2019: New Drugs in Development

Igor Puzanov, M.D., M.S.C.I., F.A.C.P.

Director, Early Phase Clinical Trials Program
Co-Leader, Developmental Therapeutics
Chief, Melanoma Section
Professor of Medicine
Roswell Park Comprehensive Cancer Center

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Disclosures:

- Consultant: Amgen, Hoffmann-La Roche
- Clinical Trial Support: Merck, Amgen, Plexxikon, Hoffmann-La Roche, GlaxoSmithKline, Bristol Myers Squibb


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Learning Objectives:

- Discuss the novel classes of promising agents in development
- Enhancing immune response in patients
- Describe the promise of precision therapy (targeting old targets in a novel way-Ras, synthetic lethality)

Pretest Question 1:

NKTR-214 is a pegylated form of:

1. IL-15
2. IL-12
3. IL-2
4. IL-10

Pretest Question 2:

AMG-510 showed best activity in patients with:

1. Melanoma with $BRAF^{V600E}$ mutation
2. CRC with $BRAF^{V600E}$ mutation
3. CRC with $KRAS^{G12C}$ mutation
4. NSCLC with $KRAS^{G12C}$ mutation

Pretest Question 3:

Synthetic lethality concept refers to the situation where loss of either one gene which interact leaves the cell viable. However, if both are lost, the cell dies. Examples include genes pairs ATM/ATR; BRCA/PARP.

1. True
2. False

Learning Objectives:

- **Enhancing immune response in patients**

- Targeting old targets in a novel way (Ras, synthetic lethality)

Enhancing Immune Responses in Patients

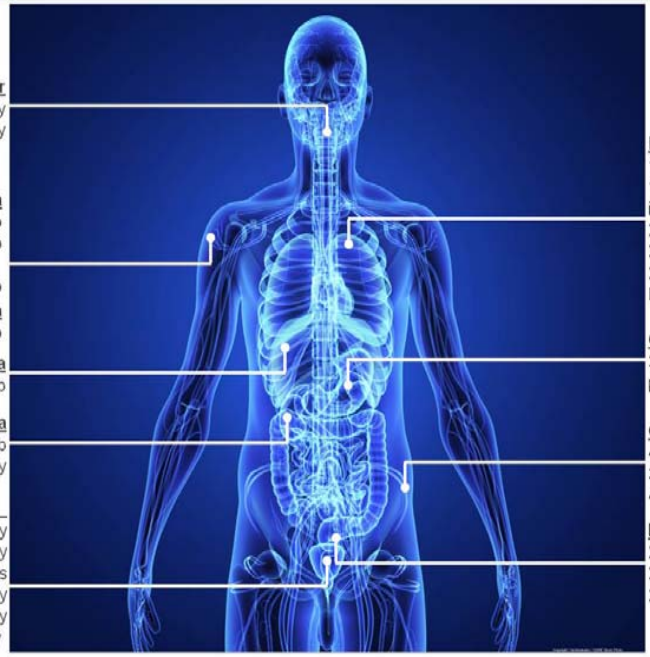
T-cells

- Block Inhibitory Signals
  - αCTLA4
  - αPD-1
- Transfer cultured T-cells
  - TIL
  - CAR-transduced
  - TCR transduced
- Enhance Positive Signals
  - Cytokines
  - Receptor Agonists

Microenvironment

- Inhibitory Proteins
  - TGFβ
- Other Immune Cells
  - Treg
  - Macrophages

U.S. FDA Approved Immune-Checkpoint Inhibitors



Squamous Cell Head & Neck Cancer
1L nivolumab after platinum chemotherapy
1L pembrolizumab after platinum chemotherapy

Malignant Melanoma
Adj./1L ipilimumab
1L nivolumab ± ipilimumab
Adj. nivolumab
1L pembrolizumab

Merkel Cell Carcinoma
2L avelumab

Hepatocellular Carcinoma
2L nivolumab after sorafenib

Adv. Renal Cell Carcinoma
1L nivolumab plus ipilimumab
2L nivolumab after anti-angiogenic therapy

Locally Adv. or Met. Urothelial Cancer
1L nivolumab after platinum chemotherapy
1L pembrolizumab after platinum chemotherapy
or in platinum-ineligible patients
1/L atezolizumab after platinum chemotherapy
1L avelumab after platinum chemotherapy
1L durvalumab after platinum chemotherapy

Non-Small Cell Lung Cancer
1L pembrolizumab TPS≥50%
1L pembrolizumab + pemetrexed/carboplatin
in non-squamous NSCLC
2L pembrolizumab TPS≥1%
2L nivolumab
2L atezolizumab NSCLC
Maintenance durvalumab after chemoradiation

Gastric & GEJ Carcinoma
3L pembrolizumab after fluoropyrimidine- and
platinum-Chemotherapy +/- HER2 therapy & CPS≥1

Classical Hodkin Lymphoma
4L pembrolizumab
3L nivolumab after auto-HSCT and BV
4L nivolumab and after auto-HSCT

MSI-H or dMMR Cancers
2L nivolumab in CRC after FOLFOXIRI
2L pembrolizumab in CRC after FOLFOXIRI
2L pembrolizumab in any MSI-H/dMMR cancer

1 Prescribing information pembrolizumab (Keytruda®), revised: 11/2017
2 Prescribing information durvalumab (Imfinzi®), revised: 05/2017
3 Prescribing information nivolumab (Opdivo®), revised: 04/2018
4 Prescribing information ipilimumab (Yervoy®), revised: 04/2018
5 Prescribing information atezolizumab (Tecentriq®), revised: 04/2017
6 Prescribing information avelumab (Bavencio®), revised: 10/2017

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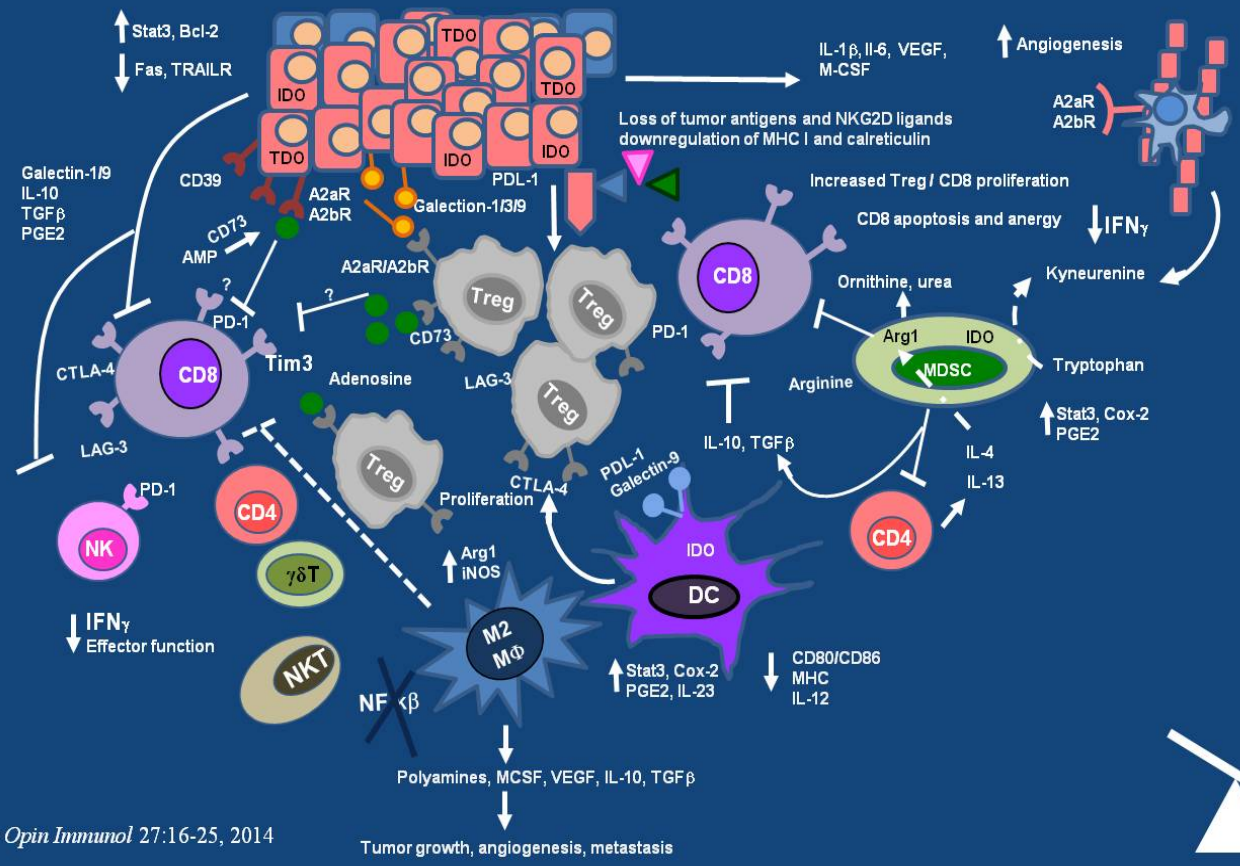
A Comprehensive Look at the Immune Microenvironment



Adapted from Mittal D et al. *Curr Opin Immunol* 27:16-25, 2014

NKTR-214 (CD-122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT

ClinicalTrials.gov Identifier: NCT02983045

Adi Diab[1], Michael Hurwitz[2], Daniel Cho[3], Vali Papadimitrakopoulou[1], Brendan Curti[4], Scott Tykodi[5], Igor Puzanov[6], Nuhad K. Ibrahim[1], Sara M. Tolaney[7], Debu Tripathy[1], Jianjun Gao[1], Arlene O. Siefker-Radtke[1], Wendy Clemens[8], Mary Tagliaferri[9], Scott N. Gettinger[2], Harriet Kluger[2], James M. G. Larkin[10], Giovanni Grignani[11], Mario Sznol[2], Nizar Tannir[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Yale School of Medicine, New Haven, CT, USA, [3]NYU Medical Oncology Associates, New York, NY, USA; [4]Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR, USA; [5]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [6]Roswell Park Cancer Institute, Buffalo, NY, USA; [7]Dana Farber Cancer Institute, Boston, MA, USA; [8]Bristol-Myers Squibb, New York, NY, USA; [9]Nektar Therapeutics, San Francisco, CA, USA; [10]Royal Marsden NHS Foundation Trust London, United Kingdom; [11]Candiolo Cancer Institute, Turin, Italy, Europe.

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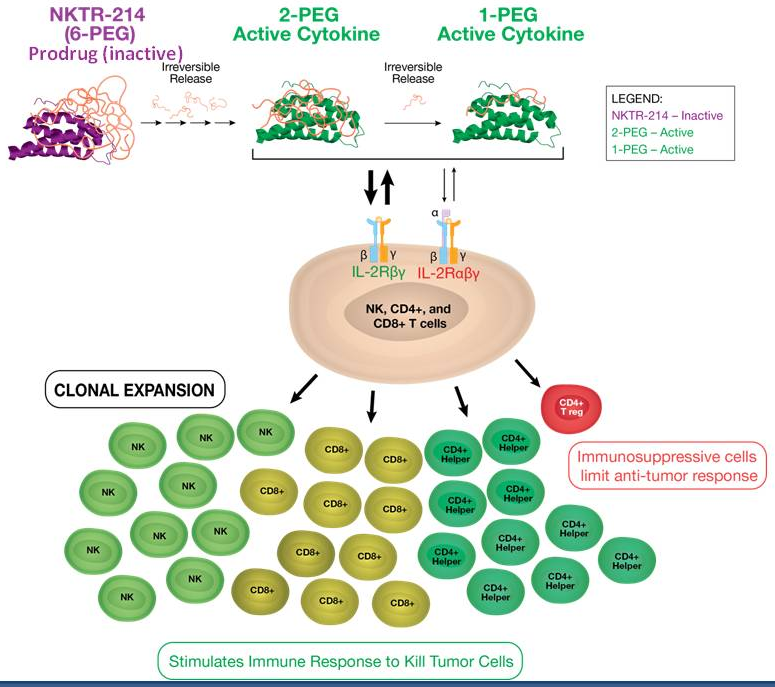
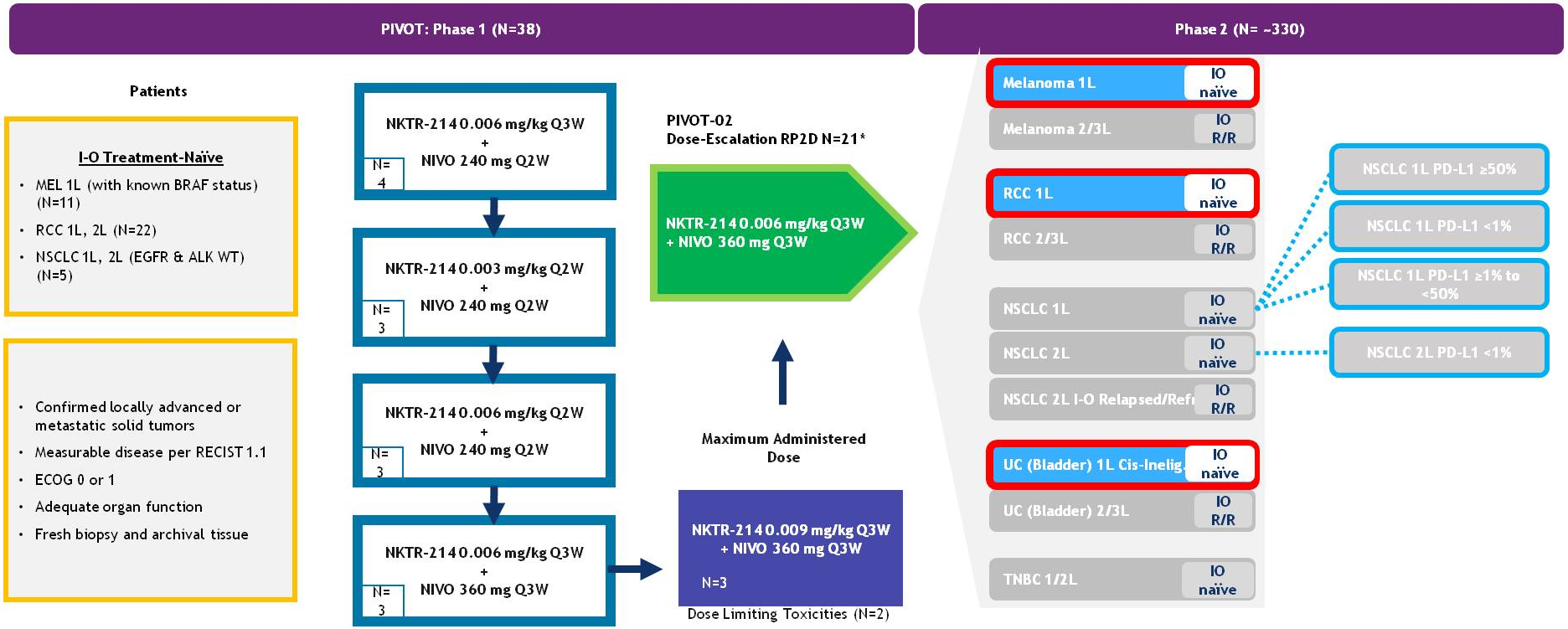
NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs



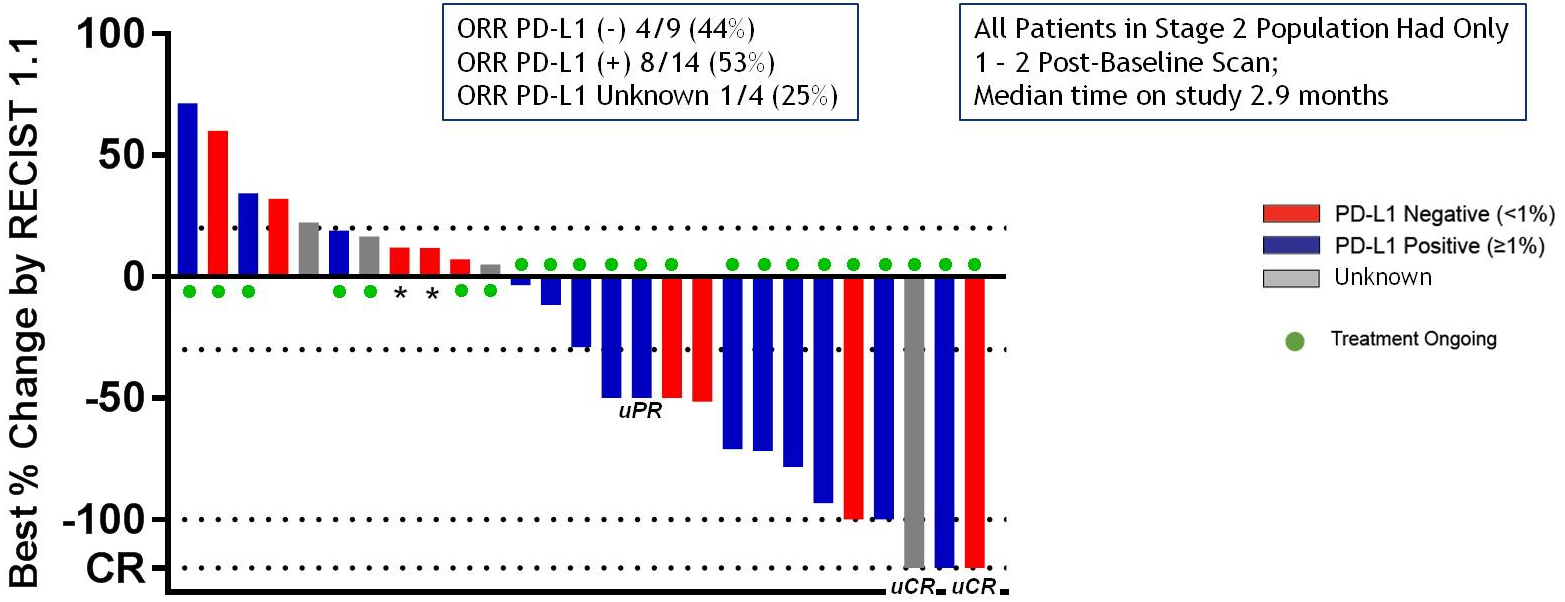
- NKTR-214 prodrug design with sustained signaling
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen administered every 3 week IV dosing
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- NKTR-214 increases proliferation of TILs and PD-1 expression on the surface of CD8+ T cells providing a mechanistic rationale for combining with nivolumab

PIVOT-02 Study Design in I-O Treatment-Naïve Patients



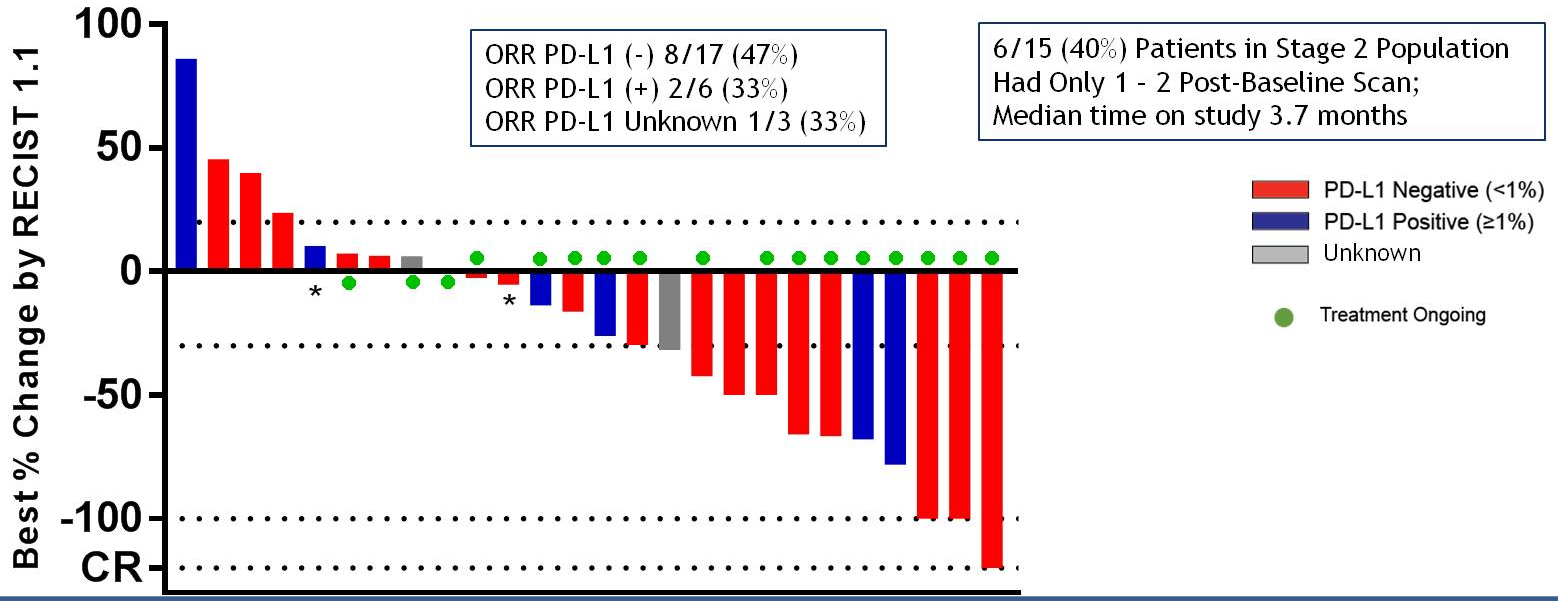
Stage IV IO-Naïve 1L Melanoma Cohort at RP2D: Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 11/13 (85%)
Stage 2: Best Overall Response ORR=13/28 (46%); DCR=2/28 (71%)



Stage IV IO-Naïve 1L RCC Cohort Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 7/11 (64%)
Stage 2: Best Overall Response ORR=11/26 (42%); DCR=20/26 (77%)



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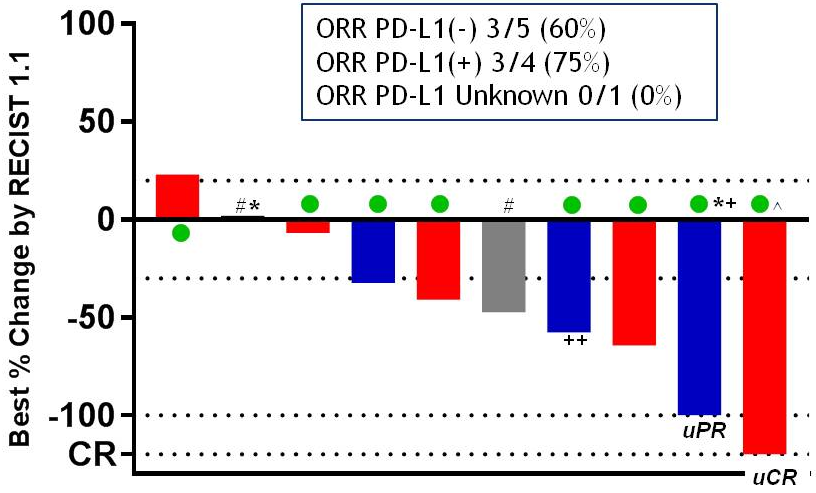
Stage IV IO-Naïve 1L Urothelial Cohort (Cisplatin-Ineligible) Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR=6/10 (60%)
Stage 2: Best Overall Response ORR=6/10 (60%); DCR=7/10 (70%)

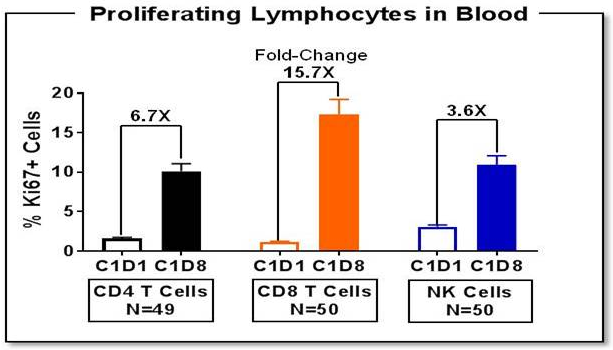
% Change From Baseline in Target Lesions

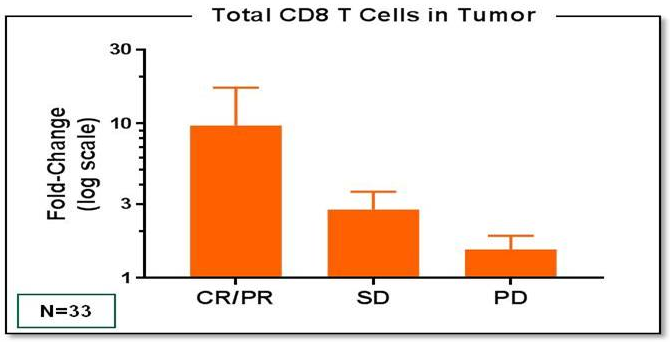


6/10 (60%) Patients in Stage 2 Population Had Only 1 - 2 Post-Baseline Scan; Median time on study 2.1 months

PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
Unknown
Treatment Ongoing

NKTR-214 + Nivolumab Increased Lymphocyte Proliferation in Blood and CD8 T Cells in Tumor





"Proliferating Lymphocytes in Blood" were measured using flow cytometry of fresh whole blood for all patients that the met inclusion criteria and had matched Cycle 1 Day 1 (C1D1) and Cycle 1 Day 8 (C1D8) blood collections. Data presented as mean ± standard error. Fold-change calculated for C1D8/C1D1. Ki67 is a marker of proliferation. "Total CD8 T Cells in Tumor" measured using immunohistochemistry using biopsy specimens collected at baseline and week 3. Cells/mm² were counted and fold-change calculated for week3/baseline, data presented as mean ± standard error.

