Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Neoadjuvant Therapy

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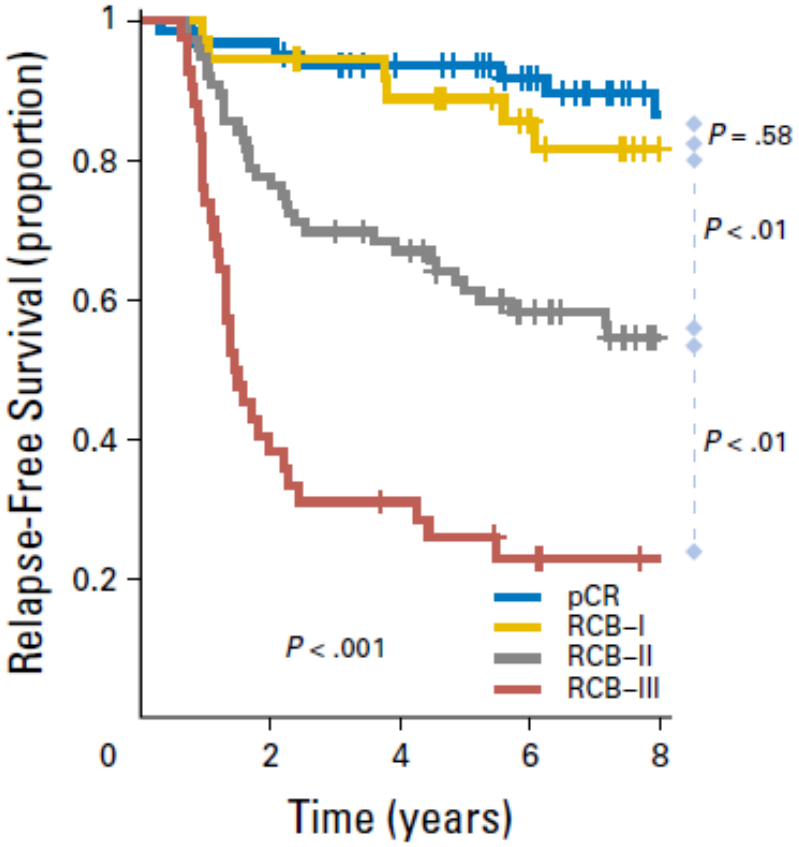
Disclosures

- No relevant financial relationships to disclose.

Outline

- Keynote-522 regimen
  - Benefits
  - Regimen details
  - Adjuvant pembrolizumab
  - Toxicity
- Optimization and questions of interest

