Treatment Decision-Making for Patients with Advanced Gastric & GE Junction Cancer

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Disclosures

Consulting Agreements	Amgen Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Dicerna Pharmaceuticals, Entrinsic Health Solutions LLC, Five Prime Therapeutics Inc, Genentech BioOncology, Gilead Sciences Inc, Lilly, MacroGenics Inc, Merck, Pfizer Inc, Sanofi Genzyme

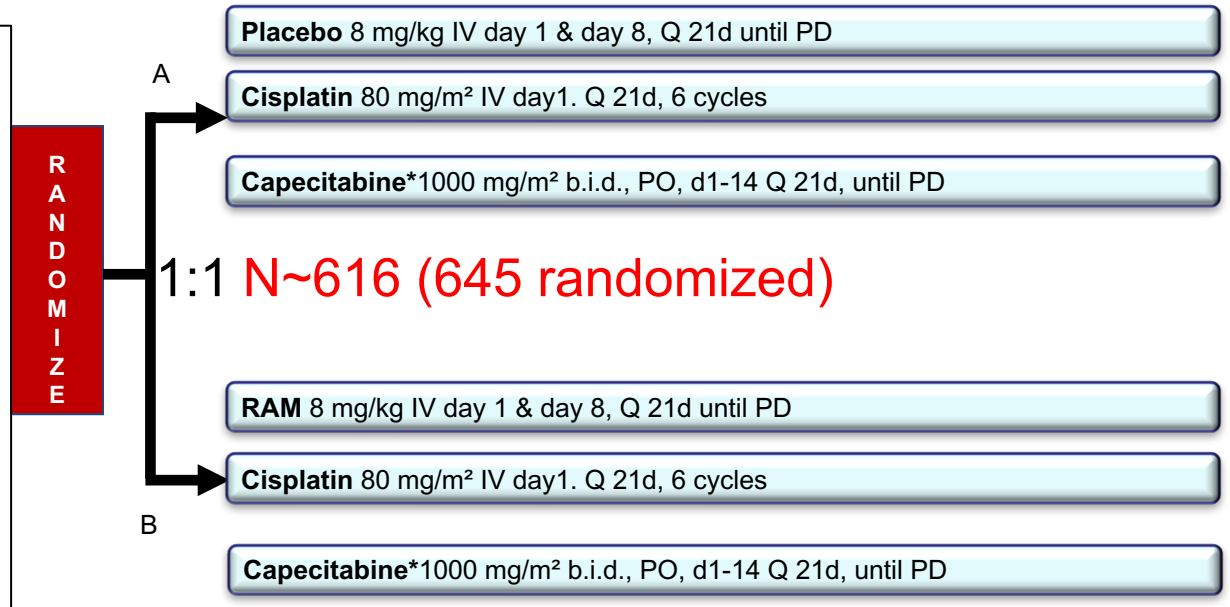
Ramucirumab in Advanced Gastric/GEJ Cancer

- MoAb targeting VEGFR2
- REGARD: Ram vs. Placebo in 2nd line: 22% improvement in OS
- RAINBOW: Paclitaxel/Ram vs. Paclitaxel/Placebo in 2nd line:
  - Median OS: 9.6 vs. 7.3 mos; p = 0.0169
  - ORR: 28% vs. 16%; p = 0.0001

RAINFALL –Phase 3 Study of Capecitabine/Cisplatin +/- Ramucirumab in 1st-line Therapy of Patients With Metastatic Gastric/GEJ Adenocarcinoma

Inclusion:
- Metastatic Gastric or GEJ adenocarcinoma
- No prior systemic chemoRx except for (neo)adjuvant
- ECOG PS: 0-1
- Measurable or non-measurable but evaluable disease

Exclusion:
- Inadequate nutritional status (albumin less than 2.5 g/dl in non-dehydrated state)
- CNS mets
- HER2+ tumor

