Rajiv Gandhi Cancer Institute and Research Centre

A Unit of Indraprastha Cancer Society
Registered under "Societies Registration Act 1860"

Sector-5, Rohini, Delhi-110 085, INDIA

Architect's Impression of RGCI & RC (post expansion)

Rajiv Gandhi Cancer Institute
and Research Centre

SURGERY AFTER NACT IN LOCALLY ADVANCED LUNG CANCER

Dr LM.Darlong
Sr Consultant Thoracic Surgery
Head Thoracic Oncosurgery
Rajiv Gandhi cancer institute Delhi

Rajiv Gandhi Cancer Institute
and Research Centre

NACT [CHEMOTHERAPY]

- CHEMOTHERAPY BEFORE MAIN TREATMENT
  - SURGERY
- GOAL
  - R0 - SURGERY

INDICATIONS

- RESECTABLE N2 NODAL DISEASE
- POTENTIALLY RESECTABLE CENTRAL TUMOR
  - CLOSE TO VESSELS
- DOES NOT MAKE
  - UNRESECTABLE —- RESECTABLE

NOT ESTABLISHED

- RESECTABLE LESION INVOLVING
  - CHEST WALL / RIBS
  - DIAPHRAGM
  - PERICARDIUM

LOCALLY ADVANCED

- BULKY TUMOR [T SIZE]
- INVOLVING ADJACENT STRUCTURE
- METASTASIS TO REGIONAL NODES [N1/N2]

LAST 30 YEARS - PREIMMUNO ERA

- ADJUVANT / NACT FOR RESECTED NSCLC
  - OS BY 4 TO 5 % AT 5 YEARS
- META-ANALYSIS OF CISPLATIN BASED INDUCTION
  - RISK OF DEATH 13% [REDUCTION]
  - ABSOLUTE 5YR SURVIVAL 5% [INCREASED]

- OUTSIDE CLINICAL TRIAL - NACT [IIIA N2 DIS]
  - 34% 3YR SURVIVAL
  - HIGH VOLUME CENTRE
    - 40% 5 YRS SURVIVAL [SUBOPTIMAL]
- PACIFIC TRAIL -
  - UNRESECTABLE STAGE III DIS
  - 42 % 5YRS OS [ADDITION OF IO]

PREDICTORS IN PRE -IMMUNOTHERAPY ERA

- CLASSIC PREDICTORS OF LONG TERM SURVIVAL
  - R0 RESECTION
  - DOWNSTAGING
  - pCR [PATH COMPLETE RESPONSE]
- MPR [MAJOR PATH RESPONSE]
  - 10 % OR LESS RESIDUAL TUMOR
  - SURROGATE FOR OS
    - UNPROVEN IN RCT

PCR - PREIMMUNOTHERAPY

TABLE 2. Pathologic Complete Response After Neoadjuvant Chemotherapy in Stage IIIA (N2) During Preimmunotherapy Era

Study	No. of Patients	Treatment	Resection Rate	pCR	3–Year OS
Martini et al[38]	41	MVd/VP	68%	20%	34%
Betticher et al[39]	90	Docetaxel + cisplatin	87%	12%	36%, median EFS: 11.7 mo
Garrido et al[40]	129	Docetaxel + cisplatin	70%	8.9%	36.8%, median EFS: 9.9 mo
Burkes et al[41]	35	MVP	56%	4.6%	26%, median EFS: 19 mo
Chaft et al[37]	50	Bevacizumab + docetaxel + cisplatin	88%	MPR: 27%	52%, TTP: 20 mo

IMMUNOTHERAPY ERA

- NEOADJUVANT [ICI]
  - MONOTHERAPY
  - ICI WITH CHEMOTHERAPY
  - DUAL ICI
    - ANTI PDL -1 WITH CTLA-4
- NUMEROUS TRAILS
  - PHASE II / PHASE III

