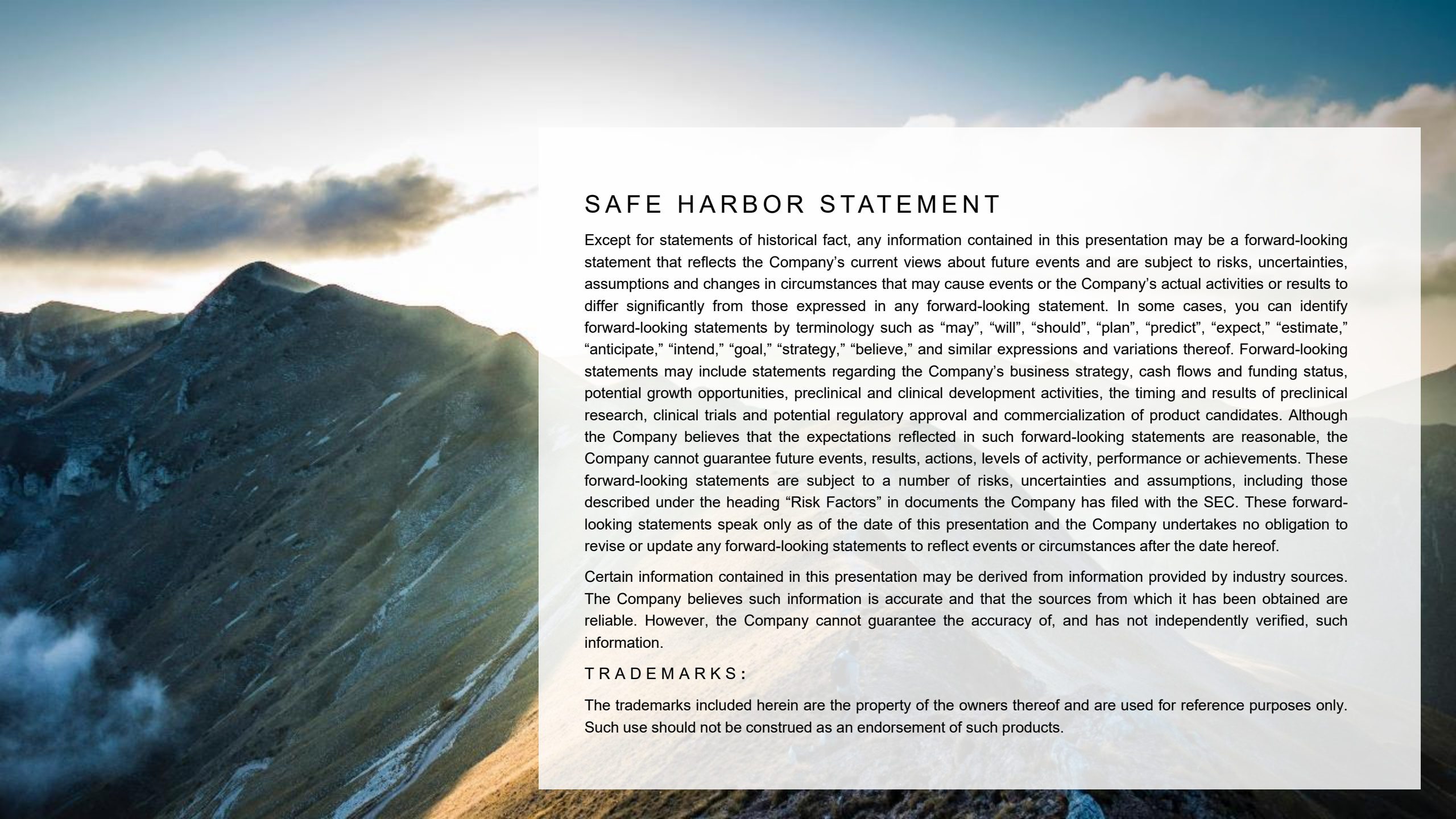
SIERRA ONCOLOGY

# SRA737 Analyst & Investor Call

June 3, 2019

American Society of Clinical Oncology Annual Meeting

**NASDAQ: SRRA**



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# Addressing Unmet Medical Needs with a Broad Pipeline

DDR Network Programs

## momelotinib

MOMELOTINIB
JAK1/2 ACVR1

TARGETING JAK1/2 AND ACVR1

THERAPEUTIC FOCUS

Myelofibrosis

## SRA737

SRA737
Chk1

TARGETING Chk1

THERAPEUTIC FOCUS

Anogenital Cancer
& Other Solid Tumors

## SRA141

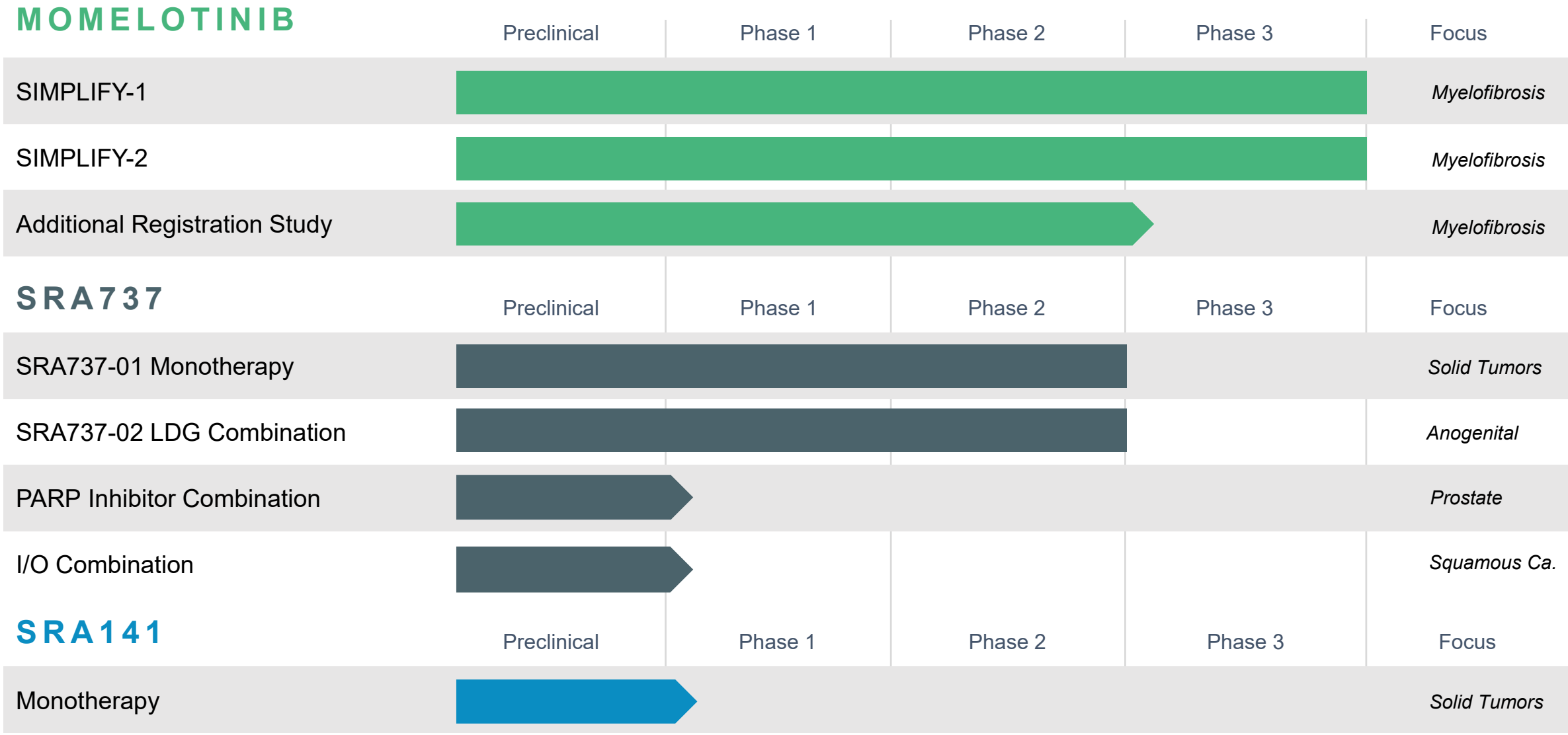
SRA141
Cdc7

TARGETING Cdc7

THERAPEUTIC FOCUS

Colorectal Cancer

# Our Pipeline of Targeted Therapeutics



# ASCO 2019:
# **SRA737 Poster Presentations**

***A Phase 1/2 First-in-Human Trial of Oral SRA737 (a Chk1 Inhibitor) in Subjects with Advanced Cancer*.**

Abstract: 3094

***A Phase 1/2 First-in-Human Trial of Oral SRA737 (a Chk1 inhibitor) Given in Combination with Low Dose Gemcitabine in Subjects with Advanced Cancer.***

Abstract: 3095

Data Cut Off: May 3, 2019. Data not final.

# Dr. Rebecca Kristeleit

## University College London Cancer Institute & UCLH Dept. of Oncology

- Dr. Rebecca Kristeleit is Clinical Senior Lecturer and Honorary Consultant Medical Oncologist at University College London (UCL) Cancer Institute & UCLH Dept. of Oncology.
- Through her work within the gynaecological oncology team and the clinical research facility at UCLH and UCL Cancer Institute, Rebecca has developed a comprehensive portfolio of cutting-edge early phase trials and translational research studies to identify and evaluate innovative treatment strategies for cancer, particularly gynaecologic malignancies.
- She has received grant-funding for trials and translational projects in endometrial and ovarian cancer and is Chief Investigator for a number of early phase studies.
- She was the 2016 Chair of the ASCO Gynaecologic Scientific Committee, 2018 Scientific Chair of the BGCS Conference, is a member of the Target Ovarian Cancer Scientific Research Committee, the NCRI and is gynaecology cancer research lead for North Thames.

Clinical Senior Lecturer and Honorary Consultant Medical Oncologist

**University College London Cancer Institute & UCLH Dept. of Oncology**

# Professor Johann de Bono
## Institute of Cancer Research UK

- Professor Johann de Bono is Regius Professor of Cancer Research and a Professor in Experimental Cancer Medicine at The Institute of Cancer Research and Royal Marsden. He is also the Head of the Division of Clinical Studies at The ICR and the Director of the Royal Marsden Drug Development Unit, leading the NIHR Experimental Cancer Medicine Centre team and co-leads the NIHR Biomedical Research Centre overseeing the Systemic Therapies theme.
- The Royal Marsden Drug Development Unit is one of the world's largest Phase I clinical trials units for cancer, run jointly between The Institute of Cancer Research (ICR) and The Royal Marsden and The London Movember Prostate Cancer Centre of Excellence.
- He leads the Prostate Cancer Targeted Therapies team and has also led on multiple phase III trials that have changed the standard of care for prostate cancer, including trials of the ICR-discovered drug abiraterone, cabazitaxel and enzalutamide and has published more than 400 manuscripts including multiple publications in the New England Journal of Medicine and The Lancet.

Regius Professor of Cancer Research
Professor of Experimental Cancer Medicine
Director of the Drug Development Unit and Head of the Prostate Cancer Targeted Therapy Group

**The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust**

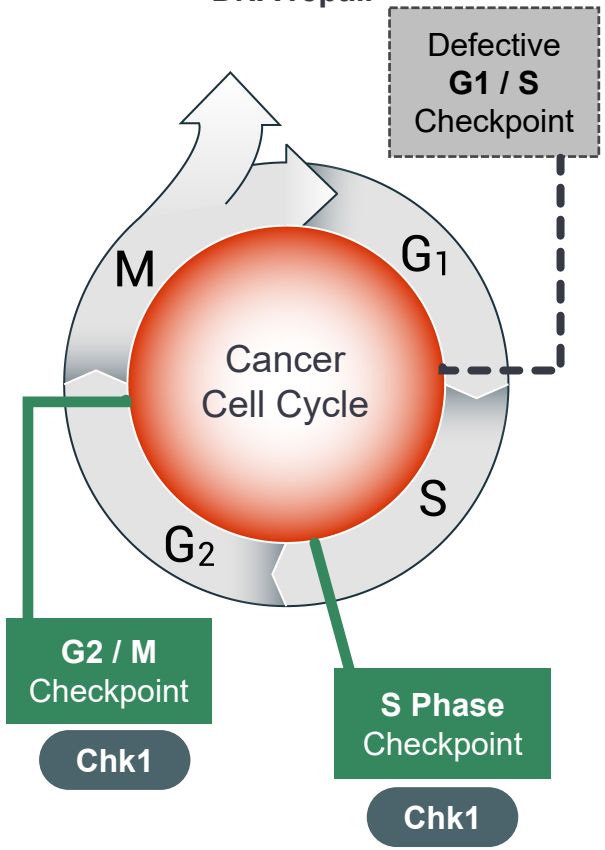
# SRA737

Highlights of SRA737-01 & SRA737-02 Clinical Studies

# Chk1:
## Next-generation DDR target & Master Regulator of Replication Stress

### CELL CYCLE

**Chk1 pauses the cell cycle to enable DNA repair**

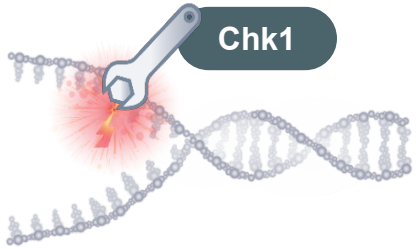



G1/S-defective cancer cells are reliant on Chk1-regulated cell cycle checkpoints

### DNA DAMAGE RESPONSE

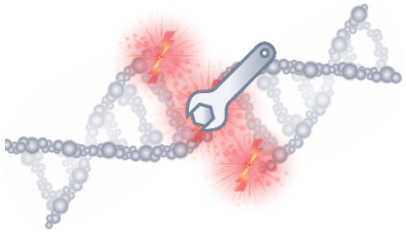
**Chk1 regulates origin firing to manage replication stress**