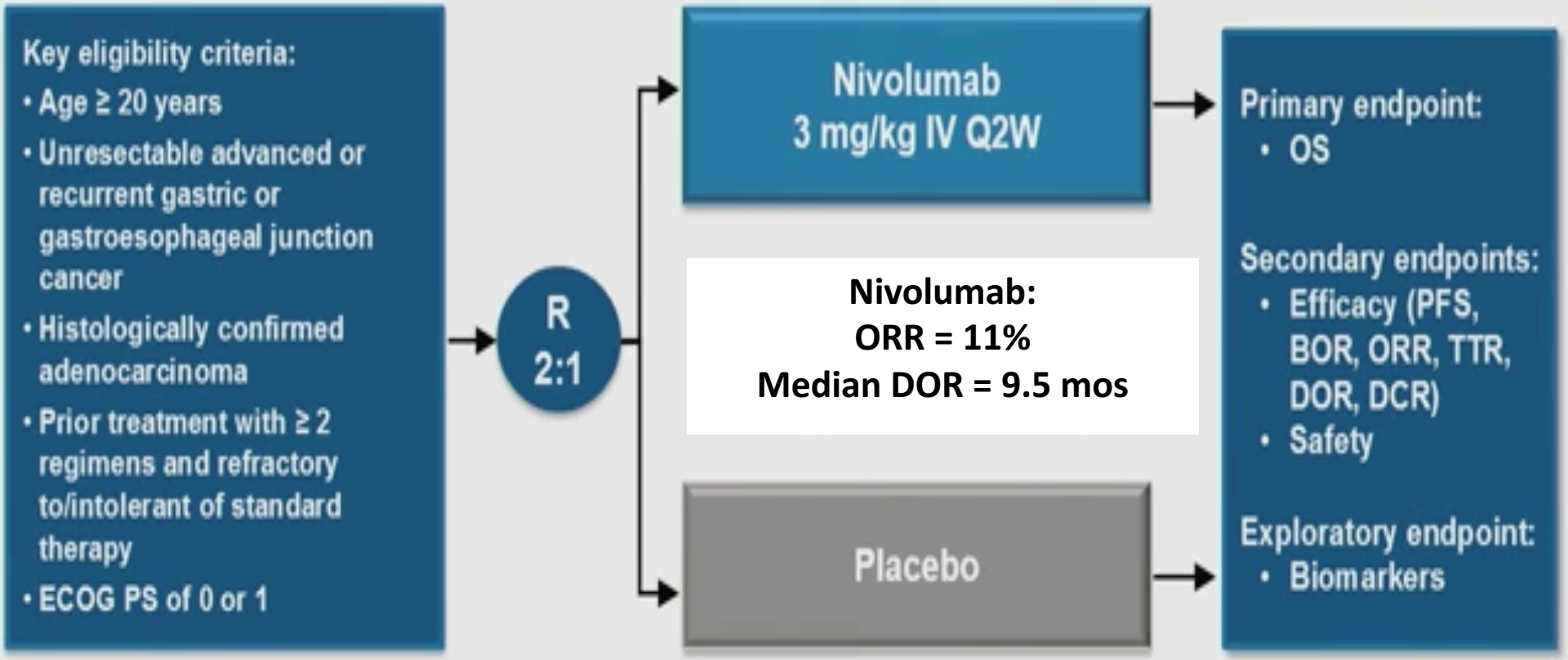


Stratification factors: ECOG PS (0 vs 1),Primary tumor location (gastric vs GEJ), Disease measurability (measurable vs nonmeasurable), Geographic region (N America, EU, ROW vs Japan)

1° Endpoint: PFS (5.6 vs. 8m, HR=0.70, 95% power).
2° Endpoints:OS (10 vs.13m, HR=0.77, 80% power), PFS2,safety,ORR,TTP,QOL,PK. **Final Readout:**Q1'18 (467 OS events)
Study Location: Global (19 countries, 139 sites) **Enrollment period:** Jan'15-Aug'16

IDMC: RAINFALL met its primary endpoint of PFS in this analysis.
Allow the OS data to mature before unblinding and considering a regulatory submission. Final OS data expected in 2018.

Phase III Study of Nivolumab as Salvage Treatment for Advanced Gastric/GEJ Cancer

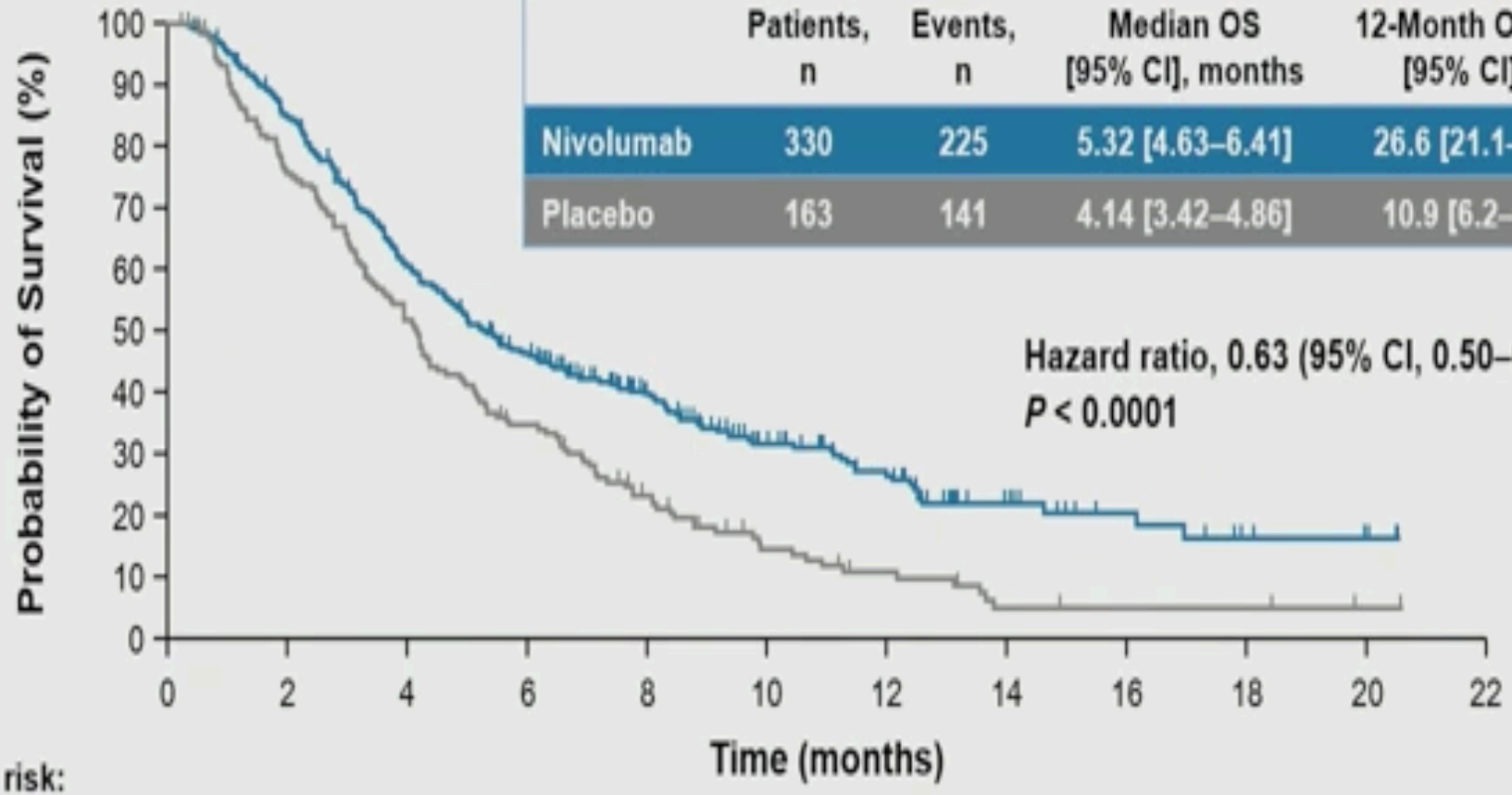


- Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug

BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response.