Enhancing Immune Responses in Patients

T-cells

- Block Inhibitory Signals
  - αCTLA4
  - αPD-1
- Transfer cultured T-cells
  - TIL
  - CAR-transduced
  - TCR transduced
- Enhance Positive Signals
  - Cytokines
  - Receptor Agonists

Microenvironment

- Inhibitory Proteins
  - TGFβ
- Other Immune Cells
  - Treg
  - Macrophages

A First-in-class, First-in-human Phase 1 Pharmacokinetic (PK) and Pharmacodynamic (PD) Study of Hu5F9-G4 (5F9), an Anti-CD47 Monoclonal Antibody (mAb), in Patients with Advanced Solid Tumors

Branimir I. Sikic[1], Nehal Lakhani[2], Amita Patnaik[3], Sumit Shah[1], Sreenivasa Chandana[2], Drew Rasco[3], A. Dimitrios Colevas[1], Timothy O'Rourke[2], Kyriakos Papadopoulos[3], George A. Fisher[1], Victor Villalobos[1], Mark Chao[4], Balaji Agoram[4], James Y. Chen[4], Jenny Huang[4], Matthew Axt[4], Jen-Peter Volkmer[4], Ravindra Majeti[5,6], Irving L Weissman[6], Chris H. Takimoto[4], Mark Daniel Pegram[1], Sukhmani K. Padda[1]

[1]Stanford University School of Medicine, Stanford, CA; [2]South Texas Accelerated Therapeutics (START) Midwest, Grand Rapids, MI; [3]START San Antonio, TX; [4]Forty Seven, Inc., Menlo Park, CA, [5]Department of Medicine, Division of Hematology, Stanford University School of Medicine; and [6]Cancer Institute and Institute for Stem Cell Biology and Regenerative Medicine - Stanford University

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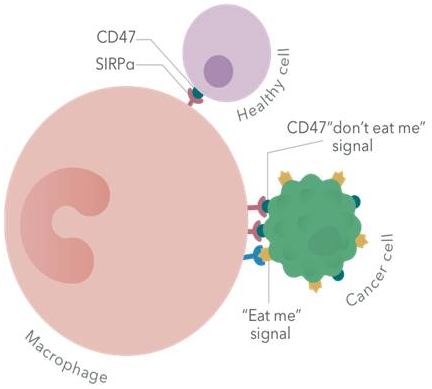
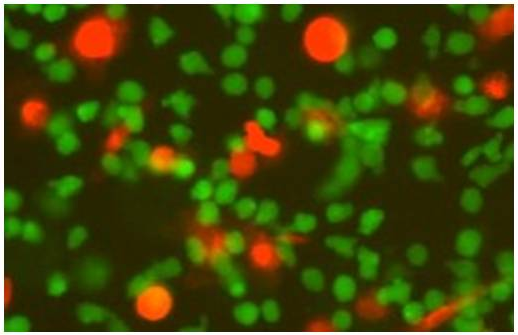
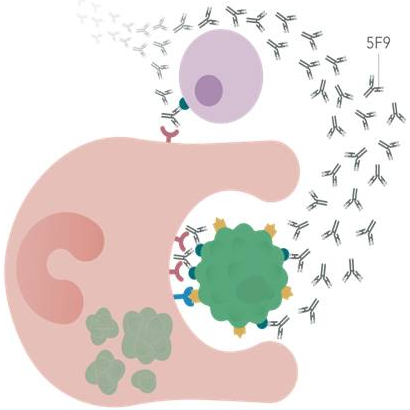
5F9 is a Novel Macrophage Immune Checkpoint Inhibitor Targeting CD47



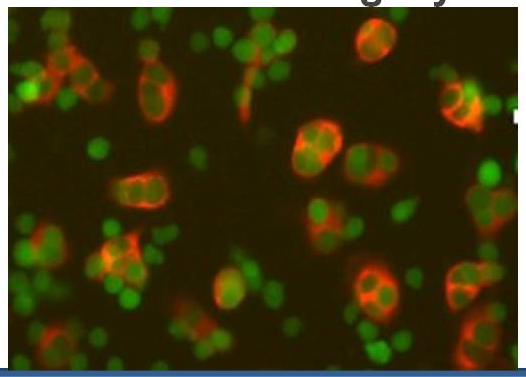
Control mAb: No Phagocytosis



Macrophages
Cancer cells

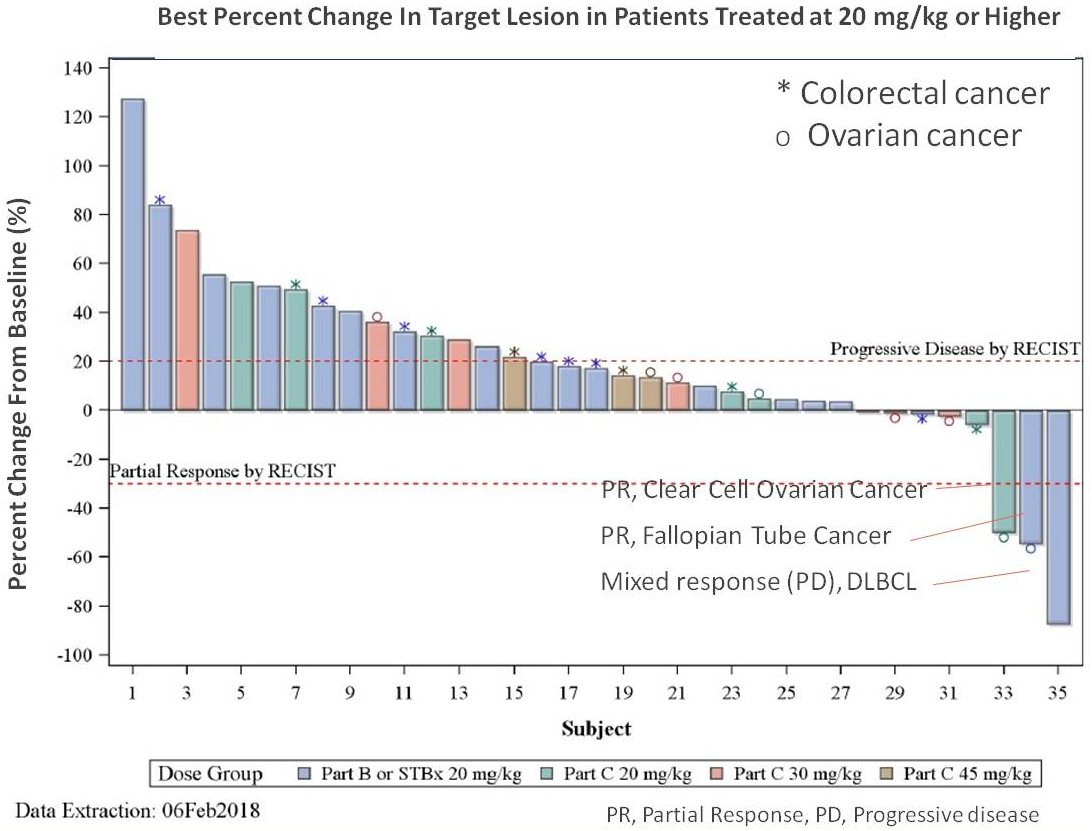


Anti-CD47 mAb: Phagocytosis



Preliminary Efficacy for Patients Treated at 20 mg/kg or Higher

- Two ovarian or fallopian tube cancer patients had confirmed partial responses by RECIST
  - Both patients heavily pre-treated with more than 6 prior lines of systemic therapy
  - Both received weekly maintenance doses at 20 mg/kg
- A patient with DLBCL had shrinkage of target lesions and a mixed response (progressive disease) by Lugano criteria



Data Extraction: 06Feb2018

PR, Partial Response, PD, Progressive disease

CONCLUSIONS:

- Immunotherapies for solid tumor patients are promising new field, obstacles have to be overcome: patient selection, side effect management, logistics
- Cytokine like molecules (NKTR-214) with exciting data, awaiting randomized results
- Other I-O targeting is promising (ICOS, TGFb, CD47, TLR, STING)-we are in need of biomarkers for patient selection
- CD47-better performance in NHL/MDS/leukemia

Learning Objectives:

- Enhancing immune response in patients
- **Targeting old targets in a novel way (Ras, synthetic lethality)**

Highlights in Signal Transduction and DNA Repair

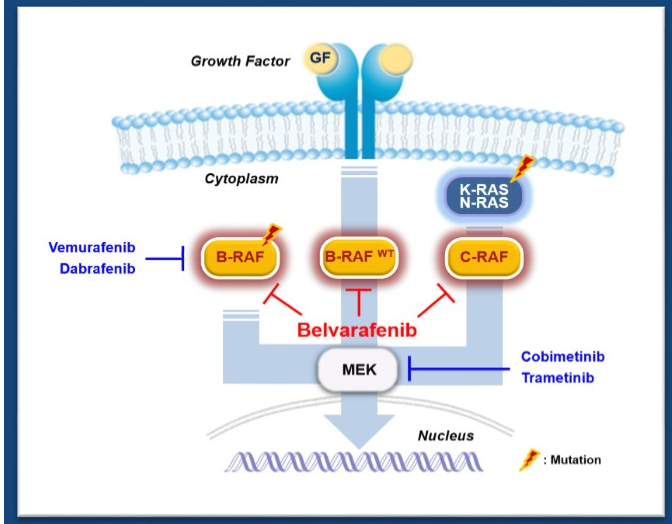
Targeting *RAS*-mutant cancers

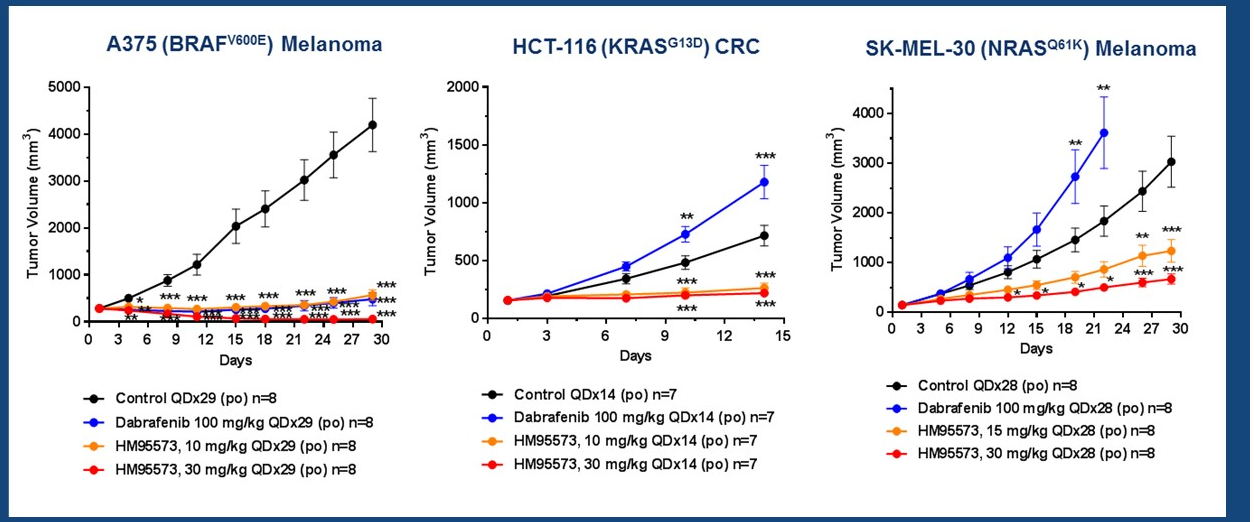
- Phase 1 Study of belvarafenib, a pan-RAF inhibitor (abstract 3000)
- Phase 1 Study of AMG510, a first-in-class $KRAS^{G12C}$ inhibitor (abstract 3003)

Expanding Synthetic Lethality

- Phase 2 study of talazoparib beyond *BRCA* (abstract 3006)
- Phase 1 study of BAY 1895344, an ATR inhibitor (abstract 3007)