**Chk1 stabilizes stalled replication forks**

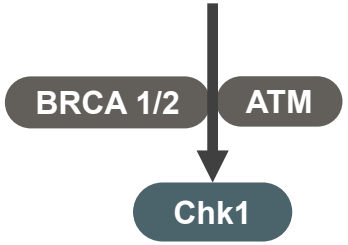



Stalled replication forks

**Chk1 mediates DNA repair via HRR**



Double strand breaks




HRR = Homologous Recombination Repair

# Intrinsic & Extrinsic Inducers of Replication Stress (RS): **Elevated Genomic Instability & Reliance on Chk1**

## INTRINSIC RS INDUCERS

**Cell cycle dysregulation**
Loss of G1/S

e.g. TP53* / HPV* → Defective **G1 / S** Checkpoint

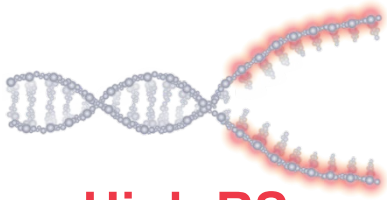
**Oncogenic drivers**
Dysregulation of replication, transcription/replication collision

e.g. MYC* CCNE1*

**Defective DNA damage repair**
Single strand breaks, double strand breaks

e.g. BRCA 1/2*

*Illustrative genes and drivers only



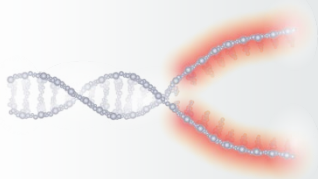
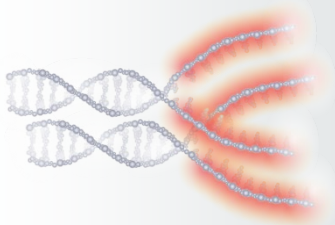
**High RS results in:**


## EXTRINSIC RS INDUCERS

**Depleted replication building blocks**
Low dose gemcitabine (LDG)


***Increased reliance on Chk1 in tumor***

# SRA737 Program Overview:
# **Broad Signal Seeking Across Indications & Genetics**

| Clinical Trial | Clinical Hypothesis | Indications | Tumor Genetics | Ph2 Directional Efficacy Signal |
|---|---|---|---|---|
| SRA737<br>**SRA737 Monotherapy (-01)** |  <br>Intrinsic RS | **HGSOC**<br>**SCC (H&N, anogenital)**<br>**NSCLC**<br>**mCRPC**<br>**mCRC** |  <br>Tumor Suppressor<br>*TP53, RAD50...*<br>Oncogenic Drivers<br>*CCNE1, MYC…*<br>Replicative Stress<br>*ATR, CHEK1…*<br>DNA Repair Machinery<br>*BRCA1, FANCA…* | **Indication / genomic signature with enriched response to SRA737 +/-LDG** |
| SRA737 + LDG<br>**SRA737 + LDG (-02)** |  <br>Intrinsic + Extrinsic RS | **HGSOC**<br>**Cervical / Anogenital**<br>**SCLC**<br>**STS** | | |

# SRA737:
# Subject Characteristics and Dose Evaluation

## SRA737 MONOTHERAPY

**Dose Escalation phase:**

- 18 subjects received SRA737 across 9 dose level cohorts (20 - 1300 mg QD. 3 experienced DLTs (inability to receive 75% of the planned dose); 2 at 1300 mg QD (gastrointestinal intolerability), 1 at 500 mg BID (thrombocytopenia).
- The maximum tolerated dose (MTD) was established at 1000 mg QD or 500 mg BID.
- **The recommended Phase 2 dose is 800 mg QD (RP2D).**

**Cohort Expansion phase:**

- 512 subjects prospectively identified, 355 screened for genetic alterations associated with Chk1 sensitivity, 237 (67%) met genetic eligibility criteria, 94 treated in expansion cohorts across six tumor types.

**Dosing Schedule**

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| SRA737 po | ■ | ■ | ■ | ■ | ■ | ■ | ■ |

## SRA737 + LOW DOSE GEMCITABINE

**Dose Escalation phase:**

- 58 subjects received SRA737 in 13 escalation cohorts (50 - 600 mg SRA737, variously combined with LDG doses (50 - 300 mg/m$^2$).
- No protocol-defined dose limiting toxicities (DLTs) were observed; intolerability was notably evident at the highest doses tested.
- **The recommended Phase 2 dose is 500 mg SRA737 + 250 mg/m$^2$ LDG (RP2D).**

**Cohort Expansion phase:**

- 335 subjects prospectively identified, 204 screened for genetic alterations associated with Chk1 sensitivity, 176 (86%) met genetic eligibility criteria, 85 enrolled into four expansion cohorts.

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| LDG (IV) | ■ | | | | | | |
| SRA737 po | | ■ | ■ | | | | |

LDG and SRA737 administered weekly for 3 weeks on a 28-day cycle

# SRA737:
# Baseline & Demographic Data

## SRA737 MONOTHERAPY

| Characteristic | Overall (Escalation + Expansion) | Tumor types of Interest (Expansion)* | | | |
|---|---|---|---|---|---|
| | | HGSOC (inc. CCNE1 enriched)** | CRC** | NSCLC | mCRPC** |
| Number of subjects treated | 107 | 38 | 27 | 10 | 15 |
| Prior systemic therapy regimens; mean (min, max)*** | 4.2 (1, 10) | 4.7 (2, 10) | 3.5 (2, 5) | 3.2 (2, 6) | 5.7 (2, 10) |
| Treatment delay from consent to C1D1; median (min, max) | 61 (9, 329) | 59 (11, 329) | 74 (10, 154) | 86 (15, 314) | 63 (9, 296) |
| Subjects evaluable for target-tumor response****; [# with genetic profile available] | 71 [64] | 24 [21] | 22 [21] | 7 [7] | 9 [8] |

* In addition to the subjects shown, 4 subjects with HNSCC were enrolled; no SCCA subjects were enrolled
** Includes subjects in the Dose Escalation phase concurrently enrolled in Cohort Expansion (3 CRC; 1 HGSOC; 1 mCRPC)
*** Prior radiation therapy regimens: n=44
****Subjects with pre- and post-treatment target tumor measurements who received ≥ 75% of total planned C1 dose at ≥ 300mg, or continued on-study after 2 cycles of treatment at any dose level
Data cut off: 03 May 2019.

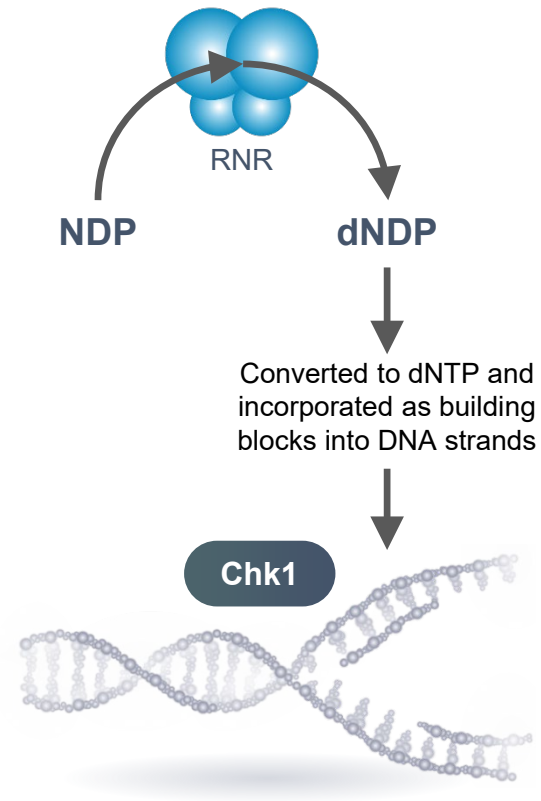
## SRA737 + LOW DOSE GEMCITABINE

| Characteristic | Overall SRA737 + LDG (Escalation & Expansion) | Tumor Types of Interest | | | |
|---|---|---|---|---|---|
| | | Anogenital/ Cervical Cancer | | Rectal cancer | HGSOC |
| | | Anogenital | Cervical | | |
| Number of subjects treated | 141 | 18 | 17 | 14 | 28 |
| Prior systemic therapy regimens; mean (min, max) | 2.8 (1, 9) | 2.0 (1, 5) | 2.2 (1, 4) | 3.5 (2, 5) | 4.2 (1, 9) |
| Prior radiation therapy regimens; mean (min, max) | 1.6 (1, 3) n=76 | 1.6 (1, 3) n=14 | 1.9 (1, 3) n=14 | 1.4 (1, 2) n=8 | 1.0 (1, 1) n=2 |
| Treatment delay from consent to C1D1; median (min, max)* | 24 (7, 157) | 26 (11, 147) | 43 (8, 89) | 22 (13, 36) | 28 (8, 84) |
| Subjects evaluable for target-tumor response**; [# with genetic profile available] | 81 [54] | 10 [7] | 12# [9] | 8 [6] | 15 [10] |

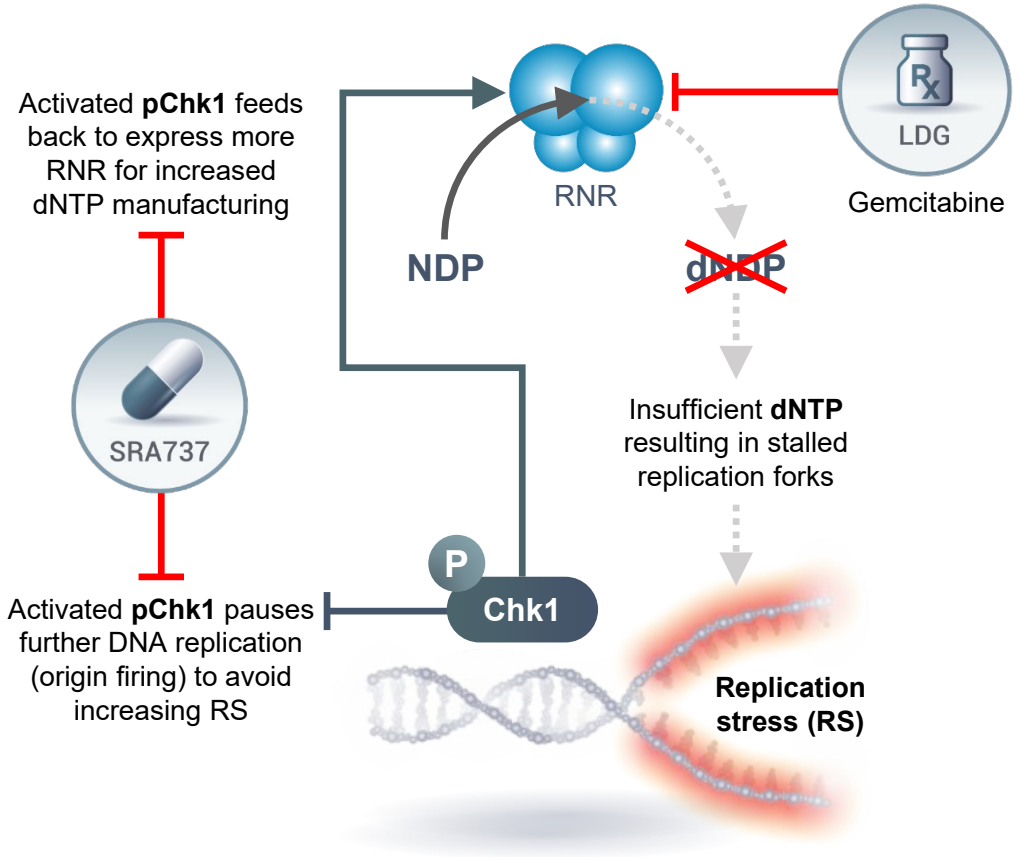
* Subjects with pre- and post-treatment target tumor measurements who received ≥ 83% of total planned SRA737 in C1 at ≥ 150mg SRA737 and ≥ 100 mg/m2 GEM, or continued on-study after 3 cycles of treatment at any dose level
# 8/12 subjects were noted to be squamous
Data cut off: 03 May 2019