Overall Survival

	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]



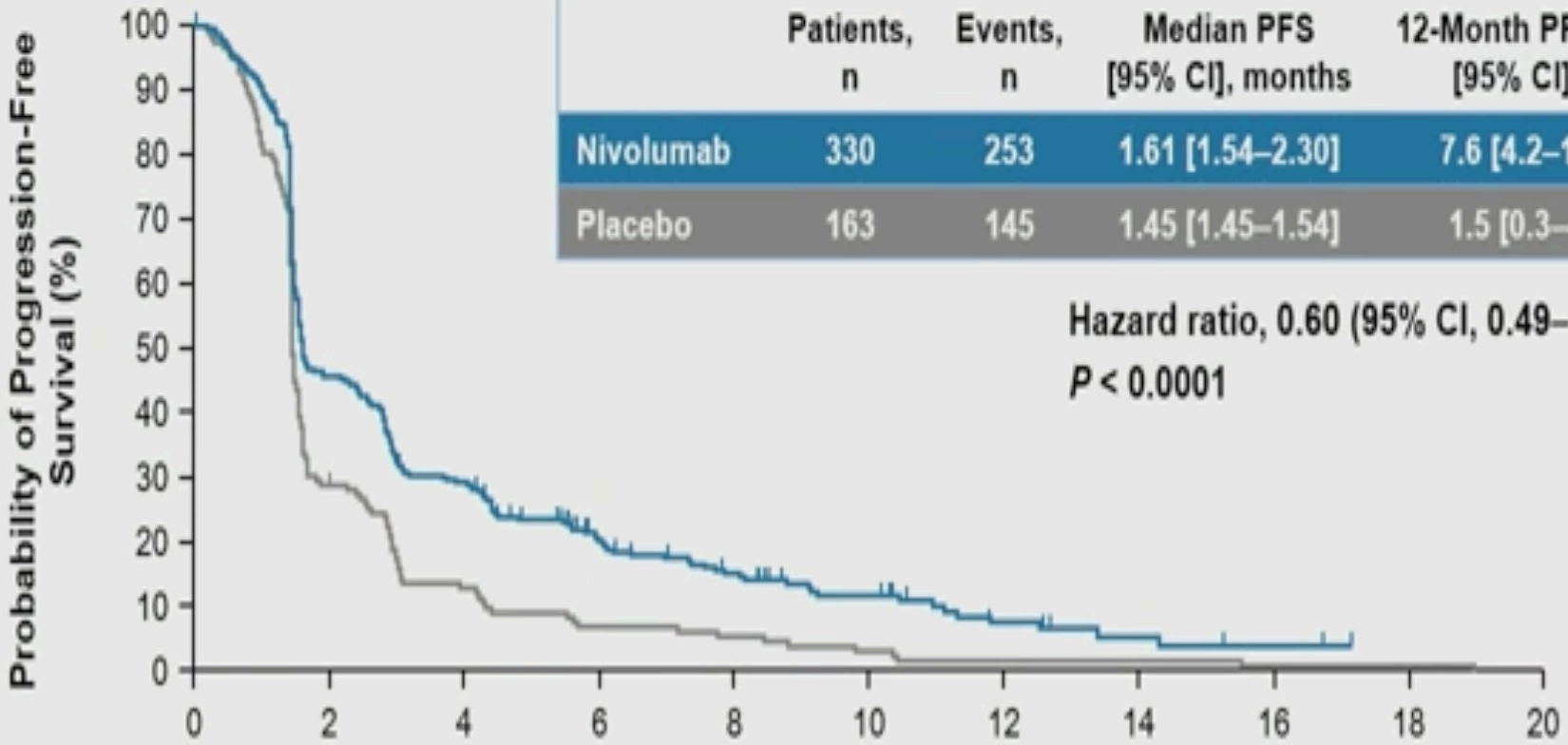
At risk:												
Nivolumab	330	275	193	142	95	57	39	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

Progression-Free Survival

	Patients, n	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], %
Nivolumab	330	253	1.61 [1.54–2.30]	7.6 [4.2–12.2]
Placebo	163	145	1.45 [1.45–1.54]	1.5 [0.3–4.8]

