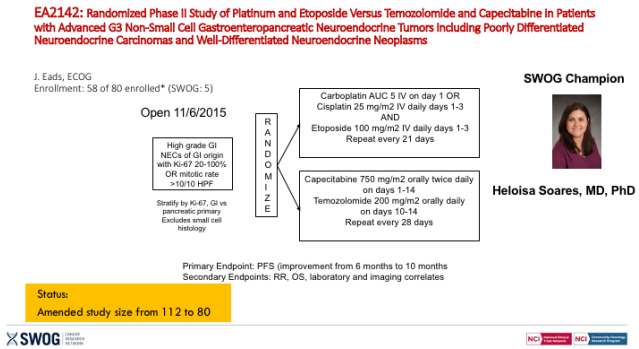
Dasari also mentioned RETNET trial.

- Evaluate best modality for liver-directed therapy

2:04:42
Dasari reviewed the ongoing NCTN studies in the field.

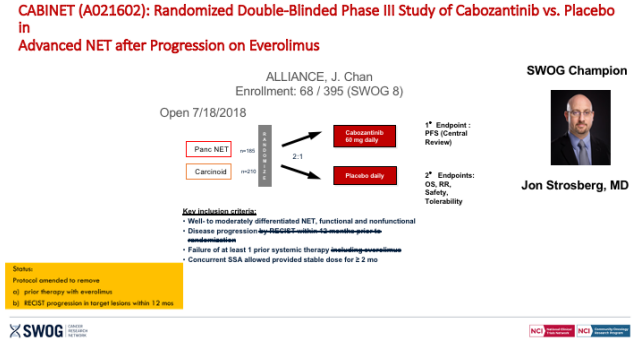
Heloisa Soares presented EA2142.

- First line randomized phase 2 trial using platinum/etoposide vs cape/tem for patients with grade 3 non-small-cell NETs
- Trial had slow accrual
- Amendment to total of 80 patients
- Around 50 patients enrolled



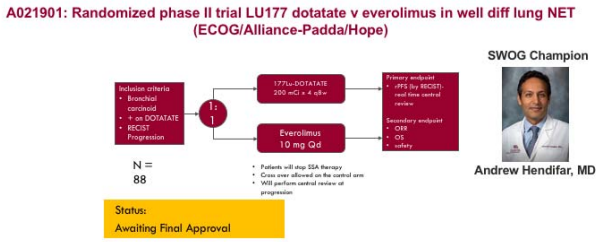
2:05:50
Jon Strosberg presented CABINET (A021602).

- Looks at another VEGF-inhibiting TKI, cabozantinib, vs placebo in both pancreatic and nonpancreatic GI and NE tumors
- Study is being amended; should come through soon
    - Everolimus no longer required
    - Loosened criteria for RECIST progression within 12 months prerandomization
- Both changes should make trial easier to enroll to
- Patients will require at least one prior therapy but not much more

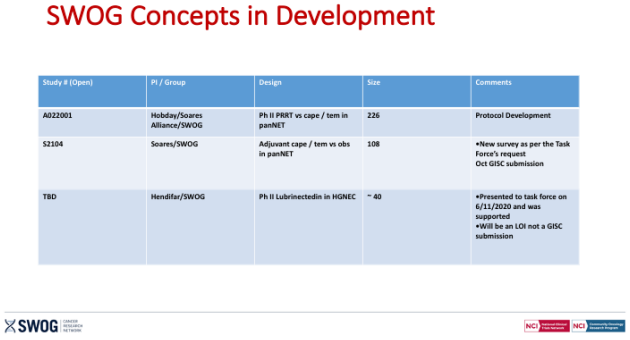


2:07:03
Dasari presented A021901.

- Trial is about to open
- Randomized phase 2 trial of Lu-Dotatate vs everolimus in well-differentiated NETs
- Total of 88 patients randomized 1:1
- Primary endpoint of PFS
- Awaiting final approval



2:07:43
Dasari presented the set of concepts in development being led or co-led by SWOG.



Soares presented A022001.

- Had some feedback from Alliance executive committee
- Working to address questions
- Hopes it will go back to Alliance executive committee and then GI steering committee
- Trial that randomizes pancreatic NETs to PRRT vs cape/tem
- Soares said trial does not address sequencing statistically but should give idea about whether best strategy is cape/tem followed by PRRT
- Will need to enroll >200 patients

Soares also presented S2104.

- SWOG trial for patients at high risk for recurrence after resected pancreatic NET
- Grade 2 or 3
- Good collaboration with Surgical Committee
- Have SWOG approval and going to GI steering committee in October

Dasari presented the last concept.

- Single-arm phase 2 trial of lurbinectedin, a transcription factor inhibitor recently FDA approved for small-cell lung cancer

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- Trial evaluates it in high-grade NE carcinomas
- Will be an LoI in the SWOG network
- Concept in development
- Estimate enrollment of around 40 patients

Jon Strosberg spoke of the two SWOG concepts in development.

- Adjuvant study is first one they've done
- Know these patients tend to recur
- Know there's effective cytotoxic treatment
- Thinks it will be a positive study
- Strosberg noted there is nothing for high-grade NE carcinomas beyond platinum/etoposide, so great to have novel drug
- Said he had just scanned first patient with small-cell cervical NE carcinoma who had a nice response to lurbinectedin, so he's optimistic

Philip made announcement.

- Have two interventional radiologists joining GI Committee:
    - Daniel Brown from Vanderbilt
    - Armeen Mahvash a very experienced interventional radiologist from MD Anderson
- He sees them helping group a lot in NET area
- Hopes group can develop some studies of liver-directed therapy
- Issue of liver-directed therapy vs PRRT and sequencing is open one group should keep in mind
- Philip said he also assumed immunotherapy would not be major player in this area

Strosberg responded:

- Re immunotherapy question, had demonstrated single-agent PD-1 inhibition works for neither well-differentiated nor poorly differentiated carcinomas
- Also can say that combo CTLA4/PD-1 doesn't work for well-differentiated
- Mixed data on combo immunotherapy in high-grade tumors

- Strosberg referred to basket study of ipi/nivo in which small, unplanned subset analysis showed high response rate of 44%
- At ESMO, Spanish study looking at durvalumab and tremelimumab reported response rate of only 7% in same population
- His personal experience with combo is it has not been effective
    - Just submitted abstract to GI ASCO in which responses were lower
- Agreed that immunotherapy is probably not going to play a big role

Dasari responded:

- Dasari said he wanted to plug efforts by Chiorean looking at combining immunotherapy with chemo in high-grade NE carcinomas
- Effort is through rare tumor subcommittee
- Strosberg acknowledged that many oncologists are adding atezo to first line platinum/etoposide
- Said we really have no data outside of small-cell lung cancer

Gold asked of the cabozantinib trial presented a few minutes earlier are they comfortable randomizing to placebo when there are other agents available?

- Gold said there was a randomization to placebo, yet agents such as Sutent are available
- Strosberg acknowledged Sutent was an option
- Also said with removal of everolimus as requirement, everolimus is option, as is PRRT
- Noted it's a 2:1 randomization for cabozantinib and amendment also added crossover
- Said if patient has high disease burden and standard of care drugs are available, wouldn't randomize someone to placebo

Comment by Sandip Patel:
SWOG S1609 (not available for follow-up)

Gold asked about high-grade poorly differentiated NE carcinomas that are platinum/etoposide refractory: would they not give nivo/ipi a try?

- Strosberg said he would when reasonable
- But response rate of 44% is probably overestimation
- Will be new update to this with a prespecified …

Comment by Joaquina Baranda that there is an ETCTN trial on high grade tumors using ipi/nivo with cabo.

- Dasari said he thought it was a phase 1 with an expansion cohort

Philip invited Patel to follow-up on his earlier comment.

Concluding remarks and adjournment

2:17:37

Philip thanked all speakers and presenters; thought meeting was great.

Philip said they're working hard to help people come up with new concepts.

- Also are eager to help young investigators.
- Or older investigators who have not been involved with SWOG.
- Said he would like to involve everyone.
- Said it is easy to contact him and leadership
- Wants to encourage people to get involved

Eng said it was important that everyone be aware there are now subcommittee working groups.

- Started since last meeting
- Eng said for those who have a concept, a good approach is to work with those in the working group with malignancy of your choice
- Can develop concept fully and vet it almost completely before bringing it to monthly meeting to increase chances that Committee will approve it
- Said initiative has been extremely productive
- Said they have met with each of the malignancies each month, even for just 20 or 30 minutes

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Philip said last question submitted is whether group can open earlier phase trials.

- Philip said yes, and group has done it before
- Must first come up with idea and see if it's appropriate for GI Committee

2:21:12
Meeting was adjourned.