Role of Neoadjuvant Therapy

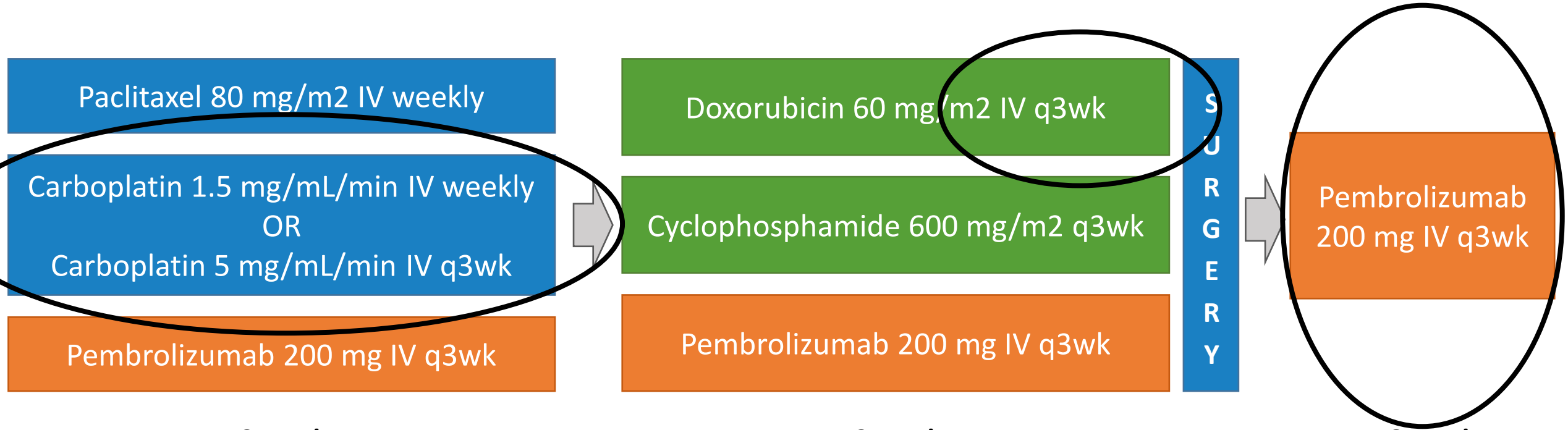


Fraser-Symmans et al. JCO (2017) 35:1049-1060

- Optimize surgical outcome
- Reduce breast cancer recurrence risk
- Triple-negative (TNBC) and HER2+ breast cancer – estimate prognosis and individualize adjuvant therapy

Keynote-522 Treatment Regimen

- Approved in 2021 for early high-risk TNBC based on EFS benefit



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Keynote-522 Enrollment Criteria

Inclusion Criteria

- Triple-negative breast cancer
  - T1c, N1-2
  - T2-4, N0-2
- ECOG 0-1
- Adequate organ function

Exclusion Criteria

- Active autoimmune disease requiring systemic therapy
- Immunodeficiency diagnosis
- Steroid or other immunosuppressive therapy within 7 days of tx start
- History of non-infectious pneumonitis

Keynote-522 Patient Demographics

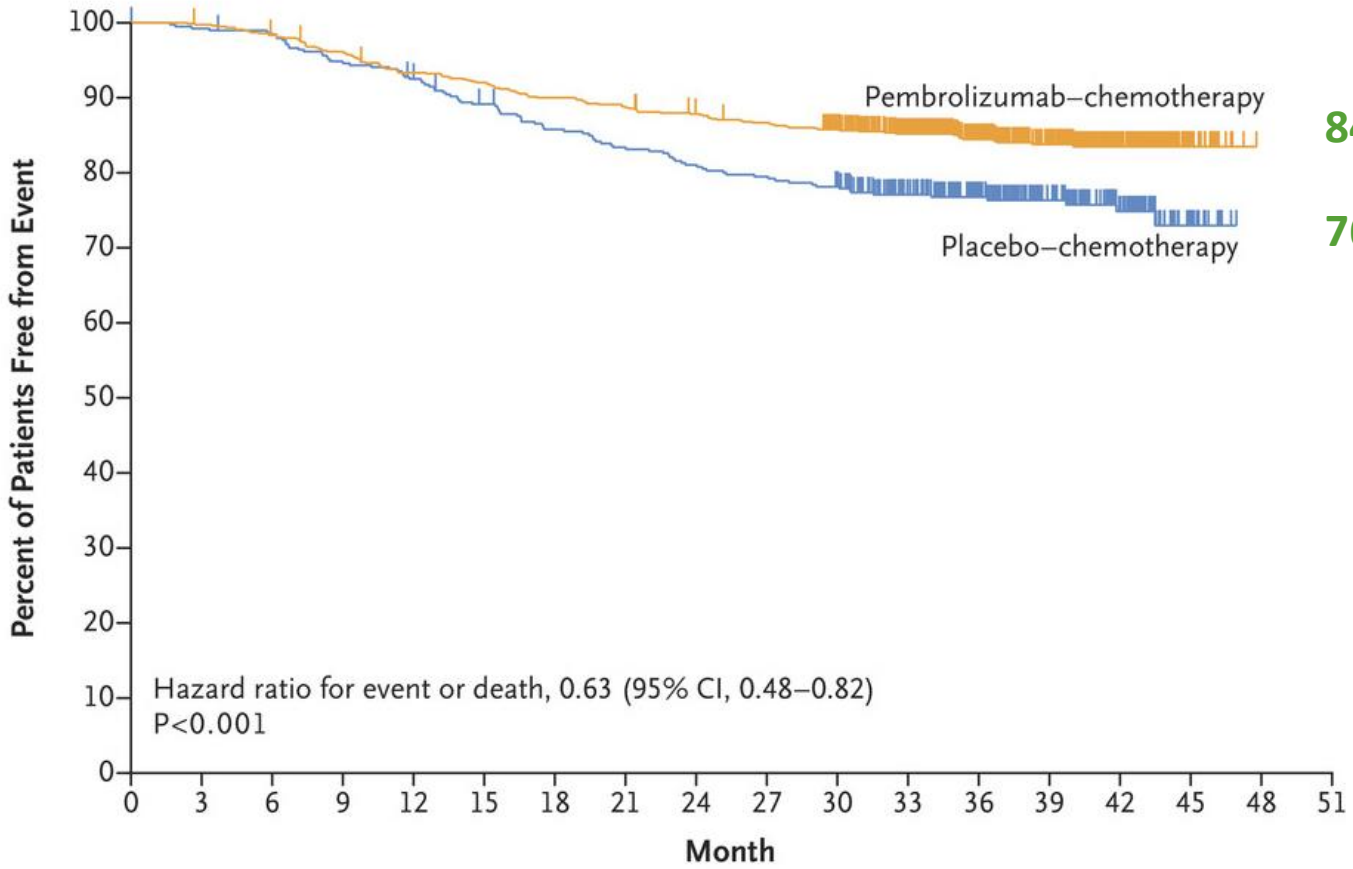
- Over 85% of patients were under the age of 65
- ~80% were PD-L1+
- T1 and T2 tumors made up about 75% of study population
- About half of the patients were node-positive

Table 2. Pathological Complete Response, According to Pathological Stage.*

Variable	Pembrolizumab–Chemotherapy (N=401)	Placebo–Chemotherapy (N=201)	Estimated Treatment Difference†	P Value
			percentage points (95% CI)	
Pathological stage ypT0/Tis ypN0				
No. of patients	260	103		
Percentage of patients with response (95% CI)	64.8 (59.9–69.5)	51.2 (44.1–58.3)	13.6 (5.4–21.8)	P<0.001
Pathological stage ypT0 ypN0				
No. of patients	240	91		
Percentage of patients with response (95% CI)	59.9 (54.9–64.7)	45.3 (38.3–52.4)	14.5 (6.2–22.7)	
Pathological stage ypT0/Tis				
No. of patients	275	108		
Percentage of patients with response (95% CI)	68.6 (63.8–73.1)	53.7 (46.6–60.8)	14.8 (6.8–23.0)	

Schmid et al. NEJM 2020 382:810-821.

Keynote-522 Event-Free Survival



No. at Risk																	
Pembrolizumab–chemotherapy	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo–chemotherapy	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

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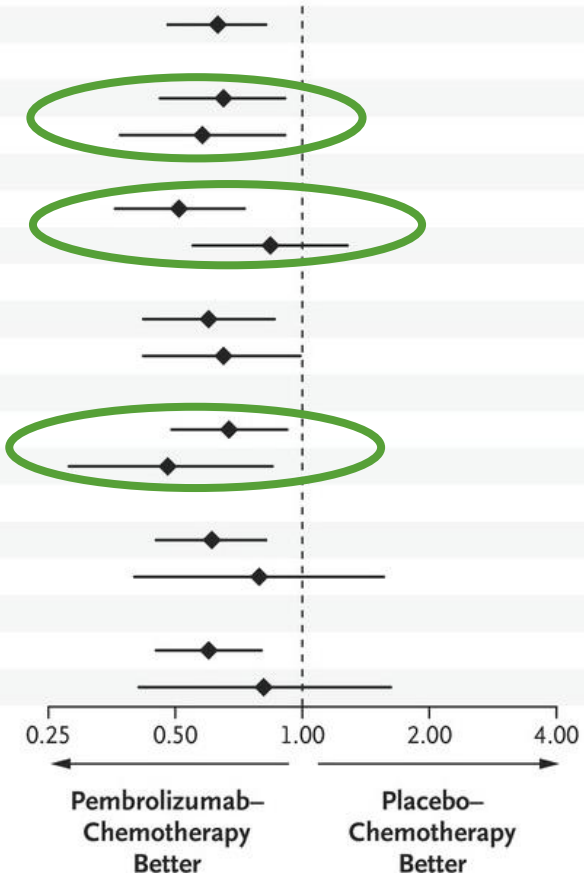
Schmid et al. NEJM 2022 386:556-567.

Keynote-522 Event-Free Survival

Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no. (%)		
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48–0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46–0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37–0.91)
Tumor size			
T1 to T2	64/581 (11.0)	59/290 (20.3)	0.51 (0.36–0.73)
T3 to T4	59/203 (29.1)	34/100 (34.0)	0.84 (0.55–1.28)
Carboplatin schedule			
Weekly	71/444 (16.0)	56/220 (25.5)	0.60 (0.42–0.86)
Every 3 wk	50/334 (15.0)	37/167 (22.2)	0.65 (0.42–0.99)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49–0.92)
Negative	25/128 (19.5)	25/69 (36)	0.48 (0.28–0.85)
Age			
<65 yr	103/700 (14.7)	79/342 (23.1)	0.61 (0.45–0.82)
≥65 yr	20/84 (24)	14/48 (29)	0.79 (0.40–1.56)
ECOG performance-status score			
0	101/678 (14.9)	80/341 (23.5)	0.60 (0.45–0.80)
1	22/106 (20.8)	13/49 (27)	0.81 (0.41–1.62)



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Schmid et al. NEJM 2022 386:556-567.

Keynote-522 Adverse Effects

- Grade 3+ AEs occurred in 77% of pts that received pembrolizumab
  - Nausea, alopecia, anemia were most common AEs of any grade
- ↑ rates of pyrexia, hypothyroidism, rash, anorexia, and hypokalemia were noted with the addition of pembrolizumab
- Four deaths in the pembrolizumab arm – Multiorgan dysfunction 2/2 sepsis, PE, pneumonitis, and autoimmune encephalitis

Keynote-522 Summary

- Addition of pembrolizumab to a standard chemotherapy backbone for high-risk TNBC improved long-term outcomes
  - True regardless of nodal and PD-L1 status
  - Subgroup analysis – ?less benefit? in larger primary tumors (T3 and T4), but fewer pts in this subgroup

- Addition of pembrolizumab also increased toxicity
  - Potential for permanent AEs – hypothyroidism and adrenal insufficiency
  - Also risk of death related to irAEs – notable in a curative intent population

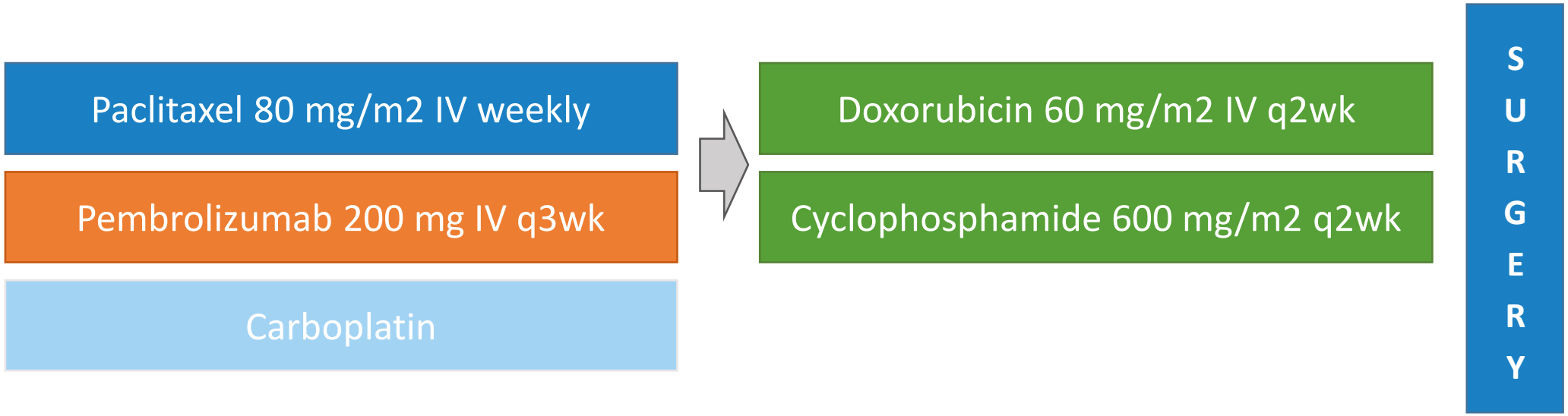
Things to Consider

- Adjuvant therapy
- Further optimization of outcomes
  - Chemotherapy backbone
  - Immunotherapy timing
- Patient selection
- Other breast cancer subtypes

Adjuvant Pembrolizumab

- Is this needed?
- For patients with residual disease, should they receive capecitabine or olaparib (if BRCA1/2+)?

I-SPY2 – 4 cycle pembrolizumab



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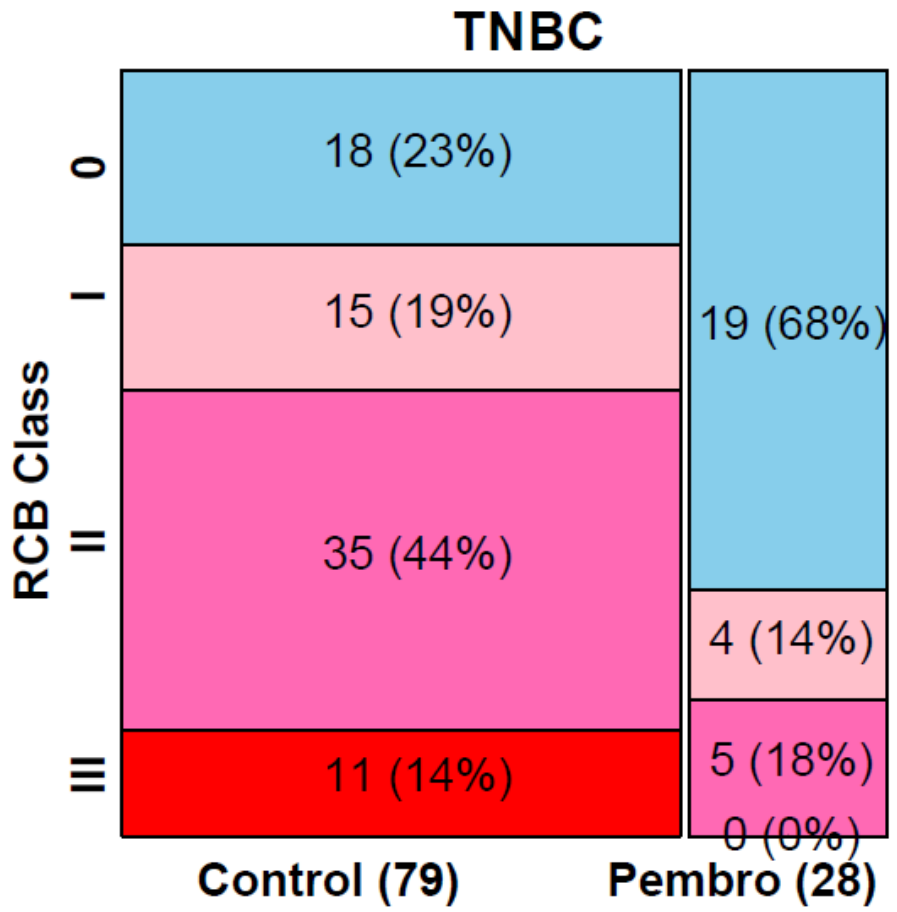