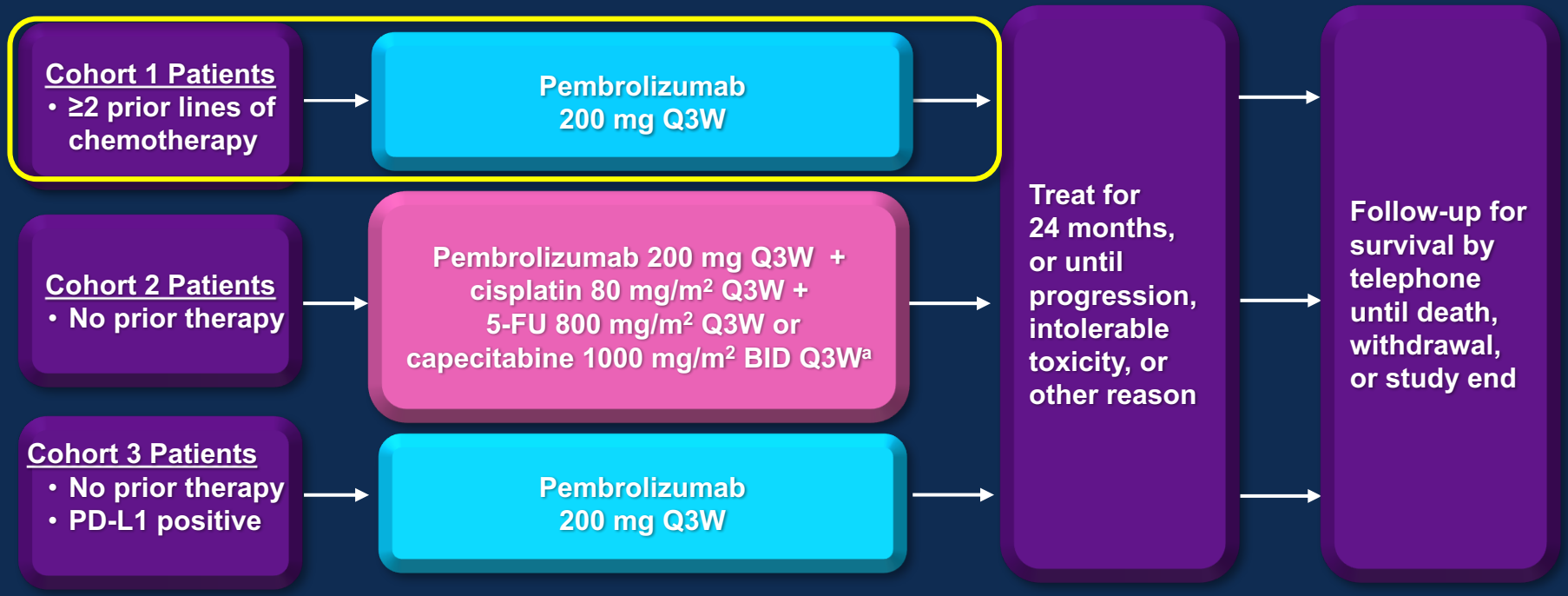
Hazard ratio, 0.60 (95% CI, 0.49–0.75)

P < 0.0001



At risk:											
Nivolumab	330	131	83	46	31	19	8	4	2	0	0
Placebo	163	41	17	9	7	4	2	2	1	1	0

KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma



Response assessment by RECIST v1.1: first scan at 9 weeks after cycle 1, every 6 weeks for 1st year, followed by every 9 weeks

[a]Capecitabine was administered *only in* Japan

KEYNOTE-059: Response in All Patients

Response	N = 259	
	%	95% CI
ORR (CR+PR)	11.6	8.0-16.1
CR	2.3	0.9-5.0
PR	9.3	6.0-13.5

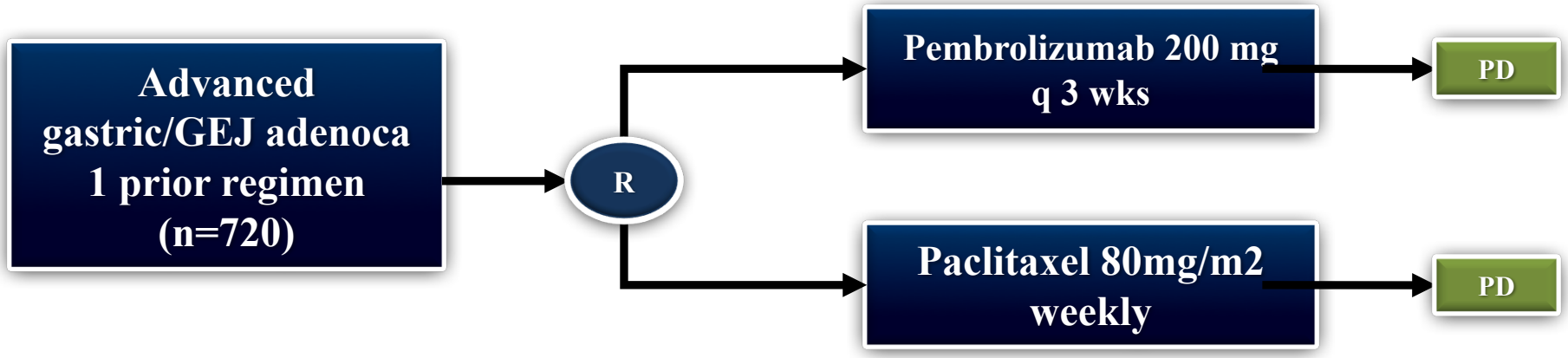
KEYNOTE-059: Response by PD-L1 Expression

Response	PD-L1 Positive (n = 148)		PD-L1 Negative (n = 109)	
	%	95% CI	%	95% CI
ORR	15.5	10.1-22.4	6.4	2.6-12.8
CR	2.0	0.4-5.8	2.8	0.6-7.8
PR	13.5	8.5-20.1	3.7	1.0-9.1

