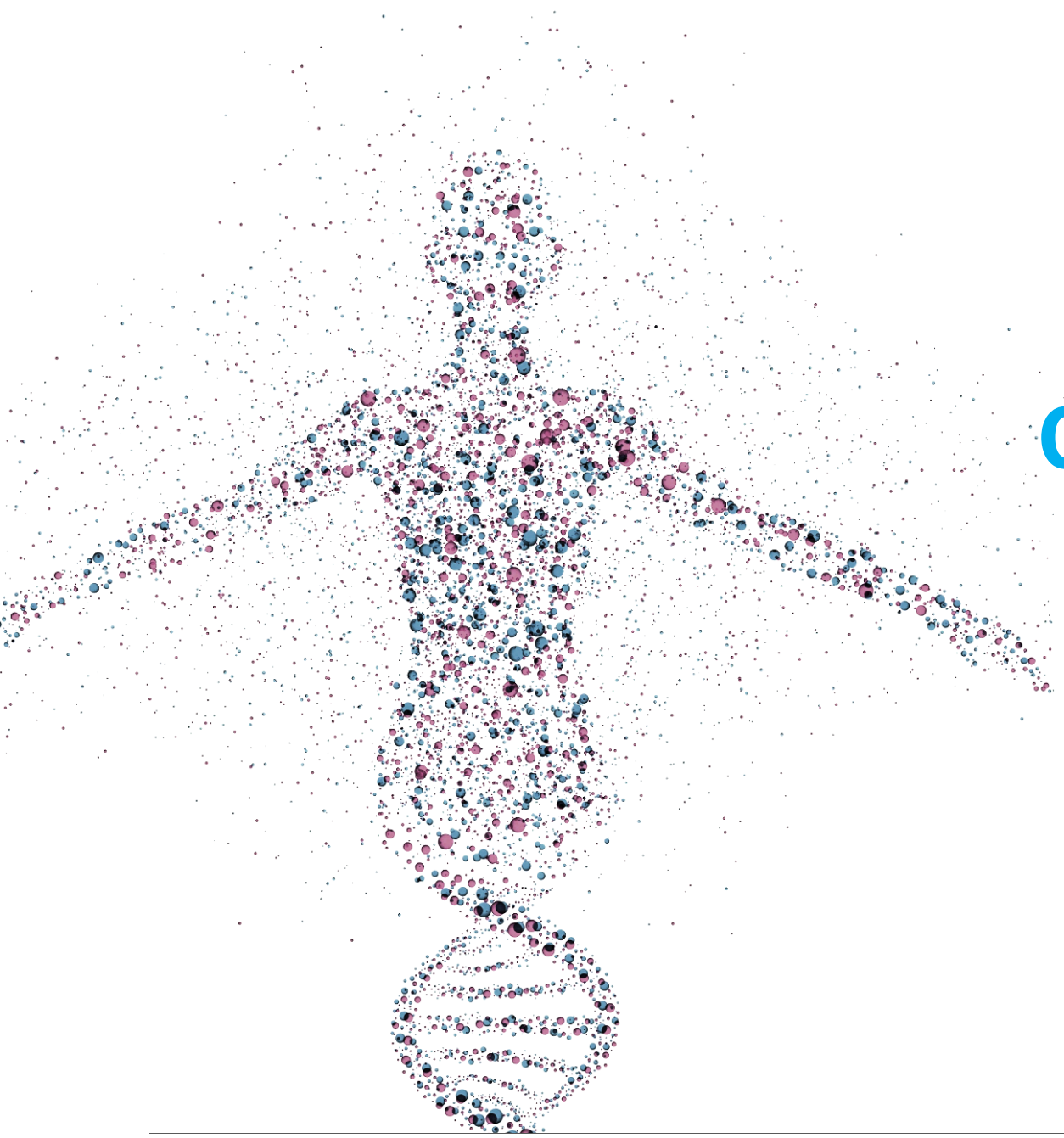

I-SPY 2 TRIAL COVID-19 Pandemic Update

April 6, 2020

Agenda

- Sponsor Update
- Safety Update
- Protocol specific changes
- Site Update
- Discussion

I-SPY 2 Sponsor COVID-19 Update

As of 3.30.2020

- I-SPY PMO
  - All members are available to perform their work by telecommuting. Note CRAs were already telecommuting. All team members are available by email and phone.
  - Clinical supply orders: SD-101 needles will be shipped within 24 hrs after site randomizes patient to manage supply. Sites need to check drug supply and maintain sufficient inventory of critical supplies.
  - E-signatures (e.g. DocuSign) is preferable, if not possible, email confirmation/approval by oncologist with this copied and uploaded as source to EDC.
  - We recognize that due to the COVID-19 pandemic, there will likely be decreased screening/enrollment, thus there will be no penalty or probation based on accrual during this period. We will continue to track enrollment.