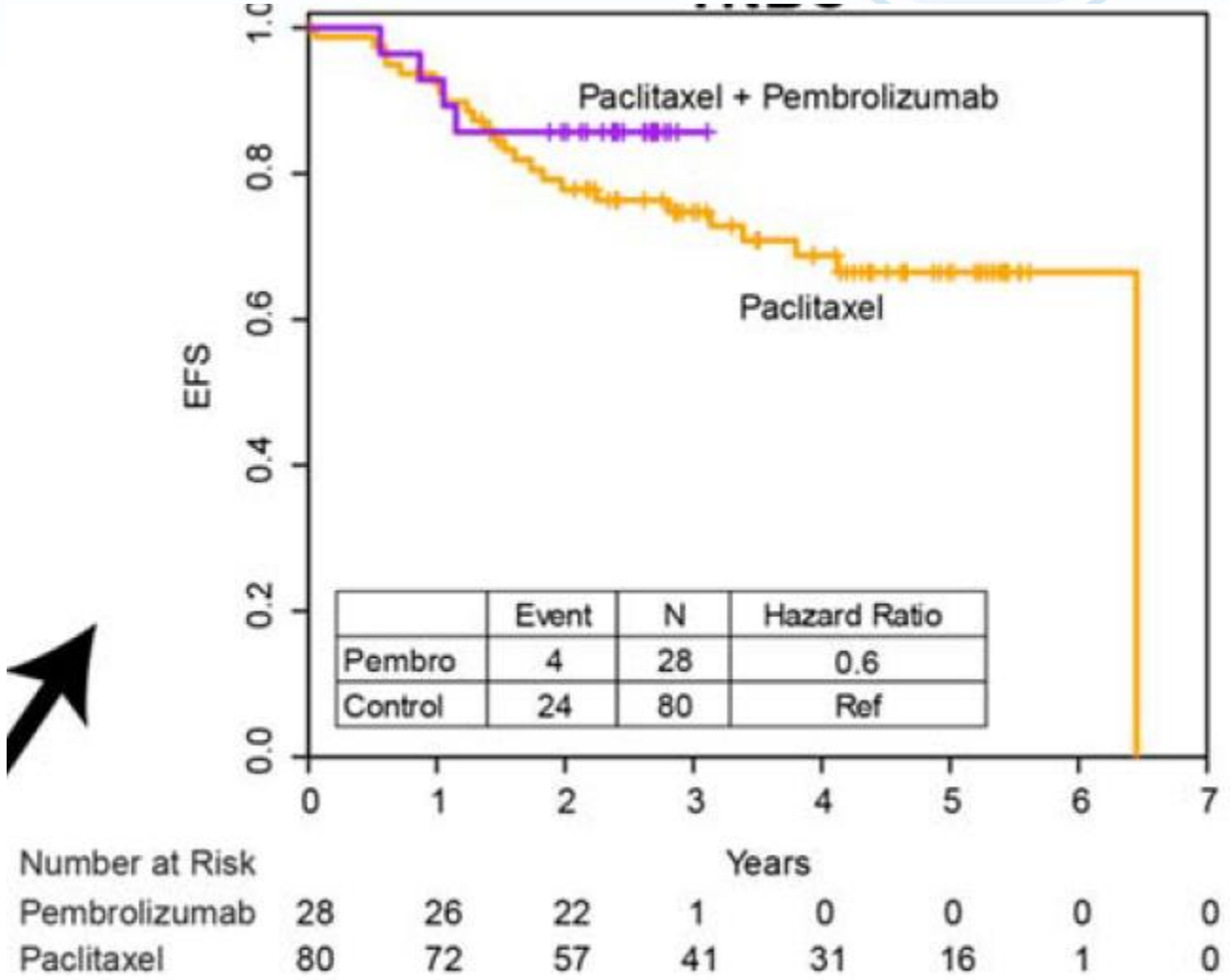

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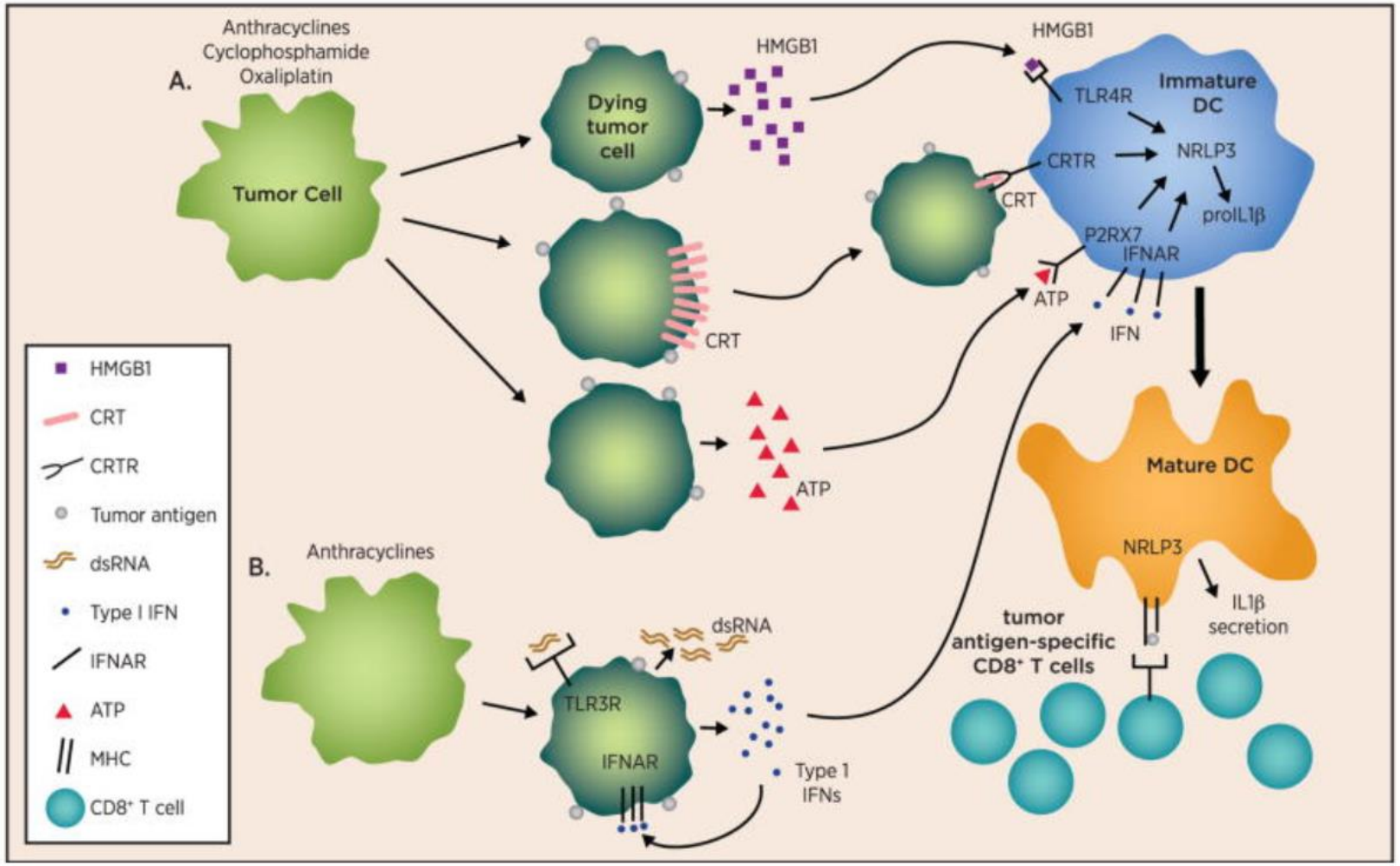
Nanda et al. JAMA Oncol 2020 6(5):1-9.

Neoadjuvant IO Trials in TNBC

Clinical Trial Name	IO Agent	Chemotherapy Backbone	Adjuvant IO therapy?	Improve pCR rate?
Keynote-522 (Schmid et al. NEJM 2020 382:810-821)	Pembrolizumab	Paclitaxel + carboplatin → AC q3wk	Yes	Yes
GeparNuevo (Loibl et al. Ann Oncol 2019 8:1279-1288.)	Durvalumab	nab-paclitaxel → EC	No	Yes – in pts who received a window dose of durvalumab
NeoTRIPaPDL1 (Gianni et al. SABCS 2019, GS3-04)	Atezolizumab	nab-paclitaxel + carboplatin	No	No
Impassion031 (Mittendorf et al. Lancet 2020 396:1090-1100.)	Atezolizumab	Nab-paclitaxel → AC q2wk	Yes	Yes
I-SPY2 (Nanda et al. JAMA Oncol 2020 6(5):1-9.)	Pembrolizumab	Paclitaxel +/- carboplatin → AC q2wk or q3wk	No	Yes

Chemotherapy and IO Interplay



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Emens L and Middleton G. Cancer Immunol Res 2015 3(5):436-443.

Patient Selection – Balancing Risk/Benefit

- Biomarkers are needed to help identify patients that benefit from addition of IO
- Consider risk of permanent toxicities – hypothyroidism and adrenal insufficiency
- TNBC with node-positive disease or tumors larger than 2 cm may benefit based on Keynote-522 analysis

Future Areas of Interest

- Biomarker-driven clinical trials to help select patients for IO + chemotherapy
- Correlative studies looking at benefit of anthracyclines in combination with IO-containing regimens
  - Risk of cardiomyopathy and leukemia with anthracyclines
- Trials in Hormone-Receptor Positive Breast Cancer
- Adjuvant studies for patients with TNBC and significant residual disease post-Keynote-522

Thank you for your attention!