In 3L pts with PD-L1^{+} tumors:
ORR = 21.3%, with 4.0% CR

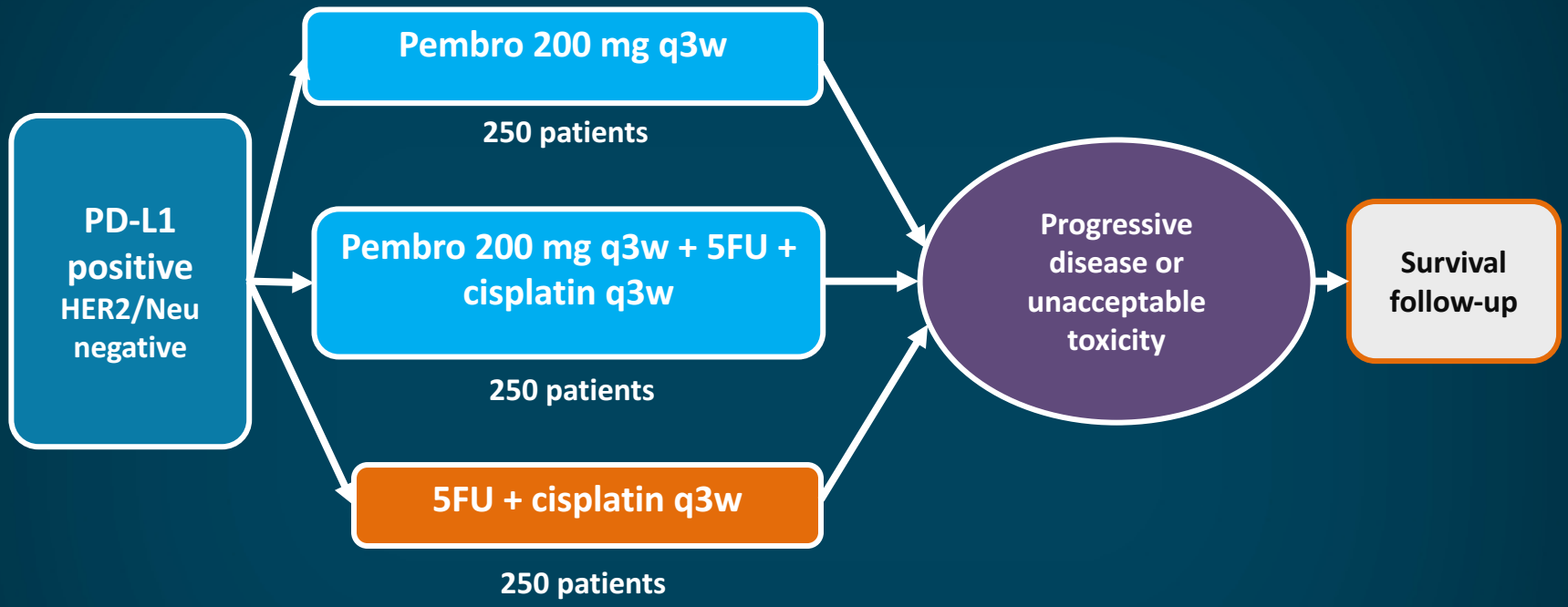
KEYNOTE-061: RCT of Pembrolizumab vs. Paclitaxel in 2nd line Gastric Cancer

720 patients who progressed on 1st line therapy



- **Primary endpoints**: PFS and OS

KEYNOTE-062—Phase 3: First-Line Patients



- Dual primary endpoints: PFS and OS
- Imaging frequency every 6 weeks until PD
- Capecitabine is allowed.

ClinicalTrials.gov Identifier: NCT02494583

Nivolumab ± Ipilimumab in Pts with Advanced (adv)/Metastatic Chemotherapy-Refractory (CTx-R) Gastric (G), Esophageal (E), or Gastroesophageal Junction (GEJ) Cancer: CheckMate 032 Study

Yelena Yuriy Janjigian et al.

Proc ASCO 2017; Abstract 4014.

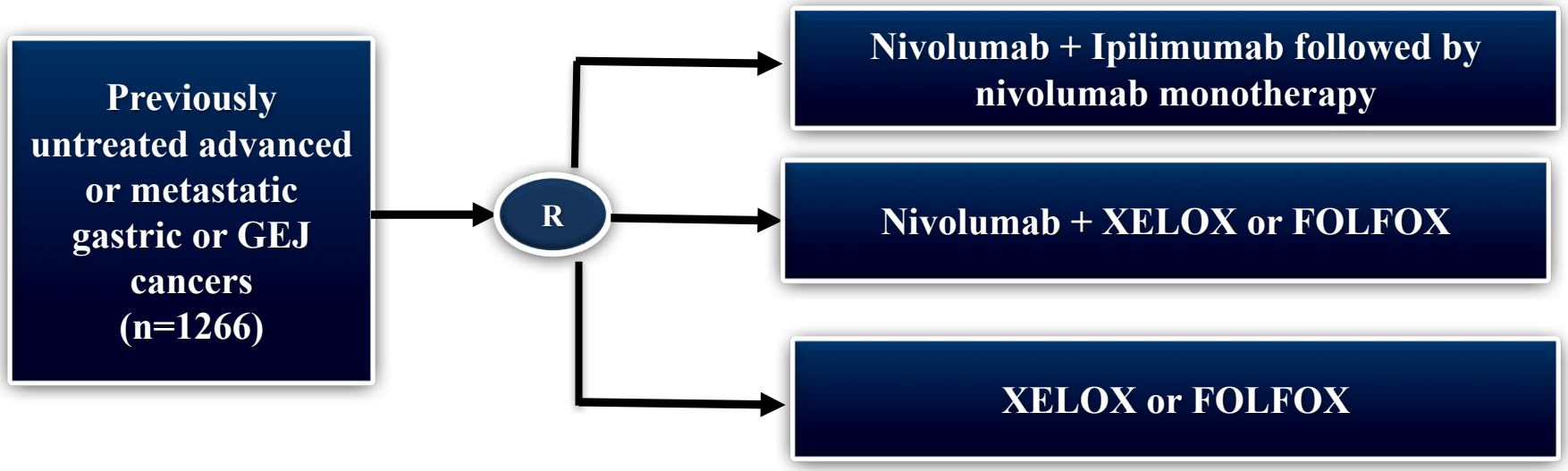
CheckMate-032: Overall Survival

	N3 (n = 59)	N1 + I3 (n = 49)	N3 + I1 (n = 52)
Median OS – All pts	6.2 mo	6.9 mo	4.8 mo
12-mos OS	39%	35%	24%
18-mos OS	25%	28%	13%
Median OS – PD-L1 ≥ 1%	6.2 mo	NA	5.6 mo
12-mos OS	34%	50%	23%
18-mos OS	13%	50%	15%

N3: N 3mg/kg Q2Wks; **N1 + I3:** N 1mg/kg + I 3 mg/kg Q3Wks; **N3 + I1:** N 3 mg/kg + I 1mg/kg Q3Wks

Janjigian YY et al. Proc ASCO 2017; Abstract 4014.