Belvarafenib (HM95573)
Potent and Selective Type II pan-RAF inhibitor





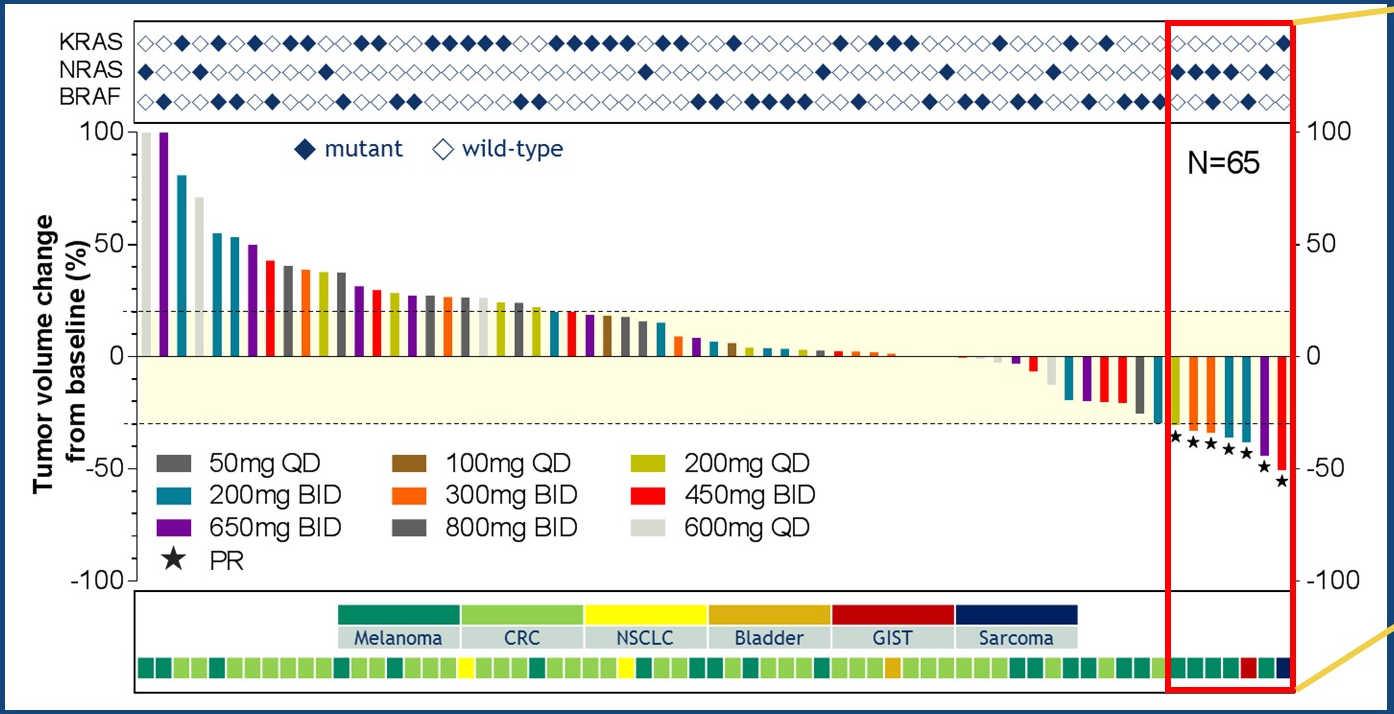
Drug Related AEs occurring in ≥ 10% of patients

This result is analyzed with pooled data of dose escalation and expansion studies.

Drug Related AEs reported in ≥ 10% of subjects	Total (N=135)		450 mg BID (N=74)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Dermatitis acneiform	50 (37.04)	**4 (2.96)**	34 (45.95)	**4 (5.41)**
Rash	31 (22.96)	**4 (2.96)**	16 (21.62)	**2 (2.70)**
Pruritus	27 (20.00)	**0**	18 (24.32)	**0**
Decreased appetite	18 (13.33)	**0**	10 (13.51)	**0**
Increased AST level	10 (7.41)	**1 (0.74)**	8 (10.81)	**0**

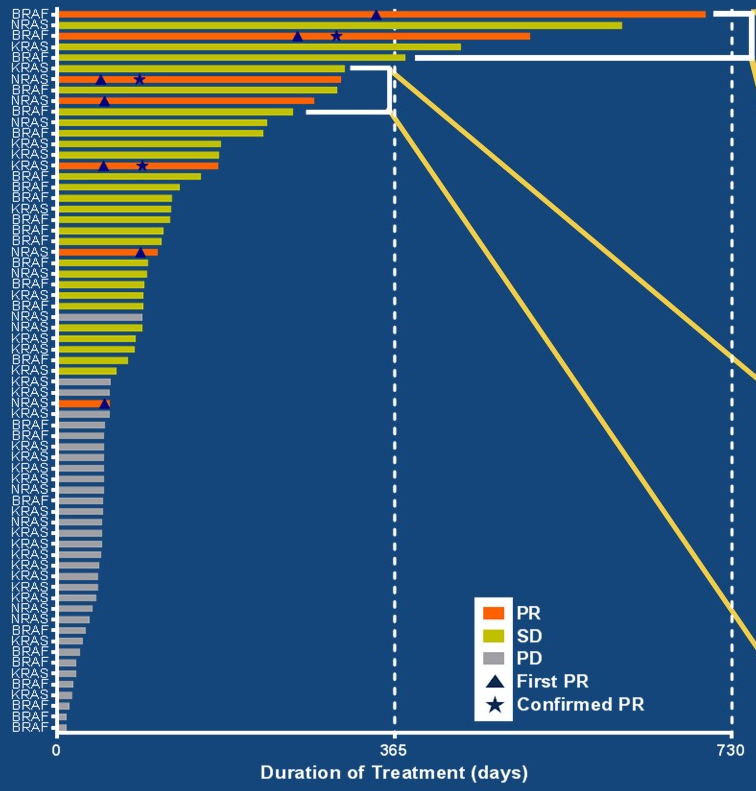
- PK guided dose escalation scheme
- Target AUC reached at 200 mg BID
- PK linear 200-650 BID;
- DLTs were rash and dermatitis
- RP2D declared at 450 mg BID

Best target percentage change from Baseline: dose escalation study



Mutation Type	Cancer Type	Dose	Best change
KRAS (G12V)	Sarcoma	450 mg BID	-50.5%
NRAS (G12D)	Melanoma	650 mg BID	-44%
BRAF (V600E)	GIST	200 mg BID	-38.1%
NRAS (Q61K)	Melanoma	200 mg BID	-36.2%
NRAS (Q61K) & BRAF (V600E)	Melanoma	300 mg BID	-33.8%
BRAF (V600E)	Melanoma	300 mg BID	-33.2%
NRAS (Q61R)	Melanoma	200 mg QD	-30.6%

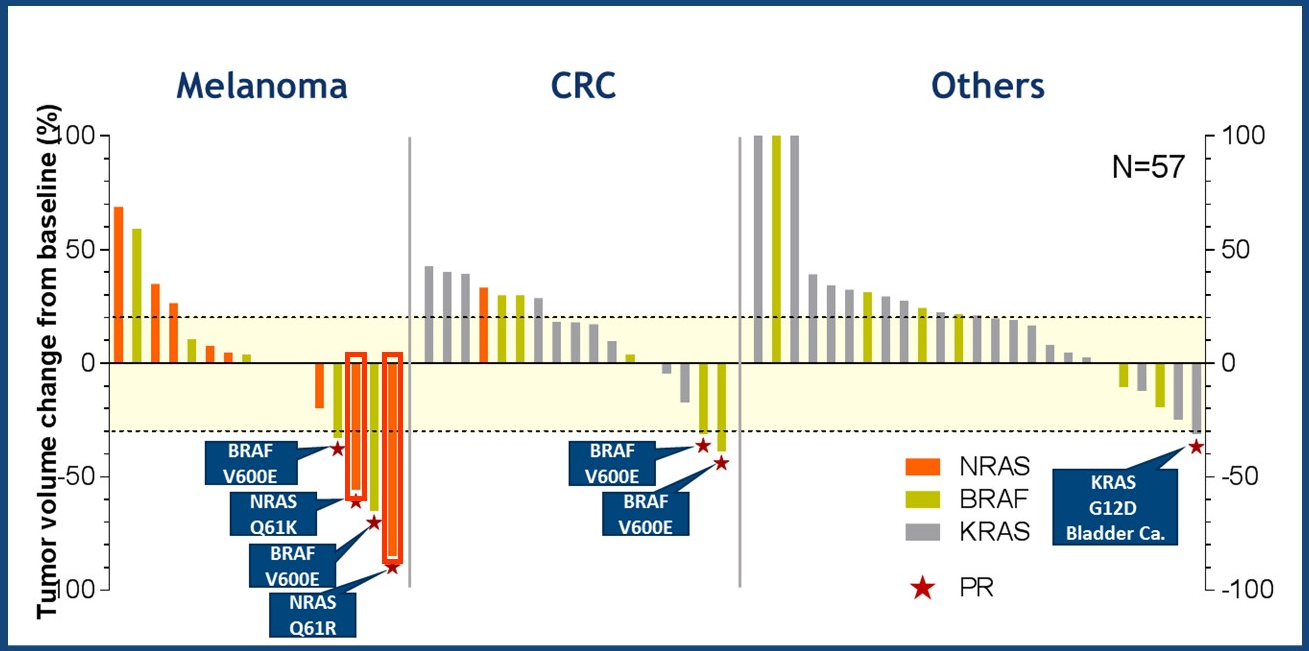
Treatment Duration: dose escalation study



Mutation Type	Cancer Type	Dose	Duration (days)
BRAF (V600E)	Melanoma	800 mg BID	702
NRAS (G12C)	Melanoma	800 mg BID	611
BRAF (V600E)	GIST	200 mg BID	512
KRAS (G12C)	CRC	100 mg QD	437
BRAF (V600E)	Melanoma	450 mg BID	377

Mutation Type	Cancer Type	Dose	Duration (days)
KRAS (G12V)	Bladder	300 mg BID	311
NRAS (Q61K)	Melanoma	200 mg BID	307
BRAF (V600E)	CRC	200 mg QD	303
NRAS (Q61K)	Melanoma	300 mg BID	278
BRAF (V600E)	CRC	200 mg BID	255

Best target percentage change from Baseline: dose expansion study



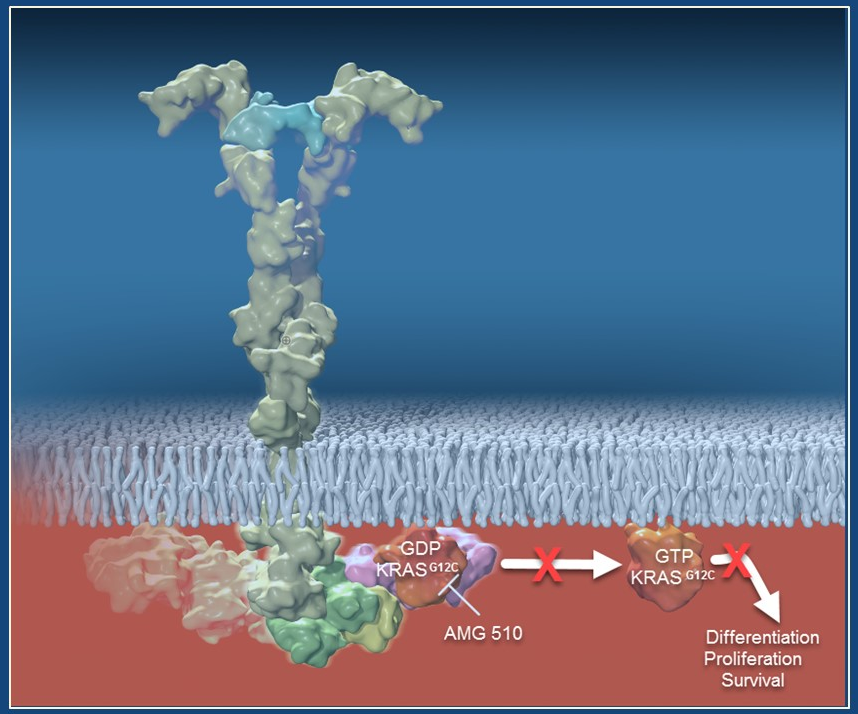
Others include gallbladder, bladder, nephroblastoma, thymic, endometrial, PDAC, amulla of vater, malignant neoplasm, NSCLC, breast, cholangiocarcinoma

Belvarafenib Summary

- Belvarafenib was well tolerated and exhibited anti-tumor activity in patients with advanced solid tumors harboring BRAF, KRAS or NRAS mutations
  - RP2D was declared as 450mg BID
  - Target exposure was achieved from 200 mg BID
  - NRAS-mutant melanoma patients had 44.4% of ORR and 24.91 weeks of PFS in dose escalation study
  - AEs that occurred in more than 20% of total patients were dermatitis acneiform, rash, and pruritus
- Belvarafenib is being further investigated in combination with the MEK inhibitor cobimetinib (NCT03284502)
- Belvarafenib with anti-PDL1 antibody Atezolizumab combination in NRAS melanoma patients will be further investigated

AMG 510 is a First in Class KRAS^{G12C} Inhibitor

- KRAS is a GTP-binding protein that links receptor tyrosine kinase activation to intracellular signaling
- Mutation of KRAS favors the GTP-bound active state and constitutive activation of downstream effects (differentiation, proliferation, survival)
- *KRAS^{G12C}* mutation is found in approximately 13% of lung cancer, 3% of colorectal (CRC) and appendix cancer, and 1-3% of other solid tumors
- AMG 510 is a novel, first in class, small molecule that specifically and irreversibly inhibits KRAS^{G12C} by locking it in an inactive GDP-bound state



