Advances in Head and Neck Cancers;
Including Thyroid Malignancies

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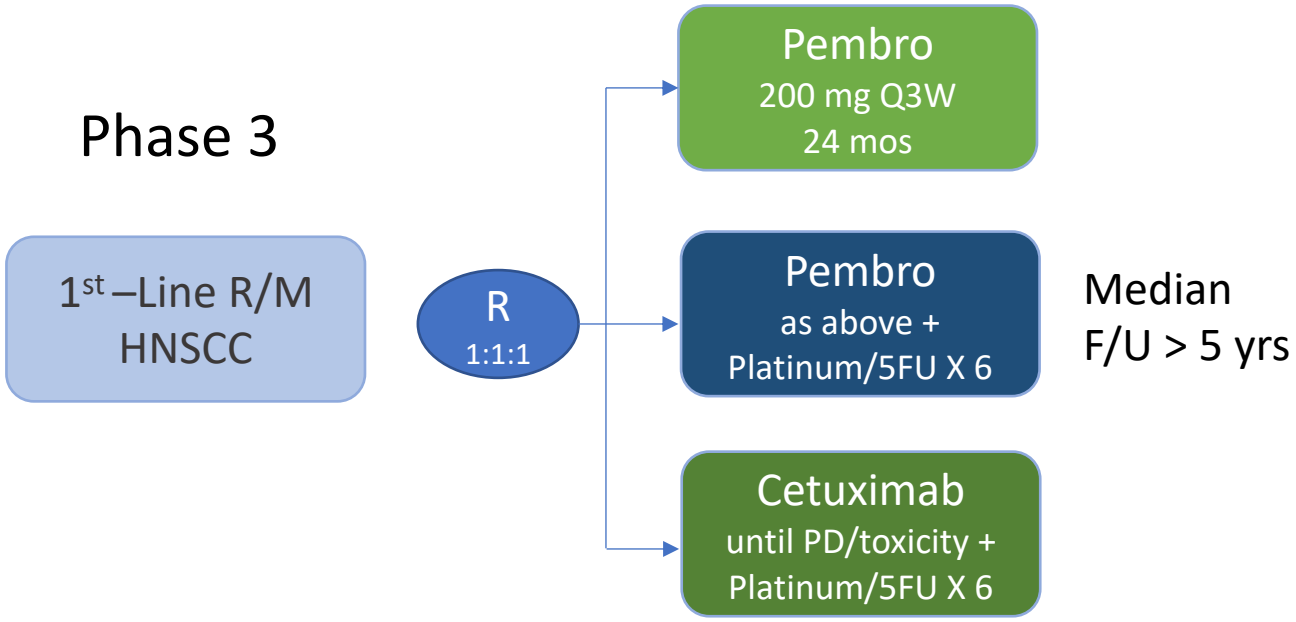
What's New in Head & Neck/Thyroid?

- It's not *all* about immunotherapy, but mostly
- Updated IO baseline: KEYNOTE-048

Phase 3



Median F/U > 5 yrs

5Y OS rate pembro vs EXTREME
CPS ≥20: 19.9% vs 7.4%
CPS ≥1: 15.4% vs 5.5%
All: 14.4% vs 6.5%

5Y OS rate pembro/chemo vs EXTREME
CPS ≥20: 23.9% vs 6.4%
CPS ≥1: 18.2% vs 4.3%
All: 16.0% vs 5.2%

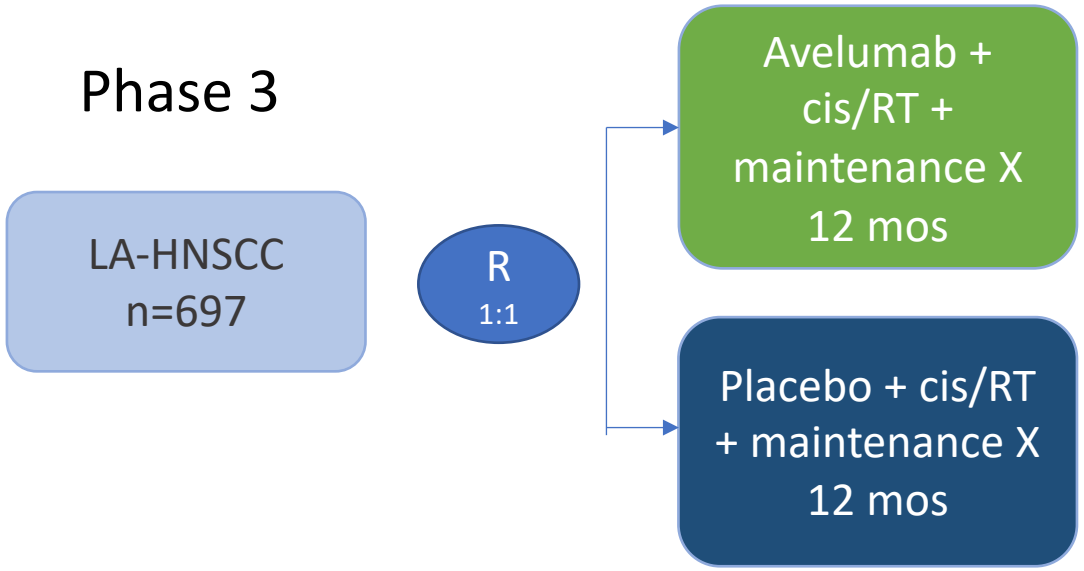
Gr 3-5 AEs	
Pembro	17.0%
Pembro/chemo	71.7%
EXTREME	69.3%

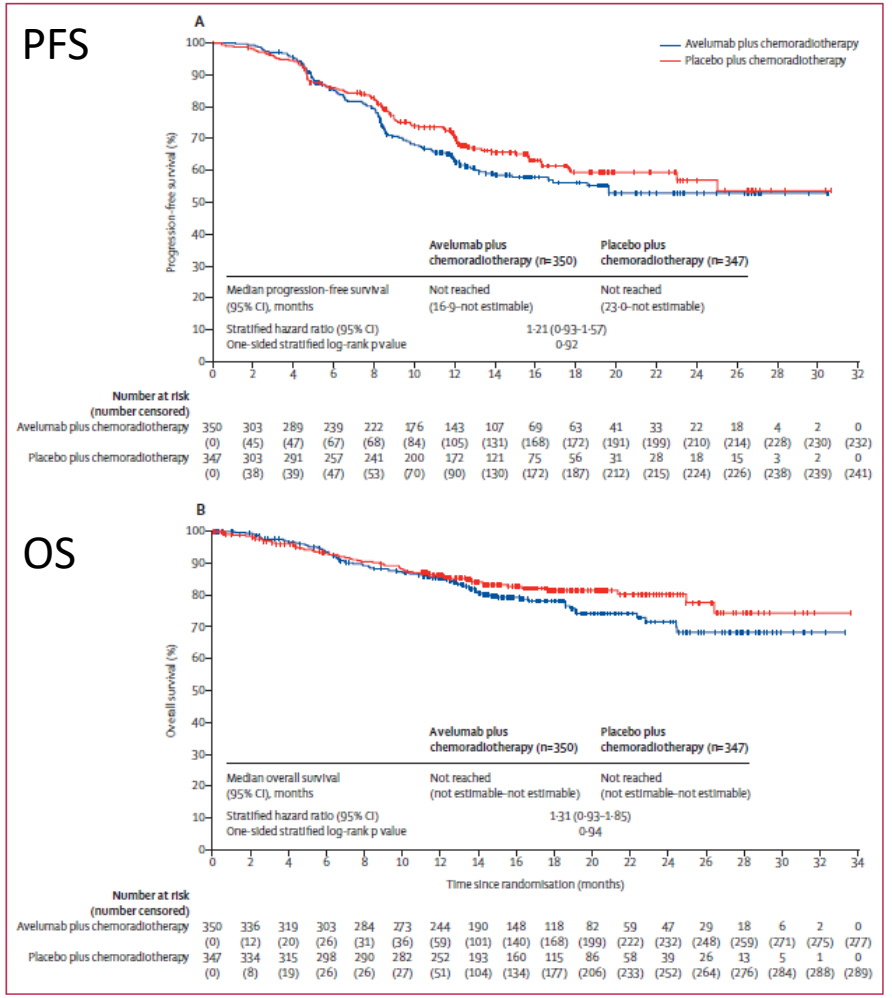
Tahara M, et al. Abstract 659MO, *ESMO*, 2022

Moving IO Up to Curative Setting?

- JAVELIN H&N 100
  - ~60% HNSCC pts present w/ potentially curable disease

Phase 3





1º endpoint: PFS

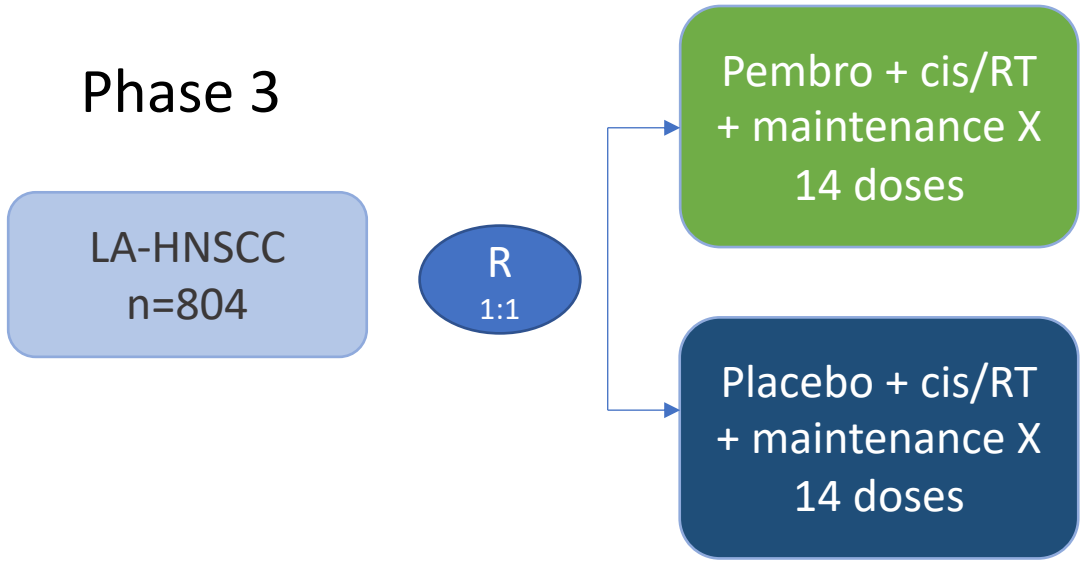
Study stopped after pre-planned interim analysis crossed futility boundary

Lee NY, et al. *Lancet Oncol*, 2021

Moving IO Up to Curative Setting?

- KEYNOTE-412

Phase 3



	Pembro/CRT	Placebo/CRT	
EFS	NR (44.7-NR)	46.6 (27.5-NR)	Med (95% CI), mo
	0.83 (0.68-1.03), *P*=0.0429		HR (95% CI), *P*
OS	NR (NR-NR)	NR (NR-NR)	Med (95% CI), mo
	0.90 (0.71-1.15)		HR (95% CI)
	CPS ≥ 1 (n=865)	**CPS < 1 (n=82)**	
EFS	0.80 (0.64-1.00)	1.09 (0.56-2.11)	

1^{o} endpoint: EFS

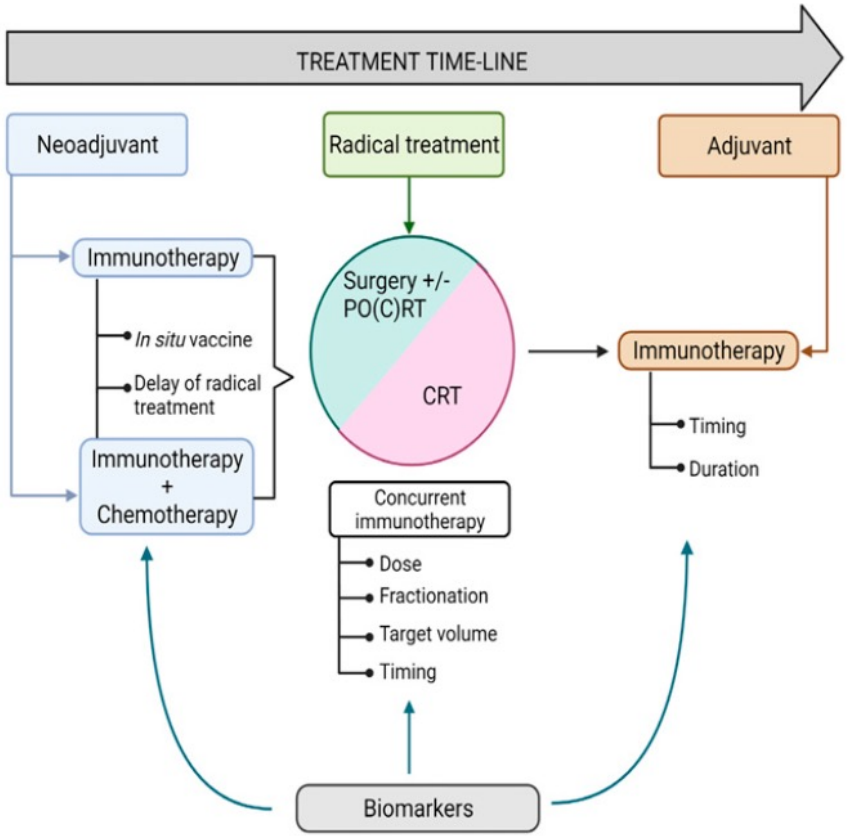
Machiels J-P, et al. LBA5, *ESMO*, 2022

JAVELIN & KEYNOTE-412: *Lessons Learned*

- Anti-PD-1 antibody (instead of anti-PD-L1) doesn't seem to matter
- Biomarker-driven patient selection may be necessary
  - Trend toward a potential benefit in JAVELIN in PD-L1 ≥ 25%
  - Can we do better than CPS alone?
- Further understanding of immune checkpoint blockade and chemoRT needed
  - Does chemoRT deplete T cells/otherwise alter TME, negating potential for immune checkpoint blockade to treat minimal residual disease?
  - Why does IO + chemoRT work in NSCLC? (PACIFIC, PACIFIC2)
- Is standard chemoRT the best backbone to which IO can be added?

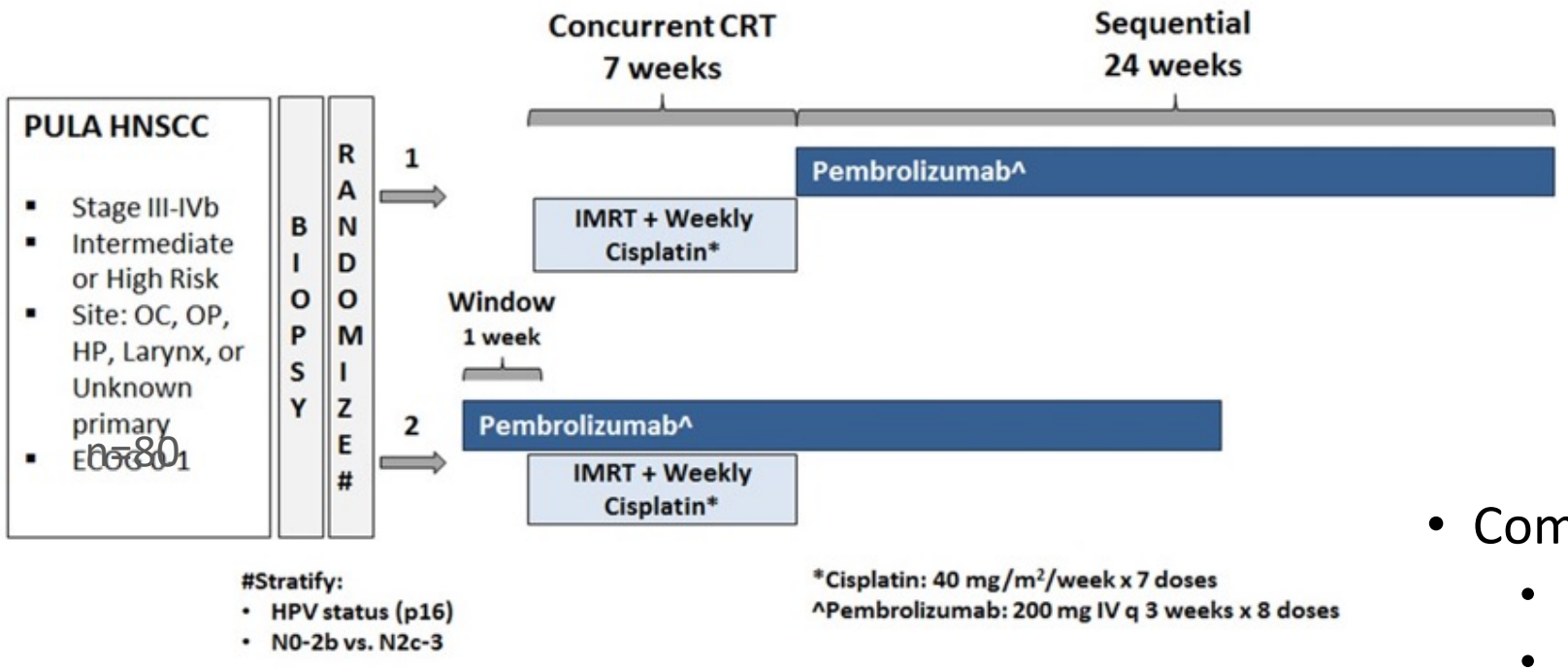
JAVELIN & KEYNOTE-412: *Lessons Learned*

- Will altering sequence of IO improve outcomes?
  - Maintenance with concurrent IO? Neoadjuvant IO? Other?