CheckMate 649: Phase III Study Schema

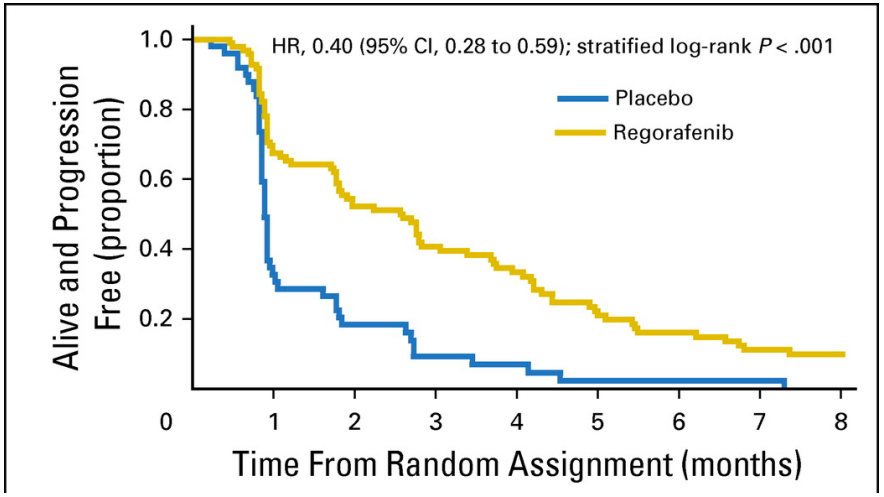


- **Primary endpoint**: OS in pts with PD-L1 expressing tumors
- **Secondary endpoints**: OS in all pts, PFS, time to symptom deterioration

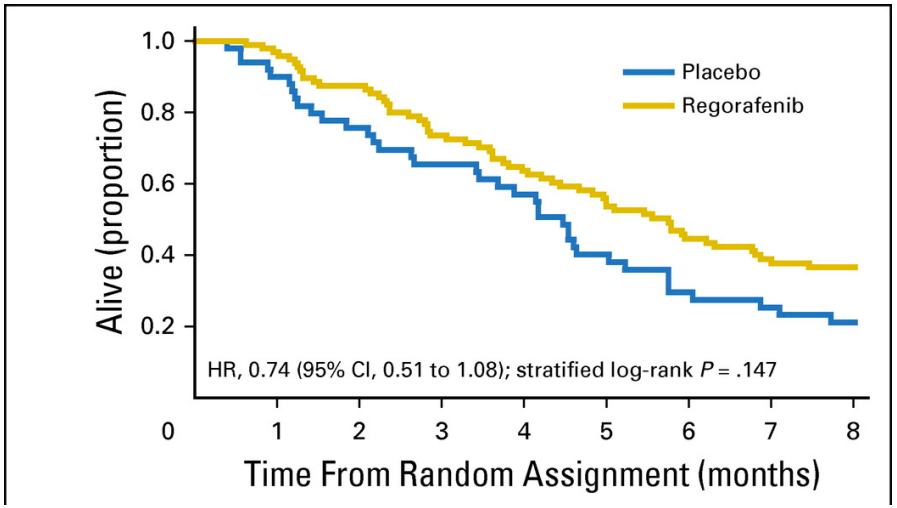
Clinicaltrials.gov, May 30, 2017 (NCT identifier: NCT02872116)

Regorafenib for the Treatment of Advanced Gastric Cancer (INTEGRATE): A Multinational Placebo-Controlled Phase II Trial

152 patients with refractory gastric cancer randomized to regorafenib vs placebo (2:1):



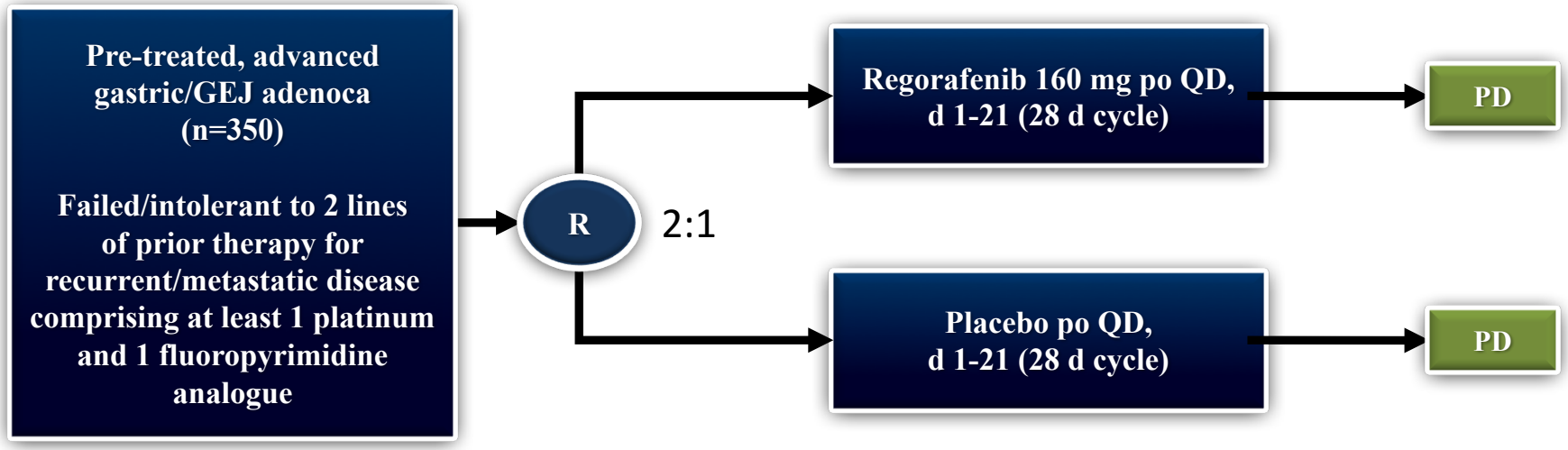
Median PFS: Regorafenib = 2.6 mos
Placebo = 0.9 mos