Be aware workforce may become sick or unable to work – timelines may be stretched during this outbreak. We will communicate with the sites as this situation is fluid.

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I-SPY 2 COVID-19 Response Communications

- Updates to I-SPY 2 COVID-19 Response will be made available on the I-SPY 2 website https://www.ispytrials.org/ by the next day of the weekly standing I-SPY 2 COVID meeting
- Links to useful resources will also be made available
- Patient Communications will be posted under For Patients https://www.ispytrials.org/patient-landing temporarily until the revised I-SPY 2 Patients website is made available

Safety Reporting for COVID-19 Infection

I-SPY 2 Safety Reporting for COVID-19 Infection

- Tracking confirmed cases of COVID-19 infection as AESIs or SAEs for all arms.
  - If suspected and tested negative, no need to report
  - If suspected and testing will be delayed by 7 days, report as suspected COVID-19 AESI or SAE
  - If suspected and tested positive, report as COVID-19 AESI or SAE (depending on seriousness)

- A follow-up report should be submitted when the status changes
  - CCSA will continue to query all events until resolution
  - If there is a repeat test, submit a follow-up report of the results

- For questions on safety reporting, please email ispy2safety@ccsainc.com

I-SPY 2 Safety Reporting for COVID-19 Infection

- Reported to ispy2safety@ccsainc.com as soon as possible as:
  - Adverse Event of Special Interest (AESI) if not serious
  - Serious Adverse Event (SAE) if it meets criteria for seriousness
- SAEs and AESIs:
  - SAEs reported to CCSA within 48 hours
  - AESIs reported to CCSA within 7 business days

Cases of I-SPY 2 COVID-19

- One case of COVID-19 has occurred:
  - Patient at Columbia tested positive on 3/27/20.
    - She had throat irritation for 2 days prior.
    - She is in follow-up (surgery date 7/11/2018).

SD-101 + Pembro (4) Fever management

- Fever from SD-101 injection within 24 hrs of injection is common
  - Patients should be informed about these injection-related fevers.
  - In the absence of other concerning clinical symptoms, patients can take acetaminophen. If acetaminophen ineffective, judicious use of NSAIDS allowed in first 24 hours.
  - SD101 injection-related fevers should resolve within 24 hours.
  - Fevers persisting longer than 24 hours and/or associated with signs/symptoms of infection should be managed per standard clinical practice.
- SD101 is also associated with neutropenia. Consider starting prophylactic growth factor support for patients receiving SD101
- G-CSF is associated with worsened outcomes in hospitalized patients with acute respiratory distress syndrome (ARDS) and should be used with caution in a patient with suspected COVID-19 or symptoms of respiratory distress

Protocol Specific Changes

I-SPY 2 Visits & Procedures

I-SPY 2 Visits & Procedures	Continue Per Protocol	Allowed modification for COVID-19 situation
Screening Activities Labs MRI MammaPrint (MP)	YES	MammaPrint: Send diagnostic specimen as may have delay with processing research formalin as this goes through a histology lab; MUST ship frozen cores needed for MP Allow clinical lab collection at external labs
Randomization and Enrollment Activities	YES	Trial is open to new accruals, recognize limitations per local site guidelines
Treatment Activities	YES	Collection of concomitant medications by phone, video call
Surgery Activities	YES	Pre-surgical visit by phone, video call
Safety Activities Clinical labs around tx	YES	Safety assessments by phone, video call Allow clinical lab collection at external labs
Follow-up Activities	YES (See modifications)	Follow up visit by phone, video call Follow up labs on hold; can be obtained if patient present for clinically indicated reason (i.e. HP infusion) In person follow-up visits, delay for 2 months unless there is an issue requiring a visit (assess by a pre-screen phone call)

FDA Guidance on COVID-19

1. Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.
2. A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.
3. Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

Acceptable On-Treatment SOC Modifications during COVID-19

Therapy	Acceptable modification
Her2+-directed therapy*	• HP can be given every 3 weeks pre-surgery • Adjuvant HP can be limited to 7 months as per current guidelines
Taxane**	• Can give paclitaxel at 175 mg/m2 or abraxane at 260 mg/m2 every 3 weeks
AC	• No deviation if any cycles dropped for COVID; indicate reason on CRF

*Exception Tucatinib treatment regimen must remain as is described in the protocol.