# Intrinsic & Extrinsic Inducers of Replication Stress (RS): **Low Dose Gemcitabine (LDG) Potentiates SRA737**

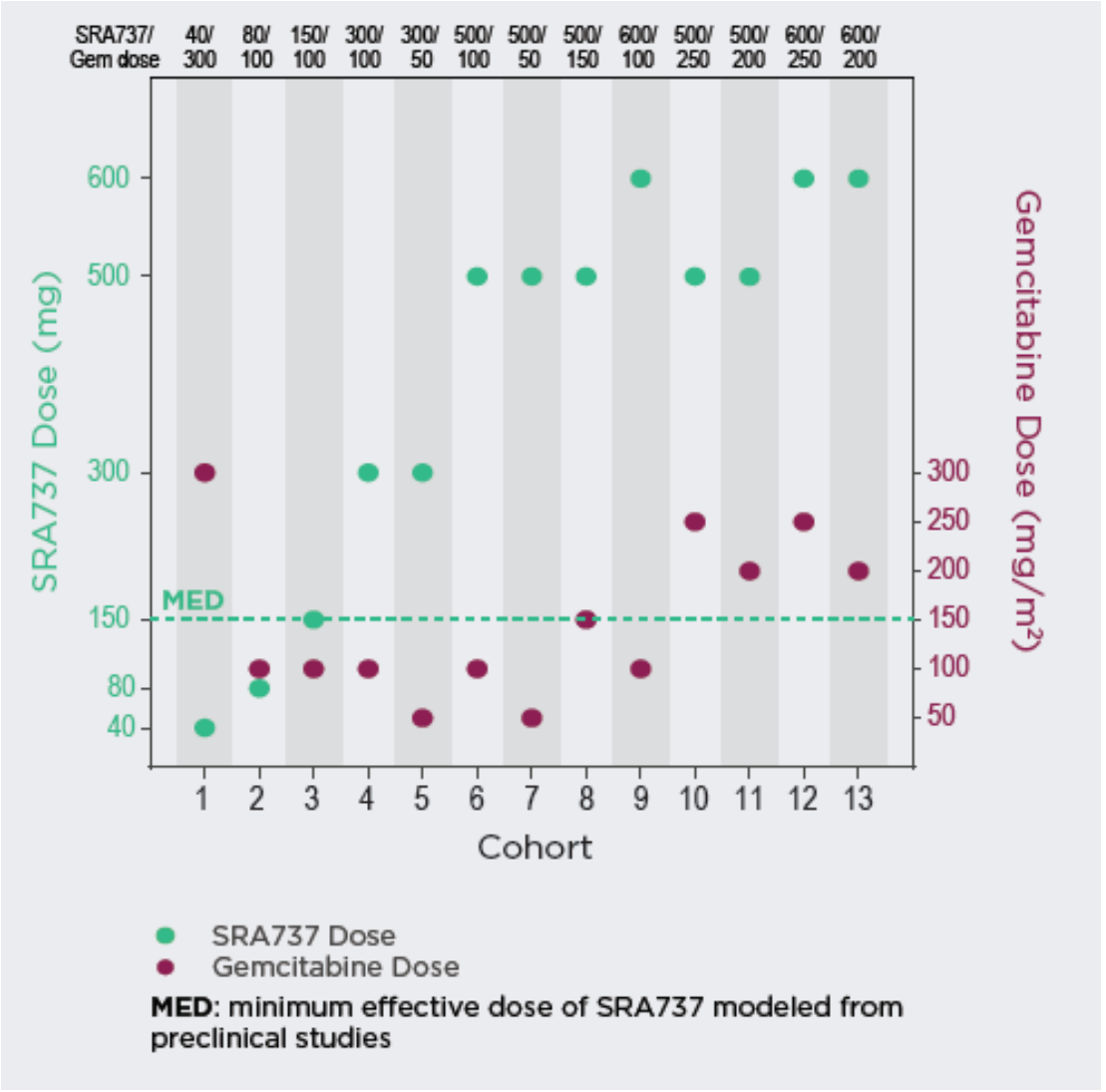
## NO TREATMENT

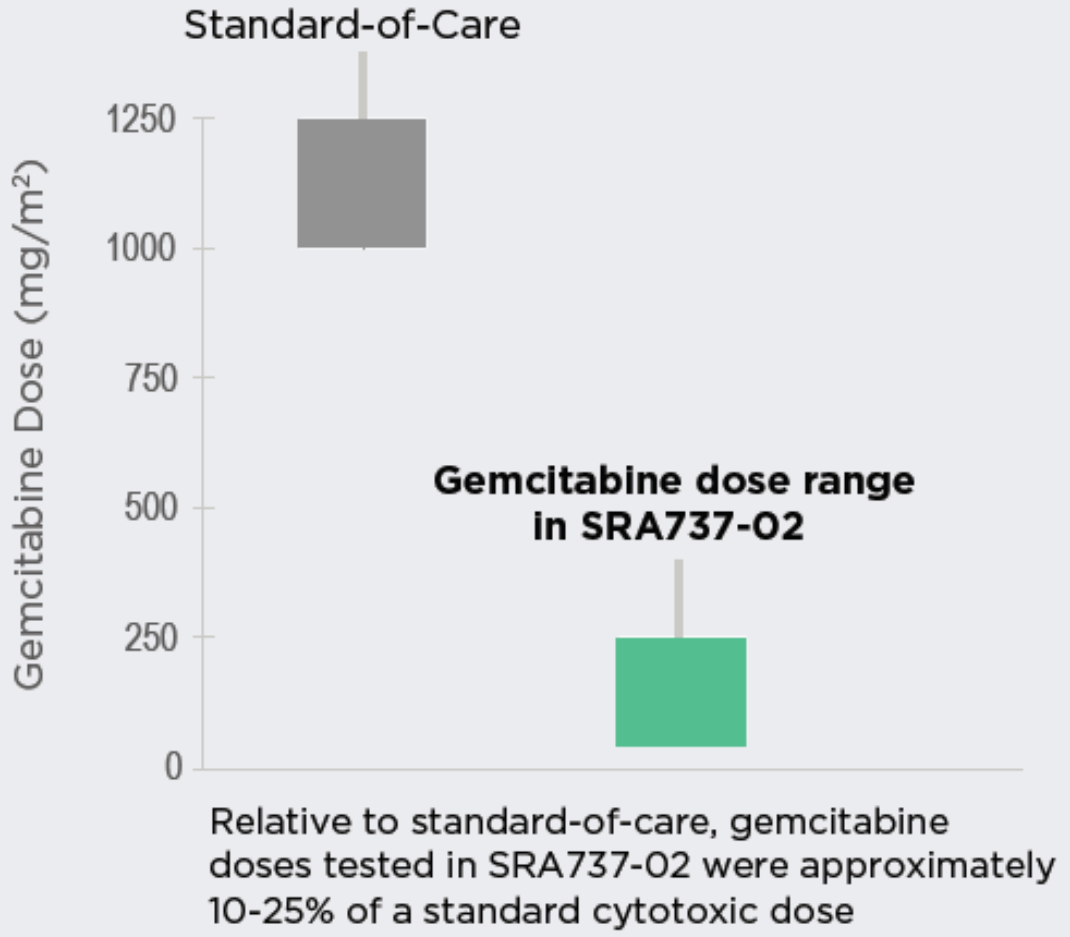



## SRA737 + LDG



# SRA737-02 LDG Combination:
# **Dose Optimization with <u>Low Dose</u> Gemcitabine**



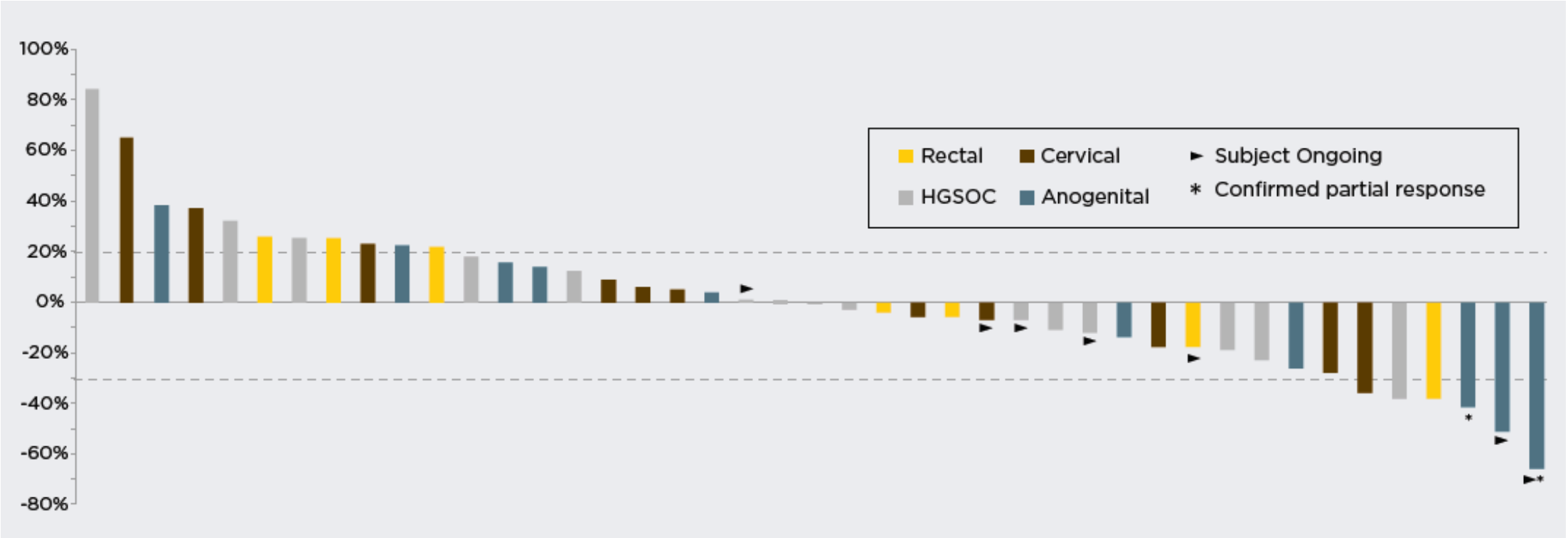
# SRA737:
# Well Tolerated Safety Profile

| | SRA737 MONOTHERAPY | | SRA737+LOW DOSE GEMCITABINE | |
|---|---|---|---|---|
| **Treatment Emergent Adverse Events (TEAEs)** | **Occurring in ≥ 20% of subjects N=107, n (%)** | **≥Grade 3% n (%) N=107, n (%)** | **Occurring in ≥ 20% of subjects N=139, n (%)** | **≥Grade 3% n (%) N=139, n (%)** |
| Subjects with any TEAE | 106 (99.1%) | 73 (68.2%) | 137 (98.6%) | 88 (63.4%) |
| Nausea | 71 (66.4%) | 3 (2.8%) | 83 (59.7%) | 1 (0.7%) |
| Vomiting | 55 (51.4%) | 1 (0.9%) | 70 (50.4%) | 3 (2.2%) |
| Diarrhea | 73 (68.2%) | 2 (1.9%) | 63 (45.3%) | 3 (2.2%) |
| Fatigue | 50 (46.7%) | 3 (2.8%) | 60 (43.2%) | 3 (2.2%) |
| Anemia | 23 (21.5%) | 2 (1.9%) | 46 (33.1%) | 8 (5.8%) |
| Pyrexia | - | - | 43 (30.9%) | 1 (0.7%) |
| Neutropenia | - | - | 36 (25.9%) | 13 (9.4%) |
| Decreased appetite | 25 (23.4%) | 0 | 33 (23.7%) | 0 |
| Thrombocytopenia | - | - | 33 (23.7%) | 5 (3.6%) |
| ALT increased | - | - | 31 (22.3%) | 8 (5.8%) |
| AST increased | - | - | 28 (20.1%) | 7 (5.0%) |
| Constipation | - | - | 28 (20.1%) | 2 (1.4%) |

- The majority of TEAEs were mild to moderate in severity (>90% Grade 1 / Grade 2).
- No evidence of emergent or cumulative toxicity and/or declining tolerability with up to 13 cycles.

TEAEs regardless of the investigator's assessment of causality; Data cut off: 23 March 2019

# SRA737+LDG:
# Demonstrates Anti-Cancer Activity Across Multiple Indications



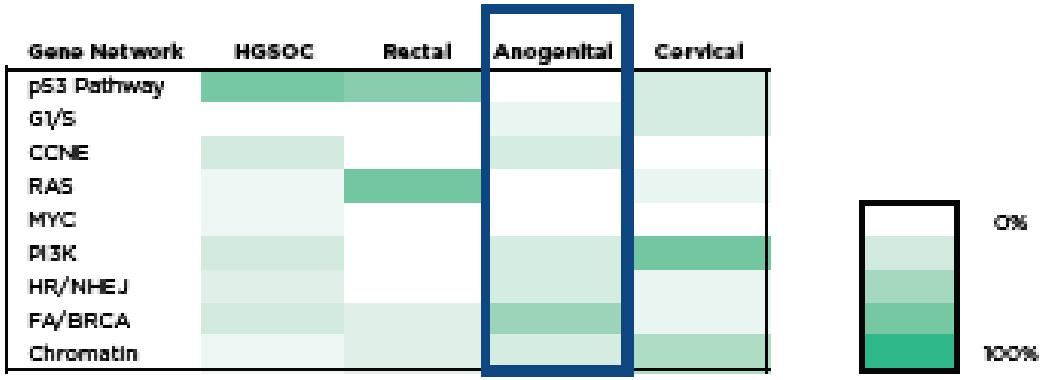

- PRs observed in six subjects (3x anogenital cancer; 1x rectal, cervical, and ovarian cancer). Generally, responses were first recorded at the end of Cycle 2 (first on-study scan).
- 41 subjects had best response of Stable Disease (SD); durable SD lasting ≥ 4 months was recorded in 32 subjects and was observed in all expansion cohorts.