Median OS: Regorafenib = 5.8 mos
Placebo = 4.5 mos

Pavlakis et al J Clin Oncol 2016

INTEGRATE II: Phase III RCT of regorafenib vs. placebo in pts with pre-treated advanced gastric/GEJ adenocarcinoma

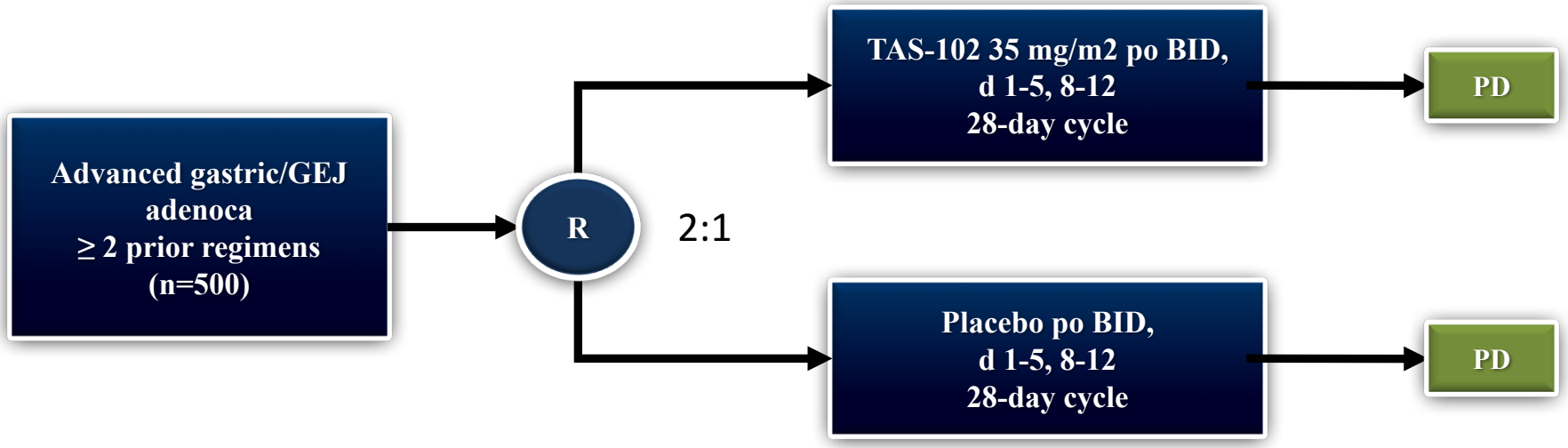


- 2:1 randomization ratio will provide 90% power to detect a hazard ratio (HR) for OS of 0.67
- **Primary endpoint**: OS
- **Secondary endpoints**: PFS, ORR, safety

NCT identifier: NCT02773524

Phase III RCT of TAS-102 vs. placebo plus BSC in pts with pre-treated advanced gastric/GEJ adenocarcinoma

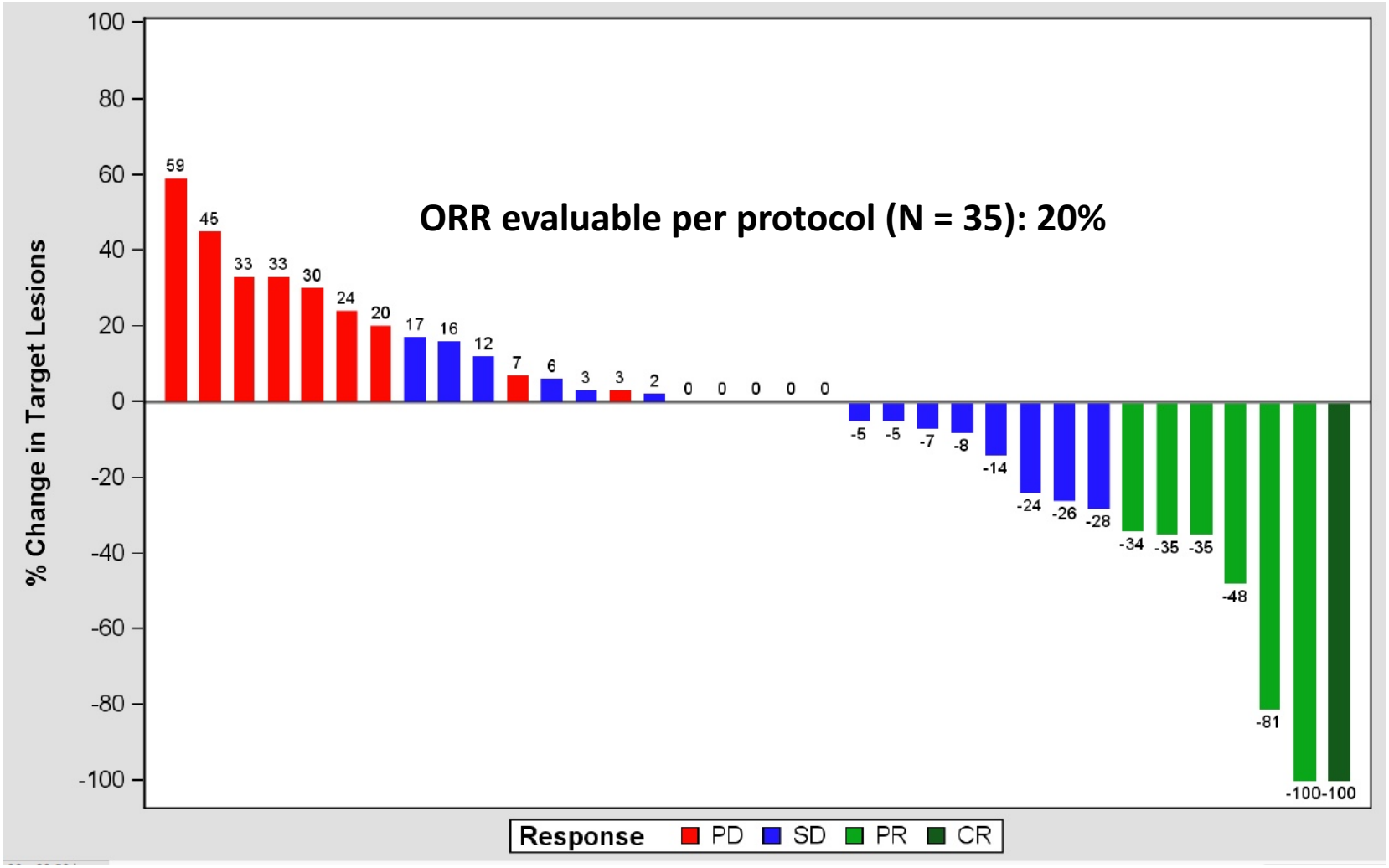
Phase 2 study of TAS-102 (n=29): median OS = 8.7 months and DCR = 65.5%



