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The Role of SHP-2 Inhibitors Alone or in Combination

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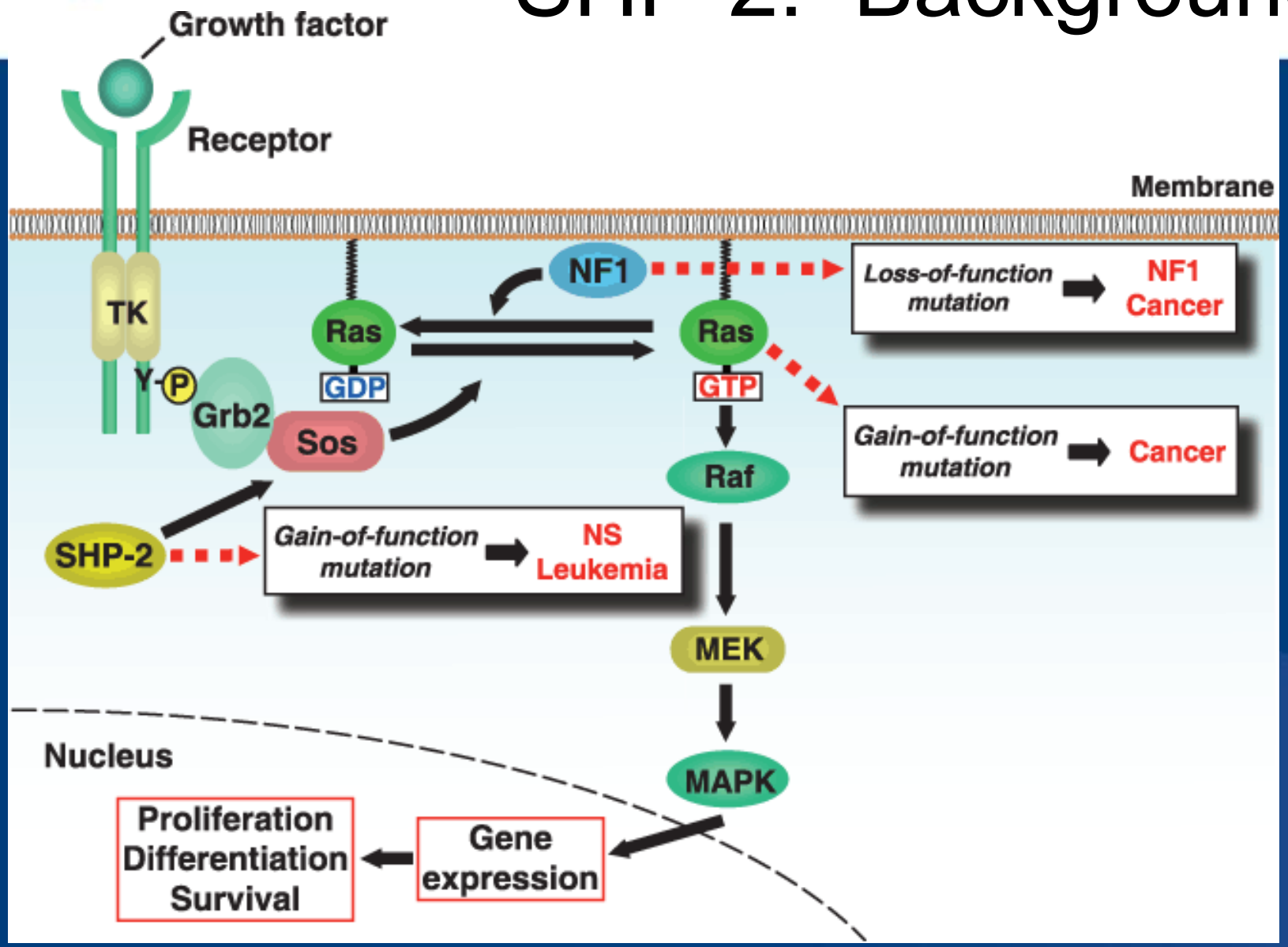
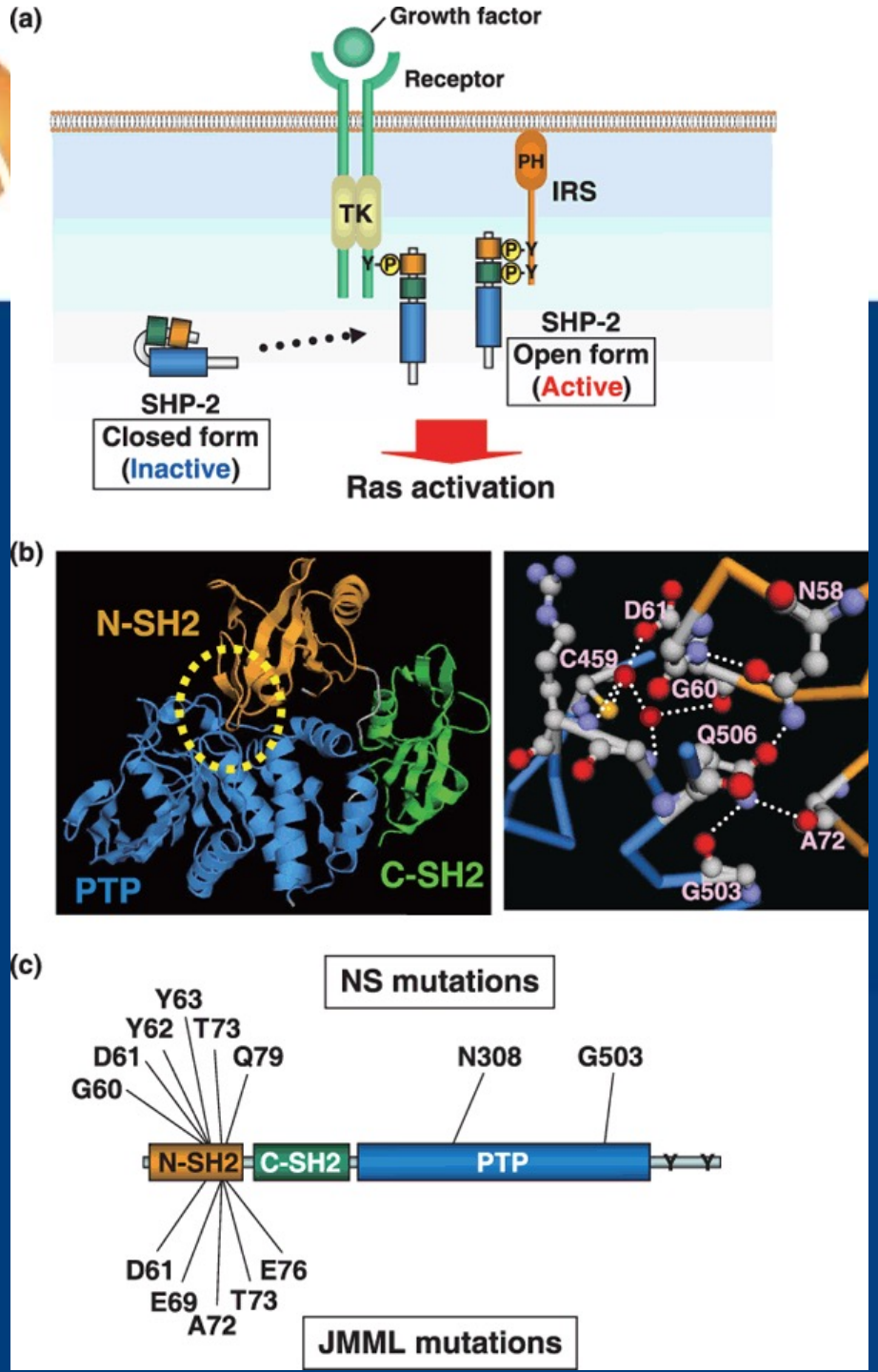
SHP-2: Background



- Protein tyrosine phosphatase SHP-2 activation promotes RAS pathway activation
- Inherited PTPN11/SHP-2 mutations (gain-of-function) lead to Noonan syndrome (developmental disorders) with myeloid malignancies, other cancers

Matozaki T et al, Cancer Sci 2009



- Closed form autoinhibits
- Activation in open conformation
- Active SH2 sites bind with phosphorylated growth factor receptors (PDGF, SIRPα, FGFR substrate, …)
- Multiple N-terminal mutations may trigger activation

Matozaki T et al, Cancer Sci 2009

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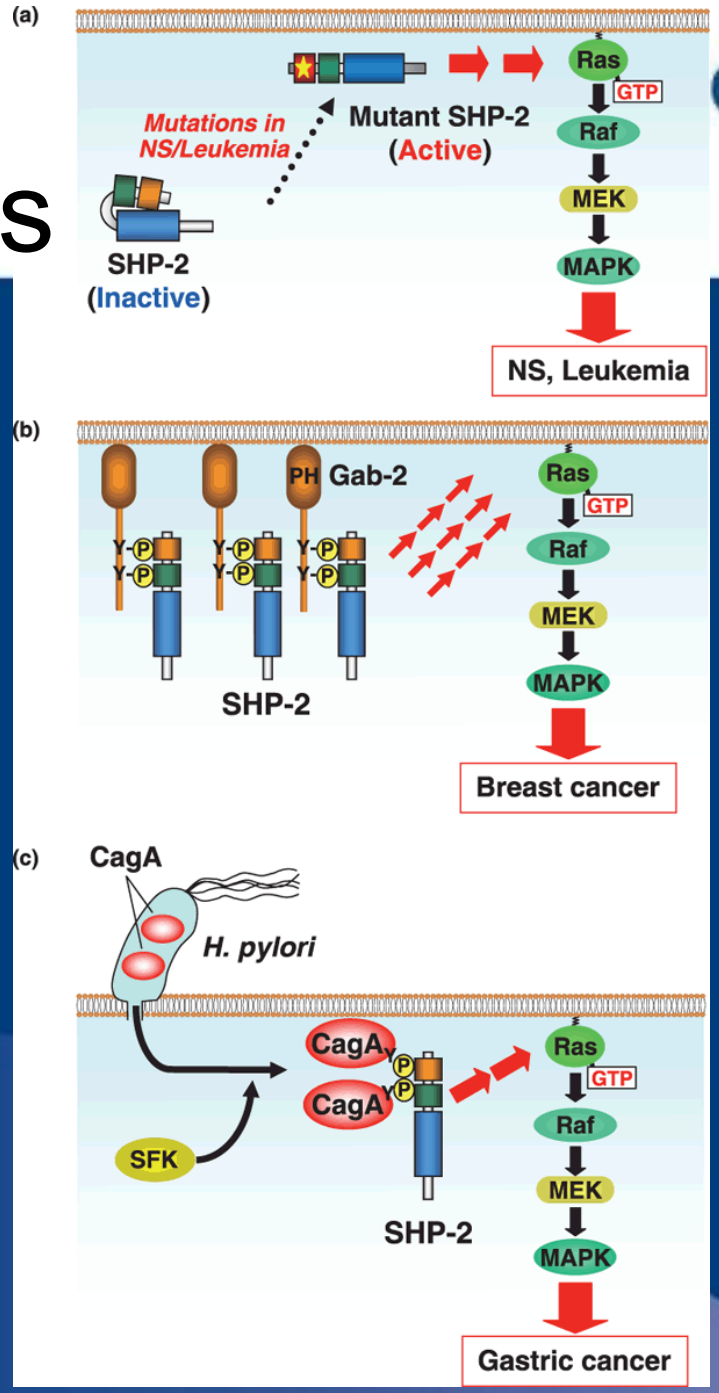
SHP-2 Proposed Pathway Actions

- SHP-2 mutation activation triggering RAS pathway
- Gab-2 activation by cytokines triggers SHP-2 binding/hyperactivation, HER2 mammary proliferation, breast cancers
- Potentiation of oncogene-addicted pathways
- H. pylori infection injects CagA into cells, docking protein for SHP-2 the MAPK activation, gastric cancer



Matozaki T et al, Cancer Sci 2009

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SHP-2 Immune Signaling

- Inactivates costimulatory receptor CD28
  - = T cell inactivation
- Inhibition may potentiate immune recognition:
  - Increase intratumoral CD8+ T lymphocytes;
  - Increase tumor-associated B lymphocytes;
  - May suppress tumor-associated macrophages (M2 TAMs)
- Potential synergy between SHP-2 inhibitors, KRAS G12C inhibitors, checkpoint inhibition

Wang J, et al. J Cancer Immunol 2021

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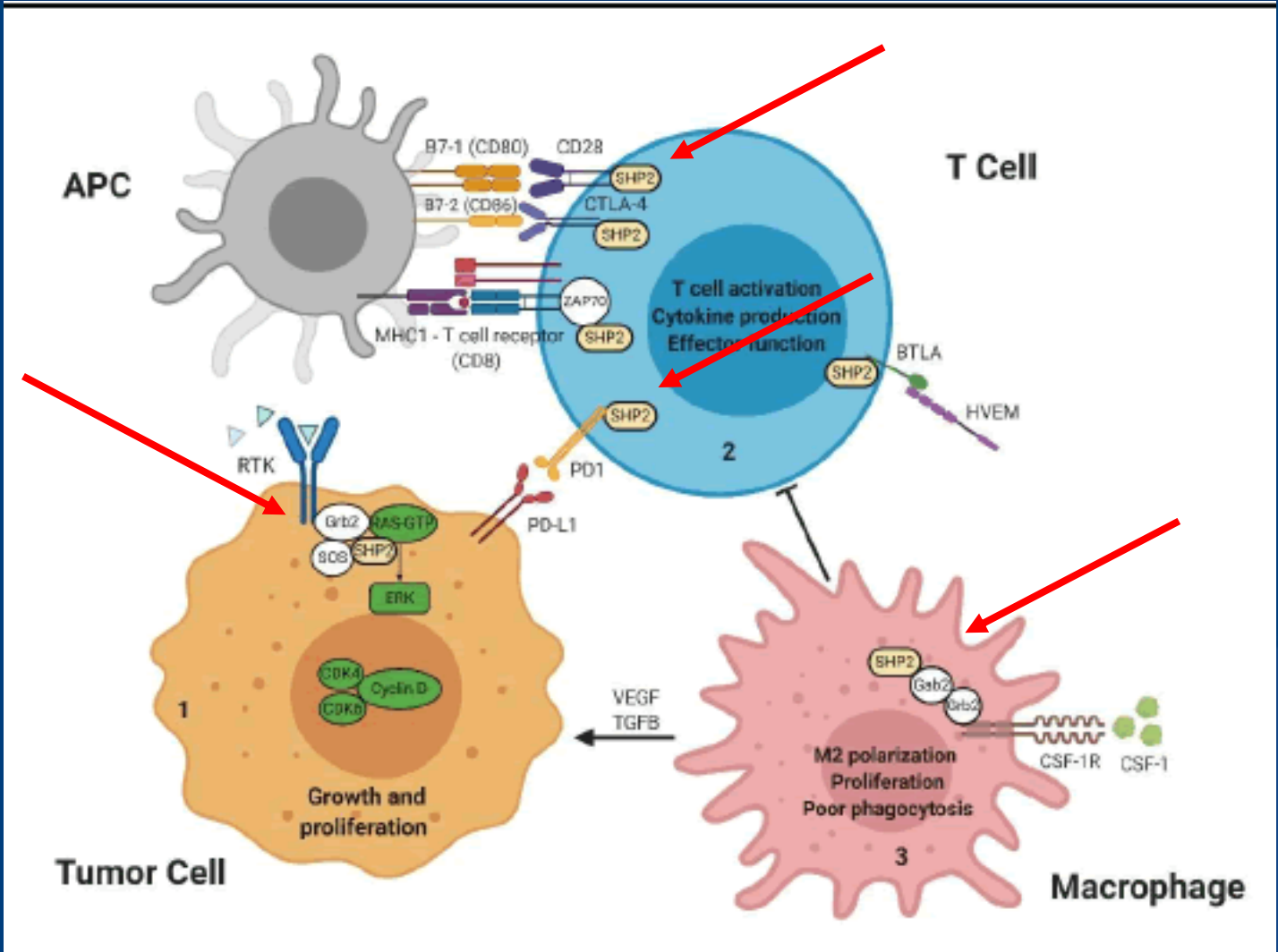
SHP-2 Immune Signaling Interactions



- RAS-ERK signaling
- Downstream signaling of TCR (exhaustion)
- CSF-1/CSF-1R axis TAMs (M2 polarization)

Wang J, et al. J Cancer Immunol 2021

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SHP-2 INHIBITOR
SINGLE AGENT STUDIES

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RMC-4630

- Phase I trial, multiple dosing schedules
- 80 efficacy-evaluable patients
  - 38 with KRASm NSCLC: DCR 61%;
  - 15 with KRAS G12Cm: DCR 80%
  - 1 PR

- Toxicities: Edema, diarrhea, fatigue, myelosuppression

Koczywas M, et al. Cancer Research 2021 AACR LBA 2021

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RMC-4630 Single Agent Immune Profiling

- AACR 2021: (Same trial)
- Immune profiling conducted for 35 patients
- SHP-2 inhibition associated with
  - Decreased monocytic myeloid-derived suppressor cells (mMDSCs)
  - Decreased total monocytes
  - No change in circulating T- or B-cell populations
- Correlation with change in tumor volumes and mMDSC/total monocyte ratio

Chen A Y-C, et al, Cancer Res 2021 LBA AACR 2021

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RMC-4630 Single Agent IHC

- AACR 2021: (Same trial)
- 3 patients with paired tumor biopsies:
  - One patient with PR; 1 Stable Disease; 1 Progression
  - Increased tumor-infiltrating lymphocytes (TILs) in biopsies from patients with PR and SD
  - Patient with PR also demonstrated reduced PD-1 expression,
  - Decreased M2 macrophages

Chen A Y-C, et al, Cancer Res 2021 LBA AACR 2021

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TNO155

- Phase I dose escalation (ongoing)
- 118 patients (12% NSCLC)

- Toxicity: Increased CPK, edema, diarrhea, dermatitis, myelosuppression, increased LFTs

- 20% Stable Disease

Brana I, et al. ASCO 2021

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ERAS-601

- FLAGSHP-1, Phase I trial
- Single agent or with Cetuximab

- Preliminary data single agent ERAS-601:
  - 27 patients, 1 PR (BRAF class III mutation)

- Toxicities: Transaminase elevations, HTN, myelosuppression, peripheral edema, diarrhea

McKean M, et al. Eur J Cancer 2022

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SHP-2 INHIBITOR COMBINATION STUDIES

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CodeBreak101

- Sotorasib + RMC-4630
- Phase I dose escalation
- Toxicities: Peripheral edema, diarrhea, fatigue
- Gr 3 = Diarrhea, ascites, transaminase elevation, colitis, dyspnea, HTN, pleural effusion
- 11 NSCLC: 3 PR, 64% DCR
- KRASi-Naive at highest doses: 3 PR, 100% DCR
- 1 NSCLC prior soto: uPR then PD

Falchook G et al. J Thoracic Oncol 2022 (OA WCLC 2022)

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KONTRAST-01

- JDQ443 (KRAS G12C i) +TNO155 (SHP-2 inhibitor)
  - Phase I dose escalation
  - 24/50 patients with NSCLC
  - (12 previously treated with KRAS G12C inh)

- Toxicities: Peripheral edema, myelosuppression, diarrhea, fatigue, increased CPK, transaminitis
  - 36% $\geq$ Grade 3

Negrao et al, WCLC 2023

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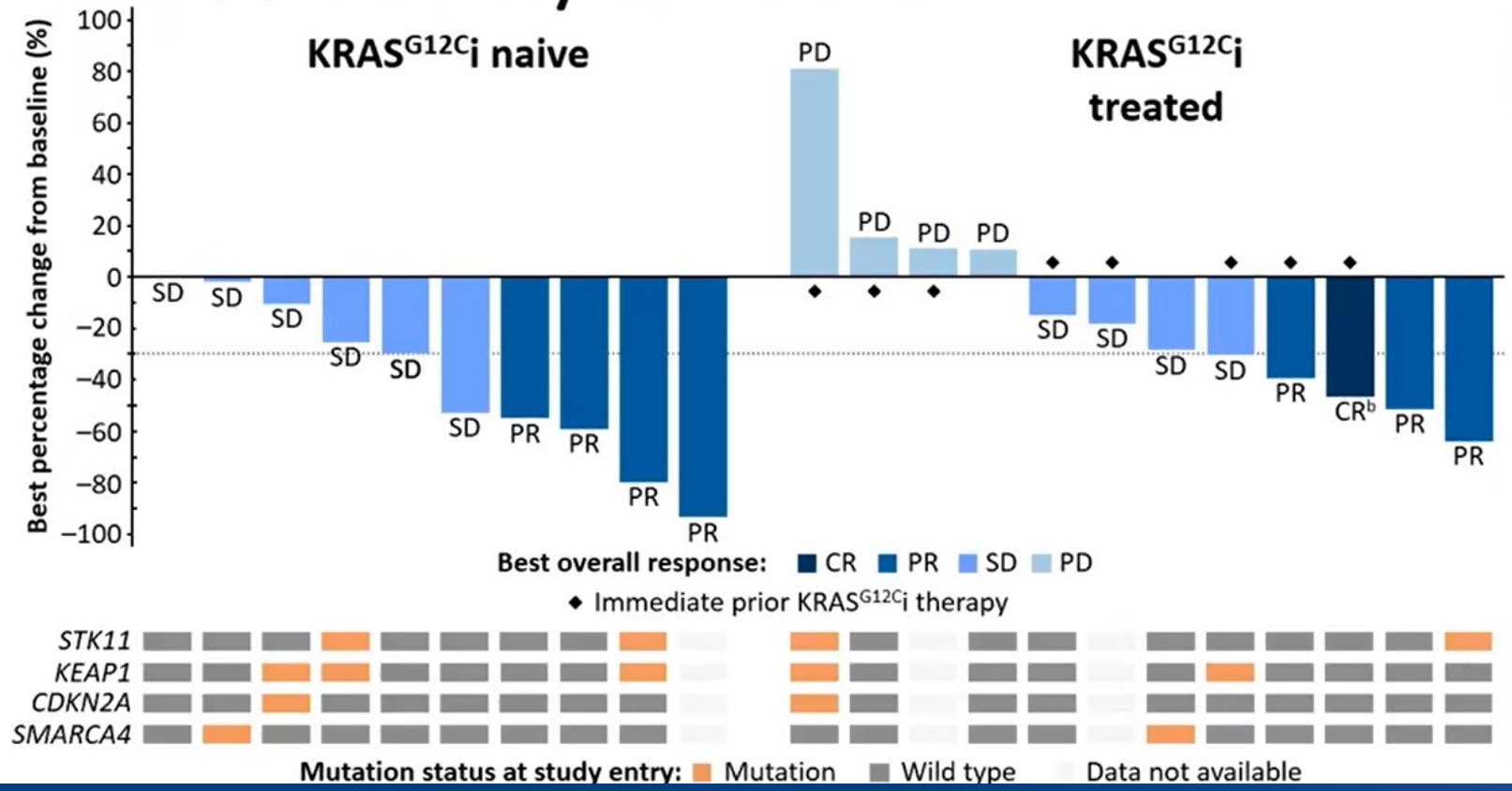
KONTRAST-01

Clinical activity in NSCLC



	NSCLC KRAS^{G12C}i naive (N=12)	NSCLC KRAS^{G12C}i treated (N=12)
BOR[a], n (n/N%)		
CR	–	1 (8.3)
PR	4 (33.3)	3 (25.0)
SD	6 (50.0)	4 (33.3)
PD	–	4 (33.3)
UNK	2 (16.7)	–
ORR: CR + PR, % (90% CI)	33.3 (12.3–60.9)	33.3 (12.3–60.9)
DCR: CR + PR + SD, % (90% CI)	83.3 (56.2–97.0)	66.7 (39.1–87.7)

Negrao et al, WCLC 2023

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Single Agent SHP-2 Inhibitor Trials

Drug	Tumor Types	Phase	Recruiting
BBP-398	MAPK-, RTK- driven Adv Solid Tumors	I	Y
ET0038	Adv Solid Tumors	I (FIRST)	Not yet
HBI-2376	KRAS or EGFRm Adv Solid Tumors	I	Y
JAB-3312	Adv Solid Tumors	I	Y
RLY-1971	Adv Solid Tumors	I	N

Clinicaltrials.gov Accessed 10-27-2023

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SHP-2 Inhibitor Combination Trials

Drug	Partner	Tumor Types	Phase	Recruiting
BBP-398	Nivolumab	NSCLC KRASm	I	Y
ERAS-601	Cetuximab; Pembrolizumab		I	Y
GDC-1971	GDC-6036 (KRAS G12Ci)	KRAS G12Cm	I	Y
PF-07284892	Single agent; Lorlatinib; Encorafenib + Cetuximab; Binimetinib	Adv Solid Tumors; ALK+, ROS-1+ NSCLC; CRC BRAF V600E; RASm, NF1m, BRAF Class III m Adv solid tumors	I	Y
RMC-4630	LY3214996 (ERK inhibitor)	KRASm CRC, PDAC, NSCLC	I	Y
TNO155	Alone or w EGF816 (nazartinib) (EGFRi)	Adv Solid Tum	I	Y
TNO155	Adagrasib	KRAS G12Cm Adv Solid Tumors	I/II (KRYSTAL 2)	N
TNO155	JDQ443 (KRAS G12Ci)	KRAS G12Cm Adv Solid Tum	I/II (KontRASt-01)	Y
TNO155	Spartalizumab Ribociclib	Adv Solid Tum	I	N

Clinicaltrials.gov Accessed 10-27-2023

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Conclusions

- SHP-2 is a rational pathway for targeting a variety of oncogenic functions
- SHP-2 inhibition is feasible
- Current published activity is limited, but multiple agents under investigation
- Likely role will be as a combination partner in multiple potential settings