IMMUNOTHERAPY IN NEOADJUVANT / ADJUVANT & STAGE III NSCLC

By Dr Pedro G Solivan Ortiz
Hematology-Oncology
Hospital San Francisco & Hosp Auxilio Mutuo Centro de Cancer

Disclosure Information

Pedro G. Solivan, MD

I have the following financial relationships to disclose:

Consultant for: Bristol-Myers Squibb,, AstraZeneca, Janssen, BI and Biodexic.

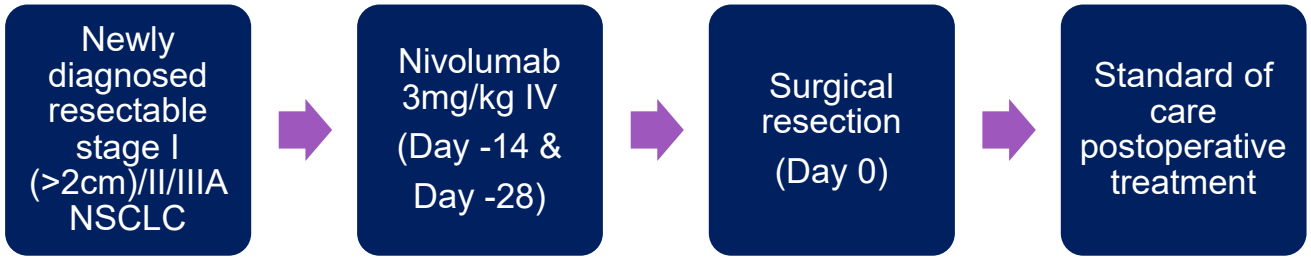
I **will discuss the following off label use and/or investigational use in my presentation:** Neoadjuvant and adjuvant immunotherapy

Rationale for Immunotherapy in Early Stage Disease

- PD-(L)1 antibodies induce durable remissions for a subset of patients with advanced NSCLC

- Early stage NSCLC may be ideal for immunotherapy
  - Patients may have a more intact immune system
  - Potential for long lasting immune priming against micro-metastases
  - Ideal opportunity for translational science in neoadjuvant setting

Neoadjuvant Nivolumab in Resectable Stage I-IIIA NSCLC - Schema



N=21

Tumor Biopsy

PBMC & plasma collection

Tumor & Lymph Node Assessment

TILS

PBMC & plasma collection

Primary Endpoint: Safety & Feasibility

Exploratory: Pathologic response (MPR rate = ≤ 10% residual viable tumor)

Immunologic correlates, Genomic and pathologic correlates

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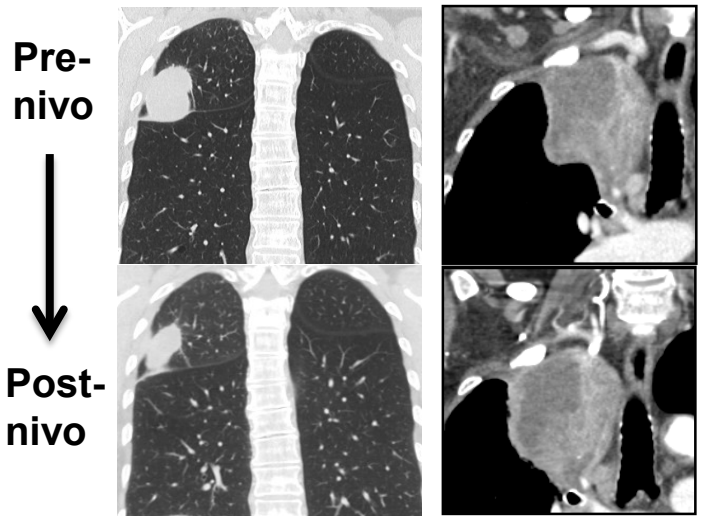
Neoadjuvant Nivolumab- Radiographic responses



RECIST*	N(%)
PR	2 (10%)
Stable Disease	18 (85%)
PD	1 (5%)

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Conclusions from Pilot Study

- Nivolumab prior to lung cancer resection did not delay surgery in any of the treated patients
- No unexpected safety signals were seen
- 45% of resected tumors demonstrated a major pathologic response post-nivolumab
- Pathologic response correlated with mutational burden
- Direct evidence for induction of tumor neoantigen-specific T cells
- Clinical follow-up encouraging but larger trials necessary: >50 neoadjuvant PD-1 blockade trials underway in 10 cancer types

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IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

NEO-ADJUVANT CHEMO-IMMUNOTHERAPY FOR THE TREATMENT OF STAGE IIIA RESECTABLE NON-SMALL-CELL LUNG CANCER (NSCLC): A PHASE II MULTICENTER EXPLORATORY STUDY