- 2:1 randomization
- **Primary endpoint**: OS
- **Secondary endpoints**: PFS, QoL, safety

NCT identifier: NCT02500043

Phase Ib/II Study of Napabucasin Combined with Paclitaxel in Advanced Gastric and GEJ Adenocarcinoma: Best Response



Becerra C et al. Proc ASCO 2015; Abstract 4069.

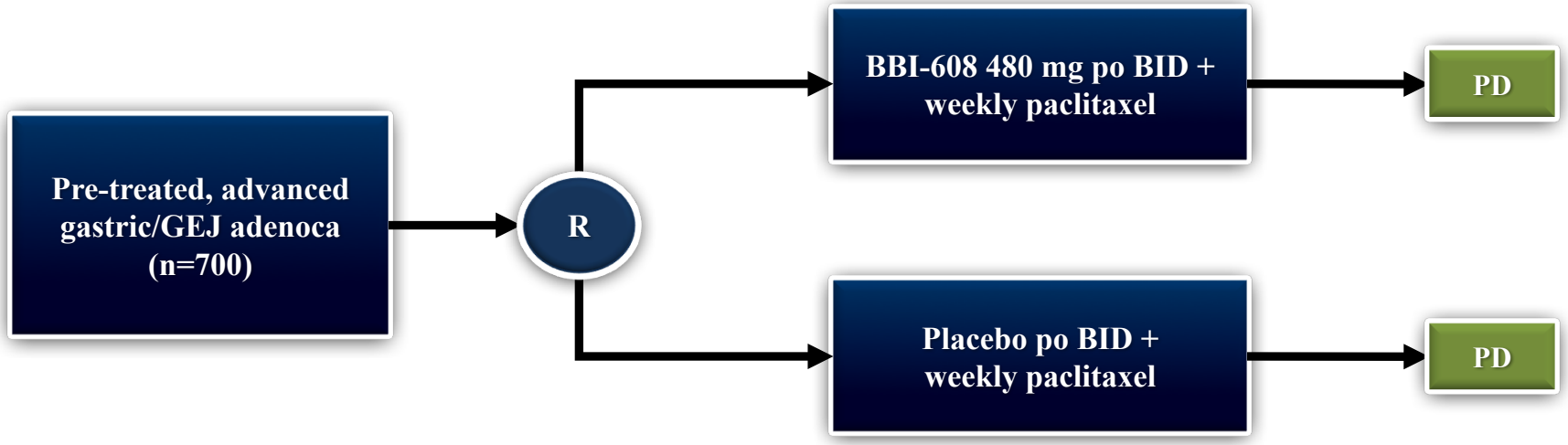
Phase Ib/II Study of Napabucasin Combined with Paclitaxel in Advanced Gastric and GEJ Adenocarcinoma: Efficacy Summary

Group	N	Avg # Prior Lines	ORR	DCR	mPFS (wks)	mOS (wks)
All patients	46	2.4	15%	54%	13.0	31.6
Evaluable per protocol	35	2.4	20%	71%	14.6	34.0
Received taxane in metastatic setting	19	2.6	11%	68%	12.6	33.1
No taxane in metastatic setting	16	2.1	31%	75%	20.6	39.3

Becerra C et al. Proc ASCO 2015; Abstract 4069.

BRIGHTER: Phase III RCT of BBI-608 + paclitaxel vs. paclitaxel in pts with pre-treated advanced gastric/GEJ adenocarcinoma

Phase 2 study of BBI-608 plus paclitaxel:
taxane-naïve (n=20): ORR = 31%; prior taxane (n=29): ORR = 11%



- **Primary endpoint**: OS
- **Secondary endpoints**: PFS, OS and PFS in biomarker group

NCT identifier: NCT02178956

Claudin18.2 in Advanced Gastric/GEJ Cancer

- Claudin18.2 is a tight junction protein expressed in gastric and GEJ adenocarcinoma.

- IMAB362 is a chimeric MoAb that mediates specific killing of CLDN18.2-positive cancer cells by activation of immune effector mechanisms.

- IMAB362 has demonstrated single-agent activity and was safe and tolerable in patients (pts) with pretreated gastric cancer.

FAST: Phase II randomized trial of EOX +/- IMAB362 in pts with advanced CLDN18.2+ gastric/GEJ adenocarcinoma

161 pts with previously untreated, advanced G/GEJ adenocarcinoma: