Neoadjuvant Therapy in Lung Cancer

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#MelanomaNeoadjuvant

Disclosures

- Advisory Board/Consultant – AstraZeneca, BMS
- Steering Committee for Clinical Trials – AstraZeneca, BMS, Janssen
- Research funding (to institution) – AstraZeneca, BMS, Corvus, Kyowa, Novartis,
- Investigational use of drugs will be discussed in context of ongoing research studies

Cresting Wave
Perioperative IO in Lung Cancer

- Ct.gov search for PD-(L)1 drug names and “surgery”
  - total of 302 actively recruiting perioperative IO trials across tumor types
  - 162/302 involve neoadjuvant anti-PD-(L)1
  - 56 neoadjuvant anti-PD-(L)1 NSCLC trials on clinicaltrials.gov

Current approach & prognosis for potentially resectable NSCLC

Stage	TNM	Treatment	5 Year OS
Stage IA/B	T1-2N0M0	Sx vs SBRT	77-92%
Stage IIA/B	T1-2N1M0 T3N0M0	CTx => Sx Sx => CTx	53-60%
Stage IIIA	T3N1M0 T4N1-0M0 T1-3N2M0	CRT vs CRT + Sx vs CTx + Sx vs Sx + CTx vs Sx vs CRT?????	36%
Stage IIIB	T1-3N3M0 T4N2-3M0	CRT	13-26%

Perioperative therapy in NSCLC
Historic Perspective - Adjuvant

Meta-analysis:
Lung Adjuvant Cisplatin Evaluation (LACE)

5 studies since 1995

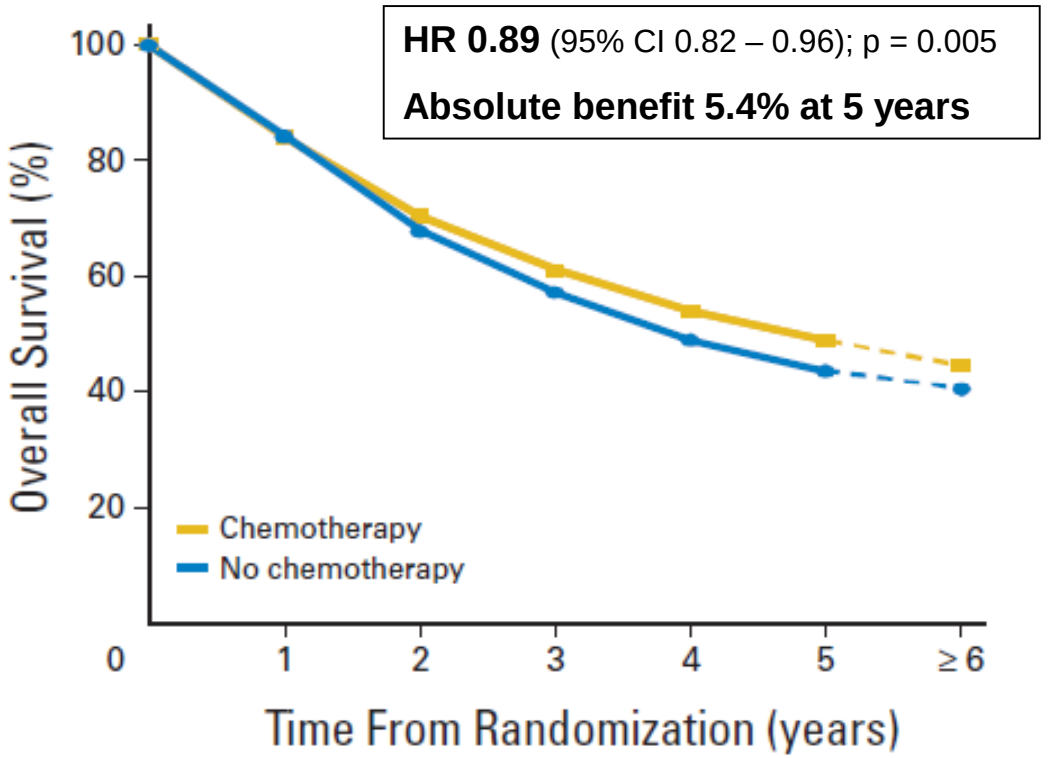
- BLT, ALPI, IALT, JBR.10, ANITA

Pooled individual data

- 4585 patients

Chemotherapy

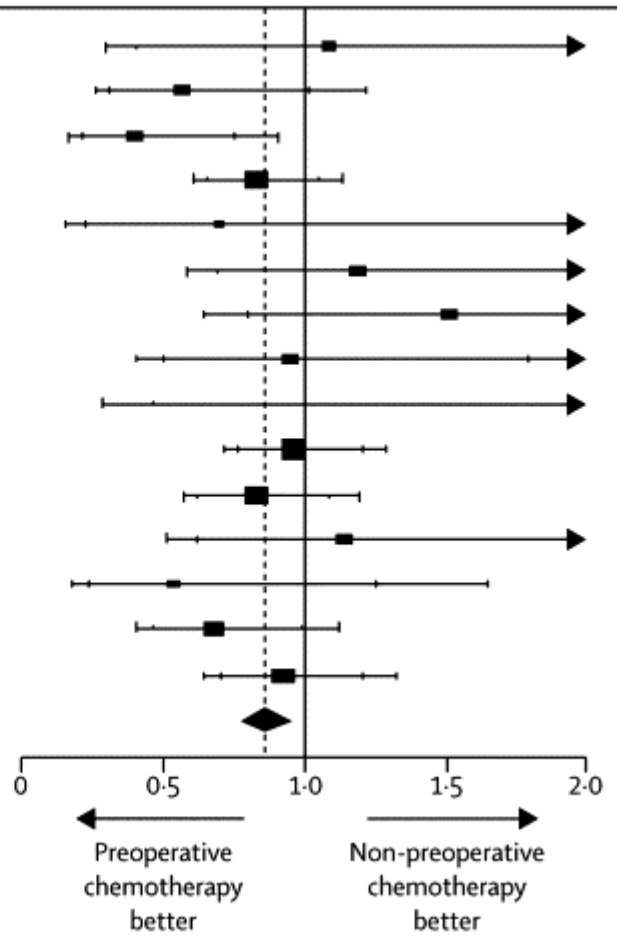
- ↓6.9% lung CA death
- ↑1.4% non-CA death



Pignon et al. *J Clin Oncol* 26:3552, 2008.

Perioperative therapy in NSCLC Historic Perspective - Neoadjuvant

	Preoperative chemotherapy*	Control*	O–E	Variance	HR (95% CI); p value
France 1990	8/13	8/13	0·32	3·97	
MD Anderson 1994	19/28	27/32	−6·40	11·19	
Spain 1994	19/29	27/30	−8·88	9·65	
MIP-91	137/179	146/176	−12·99	70·22	
SWOG S9015	3/5	12/16	−1·04	2·94	
JCOG 9209	28/31	25/31	2·25	12·97	
Netherlands 2000	23/39	15/40	3·86	9·36	
Finland 2003	19/30	19/32	−0·50	9·48	
MRC BLT	4/5	3/5	1·26	1·60	
MRC LU22	151/258	158/261	−2·92	77·01	
SWOG S9900	93/180	103/174	−9·31	48·84	
China 2002	26/32	18/23	1·42	10·78	
China 2005	8/19	14/21	−3·31	5·44	
ChEST	45/129	61/141	−10·27	26·39	
NATCH	99/201	109/212	−4·11	51·95	
Total	**682/1178**	**745/1207**	**−50·62**	**351·78**	**0·87 (0·78–0·96); p=0·007**



Overall HR
0·87 (0·78–0·96). p=0·007 (fixed effect)
0·86 (0·75–0·98), p=0·03 (random effects)
Heterogeneity: χ^2=18·75, df=14, p=0·18, I^2=25%

NSCLC Meta-analysis Collaborative Group. Lancet 2014

Drug Development in Lung Cancer

- IO & targeted therapy drug development mandates a new paradigm for resectable NSCLC
  - hundreds of candidate agents in development
  - timeline from phase 1 to 3 has shortened to 2-3 yrs
  → potential read out within 5 years of FIH study

- 2016-2019 - New FDA approved indications in advanced NSCLC

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27

- 2004-2019 – New systemic therapies for resectable NSCLC

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Current Approaches, Opportunities and Barriers

- In United States – approximately 50:50 split between neoadjuvant chemotherapy and chemoradiation for stage IIIA NSCLC

- Growing interest in neoadjuvant IO – educational sessions at all national thoracic surgery meetings in 2019

- Nearly all patients seen first by surgeons
  - incentive to resect + some concerns about progression

Limitations of Adjuvant Therapy Trials Lung Cancer

- Median time from enrollment of first patient to publication of study results for phase 3 adjuvant NSCLC studies (1990-2016)

11 years

- Absence of significant correlative science that may help enrich for benefit
  - given patient population, toxicity of chemotherapy, and modest benefit to date

Endpoints for Neoadjuvant Studies

- DFS and OS are long term endpoints for early stage lung cancer trials and take years to mature

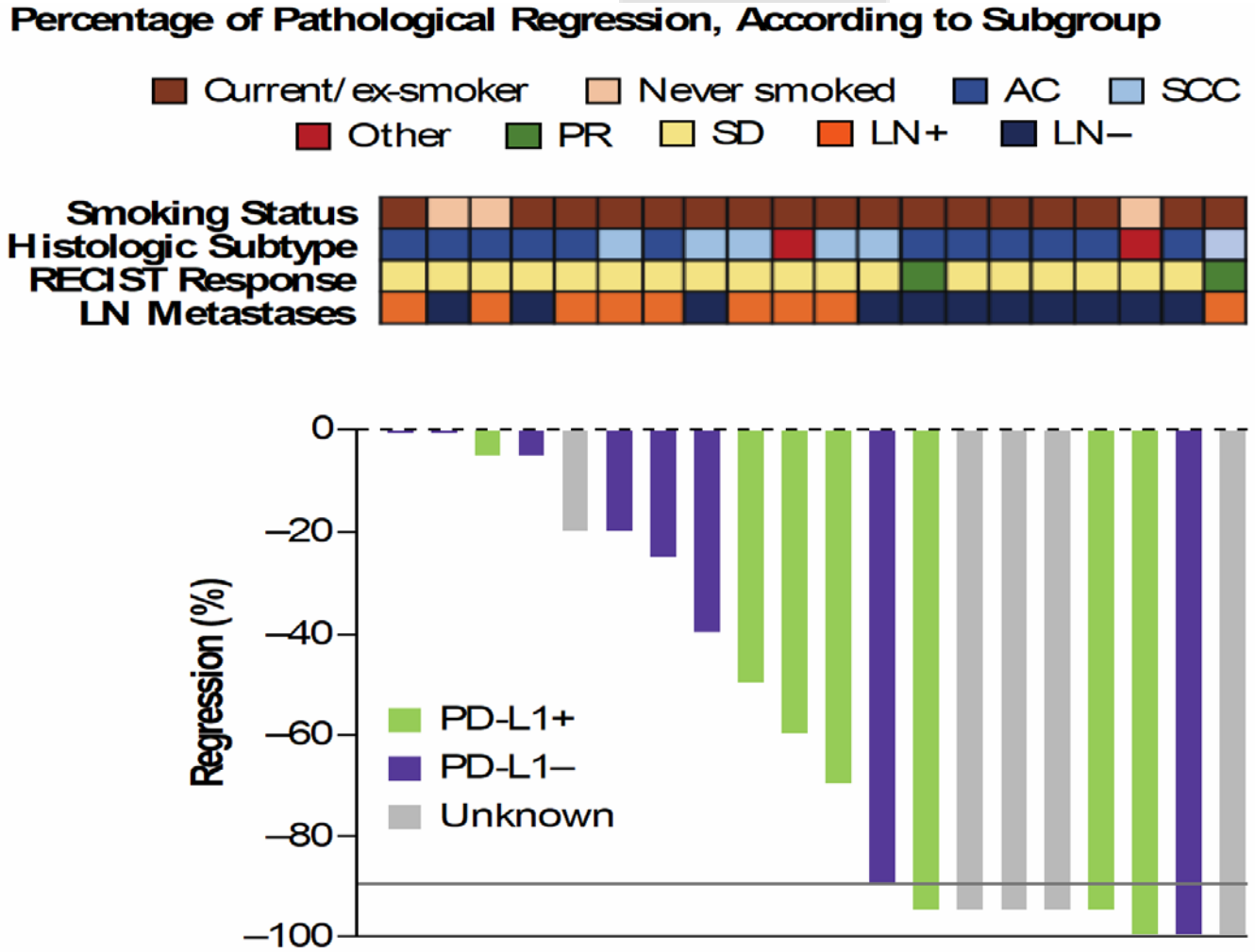
- Surrogate endpoints such as pathologic complete response (pCR) are used for breast cancer neoadjuvant studies; pCR historically has been rare after neoadjuvant chemo for lung cancer

- Major pathologic response (MPR; ≤10% residual viable tumor cells in the primary) occurs ~20% after neoadjuvant chemotherapy and may predict DFS[1]

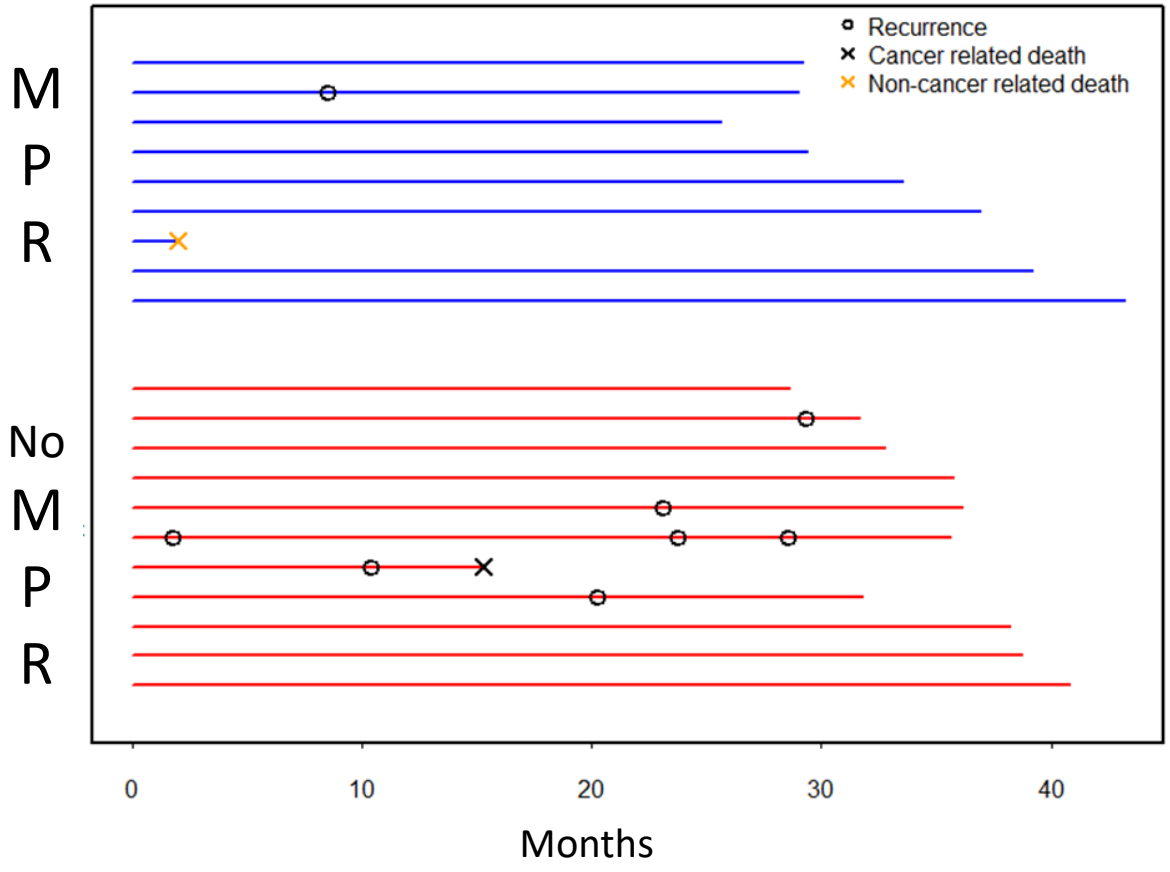
Percentage of residual viable tumor following neo-adjuvant chemotherapy	Hazard Ratio for death
1-10%	1.00
11-30%	2·51 (95% CI 0·91-6·96)
31-50%	3·39 (95% CI 1·40-8·22)
51-70%	4·57 (95% CI 1·98-10·52)
71-100%	4·78 (95% CI 2·06-11·11)

1. Pataer et al. JTO 2012; 2. Hellmann et al. Lancet Oncol 2016 3. Blumenthal et al. JTO 2018

Initial Experience with Neoadjuvant PD-1 Blockade



Longer Term Follow Up



Forde, Chaft, Smith et al. NEJM 2018

Opportunities for interdisciplinary correlative science

ANNALS OF ONCOLOGY

Clinical Cancer Research

The Journal of Thoracic and Cardiovascular Surgery
JTCVS
AATS
OFFICIAL PUBLICATION OF THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Immune-related pathologic response criteria
- Cottrell, Taube et al.