PHASE II NEO ADJ IMMUNO

TABLE 4. Neoadjuvant Immunotherapy Phase II Trials

Study	Registry No.	Stage	No. of Patients	Resected Patients	Experimental Arm	Control Arm	Primary Endpoint	MPR	pCR	1-Year OS
SKCCC-JHU Forde et al[58]	NCT02259621	IB, II, IIIA	22	20	Nivo, 2 cycles Q2W	None	Safety	9 (45%)	3 (13%)	—
LCMC3 Kwiatkowski et al[103]	NCT02927301	IB-IIIB (T3N2)	181	159	Atezolizumab, 2 cycles Q3W	None	MPR	30 (21%)	10 (7%)	
NEOSTAR Cascone et al[59]	NCT03158129	I-IIIA (single N2)	88: Nivo: 23 Nivo + Ipi: 21	39	Nivo, 3 cycles Q2W or Nivo 3 + Ipi 1	None	MPR	11: Nivo: 5 (22%) Nivo+ Ipi: 8 (38%)	8: 2 (9%) 6 (29%)	
IONESCO Wislez et al[104]	NCT03030131	IB, II, IIIA (non-N2)	50/81	46	Durva 3 cycles Q2W	None	Surgical resection R0	8 (18.6%)	3 (7%)	89.1%
COLUMBIA UNIVERSITY Shu et al[60]	NCT02716038	IB-IIIA	30	29	Atezolizumab + cCT, 4 cycles – SoC (adj)	None	MPR	17 (57%)	10 (33%)	—
NADIM Provencio et al[50]	NCT03081689	IIIA (N2)	46	41	Nivo + cCT, 3 cycles Q3W – Nivo (adj) 1 y	None	24 mo PFS	34 (83%)	26 (63%)	97.8%
SAKK 16/14 Rothschild et al[101]	NCT02572843	IIIA (N2)	67	55	Durva + cCT – Durva (adj)	None	EFS at 1 y	33 (60%)	10 (18%)	—
NADIM II Provencio et al[105]	NCT03838159	IIIA-IIIB	90	NA	Nivo + cCT - Nivo (adj) 6 mo	CT	pCR	NA	NA	—

PHASE III NEO ADJ IMMUNO

TABLE 5. Neoadjuvant immunotherapy Phase III Trials

Study	Registry No.	Stage	No. of Patients	Experimental Arm	Control Arm	Primary Endpoint
KEYNOTE-671	NCT03425643	II, IIIA, IIIB	786	Pembrolizumab + cCT, 4 cycles – pembrolizumab (adj), 13 cycles	Placebo + cCT - Placebo	EFS, OS
CheckMate-816[106]	NCT02998528	IB-IIIA	358	Nivolumab + cCT, 3 cycles or nivolumab + ipilimumab	CT	EFS, pCR
IMpower030	NCT03456063	II-IIIA-IIIB (T3N2)	450	Atezolizumab + cCT, 4 cycles – atezolizumab (adj), 16 cycles	Placebo + cCT - SoC	MPR, EFS
CheckMate-77T	NCT04025879	II-IIIB	452	Nivolumab + cCT, 4 cycles – nivolumab (adj), 1 year	Placebo + cCT - Placebo	EFS
AEGEAN	NCT03800134	II-IIIB	800	Durvalumab + cCT, 4 cycles – durvalumab (adj), 12 cycles	Placebo + cCT - Placebo	MPR, EFS

- CURRENTLY NEOADJ-IO TRIALS
  - RESECTABLE NSCLC
- PHASE II - NADIM
- PHASE III - CHECKMATE 816

PHASE II NADIM

- SINGLE ARM / OPEN LABEL / MULTICENTER
- NEODJ- IO + CHEMO X3 - SX -ADJ IO X 1YR
- RESECTABLE STAGE IIIA-B MULTISTATION [46]
- PR ENDPOINT - PFS AT 24 MONTHS
  - 66 % VS 42 %
- SEC ENDPOINT - OS AT 3YRS
  - 84 % VS 63 %