Nenclares P, et al. *ASCO Ed Book*, 2022

rPhase 2 Sequential vs. Concurrent Pembro with ChemoRT



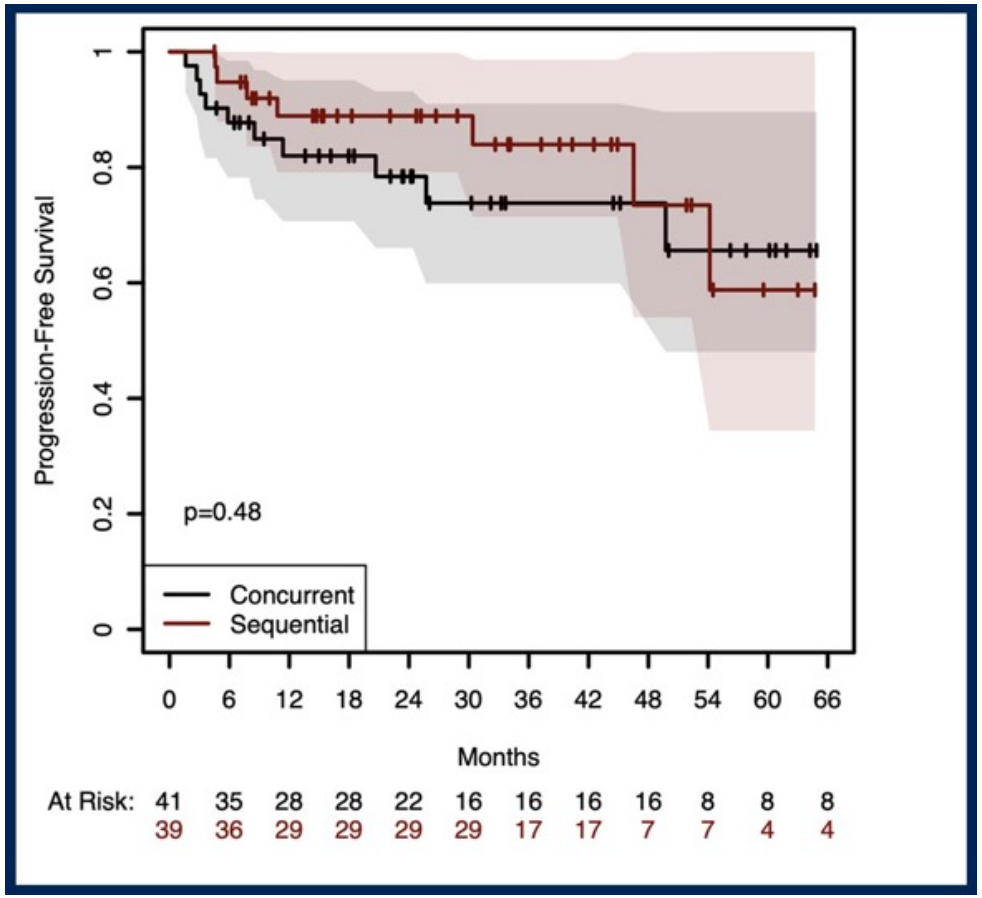
- Composite endpoint:
  - 1Y locoregional failure rate <60%
  - 1Y PFS rate ≥ 60%
  - DLT rate ≤ 20%
- If all 3 met, arm with better 1Y PFS winner for further study

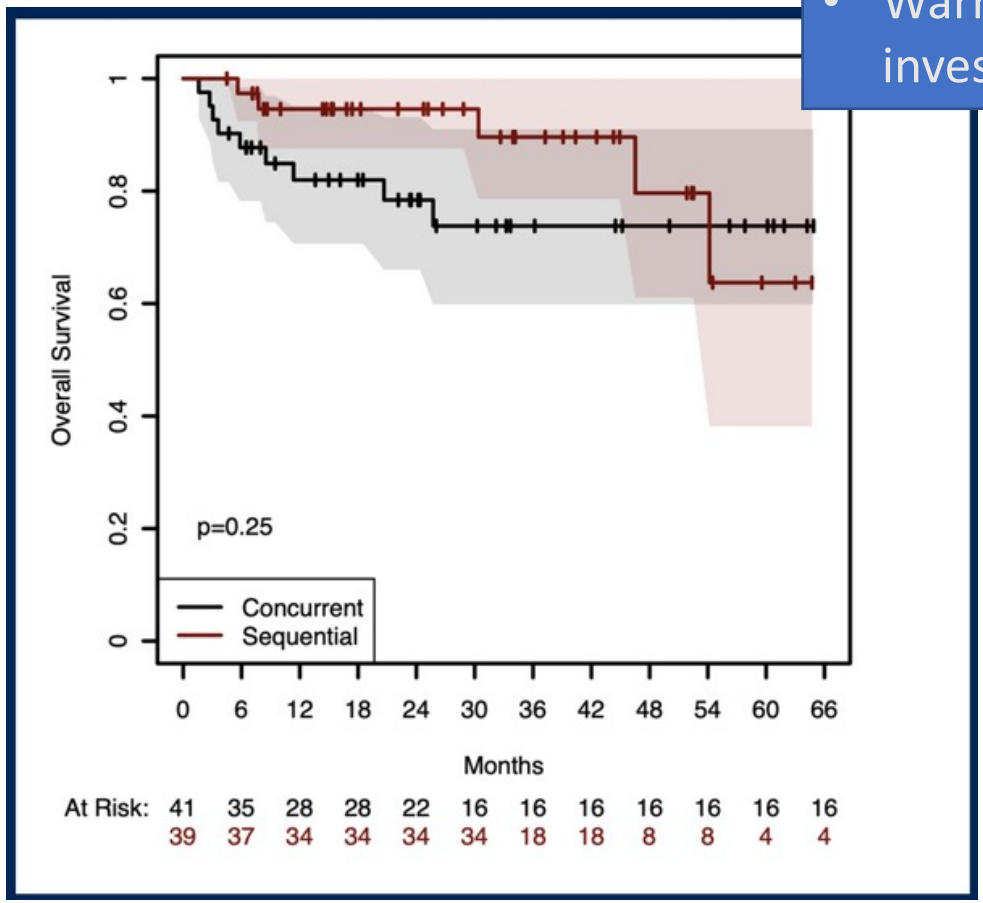
Clump DA, et al. Abstract 6007, *ASCO*, 2022

rPhase 2 Sequential vs. Concurrent Pembro with ChemoRT

- Composite endpoint met in both arms

- Sequential therapy - numerically superior PFS (and OS)
- Warrants further investigation

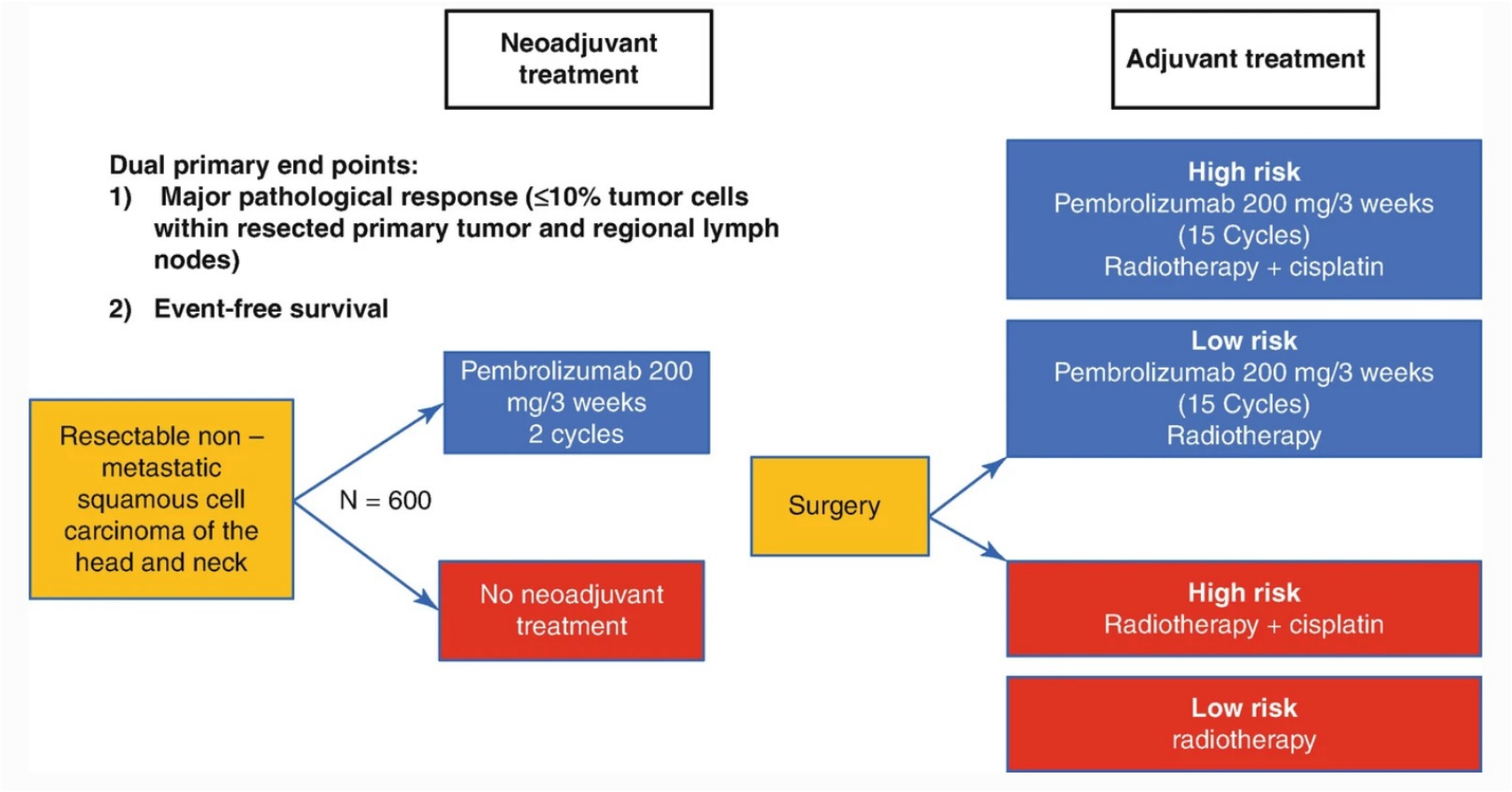




Clump DA, et al. Abstract 6007, *ASCO*, 2022

KEYNOTE-689

Phase III study of neo & adjuvant pembro + SoC in resectable LA-HNSCC

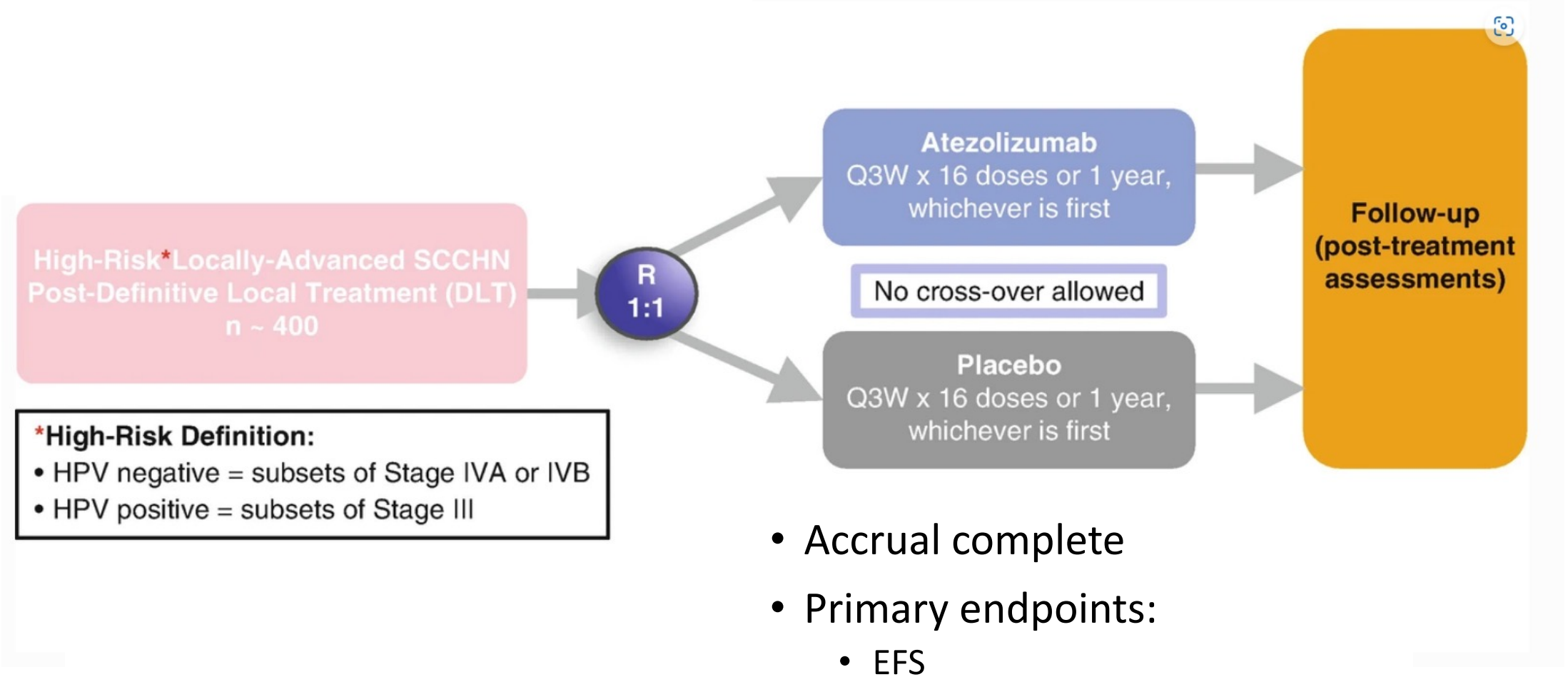


- Based on Phase II
  - 22% had ≥50% path response
  - 19% tumors down-staged
  - No delays to surgery
- Potential to
  - Reduce extent of surgery & adjuvant therapy needed
  - Decrease r/o distant mets by early introduction of systemic IO
  - Convert unresectable to resectable disease
  - Provide tissue for biomarker identification