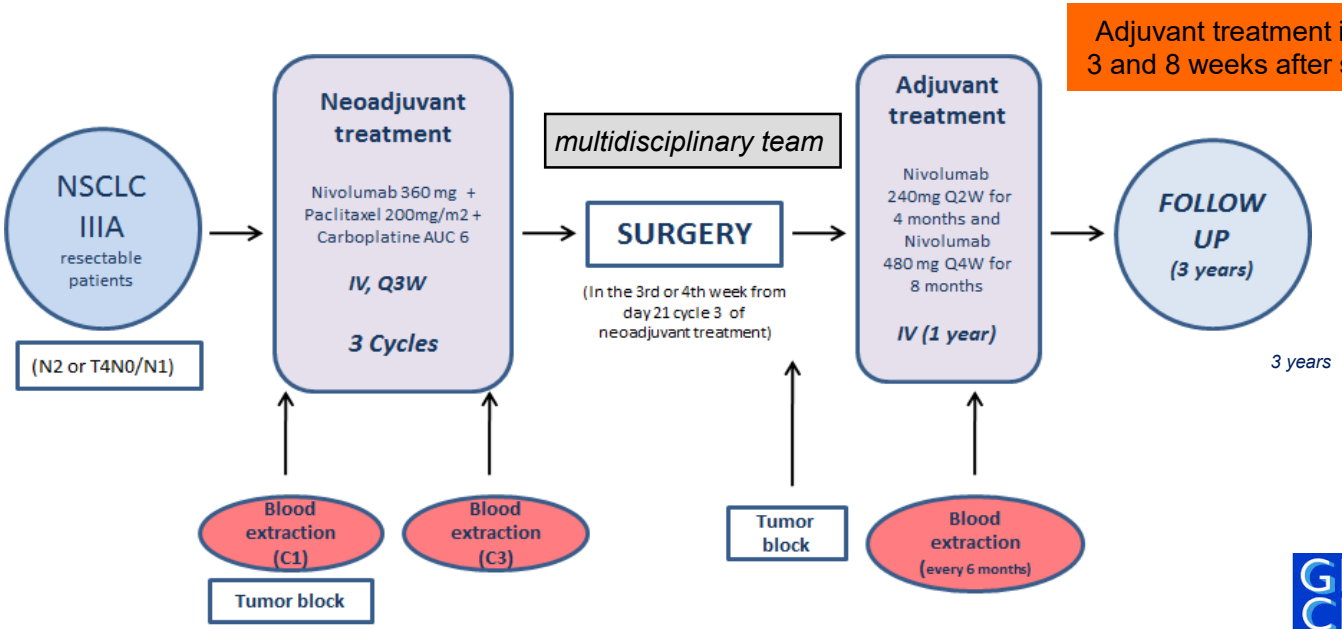
NADIM: Neo-Adjuvant Immunotherapy

GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

M. Provencio[1], E. Nadal[2], A. Insa[3], R. García-Campelo[4], G. Huidobro[5], M. Dómine[6], M. Majem[7], D. Rodríguez-Abreu[8], V. Calvo[1], A. Martínez-Martí[9], J. de Castro[10], M. Cobo[11], G. López-Vivanco[12], E. del Barco[13], R. Bernabé[14], N. Viñolas[15], I. Barneto[16], B. Massuti[17]

[1]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, [2]Institut Catalá de Oncología-Hospitalet, Barcelona, [3]Hospital Clínico Universitario, Valencia, [4]Hospital Universitario de la Coruña, La Coruña, [5]Hospital Universitario de Vigo, Pontevedra, [6]Fundación Jiménez Díaz, Madrid,[7]Hospital de la Santa Creu i Sant Pau, Barcelona, [8]Hospital Insular de Gran Canaria, Las Palmas, [9]Hospital Universitario Vall Hebrón, Barcelona, [10]Hospital Universitario la Paz, Madrid, [11]Hospital Provincial de Málaga, Málaga, [12]Hospital de Cruces, Bilbao, [13]Hospital Universitario de Salamanca, Salamanca, [14]Hospital Universitario Virgen del Rocío, Sevilla, [15]Hospital Clínic de Barcelona, Barcelona, [16]Hospital Universitario Reina Sofía, Córdoba, [17]Hospital General de Alicante, Alicante

NADIM: Study design & Flow-chart



- Phase II
- Single-arm
- Open-label
- Multicenter
- Resectable IIIA NSCLC
- 46 patients