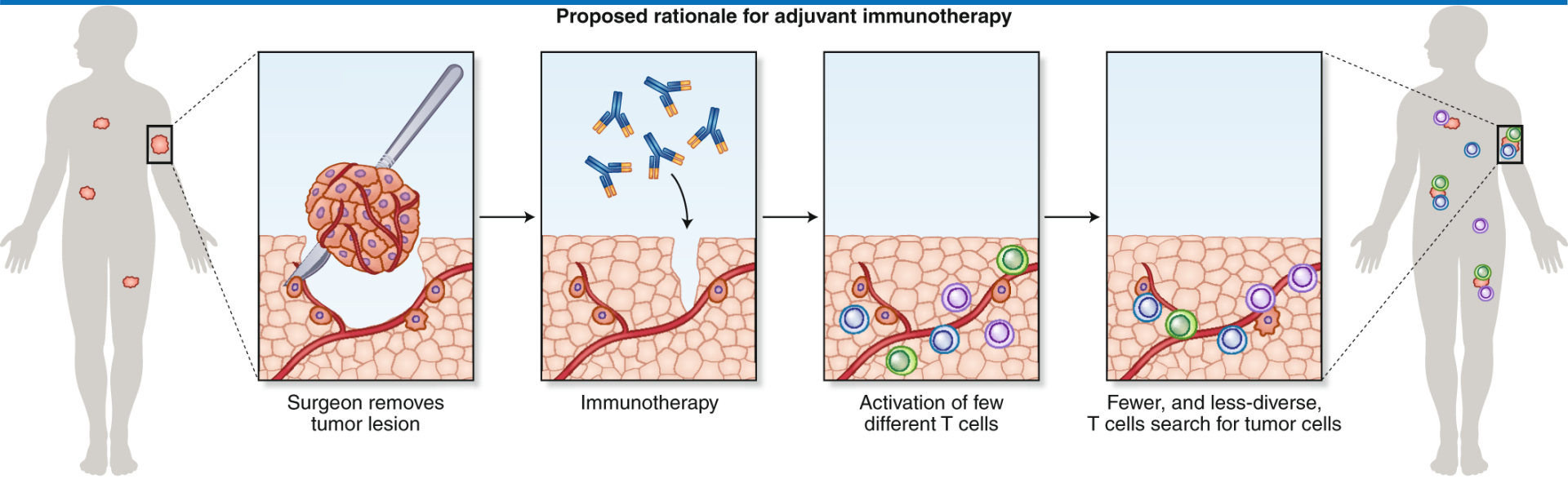
PHASE III CHECKMATE 816

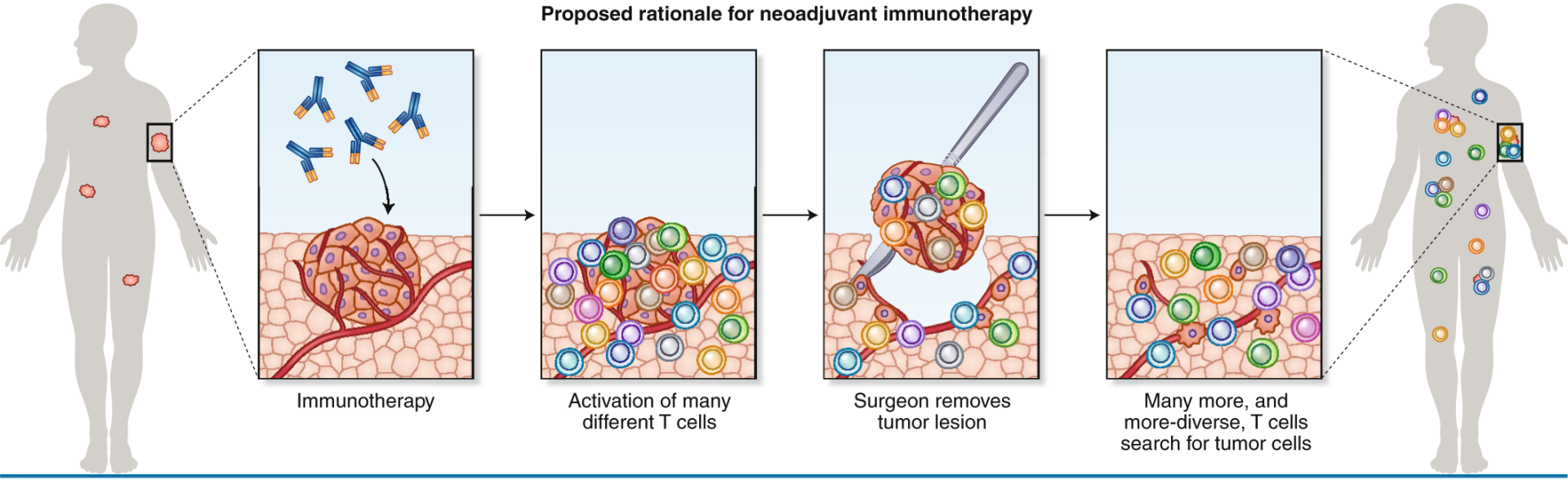
- 1ST PHASE III - RESECTABLE NSCLC
  - BENEFITS OF NEOADJ -IO+CHEMO
  - STANDARD CHEMO
- IB-IIIA / 358 PT /
- SURGERY [POST RANDOMIZATION]
  - 83.2% [CHEMO + IO] VS 75.4% [CHEMO]
- R0 RESECTION - 83% VS 78%