**Exception SD-101 + Pembrolizumab + Paclitaxel treatment which must remain weekly for the first three doses (Cycles 1-3). On cycles 4, 7, 10 provider may optionally move to q3 weeks paclitaxel/abraxane.

Once COVID-19 restrictions are relaxed at your institution, the provider may return to weekly dosing.

Acceptable Pre-Surgical Bridge Therapy in Event of Surgical Delay during COVID-19

Subtype	MRI Finding	ACCEPTABLE pre-surgical bridge therapy
Her2+/HR neg	Any	Maintain adjuvant HP every three weeks per SOC
HR+/Her2 neg	Any	Start adjuvant endocrine therapy per SOC
HR+/Her2+	Any	Start both adjuvant HP and endocrine therapy per SOC
Triple negative	Unequivocal residual disease	Start adjuvant capecitabine
Triple negative	Possible pCR	Hold any bridge therapy up to 6 weeks

I-SPY Imaging

- All team members are telecommuting and are available by email.
- Their central imaging work is not affected by telecommuting.
- E-signatures (e.g. DocuSign) is preferable, if not possible, email confirmation/approval by radiologist with this copied and uploaded as source to EDC.

I-SPY 2 COVID-19 MRI Updates (04/06/2020)

Timepoint	Continue Per Protocol	Notes
Pre-screening	YES	Mandatory.
Week 3	YES	Deviation if not performed.
6 week (MRI 2.5)	Optional	As needed for clinical care.
Week 12/Inter regimen	YES	Deviation if not performed.
Mid-AC (MRI 3.5)	NO	Do NOT perform at this time (MR 3.5)
Pre-surgery (if surgery NOT delayed)	Optional	If patient has a mastectomy, ok to omit pre-surgery MRI
Pre-surgery (if surgery delayed)	Optional	Perform at completion of AC (and prior to bridge therapy if given) Additional MRI within 7 days prior to surgery; to be used for Sales Force
Pts who have discontinued investigational therapy	NO	No MRs for patients who have discontinued investigational treatment and are on SOC

I-SPY Laboratory and Repository

- Limited staff will be handling ‘Essential’ collections, processing, and storage
- Agendia is currently staffed to handle processing
- FedEx is currently running near normal
- UCSF Histology Lab may have limited service/longer timelines; suggest diagnostic slides (note we have noticed a delay in shipping of these samples)
- Inter-regimen clinical biopsy: collect as reasonably able to do
  - Please note that patients consented prior to A22 are still eligible for clinical assessment of the biopsy

I-SPY 2 Specimens Update

Timepoint	Research Biopsy/ Clinical inter-regimen Biopsy	Research blood for plasma, serum and buffy coat	Research CPT
Pre-treatment (cannot be collected at later date)	Collect if possible or needed for MammaPrint. Ship to I-SPY lab. If not collected complete CRF.	Collect if staff available to process and freeze. Store onsite, do not ship. If not collected complete CRF. No PK testing for Tucatinib	Suspend collection Note as not collected on CRF if other blood are collected.
Early treatment (wk 3)	n/a	Collect if staff available to process and freeze. Store onsite, do not ship. If not collected plan to collect in one month. No PK testing for Tucatinib	Suspend collection If not collected, plan to collect in one month.
Inter-regimen	Collect if possible. Research: Ship formalin to I-SPY lab, store frozen. Clinical: submit to local histology Cannot be collected at later date. If not collected complete CRF.	Collect if staff available to process and freeze. Store onsite, do not ship. Plan to collect in one month. If not collected complete CRF.	Suspend collection If not collected, plan to collect in one month.
Pre-Surgery/Surgery	Collect if possible. Ship formalin to I-SPY lab, store frozen. If not collected complete CRF & request diagnostic specimen	Collect if staff available to process and freeze. Store onsite, do not ship. If not collected complete CRF.	Suspend collection Note as not collected on CRF if other blood are collected.
Post surgery and annual follow up	n/a	Can collect when patient presents for clinical reasons (i.e. HP infusion) or at a future time	n/a

Discussion/Action Items

- I-SPY 2 Memo to be released to sites this week based on decisions discussed on this call. The memo will be need to be submitted to the site IRB. Note given FDA guidance, sites can take action on updates provided by the call and slide deck as modifications are for the safety of the patient during the COVID-19 pandemic.
- I-SPY to determine the time period of safety reporting of COVID-19 confirmed cases (Safety Working Group)
- I-SPY to provide a COVID-19 Tracking Log template for the sites to track I-SPY 2 patients tested for COVID-19 (Alex Thomas and Melissa Accordino with CTO)