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ELIGIBILITY CRITERIA

- Patients aged ≥ 18 years
- Histologically or cytologically confirmed (N2) Stage IIIA NSCLC (7th edition)
- Resectable tumor
- ECOG Performance Status 0-1
- Forced expiratory volume (FEV1) ≥ 1.2 liters
- Adequate hepatic, hematological and renal functions
- EGFR and ALK mutated patients are ineligible

STUDY OBJECTIVES

- Progression-free survival (PFS) at 24 months (primary)
- Down-staging rate, complete resection rate and response rate (RR)
- Toxicity profile
- Time to progression and 3-year overall survival
- Surgical outcome and operative and post-operative complications
- To explore the expression of other biomarkers
- To determine whether PD-L1 expression is a predictive biomarker for ORR
- To determine PFS in PD-L1+ (≥ 1%) population

Neoadjuvant treatment

	N	Median	Range
Cycles	45	3.0	(1.0-3.0)

CYCLES	N	%
1	3	5
3	43	95
Total	46	100.0

All patients received three neoadjuvant cycles except for the three patients still being treated.

Clinical response

	N	%
Complete response (CR)	3	10.0
Partial response (PR)	18	60.0
Stable disease (SD)	9	30.0
Total	30	100.0

No progressive disease has been observed.

Pathological response

	N	%
Major response[1]	24	80.0
Complete response	18	75.0
Less < 90%	6	20.0
Total	30	100.0

[1]Major pathological response defined as <10% viable tumor cells in the resected specimen.

The following factors were considered to identify factors that potentially influence pathological response (complete and major):

- *Age*
- *Gender*
- *Performance status*
- *Smoking status*
- *Comorbidities*
- *Clinical stage*
- *Clinical response*
- *Primary tumor site (right vs left)*
- *Histology (adenocarcinoma vs squamous)*
- *Nodes involvement (yes/no)*
- *Nodes resected and hematological toxicities grade 3-4*

Each factor was compared between patients with pathological response (complete and major) vs those with no response. Factors with p<0.1 were considered potential factors for a logistic regression analysis (N=30).

No significant logistic regression models were obtained.

- ***Median patient follow-up = 4.1 months, range 0.2-14.6 months.***
- ***None of the patients have suffered recurrence.***

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Toxicities, neoadjuvant (n=45)

Hematological	GRADE									
	1		2		3		4		Total	
	N	%	N	%	N	%	N	%	N	%
Anemia	5	11.1	2	4.4	0	0.0	0	0.0	7	15.6
Febrile neutropenia	0	0.0	0	0.0	1	2.2	0	0.0	1	2.2
Neutropenia	0	0.0	1	2.2	2	4.4	1	2.2	4	8.9
Thrombocytopenia	2	4.4	1	2.2	0	0.0	0	0.0	3	6.7
Non-hematological	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Fatigue	12	26.7	6	13.3	1	2.2	0	0.0	19	42.2
Alopecia	2	4.4	11	26.7	0	0.0	0	0.0	14	31.1
Nausea	11	24.4	1	2.2	0	0.0	0	0.0	12	26.7
Arthralgia	8	17.8	1	2.2	0	0.0	0	0.0	9	20.0
Diarrhea	6	13.3	2	4.4	0	0.0	0	0.0	8	17.8
Decreased appetite	7	15.6	0	0.0	1	2.2	0	0.0	8	17.8
Vomiting	3	6.7	3	6.7	0	0.0	0	0.0	6	13.3
Myalgia	4	8.9	2	4.4	0	0.0	0	0.0	6	13.3
Constipation	3	6.7	2	4.4	0	0.0	0	0.0	5	11.1
Pruritus	4	8.9	1	2.2	0	0.0	0	0.0	5	11.1