# SRA737 Program Genetic Analysis:
# **Signal Seeking for Chk1i Genetic Sensitivity**

- Subjects were prospectively screened for tumor genetics harboring alterations predicted to have elevated RS and increased sensitivity to Chk1i.
- Chk1i-sensitizing genetics were divided into several functional gene categories.
- Several gene networks (or individual gene alterations) occurred with sufficient frequency to identify trends with respect to SRA737 +/- LDG sensitivity and disease control rate (DCR).

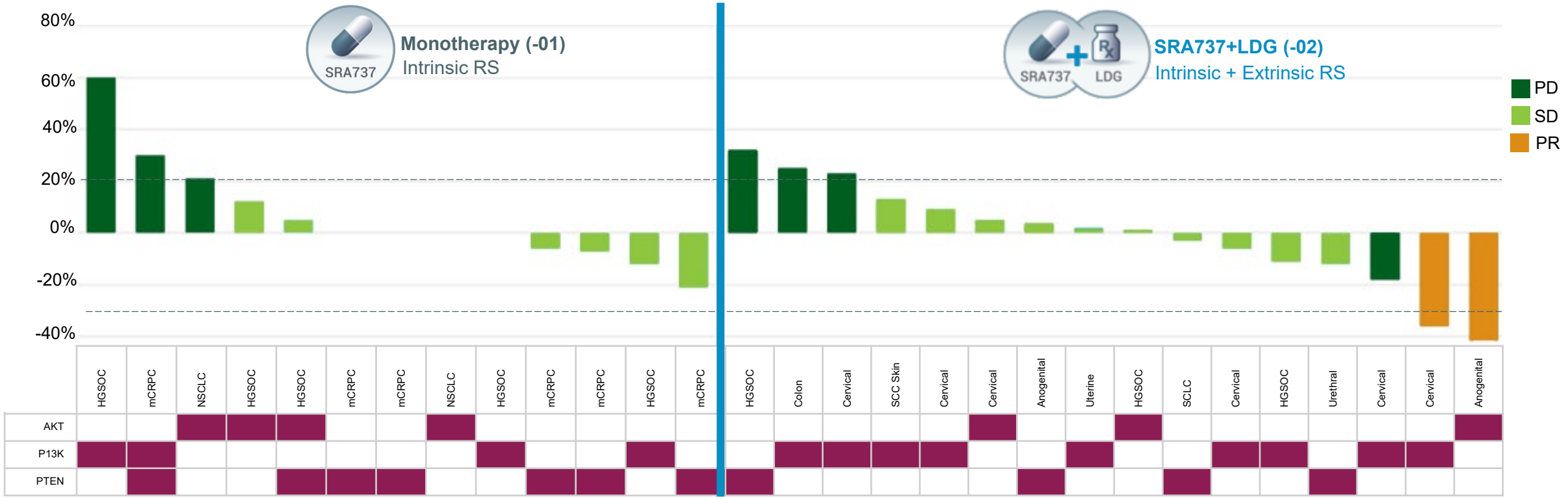
# SRA737 Program Genetic Analysis:
# **Responses Vary Across Gene Networks Surveyed**

Alterations in certain gene networks were found to be more prevalent in defined indications (e.g. RAS in rectal cancer, FA/BRCA in anogenital). Mutations in the RAS gene network were associated with relatively poor DCR (44%). Alterations in PI3K (75%) and FA/BRCA (81%) gene networks correlated with favorable DCR and were associated with several PRs.



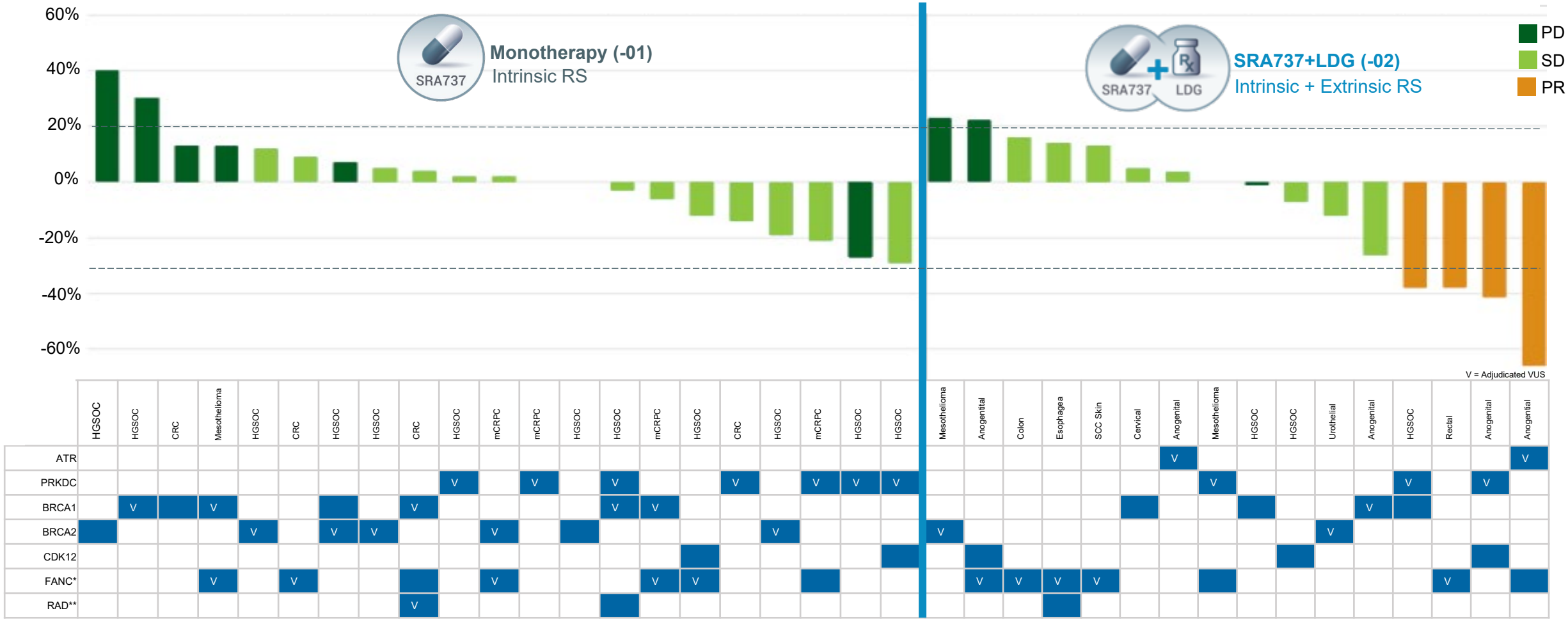

| Functional Gene Category | Gene Network | Gene | Number of Subjects | Number of RAS Wild-Type Subjects | DCR‡ (%) | Response Rate‡ (%) |
|---|---|---|---|---|---|---|
| Cell Cycle Dysregulation | p53 Pathway | *MDM2* *TP53* | 29 | 25 | 64% | 8% |
| | G1/S | *RBI* *CDKN1A/B* *CDKN2A/B/C* | 10 | 10 | 60% | 0% |
| Oncogenic Drivers | CCNE | *CCNE1* *FBXW7* *PARK2* | 6 | 6 | 67% | 17% |
| | RAS | *KRAS* *NRAS* *HRAS* | 9 | NA | 44% | 0% |
| | MYC | *MYC* *MYCN* *MYCL1* | 1 | 1 | 0% | 0% |
| | PI3K/AKT | *PIK3CA* *PTEN* *AKT1/2/3* | 19 | 16 | 75% | 13% |
| DNA Damage Response and Repair Network | FA/BRCA | *CDK12* *FANC** *RAD*** | 17 | 16 | 81% | 25% |
| | HR/NHEJ | *ATR* *BRCA1/2* *RAD51B* *RAD51C* *PRKDC* *PALB2* *ATM* | 8 | 7 | 71% | 29% |
| | Chromatin | *MLL2* *ARID1A* *ARID1B* | 9 | 8 | 38% | 13% |
| | Mismatch Repair | *MLH1* *MSH2* *MSH6* *PMS2* | 0 | 0 | NA | NA |
| | DNA Pol | *POLD1* *POLE* | 0 | 0 | NA | NA |

# SRA737 Program Genetic Analysis:
# **PI3K May Enhance SRA737 Sensitivity**



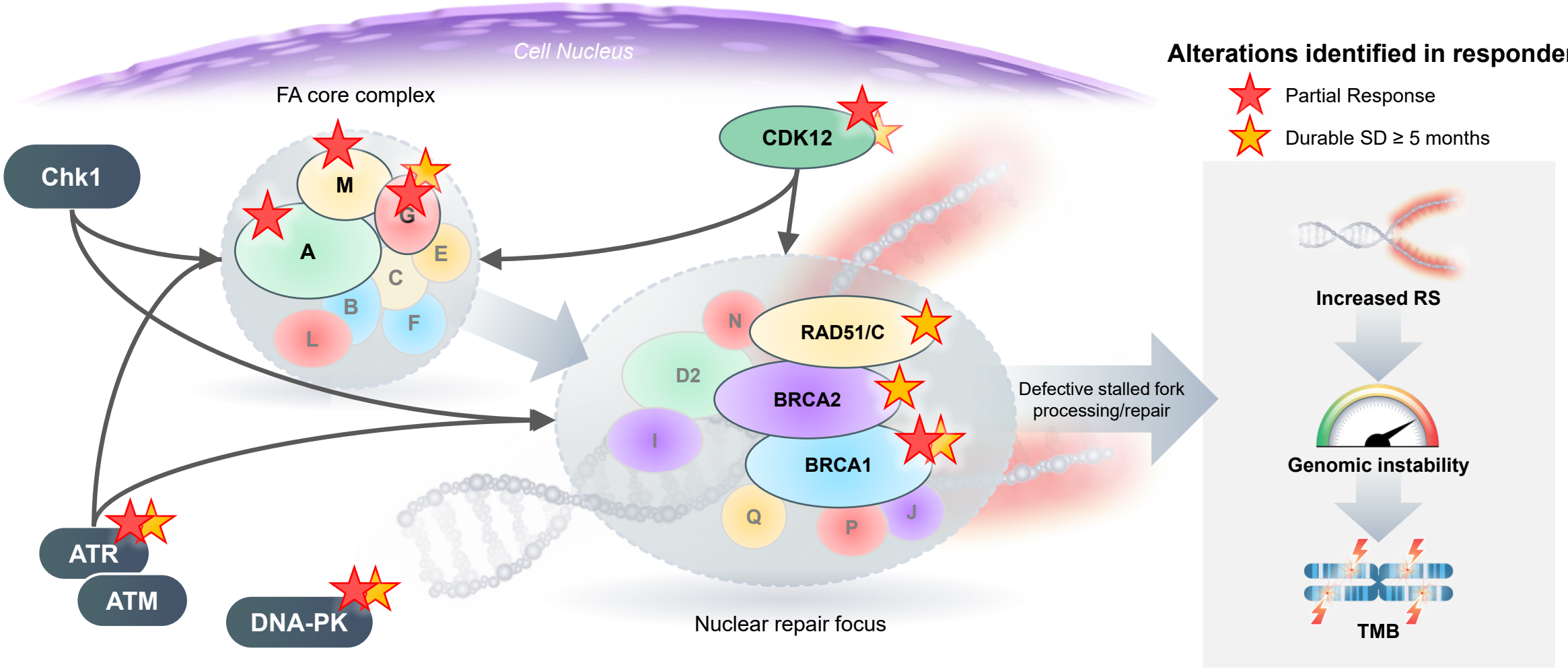

- Genomic alterations in PI3K gene network trend with improved response to SRA737 therapy in both -01 and -02 trials.
- Effects seen in multiple tumor types suggesting this oncogenic pathway may predispose to SRA737 regardless of tumor histology.

# SRA737 Program Genetic Analysis:
# **Activity Associated With FA/BRCA Replication Fork**




- Genomic alterations in *FANC* and *BRCA* genes and associated regulators (e.g. *CDK12, ATR*) trend with improved response to SRA737 therapy in both -01 and -02 trials.
- Correlation appears indication agnostic, representing a potential focused enrichment strategy.

# SRA737 Program Genetic Analysis:
# **Replication Stress - Relevance of FA/BRCA Network**



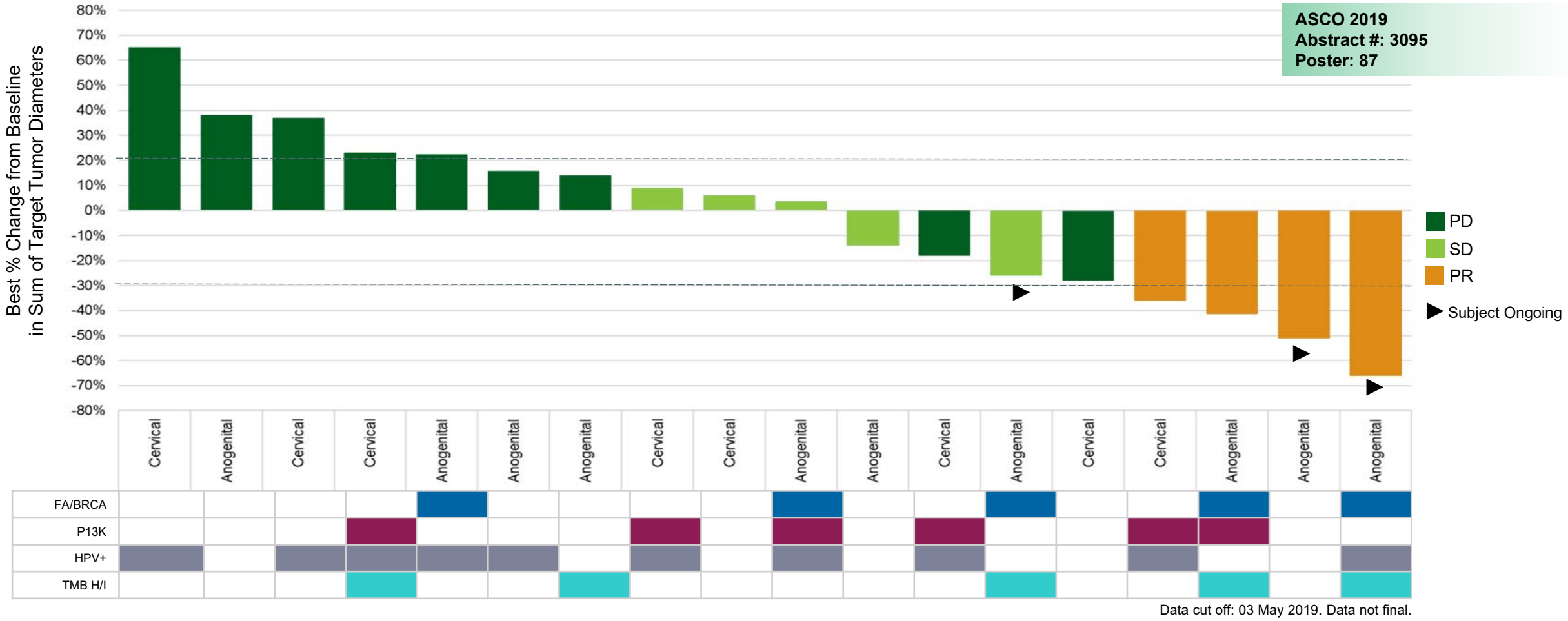

PRs and robust SDs associated with alterations in FA/BRCA gene network; many carrying secondary alteration in other DDR genes

# Anogenital Cancer

## A Potential Path to Registration

# SRA737+LDG:
# Activity in Squamous Anogenital and Cervical Cancer

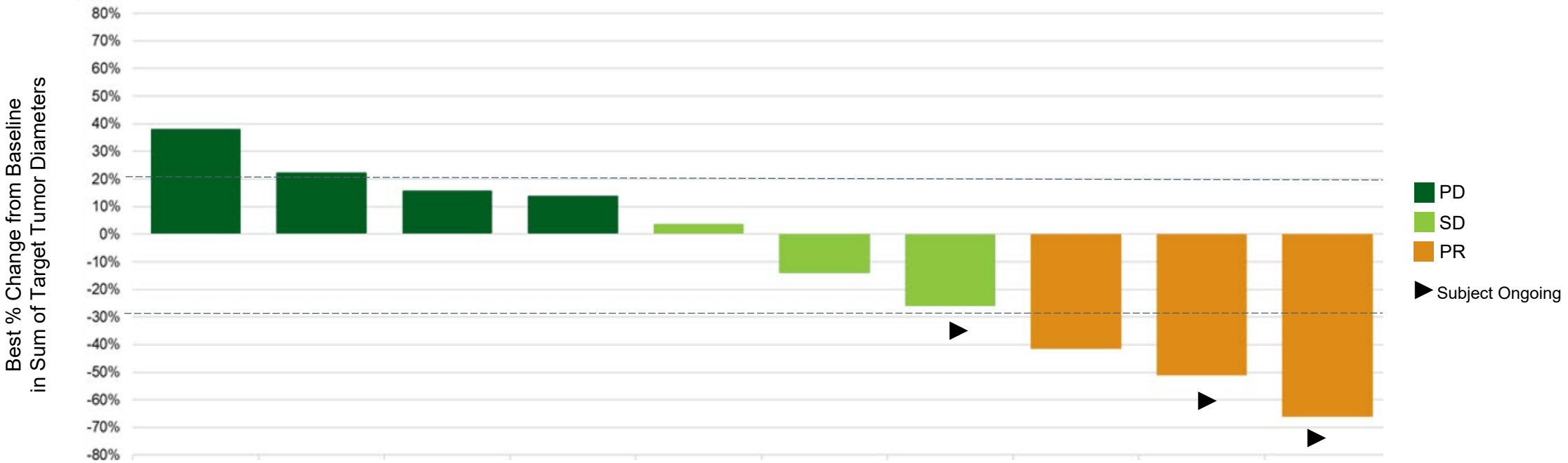
**ASCO 2019**
**Abstract #: 3095**
**Poster: 87**




Data cut off: 03 May 2019. Data not final.

- Clear activity was noted in patients with squamous anogenital and cervical cancer.
- Encouraging 4/18 (22%) response rate observed in this preliminary signal-generating study.

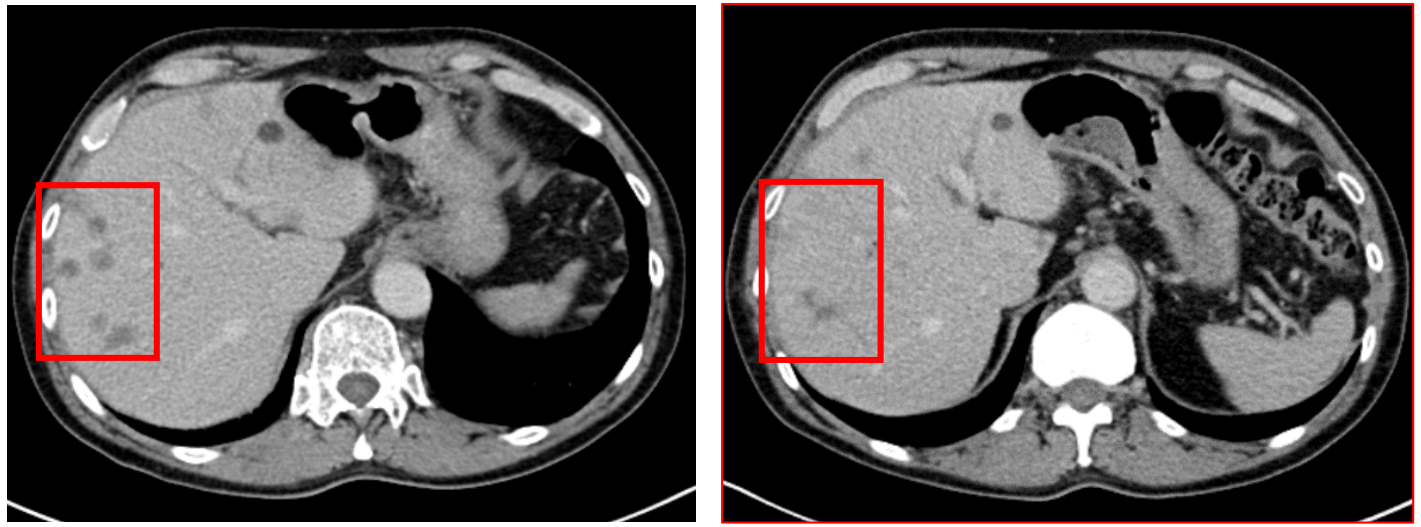
# SRA737+LDG:
# **Promising 30% Response Rate in Anogenital Cancer**




Data shown represent the best % tumor change from baseline among evaluable subjects with anogenital cancer.

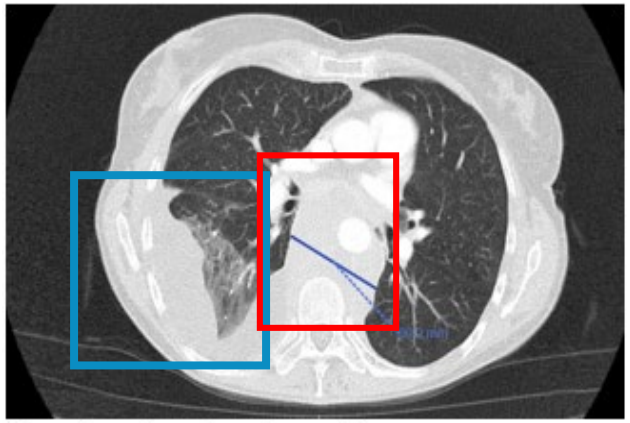
Noteworthy anti-tumor activity observed in subjects with advanced anogenital cancer (ORR = 30%; DCR=60%)

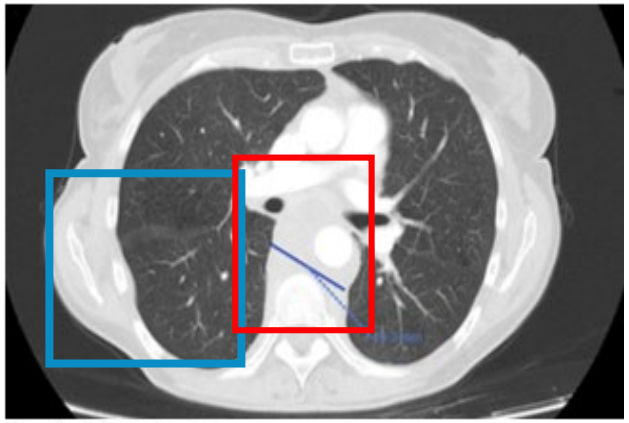
# SRA737+LDG in Anogenital Cancer: **Illustrative Clinical Activity**



70 yo male with anal cancer; extensive liver metastasis
Prior therapy: radiation and 1 line of systemic therapy
Genetic Profile: *FA/BRCA*, *PI3K* and TMB-I
Best tumor response: -41%
Duration on treatment: 11 cycles (response ongoing at discontinuation; patient decision)

# SRA737+LDG in Anogenital Cancer: **Illustrative Clinical Activity**





59 yo female with anal cancer, mediastinal mass compression and malignant pleural effusion
Prior therapy: 3 lines of systemic therapy
FMI Genetics:  FA/BRCA and TMB-I
Best tumor response: -26% + resolution of pleural effusion
Duration on treatment: 7 cycles; ongoing (as of data cut: 03 May 2019)

# Squamous cell cancer of the Anogenital Tract

## Epidemiology

- Comprises: anal, penile, vulval, vaginal, cervix
- Global annual incidence/100000: anal 1, penile <1, vulval 2.5, vaginal <1, cervix 17.8
- Approximately 2/3 cervical cancers are SCC (screening programme)
- Vulval, vaginal and penile cancer associated with older age

## Viral epidemiology

- ~80% sexually active men and women are infected with HPV in their lifetime
- Vast majority of anogenital cancer caused by HPV infection
  - cervix ~100%, anal >90%, penile 60%, vulval 70%, vaginal 75%
  - Serotypes 16 and 18 most frequent (also 6, 11, 31, 33, 45, 52, 58)
- Vaccine programme for 11-12 year olds (Gardasil 9 covers above serotypes). No therapeutic effect against existing infections. ~85% anti-HPV seropositive at 8 years.

# SCC Anogenital Cancer and HPV



Most people infected with high risk HPV do not develop cancer

Three predominant mechanisms underlie HPV oncogenic transformation:

- Deregulated expression of cell cycle regulators
  - E7 and E6 viral oncoproteins inhibit Rb and p53 preventing cell cycle arrest

    → Replication stress

- Activation of DNA damage repair pathways essential for viral replication
  - Constitutively activated ATR and ATM pathways with upregulation of CHK1

    → Replication stress

- Failure of the immune system of the host to resolve infection
  - HPV infection increases genomic instability and neoantigen expression simultaneously inducing immune suppression/evasion eg upregulating PD1, CTLA4 pathways

    → Inherent genomic instability

# So…

- The biological sequelae of each one of these three oncogenic mechanisms could hypothetically sensitise tumours to CHK1/LDG inhibition

- This may explain the observed activity in the patients with anogenital SCC in the ongoing SRA737-02 trial

# Current SOC: Recurrent or Metastatic Disease

- Anal
  - 1st line: Carboplatin/Taxol; ORR 59%, median OS 20 m
  - 2nd line: No SOC
- Penile
  - 1st line: Cisplatin/5FU; ORR 30%, median OS 7 months
  - 2nd line: No SOC
- Vulval
  - 1st line: No SOC; ORR to various platinum and/or taxane regimens 14-20%, 5 year OS 19%
- Vaginal
  - 1st line: No SOC; ORR to platinum minimal, 5 year OS 19%
- Cervix
  - 1st line:  platinum/paclitaxel/bevacizumab; ORR 48%, median OS 17 months
  - 2nd line: No SOC;  ORR 13% to various single agent regimens, median OS 9 months

# Evolving Treatment Landscape

Cervical Cancer

- Anti-PD1 monotherapy ORR 14-26% (Frenel et al, Schellens et al, Hollebecque et al)
- Pembrolizumab FDA approved for PDL1+ cervix cancer
- IO combinations eg PD1/CTLA4 increased RR but +++ toxicity
- Several ongoing Phase III trials with anti-PD1 or PARPi in the 1st line setting

Other HPV-positive cancers

- Anti-PD1 monotherapy and tumour vaccine 33% ORR H&N cancer
- Anti-PD1 monotherapy 24% ORR in SCC

- Otherwise no product class or treatment approach being systematically evaluated in anogenital cancer

# In summary

- Significant unmet need for effective treatment in patients with anogenital cancers
- SCC histology may enrich for biomarkers of sensitivity to SRA737/LDG
- Identified biomarkers could then enable broader selection of patients increasing the target population
- Should allow patients to have had prior anti-PD1 therapy – compare responses in IO-naive versus IO-exposed

# SRA737+LDG in Anogenital Cancer:
# **Potential Registration-Intent Phase 2 Trial**

University College London Hospitals NHS Foundation Trust

2nd Line Metastatic HPV+ Anal, Vulvar, Vaginal or Penile Squamous cell Carcinoma*

*Anogenital SCC excluding Cervical Cancer

→

Seamless adaptive design to optimize patient selection strategy, if or as required

Phase 2: SRA737+LDG Combination

**Dosing Schedule**

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| LDG (IV) | | | | | | | |
| SRA737 po | | | | | | | |

LDG and SRA737 administered weekly for 3 weeks on a 28-day cycle

Key Aims of the Study:

- Confirm ORR in 2nd line patients for the SRA737/LDG doublet:
  - Potential for accelerated approval if ORR >25-30% with DoR of >6 m?
- Optimized patient selection strategies, if/as required:
  - Analyses of genomic alterations, correlated with response

# SRA737+LDG in Anogenital Cancer:
# **Under-Recognized Cancer With Substantial Incidence**



| | United States | | Europe | |
|---|---|---|---|---|
| | Incidence | Mortality | Incidence | Mortality |
| Ovary | 24,469 | 14,008 | 24,469 | 14,008 |
| Cervix uteri | 14,065 | 5,266 | 25,132 | 5,266 |
| Anus | 7,894 | 1,175 | 9,865 | 2,482 |
| Vulva | 5,286 | 1,242 | 11,737 | 3,729 |
| Vagina | 1,445 | 458 | 1,782 | 790 |
| Penis | 1,510 | 336 | 4,489 | 1,084 |
| Anogenital | 16,135 | 3,211 | 27,873 | 8,085 |

*Note: Europe includes Western Europe, Southern Europe, and Northern Europe UN regions*

- Under-recognized but substantial market opportunity; ~50K diagnosed annually.

GLOBOCAN Cancer Today and Cancer Tomorrow databases (September 2018)
*International Agency for Research on Cancer; IARC Global Cancer Observatory web site (http://gco.iarc.fr/)*

# SRA737+LDG in Anogenital Cancer:
# **2L Clinical Data Reveal Need For New Therapies**



## 2L Metastatic / Advanced Recurrent Disease

| Tumor | Therapy | Pts | ORR | mPFS / mOS | Comments |
|---|---|---|---|---|---|
| Anal | Nivolumab (PD-1) | 37 | 24%, 2CR 7PR | 4.1m / 11.5m | • NCCN recommendation for 2L use |
| Anal | Pembrolizumab (PD-1) | 25 | 17%, 4PR | 3.0m / 9.3m | • NCCN recommendation for 2L use |
| Vulvar | Pembrolizumab (PD-1) | 18 | 6%, 1PR | 3.1m / 3.8m | |
| Penile | EGFR mAb | 11 | 27%, 2CR 1PR | 1.9m / 9.5m | • NCCN recommendation for 2L use |
| Penile | Paclitaxel (chemo) | 25 | 20%, 5PR | 2.75m / 5.75m | • NCCN recommendation for 2L use |

- High unmet need in this population; no 2L approved therapies.
- 2L clinical data demonstrate ~20% response rates & mPFS of ~4 months.
- Immunotherapy recommended by NCCN for 2L use (not approved), but response rates suggest scope for improvement.

# Anogenital Market Opportunity*

## Diagnosis

- 45-50K patients diagnosed annually with Anogenital cancer*
- Majority of cases are local, treated by chemo-radiation and/or curative intent surgery
- However, disease recurrence in up to 45% of patients
- Additionally, 10-30% have local or distant metastases at diagnosis

## Recurrent / Metastatic Disease

### 1st-Line (~12-20K)

25-40% of patients needing 1st-line systemic treatment for advanced recurrent or metastatic disease

- Common chemotherapeutic regimens are Cisplatin/5-FU and Carboplatin/Paclitaxel
- ~50% response rates and 6-8m PFS

### 2nd-Line (~6-10K)

~50% will need 2nd-line treatment

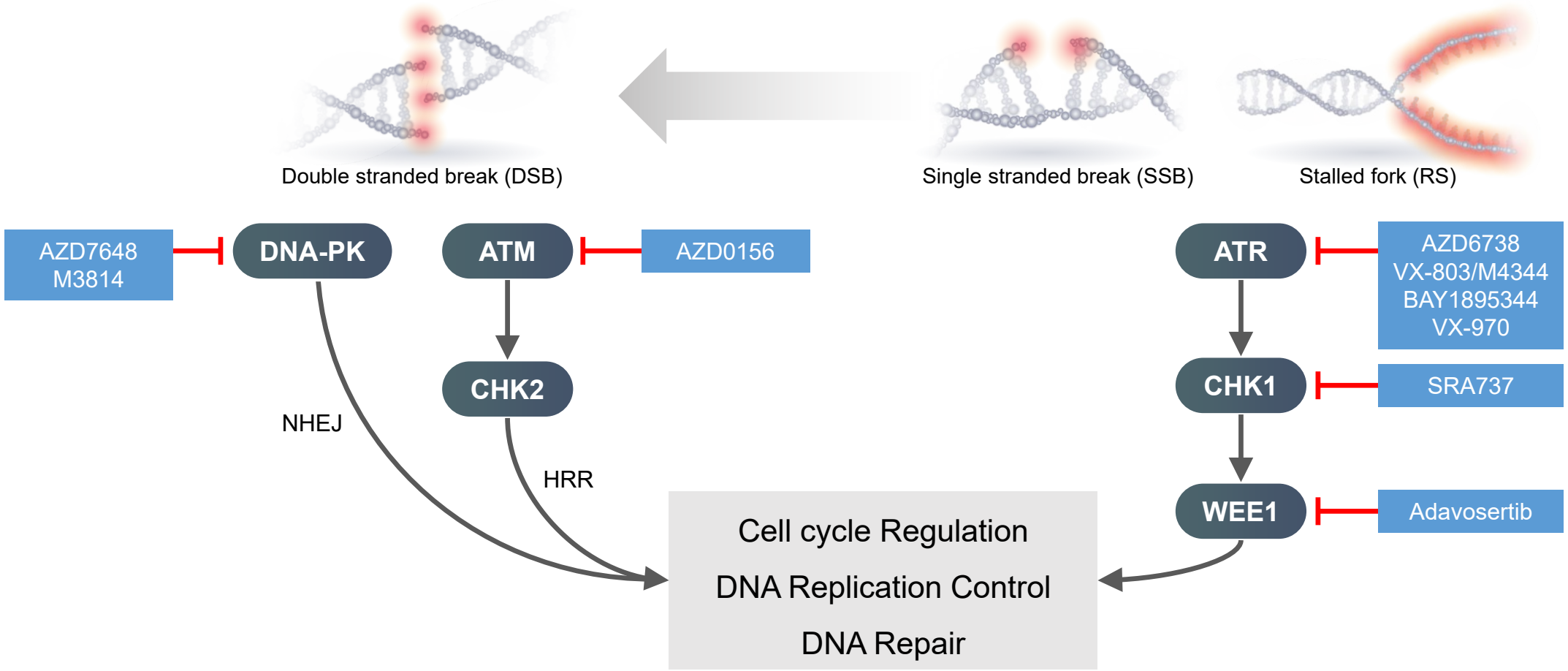
- No approved 2nd-line therapy
- Agents in development include anti-PD1, EGFRi with ~20% response rates and ~4m PFS

Sources: NCCN Guidelines, ACS Statistics Center, GLOBOCAN, Literature
*Company estimates in US and EU, not including cervical cancer

# SRA737 Competitively Positioned in Class

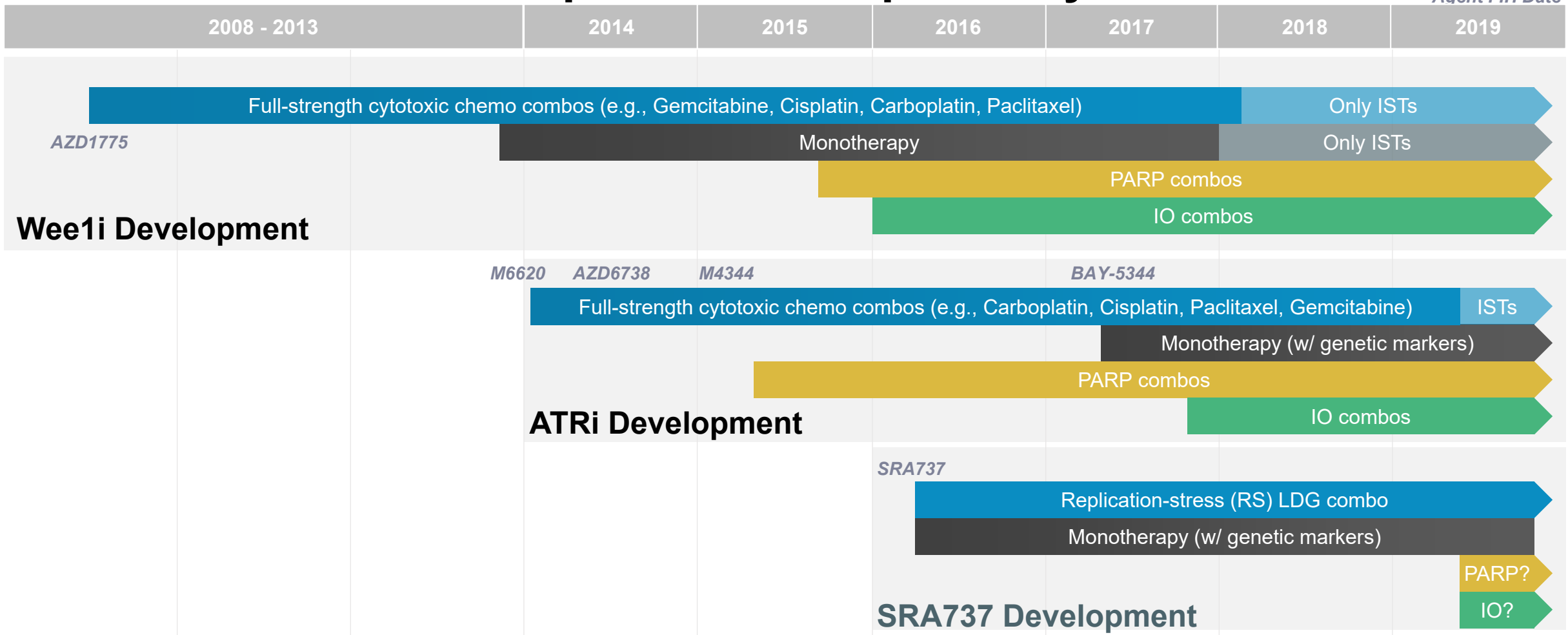
Other Development Opportunities

# Chk1 Biology:
# **Critical Role in DNA Replication & DNA Repair**




Inhibition of DDR checkpoint kinases represent a unique targeted therapeutic strategy in cancer, distinct from cytotoxic chemotherapy, that is demonstrating preliminary evidence of efficacy in clinical trials

# Chk1 Biology:
# SRA737 Development is Competitively Positioned

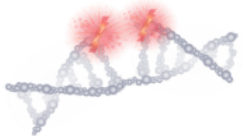



In ~3 years of development, SRA737 has reached the same point as other programs in the biological axis in terms of identifying patient selection signals for potential future development of these agents

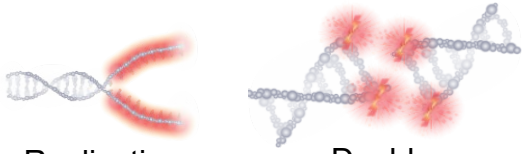
# SRA737+PARPi Combination:
# **Synergy - Compelling Biological Rationale**

## HRR DEFICIENT

'Deepen Responses'



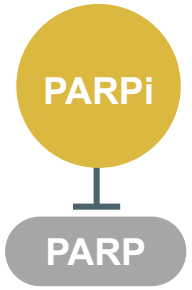
Single Strand Breaks



Replication Fork Stability & Double Strand Breaks

*mutant*

**BRCA 1/2**

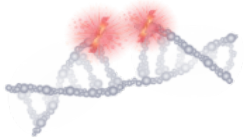



**Base Excision Repair**

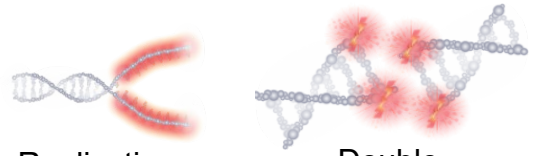

**Replication Fork Stability & HRR**

## POST PARPi RESISTANT

'Overcome Resistance'



Single Strand Breaks



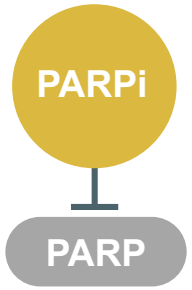
Replication Fork Stability & Double Strand Breaks