Compartmental analysis of T cell repertoire
- Zhang, Smith et al.

Dynamics of ctDNA during neoadjuvant therapy
- Anagnostou, Forde et al.

Surgical outcomes after neoadjuvant PD-1 blockade
- Broderick, Bott et al.

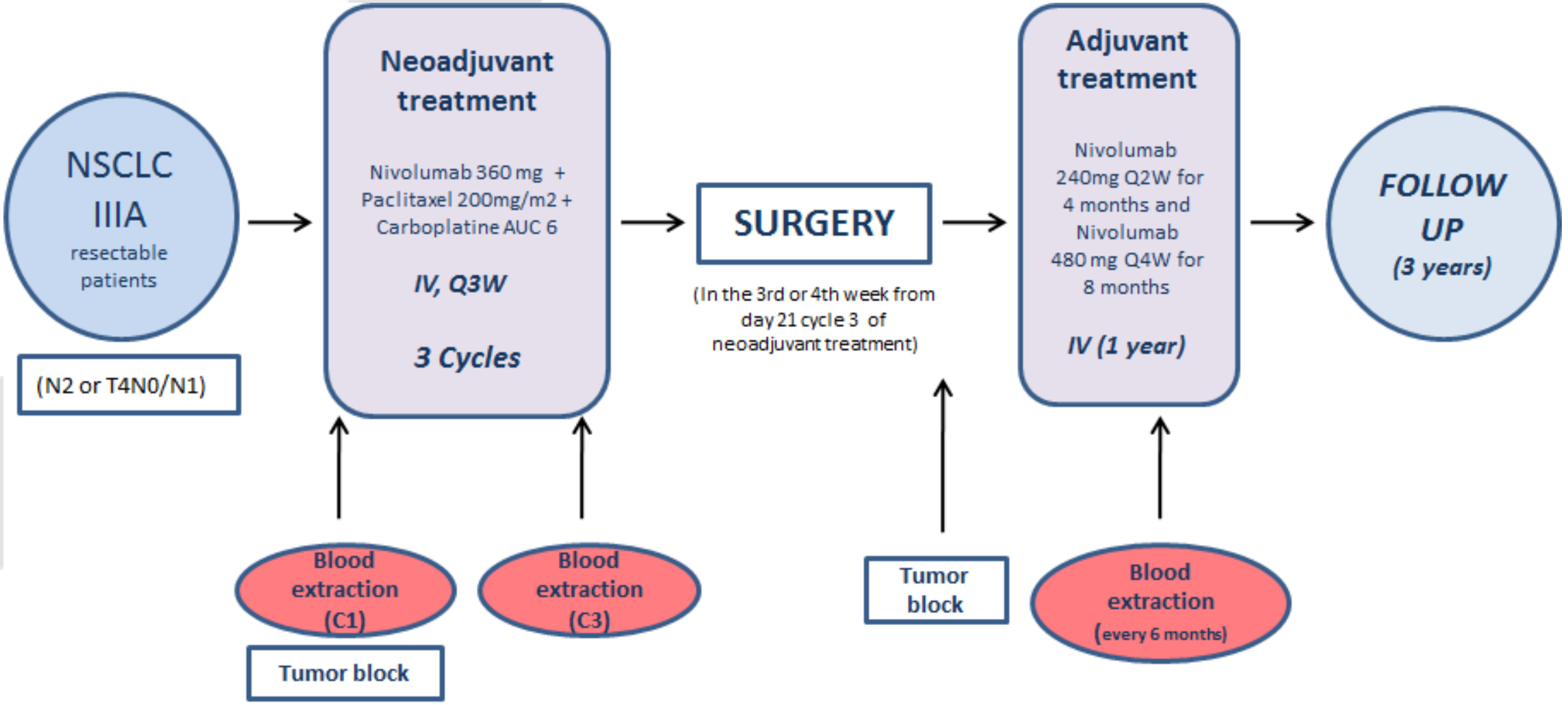
Neoadjuvant PD(L)1 is safe & feasible with encouraging MPR rates