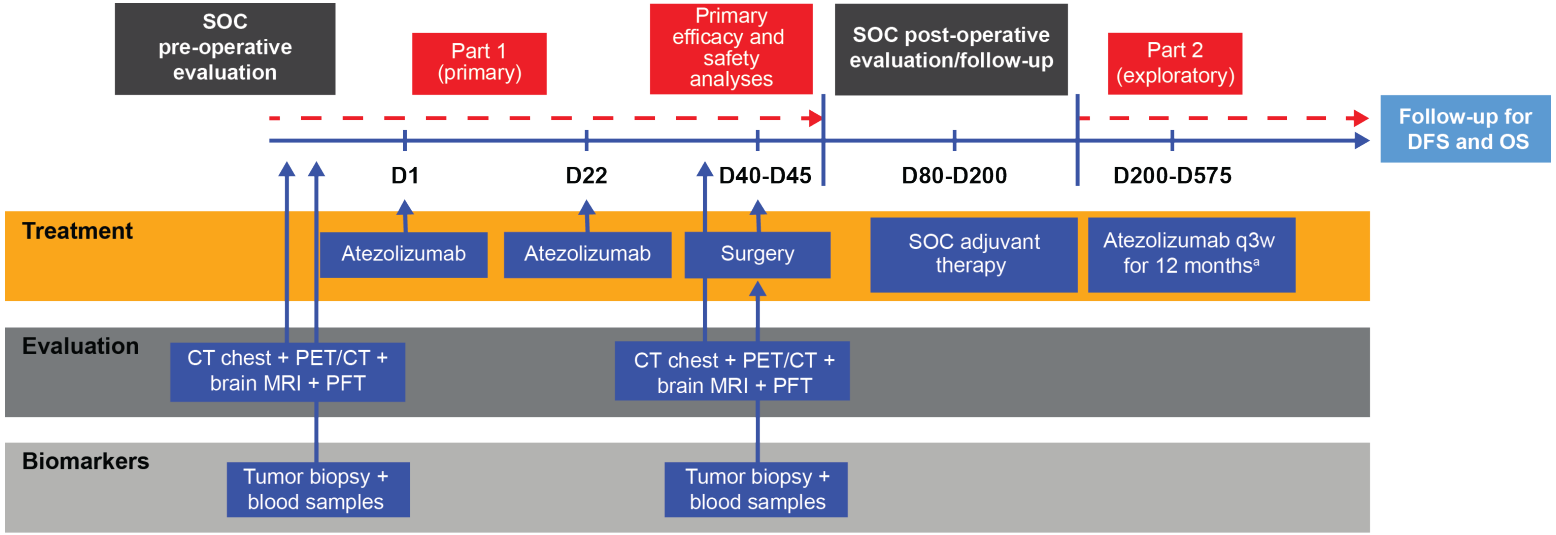
Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Updated results from a multicenter study (LCMC3)

Valerie W. Rusch,[1] Jamie E. Chaft,[1] Bruce E. Johnson,[2] Ignacio Wistuba,[3] Mark G. Kris,[1] Jay M. Lee,[4] Paul Bunn,[5] David J. Kwiatkowski,[2] Karen L. Reckamp,[6] David Finley,[7] Eric B. Haura,[8] Saiama N. Waqar,[9] Robert Doebele,[5] Edward B. Garon,[4] Justin D. Blasberg,[10] Alan Nicholas,[11] Katja Schulze,[11] See Phan,[11] Ann Johnson,[11] David P. Carbone[12]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [5]University of Colorado School of Medicine, Denver, CO, USA; [6]City of Hope, Duarte, CA, USA; [7]Dartmouth Hitchcock Medical Center, Lebanon, NH, USA; [8]Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [9]Washington University School of Medicine, St Louis, MO, USA; [10]Yale School of Medicine, New Haven, CT, USA; [11]Genentech, Inc., South San Francisco, CA, USA; [12]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

LCMC3: A Phase II, Open-Label, Multi-Center Single-Arm Study of Neoadjuvant Atezolizumab in Resectable NSCLC

- The safety interim analysis in Part 1 of the LCMC3 study (N=37) demonstrated preliminary efficacy and safety[1]



- The updated safety and efficacy in 54 patients in Part 1 of the LCMC3 study are presented here

PFT, pulmonary function testing. [a] Part 2 of this study is only for patients who demonstrate clinical benefit with neoadjuvant atezolizumab therapy in Part 1. Adjuvant atezolizumab treatment may be started directly within 60 to 90 days after surgery or within 30 days after completion of adjuvant SOC chemotherapy and/or radiotherapy (whichever occurs last). Choice of adjuvant SOC chemotherapy will be at the discretion of the treating physician, depending on the disease stage, as deemed clinically appropriate. **1.** Rush VW, et al. ASCO 2018 [poster 147].

Efficacy and Safety Summary

Outcome, n (%)	Efficacy Population (n=45)
MPR (95% CI)	10 (22%) (11%, 37%)
ORR	
PR	3 (7%)
SD	42 (93%)
PD	0

Incidence, n (%)	Safety Population (N=54)
≥1 AE	51 (94%)
Grade 3-4	15 (28%)
Grade 5[a]	1 (2%)
Treatment-related AE	32 (59%)
Grade 3-4	3 (6%)
Serious AE	16 (30%)
AE leading to withdrawal from treatment[b]	2 (4%)

Treatment-Related AEs with ≥ 5% Incidence[b]