PHASE III CHECKMATE 816

- PRIMARY ENDPOINT - EFS / pCR
  - pCR- 24 % VS 2.2%
  - EFS - 31.6 MONTHS VS 20.8%

NEOADJUVANT V/S ADJUVANT - IO





NEOADJV CHEMO + IO

- NEOADJ CHEMO [TRANSLATIONAL STUDY]
  - INCREASE IN PDL-1 + TR CELLS
  - IMMUNE INFILTRATES
  - SYNERGY WITH IO

RATIONALE FOR NEOADJ - IMMUNOTHERAPY ERA

- BIOLOGIC EFFICACY
  - NADIM - pCR 63 %
  - CHECKMATE 816 - pCR 24 % V/S 2.2 %
- COMPLIANCE
  - IM POWER 010 [ADJ-IO] - 65 %
  - CHECKMATE 816 [N-ADJ IO+CT]-94 %
  - NADIM [N-ADJ IO+CT] - 100 %

- DOWNSTAGING
- INCREASED R0 SX
- CHECKMATE 816
  - EFFECTIVE/SAFE /FEASIBLE/ACCEPTABLE SX DELAYS/AE

WHEN SURGERY AFTER N-ADJUVANT

- IIIA - > 6 WEEK POST NACT POOR SURVIVAL
- NADJ- IO + CT = 3 -6 WEEKS PERIOD
- DELAY POTENTIAL FOR
  - TUMOR REPOPULATION
  - DISTANT METASTASIS
  - ANATOMY CHANGES LOCAL SITE
    - FIBROSIS / THICKENING OF TISSUE PLANE

IMMUNE FLARE

- NODAL IMMUNE FLARE [NEOSTAR]
  - RADIOGRAPHIC NODAL PROGRESSION
  - PATHOLOGY - GRANULOMAS / SARCOID LIKE / IMMUNE MEDIATED
  - PSEUDO- PROGRESSION
  - NOT DEEMED UNRESECTABLE - PATH PROVEN

SURGICAL IMPLICATIONS

- REAL TIME
  - SURGERY MORE CHALLENGING
  - 3 - 6 WEEKS INTERVAL

CONCLUSION

- ADVANCES IN CHEMO-IO
  - SURGERY GREATER ROLE IN ADVANCED DIS
    - CURATIVE INTENT IN MIND
- BIOMARKER TESTING - ESSENTIAL FOR SX
  - EGFR [ADAURA / NEO - ADAURA]
- STAGE IB-IIIA [-VE EGFR / ALK]
  - N-ADJ+IO WILL BE PREFERRED OPTION

Thank you

Rajiv Gandhi Cancer Institute
and Research Centre