AMG 510 First in Human Study Design

This is a multicenter, open-label, phase 1, first in human study (NCT 03600883) in adult patients with locally advanced or metastatic *KRAS*^{G12C} mutant solid tumors

Key Eligibility Criteria

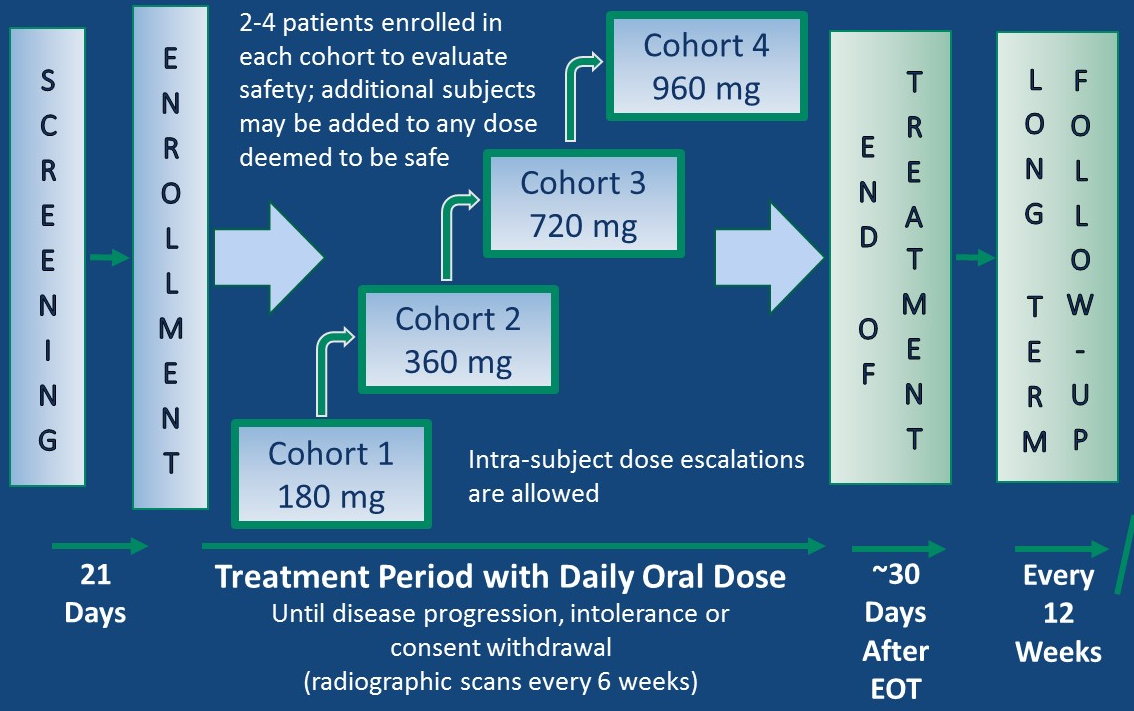
- Documented locally-advanced or metastatic *KRAS*^{G12C} measurable or evaluable solid tumors
- Received prior standard therapy appropriate for tumor type and stage of disease
- No active brain metastases

Primary Endpoints

- Safety and tolerability including the incidence of AEs and DLTs

Key Secondary Endpoints

- PK, best response, duration of response and duration of stable disease,
- Objective response rate and PFS



Patient Incidence of Treatment Related TEAE

Adverse Event	Gr 1 n	Gr 2 n	Adverse Event	Gr 1 n	Gr 2 n
Diarrhea	3		Proteinuria		1
Decreased appetite	2		Dry mouth	1	
Nausea	2		Flatulence	1	
Elevated creatine phosphokinase	2		Vomiting	1	
Elevated or change in AST	1	1	Fatigue	1	
Elevated or change in ALT	1	1	WBC Decrease	1	
Elevated alkaline phosphatase	1	1	Pyrexia	1	
Cheilitis		1	Arthralgia	1	
Hyperkalemia		1	Hot Flush	1	

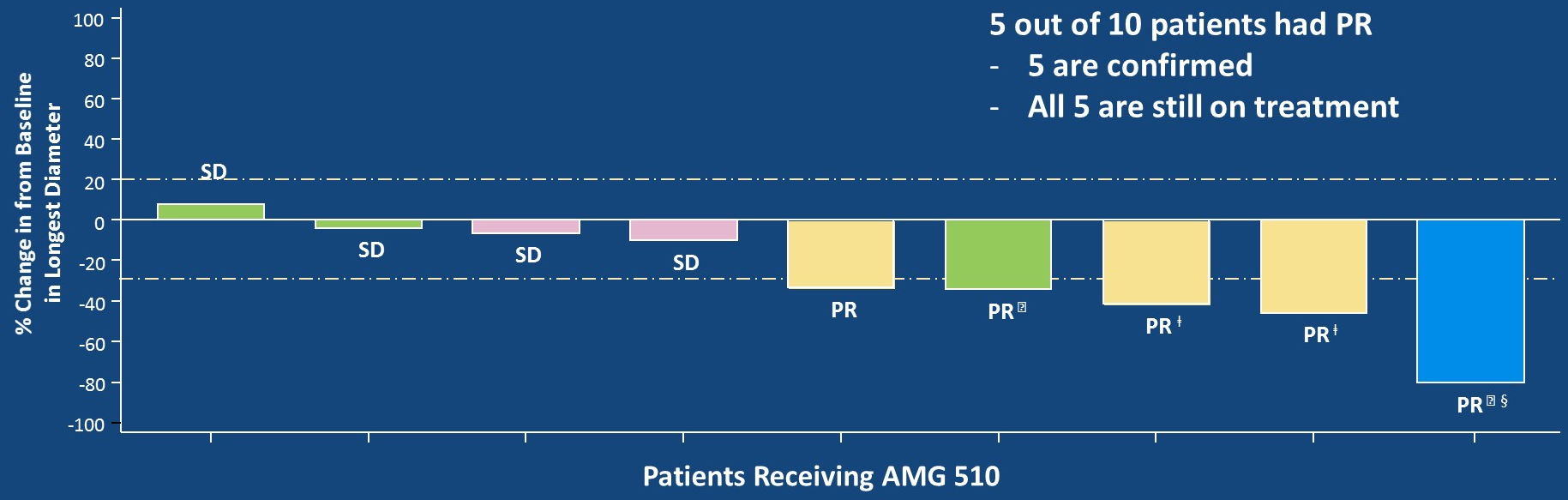
Grade 3 Adverse Event	n
Anemia[a]	1
Diarrhea[b]	1

[a]Patient had grade 2 anemia at baseline
[b]Lasting 2 days

None of the 35 patients reported:

- DLTs
- Grade 4 related AEs
- Serious related AEs

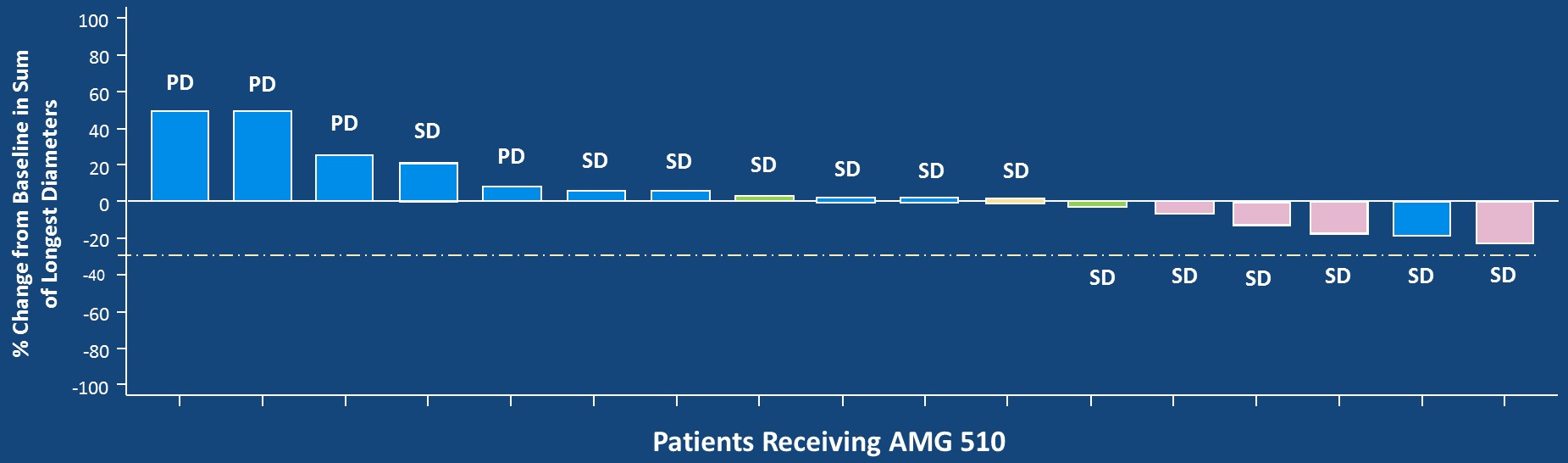
NSCLC: Best Tumor Response* (n=10)



* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 patient had clinical progression prior to week 6 and is not on this graph
⍰ Confirmed response
‡ 2 additional patients had confirmed PR post data cutoff
§Patient had a CR of the target lesions at week 18, post data cutoff

Planned Dose 180 mg 360 mg 720 mg 960 mg

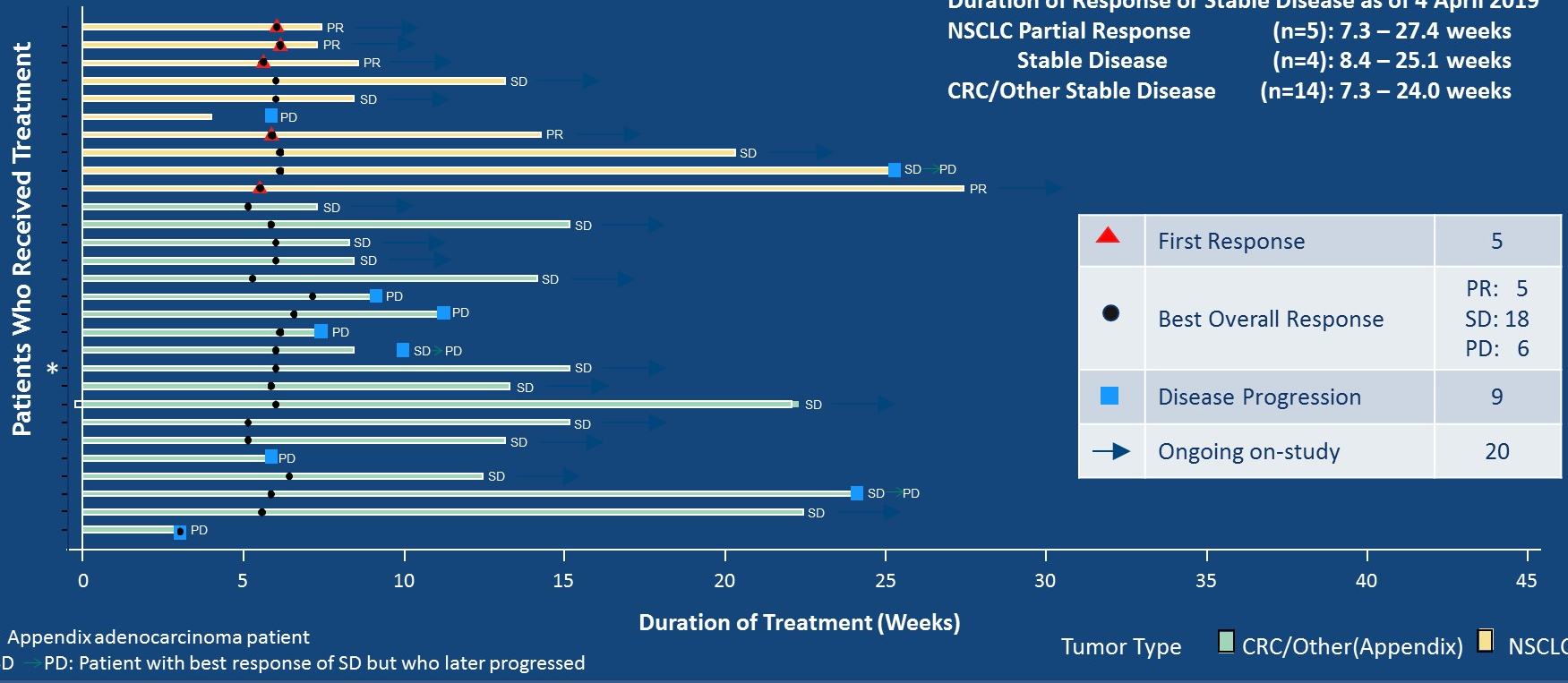
CRC and Other Solid Tumors: Best Tumor Response* (n=19)



* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 CRC patient progressed prior to week 6 and is not on this graph
1 appendix patient had clinically stable disease but is not shown on this graph

Planned Dose: 180 mg | 360 mg | 720 mg | 960 mg

Duration of Treatment by Tumor Types and Responses (n=29)



Duration of Response or Stable Disease as of 4 April 2019

NSCLC Partial Response	(n=5): 7.3 – 27.4 weeks
Stable Disease	(n=4): 8.4 – 25.1 weeks
CRC/Other Stable Disease	(n=14): 7.3 – 24.0 weeks

▲	First Response	5
●	Best Overall Response	PR: 5 SD: 18 PD: 6
■	Disease Progression	9
→	Ongoing on-study	20

* Appendix adenocarcinoma patient

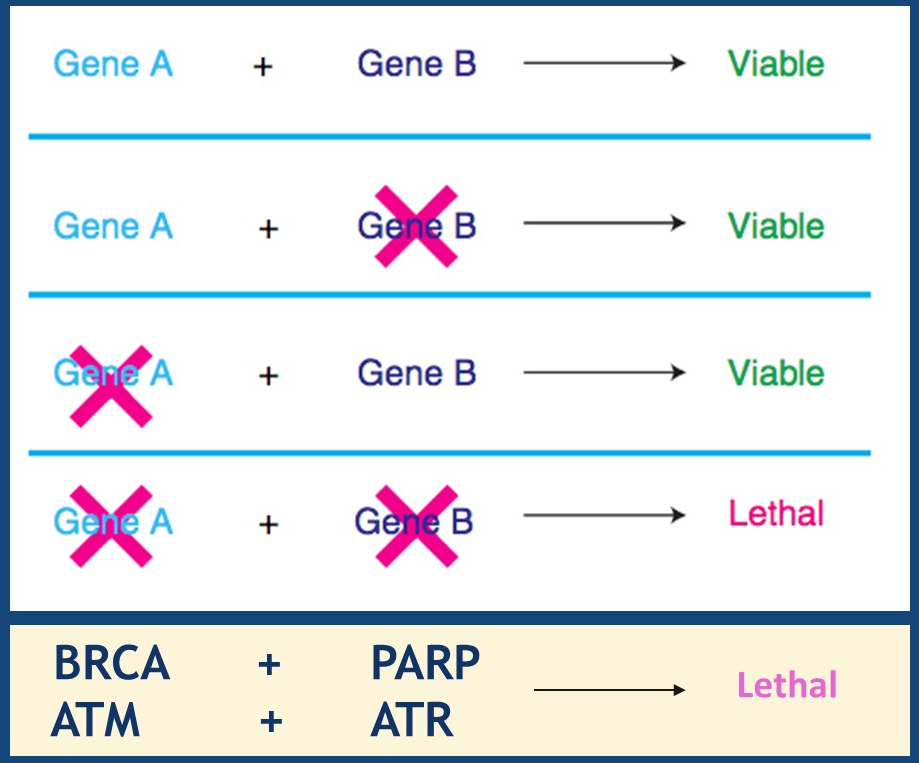
SD → PD: Patient with best response of SD but who later progressed

Tumor Type: CRC/Other(Appendix) NSCLC

AMG510 Summary

- AMG 510 is a novel, first in class, irreversible inhibitor of $KRAS^{G12C}$
- AMG 510 had a favorable PK profile with exposures exceeding the threshold for tumor growth inhibition in preclinical models
- AMG 510 has been safe and well tolerated at the dose levels tested in 35 patients in dose exploration
  - No DLTs have been observed
  - No cumulative toxicities were noted with extended treatment
- Preliminary monotherapy antitumor activity in $KRAS^{G12C}$ NSCLC was observed
  - 5 of 10 patients with NSCLC had a PR, all with confirmed PRs
- Enrollment is ongoing

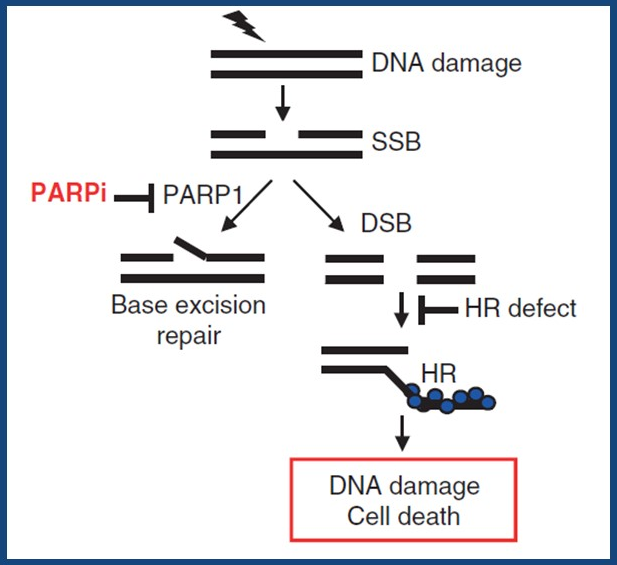
Synthetic Lethality



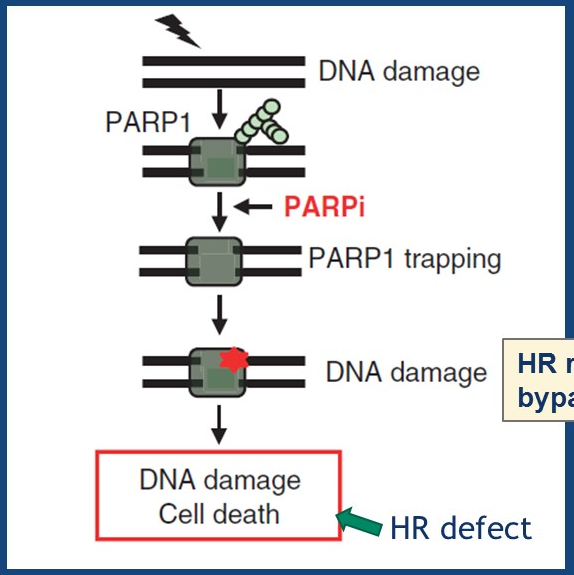
Ma e t al. Nat Commun, 2018

Synthetic Lethality of Homologous Recombination Repair Deficiency and PARP Inhibition

Inhibition of Base Excision Repair (BER)



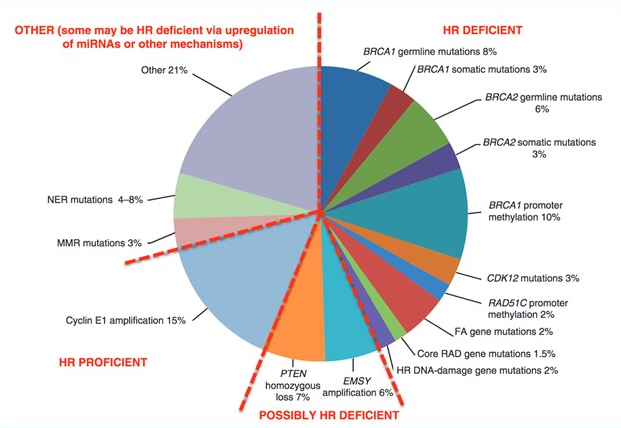
Trapping of PARP-DNA complexes



Konstantinopoulos et al., Cancer Disc 2015;5:1137-54

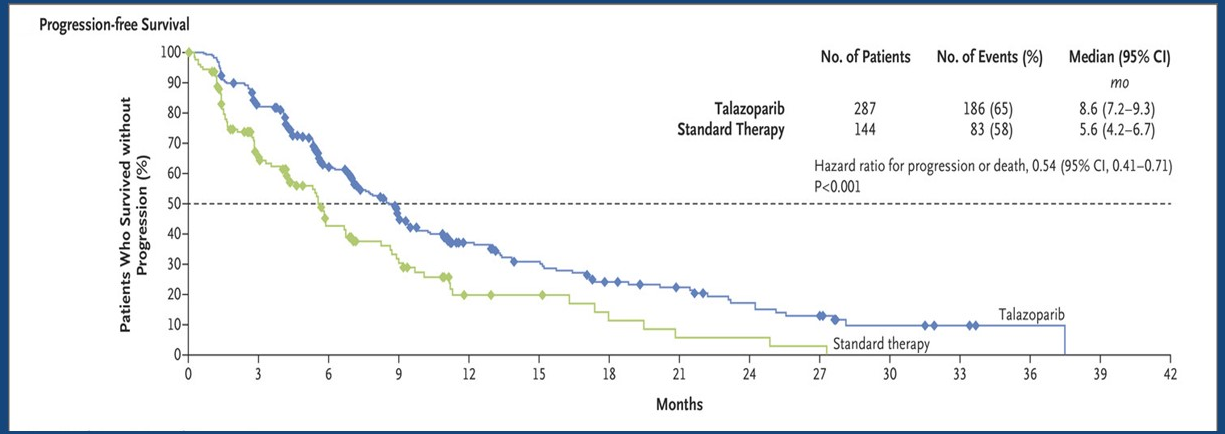
HR Deficiency in HGSOC and Breast Cancer

Ovarian Cancer



PARP inhibitors approved in advanced g/s BRCA1/2 HGSOC and in maintenance irrespective of BRCA mutation

Breast Cancer



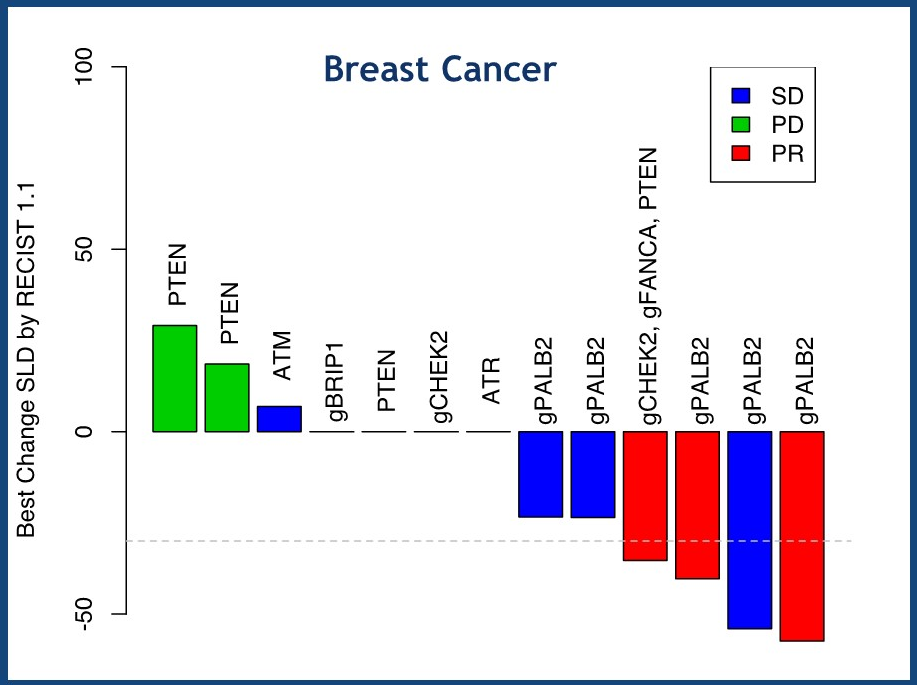
PARP inhibitors olaparib and talazoparib approved in advanced gBRCA1/2 BCa
Litton et al. EMBRACA trial, NEJM, 2018 (talazoparib)
Robson et al. OLYMPIAD trial, NEJM, 2017 (olaparib)

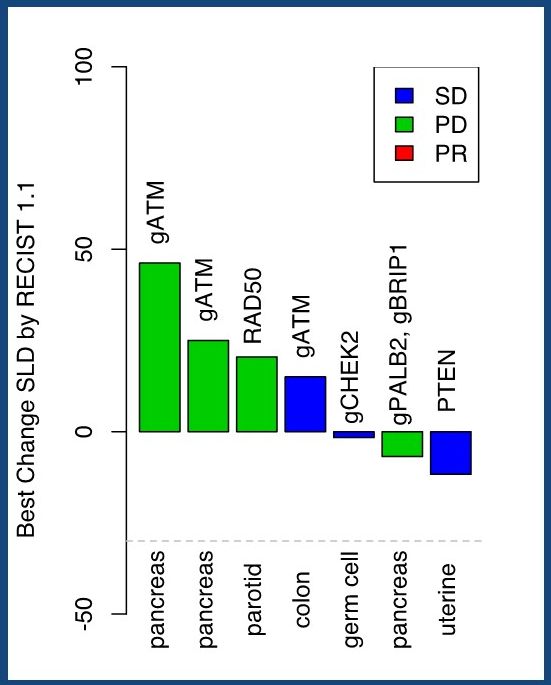
Talazoparib beyond BRCA

- Advanced HER2-negative breast cancer or other non-breast solid tumors with either a germline or somatic mutation in homologous recombination pathway genes