Incidence, n (%)	Safety Population (N=54)
Fatigue	12 (22%)
Arthalgia	6 (11%)
AST increased	5 (9%)
Pyrexia	5 (9%)
Diarrhoea	4 (7%)
Nausea	4 (7%)
ALT increased	3 (6%)
Decreased appetite	3 (6%)
Dyspnoea	3 (6%)
Infusion-related reaction	3 (6%)

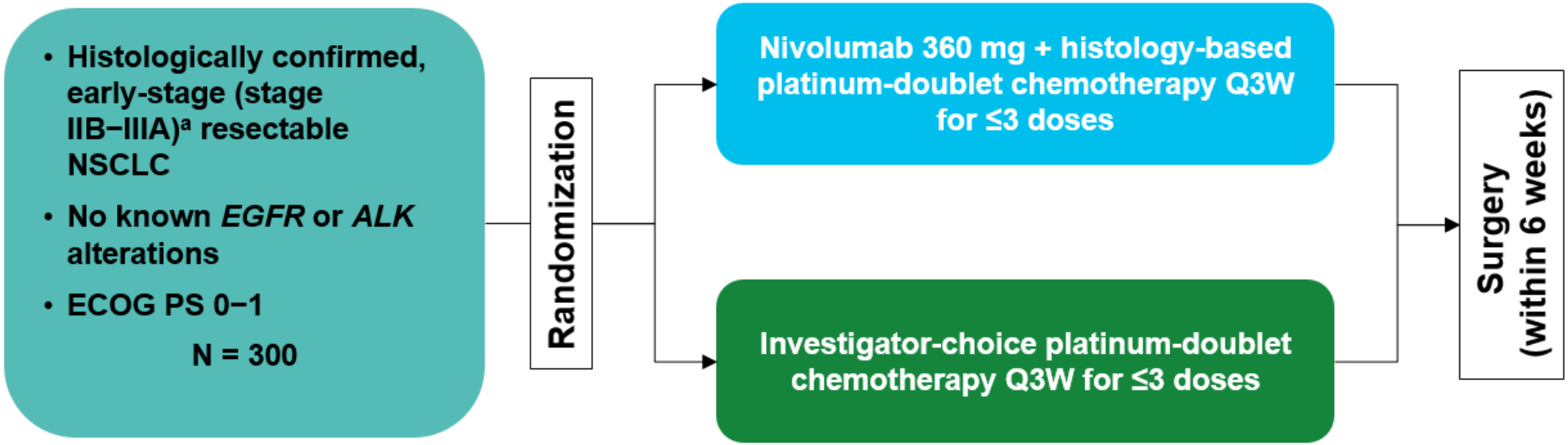
- All treatment-related AEs listed are Grade 1-2; 2 patients (4%) had Grade 3 pneumonitis and 1 patient (2%) had Grade 3 decreased lymphocyte count

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MPR, major pathologic response. [a] 1 patient with Grade 5 sudden death not related to study treatment, which occurred approximately 2 weeks after surgery. [b] 1 patient with Grade 1 pyrexia and 1 patient with Grade 2 dyspnea discontinued treatment. Data cutoff: February 2018.

Summary

- This report demonstrates that neoadjuvant atezolizumab for patients with resectable, early stage NSCLC shows promising clinical activity and was well tolerated
- 10 out of 45 patients (22% [95% CI: 11%, 37%]) without an *EGFR* or *ALK* genetic alteration treated with neoadjuvant atezolizumab had a MPR
  - There was no observable correlation between pathologic and radiographic responses
- Neoadjuvant atezolizumab did not cause major delays to surgery or interfere with surgical resection, and there were no unexpected safety findings
- A follow-up interim analysis of efficacy with 90 patients is planned

CheckMate 816: Phase 3 Neoadjuvant Trial of Nivolumab and Chemotherapy



Co-primary endpoints - EFS and pCR rate (assessed by blinded independent review) with nivolumab plus platinum-doublet chemotherapy vs platinum-doublet chemotherapy

Secondary endpoints - MPR rate, OS, Time to death or distant metastases

Ongoing Adjuvant Immunotherapy Studies in NSCLC

Ongoing Phase 3 Adjuvant Studies in Early Stage NSCLC

- **ANVIL- ECOG-ACRIN –** Adjuvant nivolumab versus observation
- **BR 31- CCTG** – Adjuvant durvalumab versus placebo
- **PEARLS – EORTC –** Adjuvant pembrolizumab versus placebo
- **IMpower 010 –** Adjuvant atezolizumab versus observation

Conclusions

- Earlier stage disease is the next frontier for immune checkpoint therapies in NSCLC
- Neoadjuvant therapy induces significant pathologic responses and potential for persistent anti-tumor immunity
- Data from large neoadjuvant and adjuvant studies are awaited and optimal endpoints are being defined

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