Study (phase)	No. Patients	Therapy	No. Cycles	MPR rate	MPR association with RECIST	MPR association with TMB	MPR association with PD-L1
JHH/MSKCC (Ib/II)	22	Nivolumab	2	45% (9/20)	No	Yes	No
NEOSTAR (II)	44	Nivolumab & Nivo/Ipi	3	19% (4/21)*	Yes	---	Yes
LCMC3 (II)	101	Atezolizumab	2	19% (15/77)	Yes	No	No

MPR rate: 23.7% (28/118)

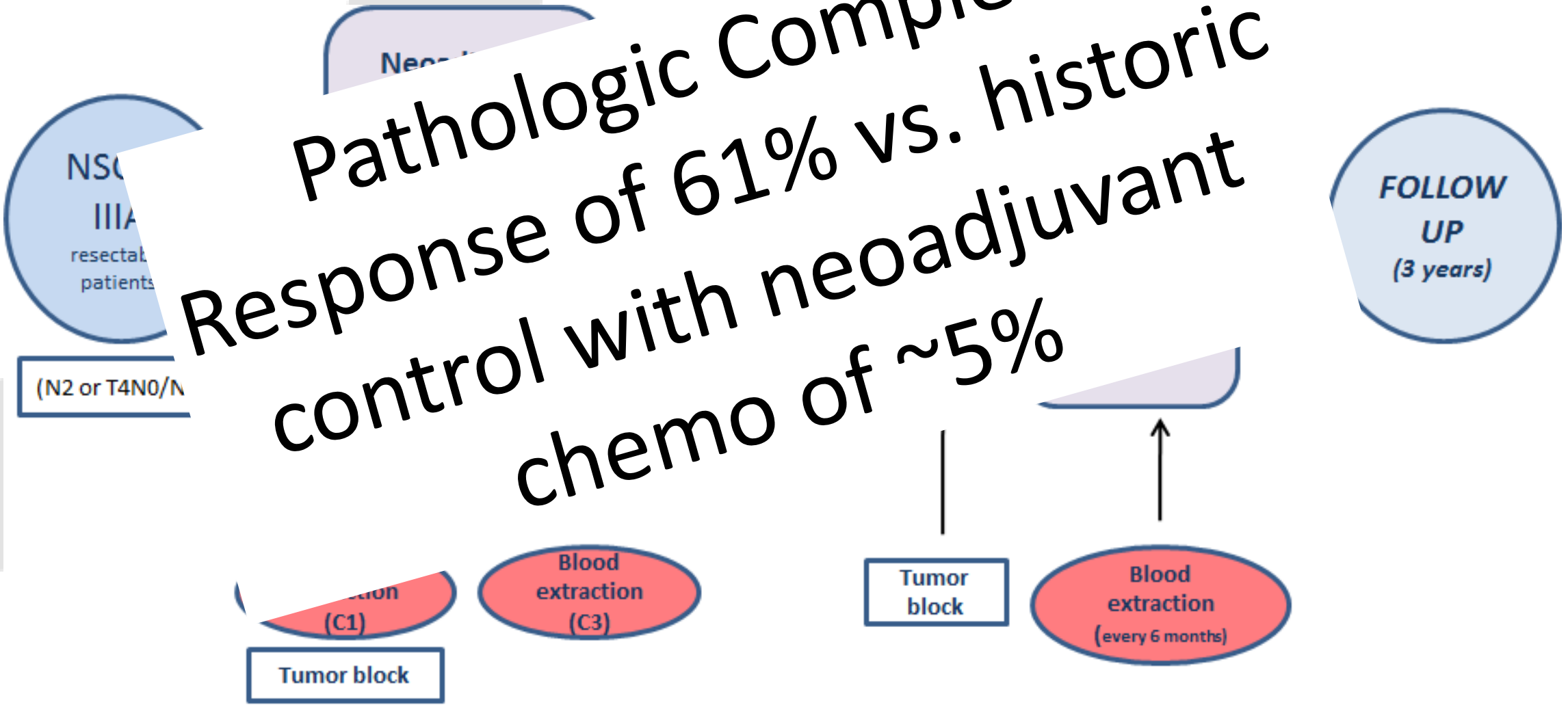
MPR with neoadjuvant chemotherapy ~20%

NADIM - Neoadjuvant Chemo-Nivolumab



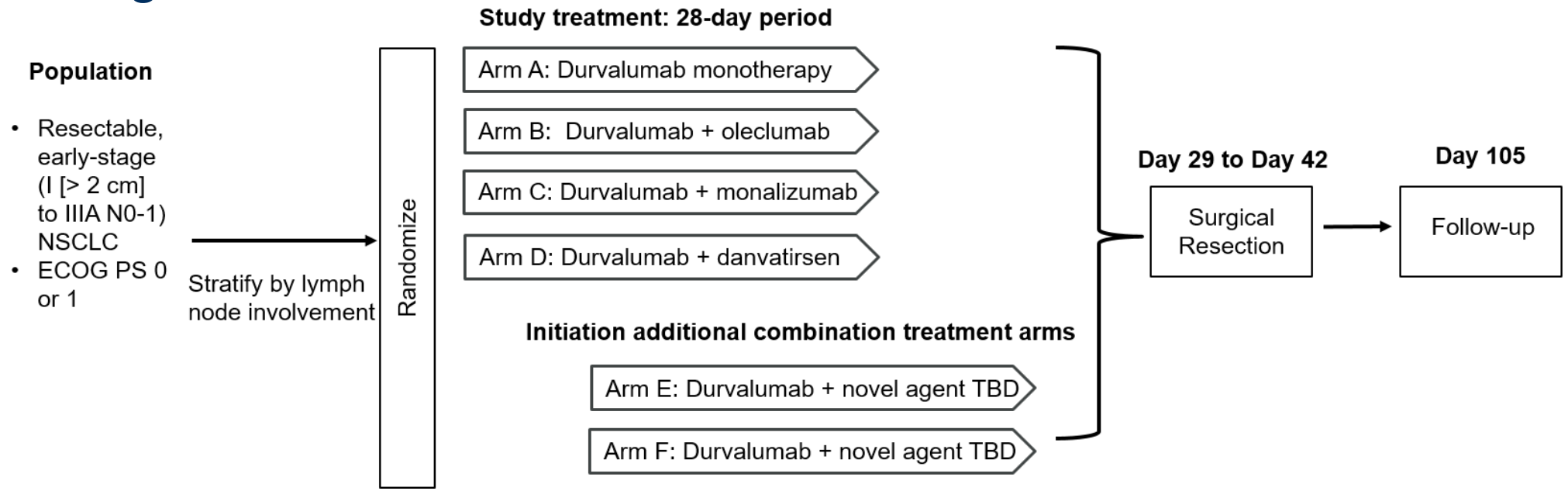
NADIM - Neoadjuvant Chemo-Ni b

Pathologic Complete Response of 61% vs. historic control with neoadjuvant chemo of ~5%