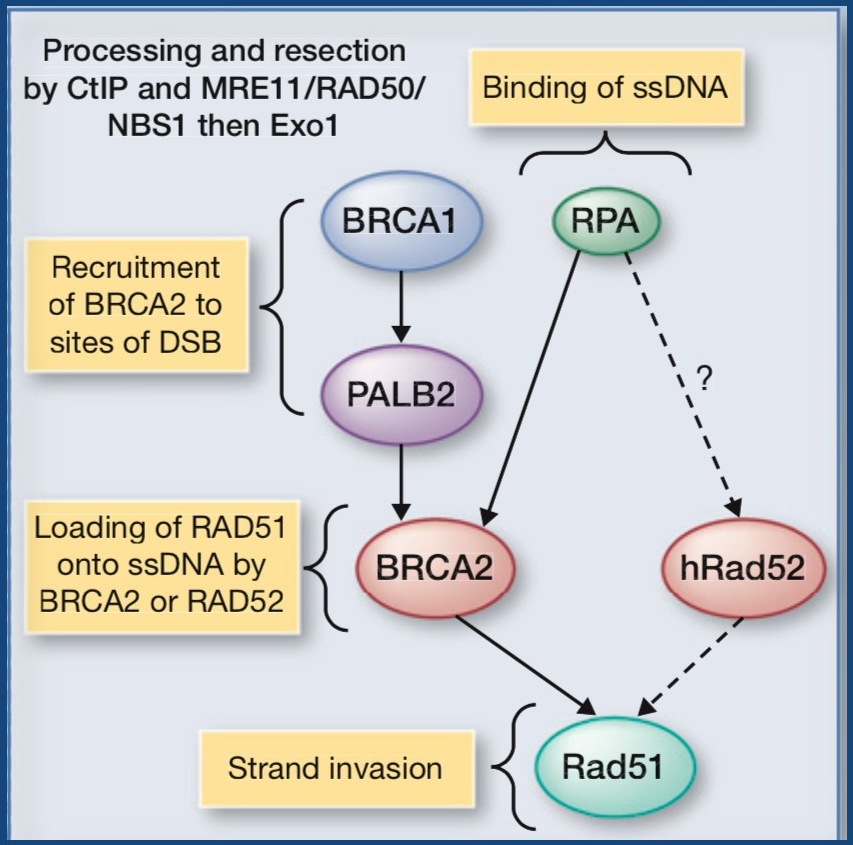
- PTEN, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, Fanconi anemia complementation group of genes (FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL)

Talazoparib beyond BRCA: Best Overall Responses





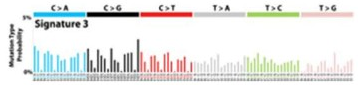
PALB2



Lok and Powell *CCR* 2012

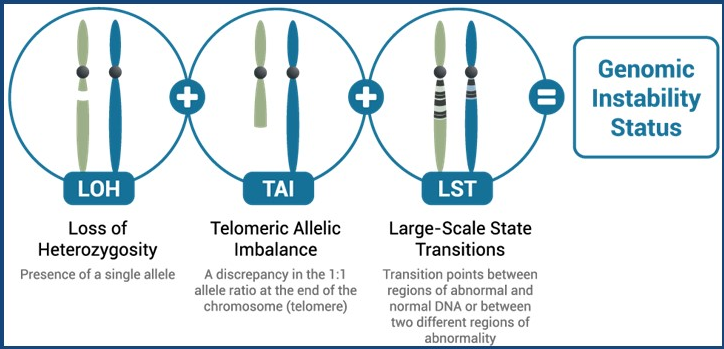
Improving predictability for PARP inhibitor sensitivity

- HRD Score
  - TNBC platinum (pCR 40% v. 11%, HRD hi v. low)
  - Ovarian high HRD predicts long olaparib maintenance
- Presence of Signature 3

Homologous Recombination			
			
Signature 3	Breast, ovarian, pancreatic	Failure of DNA double-strand break-repair by homologous recombination.	Elevated numbers of large (>3bp) insertions and deletions with overlapping microhomology at breakpoint junctions.

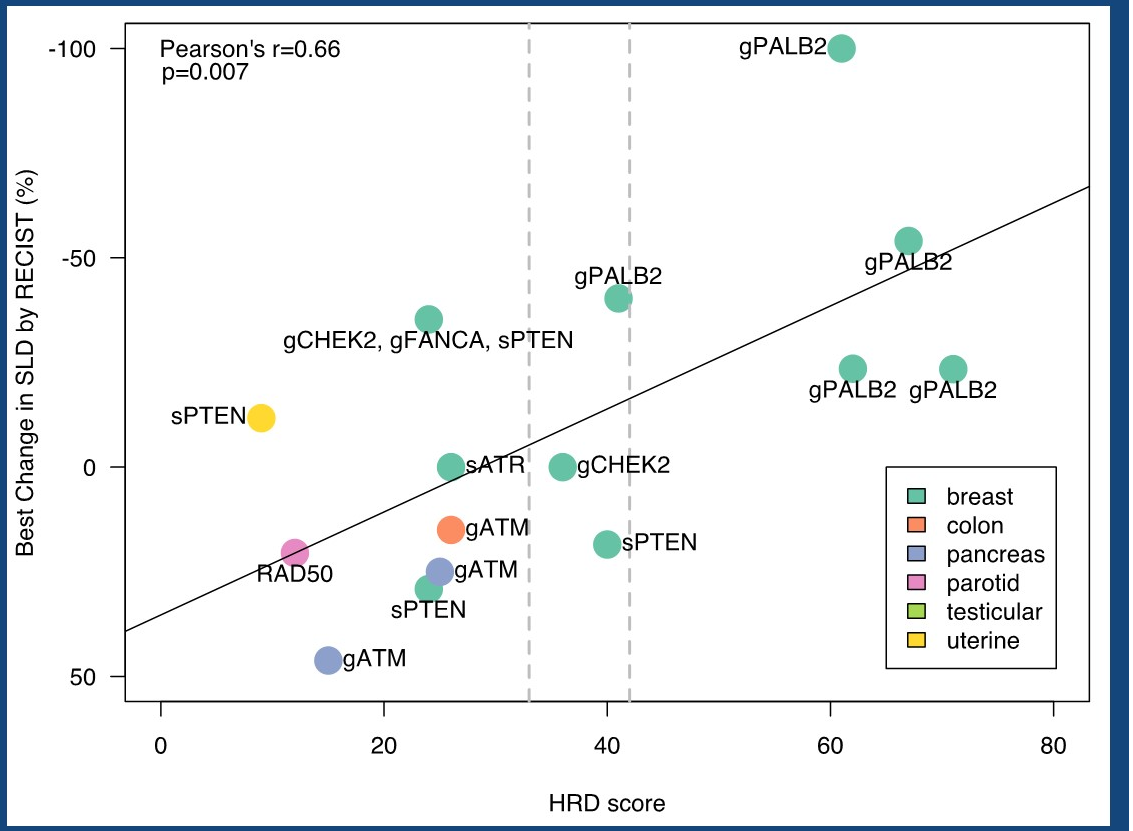
- Functional assay for HR proficiency

Homologous Recombination Deficiency (HRD) score[1] correlates with response

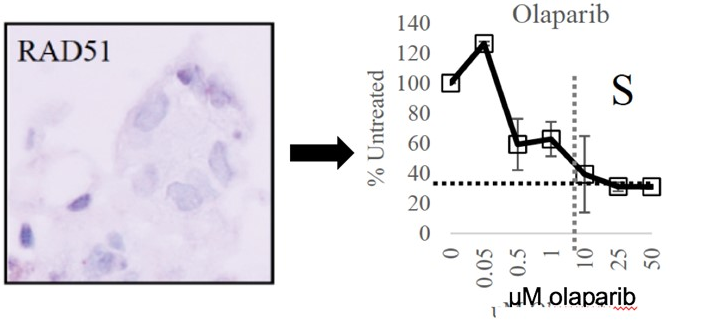


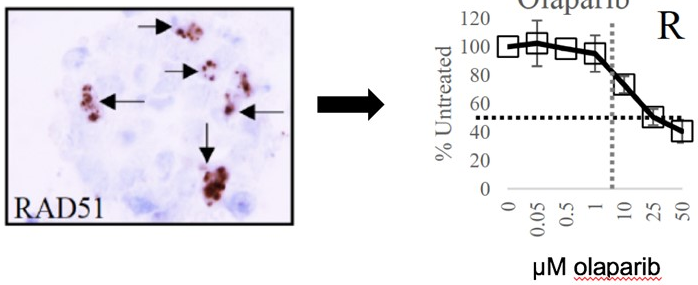
- Threshold ≥ 42 captures 95% of known BRCA1/2 deficient TNBC / ovarian cancers
- Threshold ≥ 33 captures 99%

[1]Myriad MyChoice®



RAD51 Assay for HR Proficiency distinguishes PARP inhibitor-sensitive and -resistant HGSOC organoid cultures





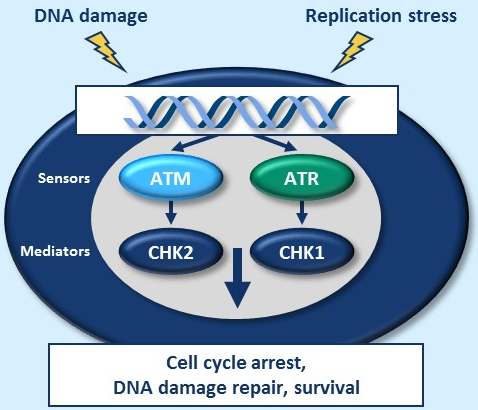
Absence of endogenous RAD51 foci correlates with PARP inhibitor sensitivity

Presence of endogenous RAD51 foci correlates with PARP inhibitor resistance

Hill et al., *Cancer Discovery*, 2018

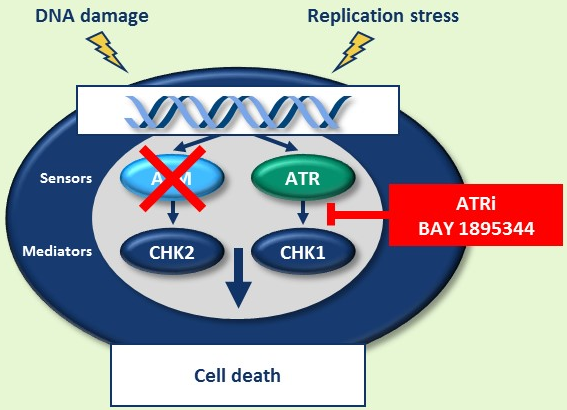
Synthetic Lethality of combined loss of ATM and ATR

Normal cell
ATM proficient



ATR is a key regulator in response to DNA damage and replication stress promoting DNA damage repair and **survival**

Cancer cell
ATM deficient



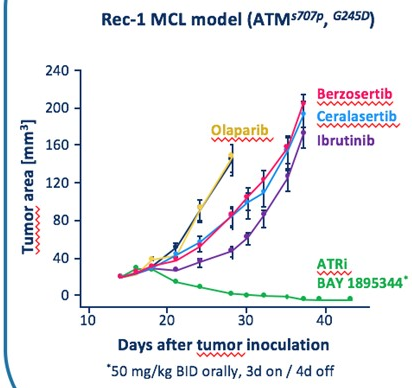
ATR inhibition in cancer cells with certain DDR defects (e.g. ATM aberrations) induces rapid cell death
→ **synthetic lethality**

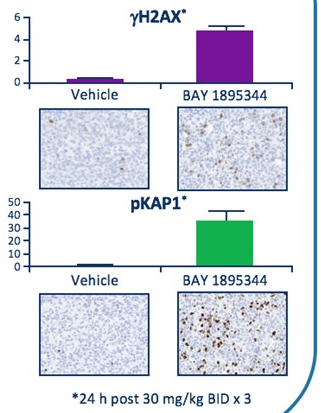
BAY1895344 – selective and potent ATR inhibitor

Biochemical and cellular activity

BAY 1895344, nM	
ATR biochemical IC_{50}	7
ATR cellular mechanistic IC_{50} Hydroxyurea induced pH2AX in HT-29	36
Kinase selectivity Hits with <50% activity at 100 nM in DiscoverX panel (395)	1
ATR selectivity against ATM Ratio of cellular mechanistic IC_{50}	200
Anti-proliferation IC_{50} range In 38 different tumor cell lines	9-490
Anti-proliferation in ATM^{loss} cells HT-144	42
Anti-proliferation in Pgp^{high} model	190

In vivo anti-tumor and PD activity





Strong single-agent activity in tumor models of **different histologies** and **DDR defects** such as ovarian, prostate, CRC, lymphoma, and lung