*mutant*

**BRCA 1/2**

***e.g.* reversion**

**BRCA 1/2**

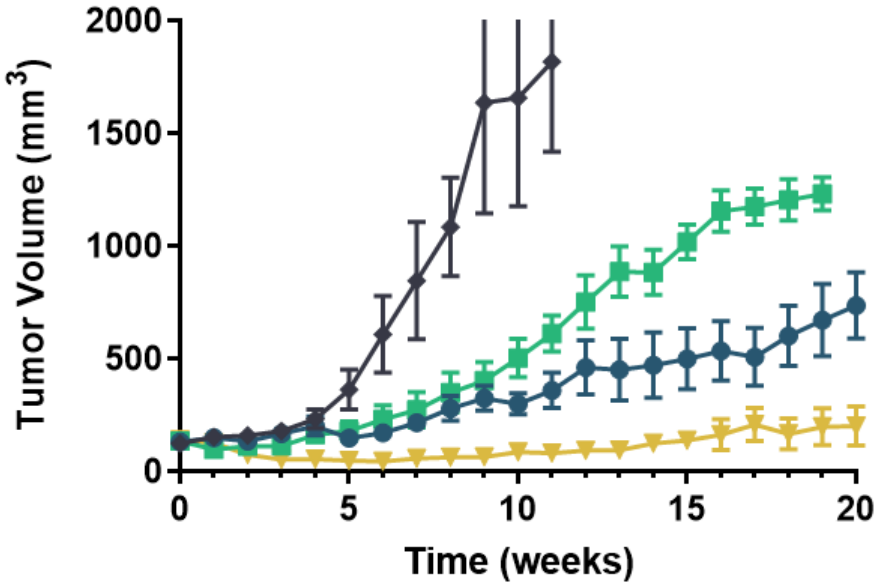


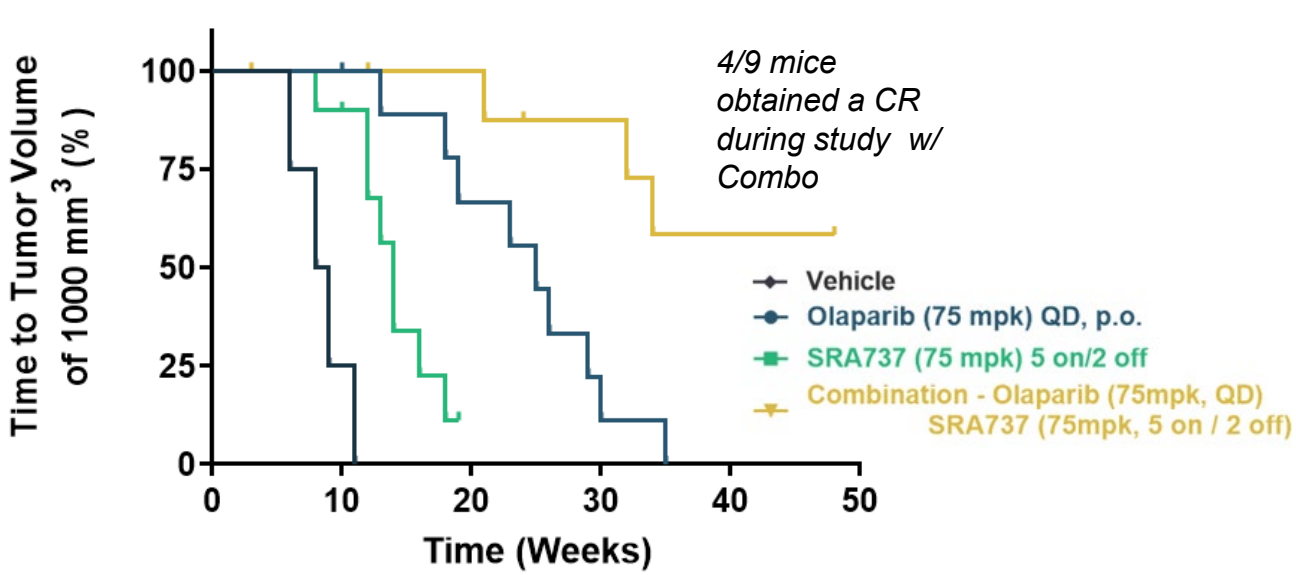

**Base Excision Repair**


**Replication Fork Stability & HRR**

**Chk1's role regulating RS & HRR facilitates various SRA737 + PARPi therapeutic scenarios.**

# SRA737+PARPi Combination:
# **Overcoming PARPi Resistance**

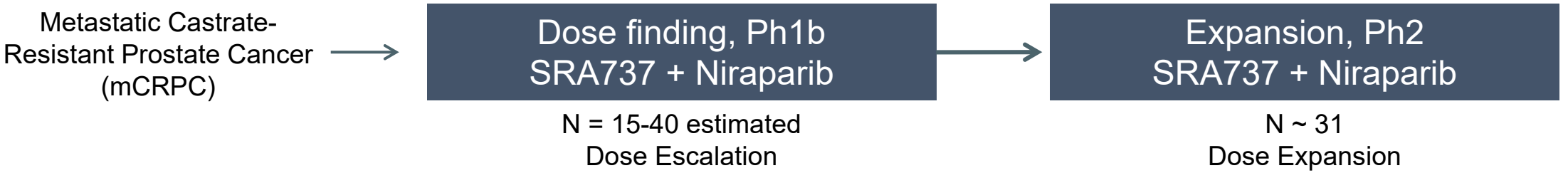



- Acquired PARPi-resistant HGSOC PDX model (Dr. Fiona Simpkins, U. Penn)
- Combination SRA737+olaparib superior to either agent alone; ~50% CRs in combination.
- SRA737 combined with olaparib well tolerated during extended treatment period (>40 wks).

# SRA737+PARPi Combination:
# **Illustrative Phase 1b/2 Clinical Trial of SRA737+Niraparib**

**Study Aim: Reversing PARP-inhibitor resistance with the SRA737 + PARP-inhibitor combination**




**Population:**

- Prior AR-targeted therapy and prior taxane-based chemotherapy
- Patients whose tumors are homologous recombination repair deficient and enriched for patients progressing on a PARP inhibitor

**Dosing Regimen**:

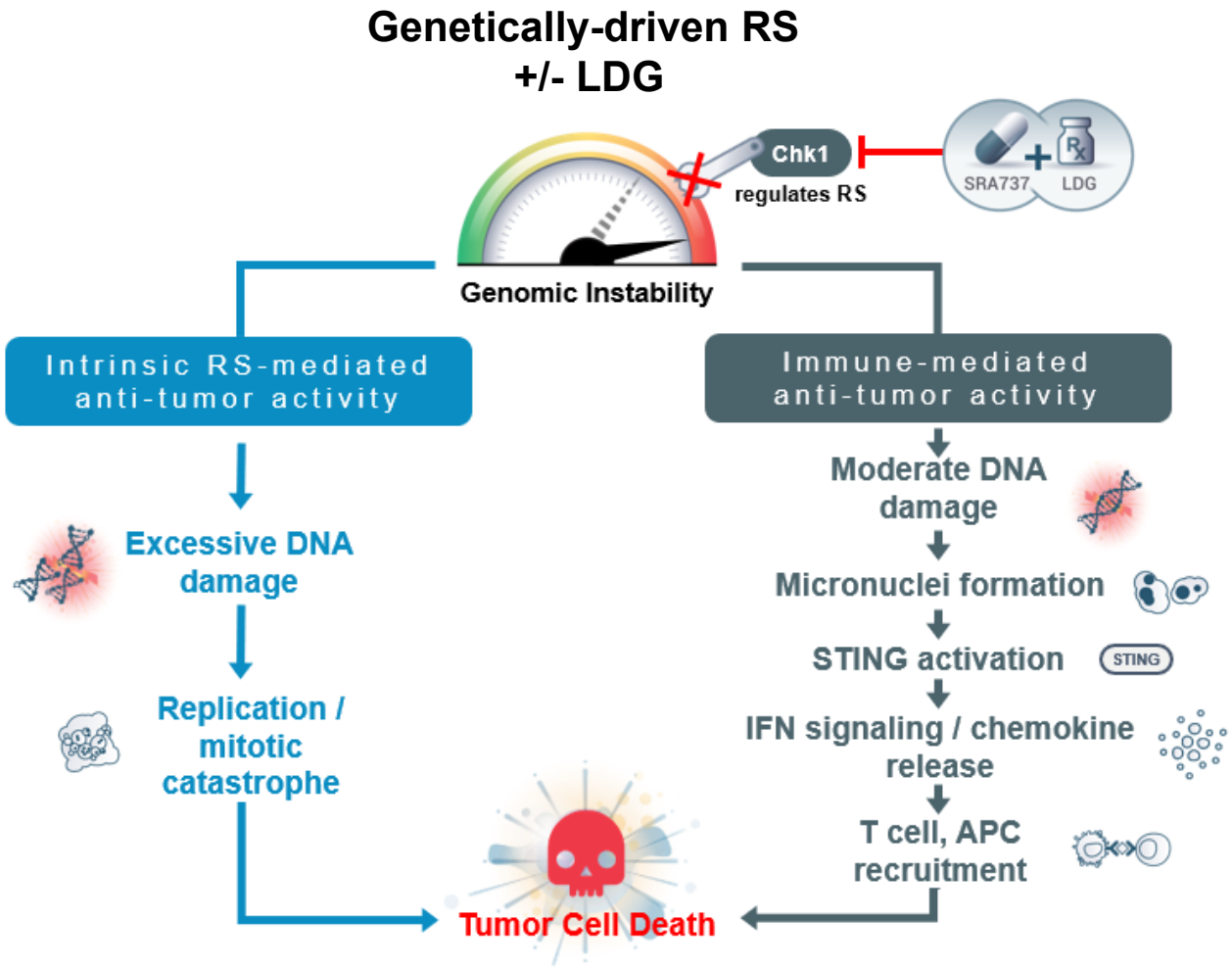
- Niraparib 200mg QD as per label with an intermittent schedule of SRA737

**Key objectives of the study:**

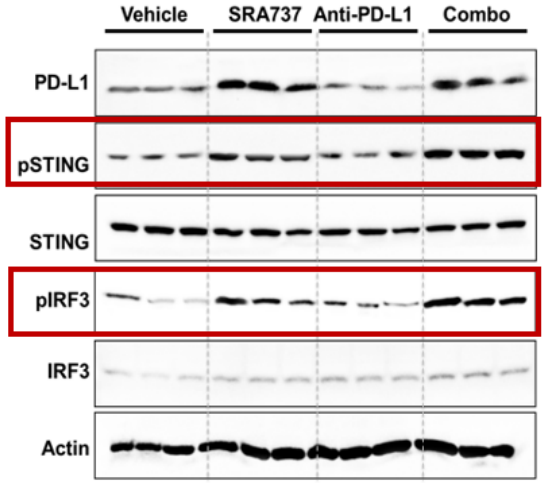
- Determine the recommended Ph2 dose, schedule for the combination
- Assess the clinical response rate of the combination
- Evaluate patient selection strategies with retrospective testing via ctDNA and tissue of genomic alterations

# SRA737+IO Combination:

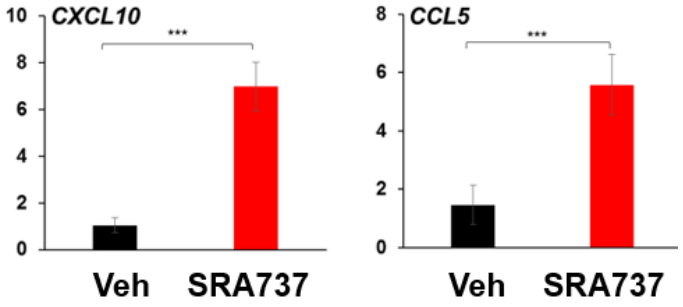
## SRA737+/-LDG Induces Intrinsic and Immune-Mediated Anti-Tumor Activity




### STING/IFN activation in tumors

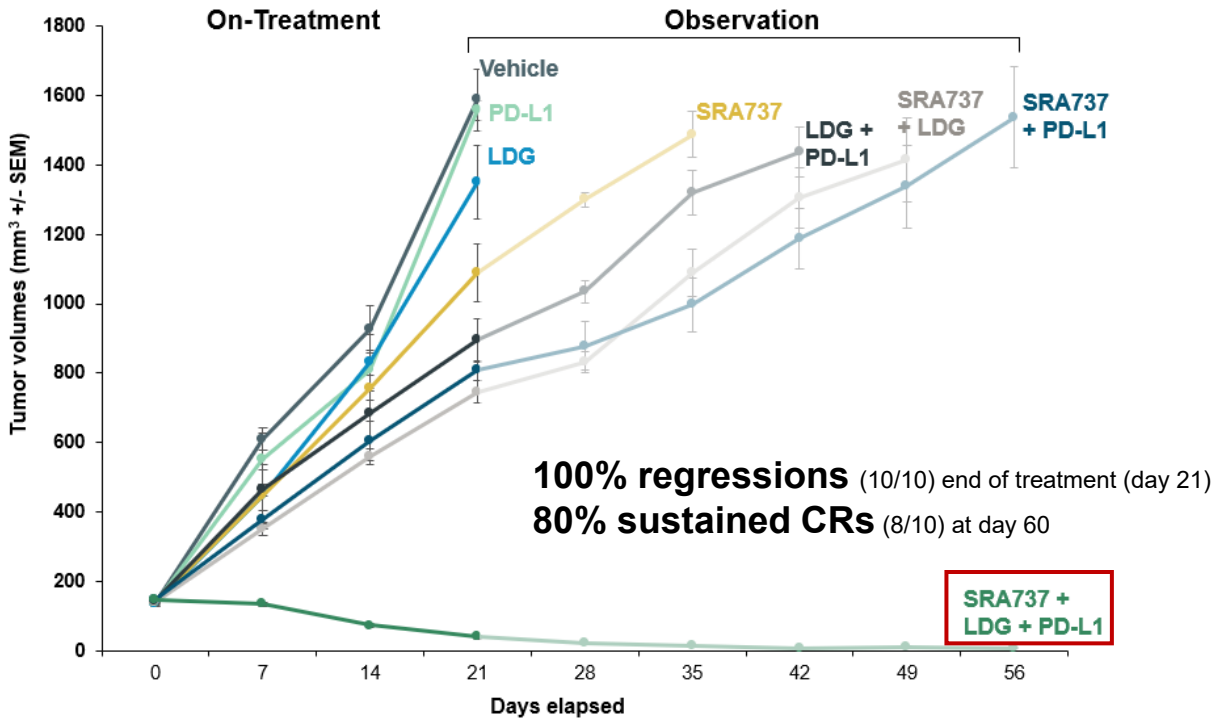



### Chemokine secretion in tumors



# SRA737+IO Combination:
# IO Synergy Reproducible Across Indications

## SCLC model

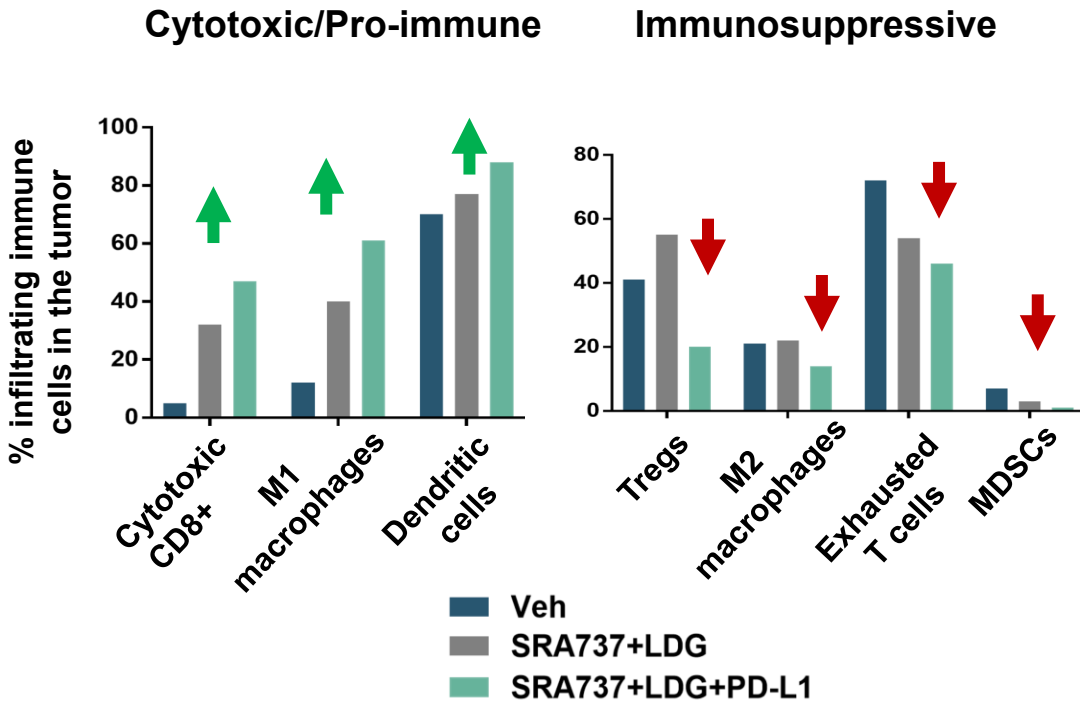



*Treatment schedule*

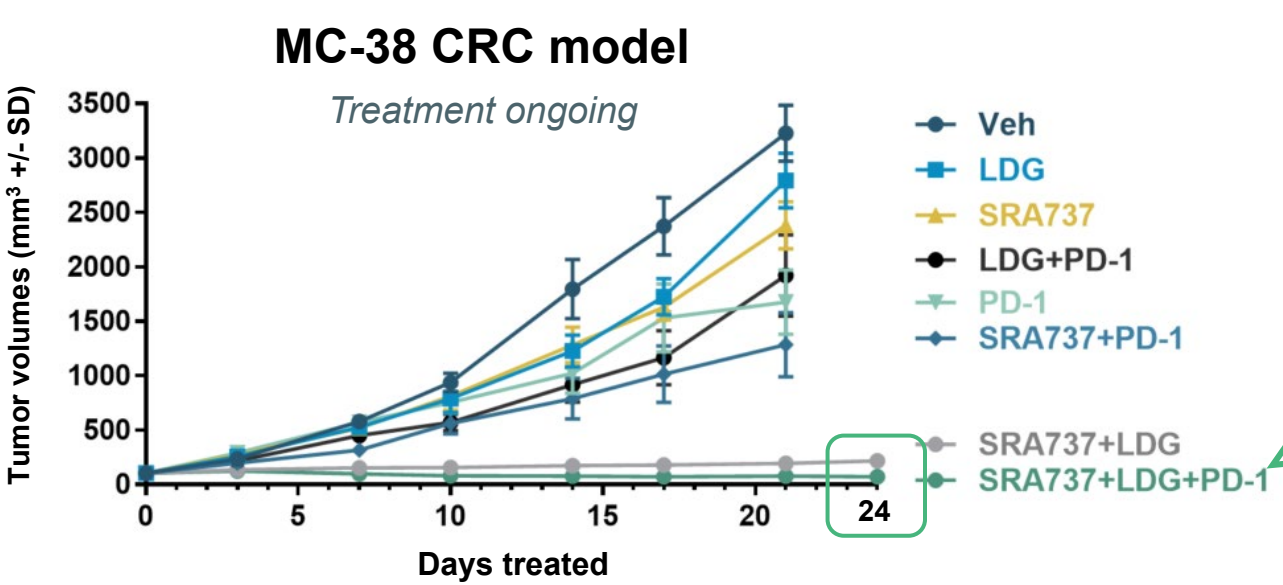
| Day | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| LDG | ■ | | | | | | |
| SRA737 | | ■ | ■ | | | | |
| ICB | | | ■ | | | | |

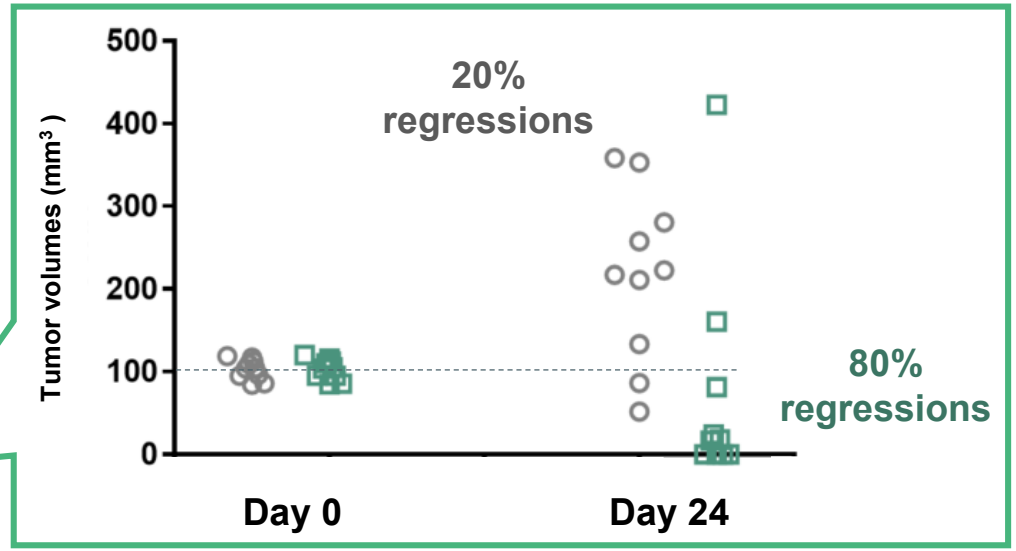
*X 3 weeks*

- Single agent IO and “LDG” inactive
- SRA737 synergizes with both i) LDG and ii) IO
- SRA737 + LDG + IO profoundly effective regimen



# SRA737+IO Combination:
# IO Synergy Reproducible Across Indications




***Treatment schedule***

| Day | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| LDG | ■ | | | | | | |
| SRA737 | | ■ | ■ | | | | |
| ICB | | | ■ | | | ■ | |

***X 4 weeks***

- All treatments well tolerated, no weight loss

- SRA737 + LDG demonstrates highly synergistic TGI
- SRA737 + LDG demonstrates disease control but limited regressions (1PR)
- Inhibition of PD-1/PD-L1 axis combined with SRA737 + LDG induces 80% regressions following 3 treatment cycles (4CR, 3PR)
- Similar results with anti-PD-L1 combination

# SRA737+IO Combination:
# **Illustrative Phase 2 SRA737+LDG+IO Clinical Trial**

Metastatic HPV+
Squamous Carcinoma

>1 prior lines

→ **Triplet dose finding, Ph1b**
**SRA737 + LDG + PD1 inhibitor**

N ~ 15
Dose Escalation

→ **Triplet Expansion, Ph2**
**SRA737 + LDG + PD1 inhibitor**

N ~ 30
Dose Expansion

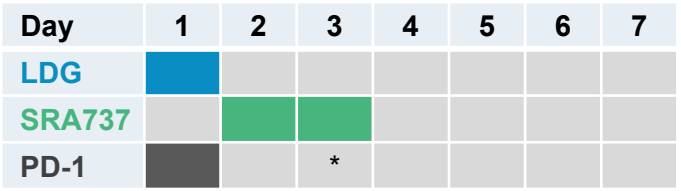
**Population**:

- Any HPV+ squamous cell cancer (anogenital cancer, head & neck cancer)

**Key objectives of the study:**

- Determine the recommended Ph2 dose, schedule for the triplet
- Explore immune activation hypothesis (paired tumor biopsies)
- Determine if the benefit of the triplet justifies additional testing with a goal of registration
  - Assess ORR, DoR for the triplet
- Evaluate patient selection strategies
  - Retrospective testing via ctDNA and tissue of HPV status and serotype; genomic alterations; tumor mutational burden; immune activation; etc

**Dosing Schedule**




*Cycle 1 only: PD-1 antibody on Day 3

LDG and SRA737 administered weekly for 3 wks on a 28-day cycle

PD-1 therapy administered on a 28-day cycle

# Exciting Future Opportunities for SRA737

- SRA737 is competitively positioned as potentially one of the leading clinical DDR assets
- Clinical safety & efficacy of SRA737 +/- LDG supports standalone development and in combination with both PARPi and IO therapy

**PARPi Combination**

- Acquired PARPi resistance is a significant and growing clinical problem that Chk1 inhibition could address
- Preclinically, SRA737+PARPi demonstrates efficacy in HRD and acquired PARPi resistance settings

**IO Combination**

- Evidence for synergistic interplay between the DDR network and tumor immune response
- SRA737+LDG activates innate immunity (STING, IFN), resulting in a highly favorable immune anti-tumor microenvironment and profound tumor regressions in preclinical models

# Summary

# SRA737 Program Summary & Potential Next Steps

- Sierra executed a cutting-edge **signal-seeking survey**
  - broad cancer landscape
  - range of indications, and
  - spectrum of genetic contexts associated with replication stress

- Goals of SRA737 Clinical Program:
  - define safety profile and Phase 2 dose(s)
  - establish proof-of-concept clinical data
  - identify sensitizing genetic contexts
  - determine whether LDG potentiates SRA737 activity
  - identify a clinical indication that could be pursued towards registration

# SRA737 Program Summary & Potential Next Steps

**Successful Outcomes:**

- Proof-of-concept activity in multiple indications
- Anti-cancer activity correlated with genetics
- Very promising anogenital cancer signal
- Anogenital cancer: tractable opportunity to potentially pursue registration-intent studies
  - unmet medical need; low historical ORR/PFS in 2L
  - substantial potential market opportunity
- PARPi & IO combinations provide compelling additional opportunities

**Next Steps:**

- Evaluate in context of our emerging pipeline
  - anogenital P2 cost estimated at ~$10M
  - exploring options to enable continued advancement of SRA737

# 2019 Milestones


## MOMELOTINIB

| | | |
|---|---|---|
| 1H 2019 | Registration Plan Clarity | |


## SRA737

| | | |
|---|---|---|
| SRA737-01 Monotherapy | 1H 2019 | Preliminary Clinical Data ✓ |
| SRA737-02 LDG Combination | 1H 2019 | Preliminary Clinical Data ✓ |
| SRA737-03 PARP Inhibitor Combination | TBD | Initiate Phase 1b/2 |


## SRA141

| | |
|---|---|
| TBD | Initiate Phase 1/2 |

# Targeted Hematology and Oncology Therapeutics

- Bold drug development company oriented to registration and commercialization
- Lead Phase 3 asset, momelotinib, for the treatment of myelofibrosis with large 2nd-line market opportunity
- SRA737 oriented to potential registration-intent studies in anogenital cancer
- Highly experienced management team with proven track record in drug development
- Strong financial standing:
  - Shares (as of March 31):
    - 74.7M outstanding
    - 87.9M fully diluted
  - $90.9M in cash and cash equivalents (as of March 31)
  - $5M borrowed in structured debt


Questions