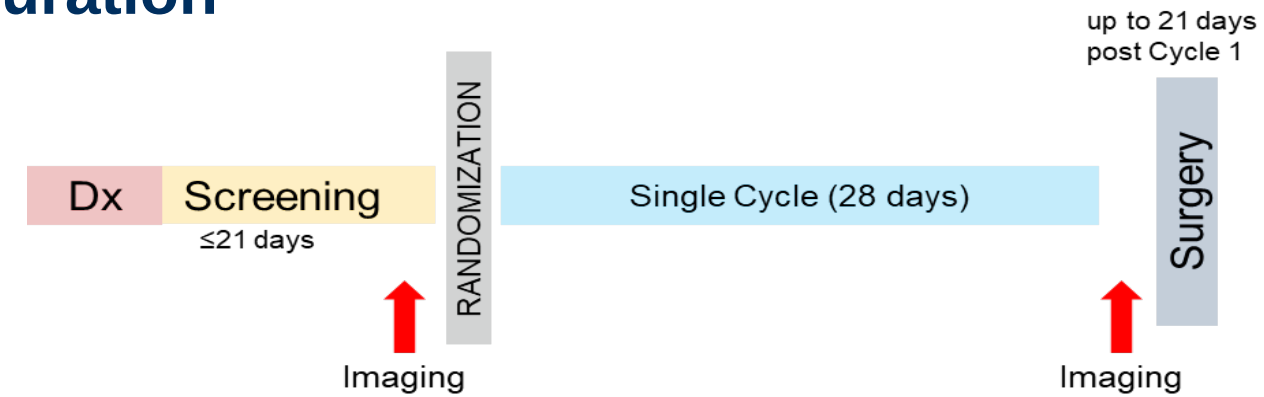


Novel Designs – Platform Neoadjuvant Studies: NeoCOAST

Study Design

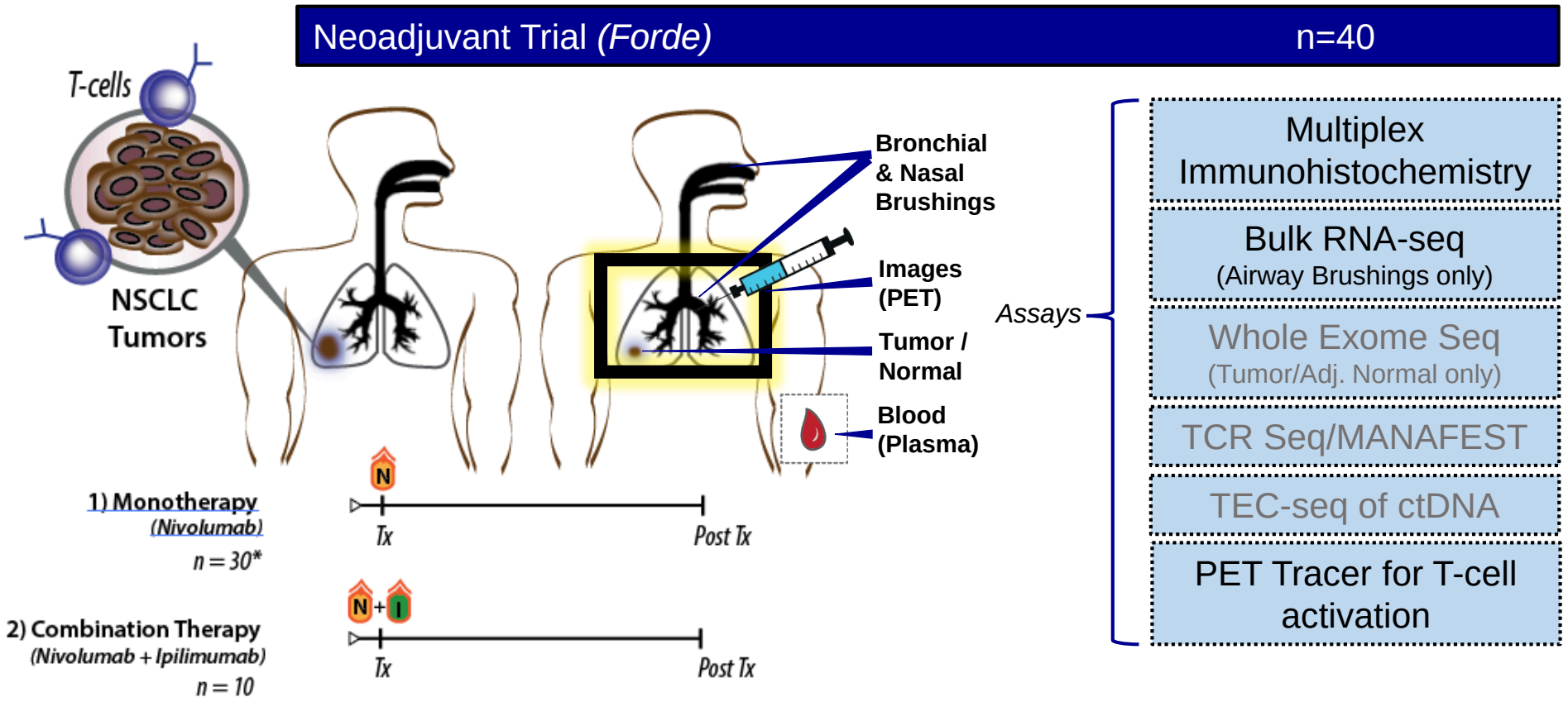


Study Period Duration



AACR-SU2C

Study Design: Predicting Therapeutic Response to Immunotherapy



Deliverable: Discover cellular, molecular and imaging features that **distinguish patients who respond to neoadjuvant nivolumab** +/- chemotherapy

Conclusions

- Neoadjuvant IO-based trials
  - accelerate drug development
  - offer crucial insights to guide rationale combination therapy
- Platform studies offer the opportunity to rapidly evaluate pathologic response to novel combinations
- Buy in from multidisciplinary cancer care team is vital
  - surgeons, pulmonary, rad onc, med onc and patient advocates

- Enthusiasm is building in lung cancer community with initial phase 3 results expected in 2020