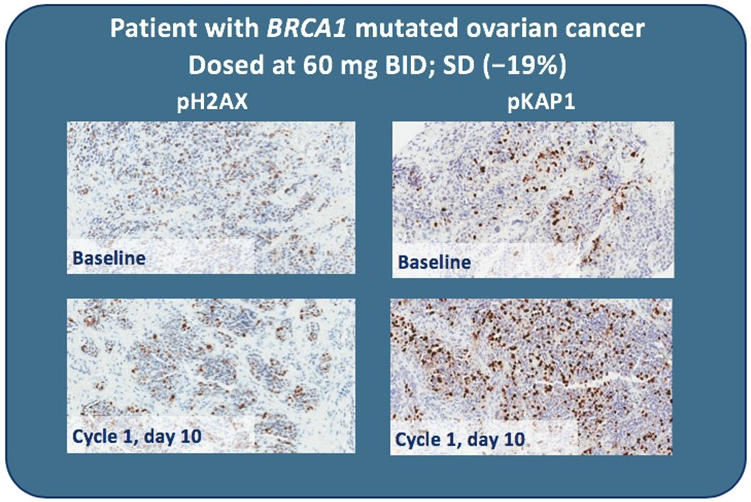
MTD Determination

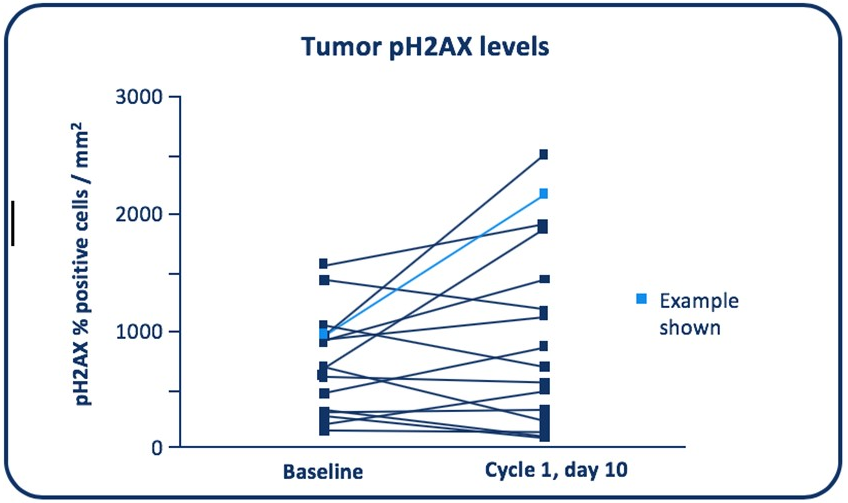
Cohort	Dose level, mg	All patients / evaluable patients, n	DLTs, n	DLT description
1	5	1 / 1	0	-
2	10	2 / 1	0	-
3	20	2 / 1	0	-
4 (MTD)	40	2 / 2	0	-
5	80	3 / 2	2	G4 neutropenia; G4 leukopenia / G4 thrombocytopenia
6	60 (schedule 1)	8 / 7	2	G4 neutropenia / G3 leukopenia; G2 fatigue
7	60 (schedule 2)	4 / 3	2	G3 thrombocytopenia; G3 neutropenia

- MTD was determined to be 40 mg BID 3 days on / 4 days off
- A dose-dependent increase in grade ≥3 cytopenia was observed during cycle 1 at doses >MTD

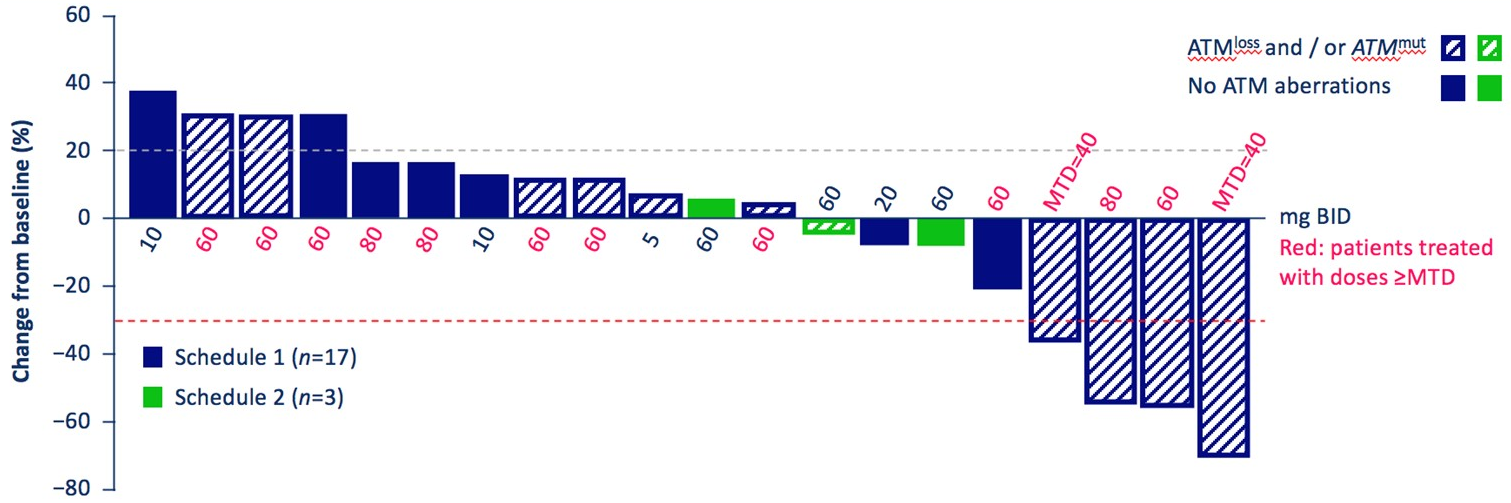
At MTD, most common AEs were anemia, neutropenia and fatigue

Pharmacodynamics: Increased γH2AX and pKAP1 in paired tumor biopsies as evidence of target engagement





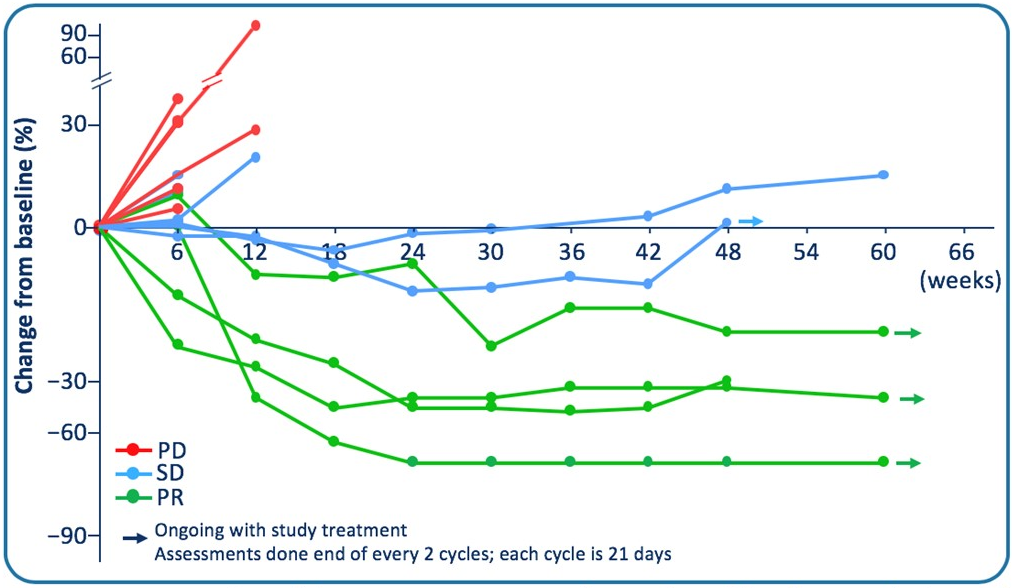
Dose escalation: RECIST and PCWG3 responses



- 20 patients with post-baseline CT scans were treated at doses from 5 mg to 80 mg BID
- 4/13 confirmed PRs were observed in ***patients treated with schedule 1 at dose levels ≥MTD → ORR=30.7%***
- All responders showed ATM aberrations ***(ATM^loss and / or ATM^mut)*** in tumors collected at screening or from archival tissue

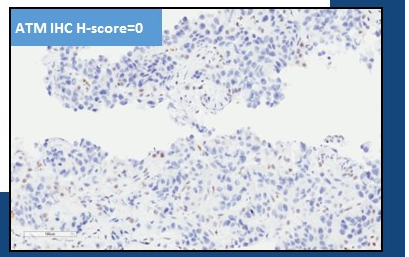
mut, mutation; PCWG3, Prostate Cancer Working Group 3; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1

Durability of responses



IHC 0 Germline DN?

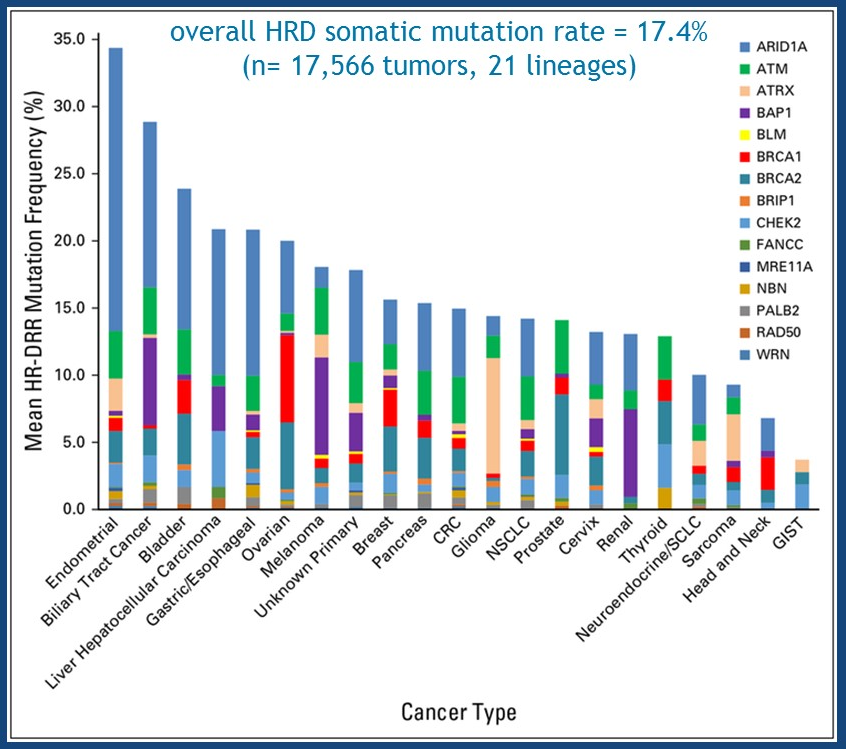
Tumor type	Dose	Best response	DDR status	Days on treatment	Treatment status
Urothelial duct	40	PR; −69%	ATM^{loss}	475	Ongoing
Clear cell endometrial	80→40	PR; −53%	ATM^{loss}/mut	445	Ongoing
HR+ HER2- breast	60→40	PR; −54%	ATM^{loss}/mut	356	Off treatment
Appendix	40	PR; −35%	ATM^{mut}	481	Ongoing
Ovary	60→40	SD; −19%	$BRCA1^{mut}$	385	Ongoing



Durable responses or prolonged stable disease (>1 year) were observed in patients with a variety of cancers and ATM / *BRCA1* DDR defect

Synthetic Lethal Interactions involving DNA repair pathways

- An increasing number of patients will ultimately benefit from these approaches
- Defining the tumors truly harboring DNA repair deficiency at the time of drug exposure will be critical for identifying those destined to respond
- Will likely require complementary genomic, protein-level and functional assays of pathway proficiency



Heeke et al. JCO Precision Onc. 2018

Belvarafenib, AMG510, Talazoparib, BAY1895344

- Tolerable doses achieved that meet or exceed threshold concentration for target engagement
- Pharmacodynamic effects demonstrated for BAY1895344
- Responses observed in predicted biomarker-driven populations
- Further work to define/refine optimal populations for DNA repair inhibitors is ongoing
- Responses frequently highly durable
- Trials ongoing to confirm initial promising responses o
- In all cases, definition of mechanisms of resistance will be critical

Acknowledgements

Patients and families who have dedicated their trust to the investigators and participated in clinical trials

Posttest Question 1:

NKTR-214 is a pegylated form of:

1. IL-15
2. IL-12
3. IL-2
4. IL-10

Posttest Question 2:

AMG-510 showed best activity in patients with:

1. Melanoma with $BRAF^{V600E}$ mutation
2. CRC with $BRAF^{V600E}$ mutation
3. CRC with $KRAS^{G12C}$ mutation
4. NSCLC with $KRAS^{G12C}$ mutation

Posttest Question 3:

Synthetic lethality concept refers to the situation where loss of either one gene which interact leaves the cell viable. However, if both are lost, the cell dies. Examples include genes pairs ATM/ATR; BRCA/PARP.

1. True
2. False