Uppaluri R, et al. *Clin Cancer Res*, 2020

Additional Efforts Underway: *IMvoke010*

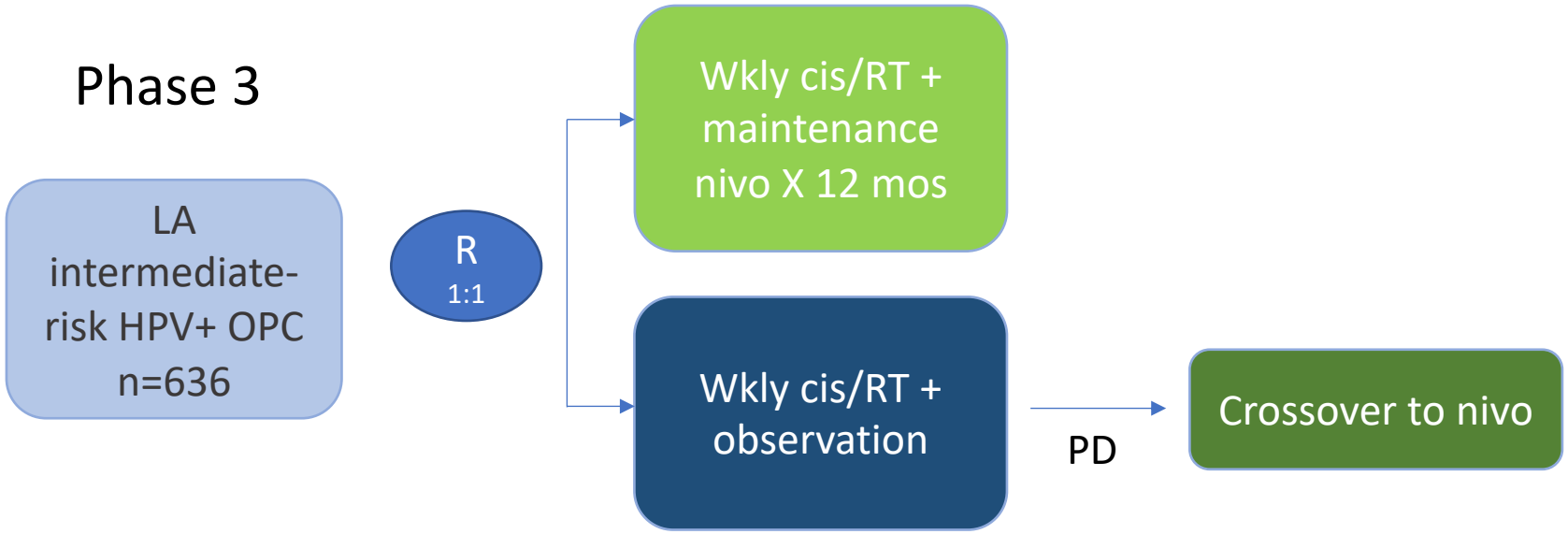
Phase III study of post-op atezo in HPV+ OPC



- Accrual complete
- Primary endpoints:
  - EFS
  - OS

NCT03452137

Additional Efforts Underway: *EA3161*

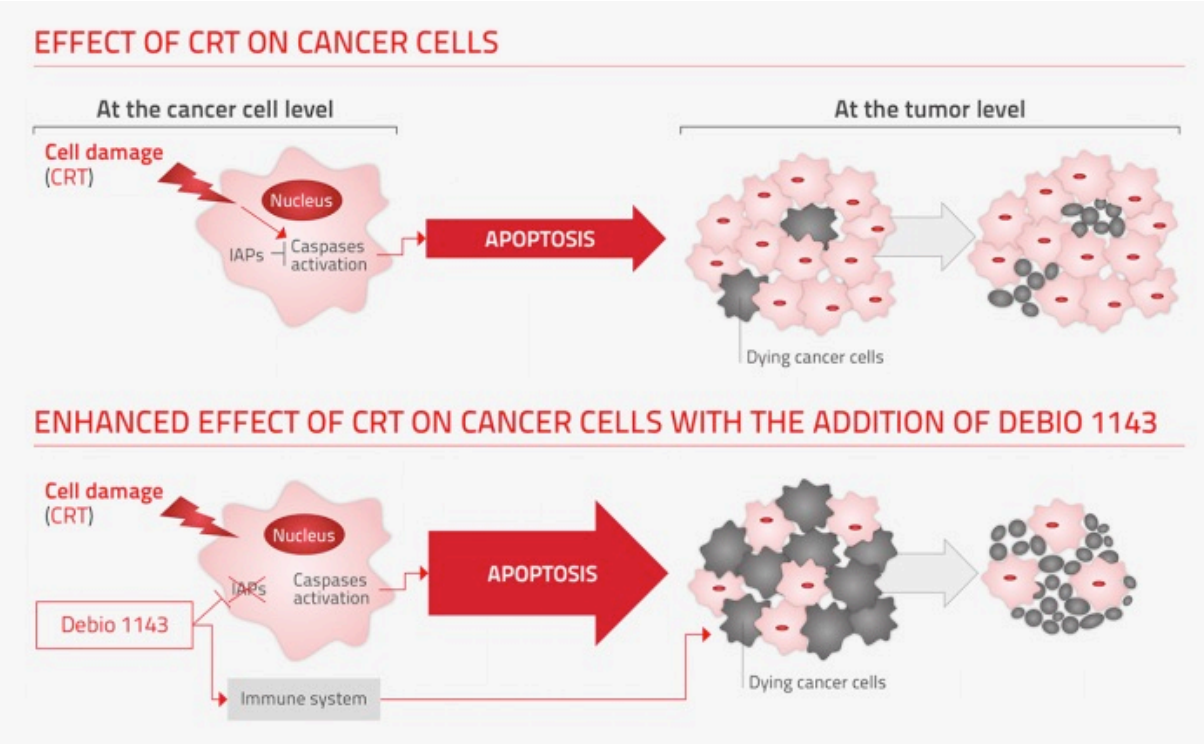


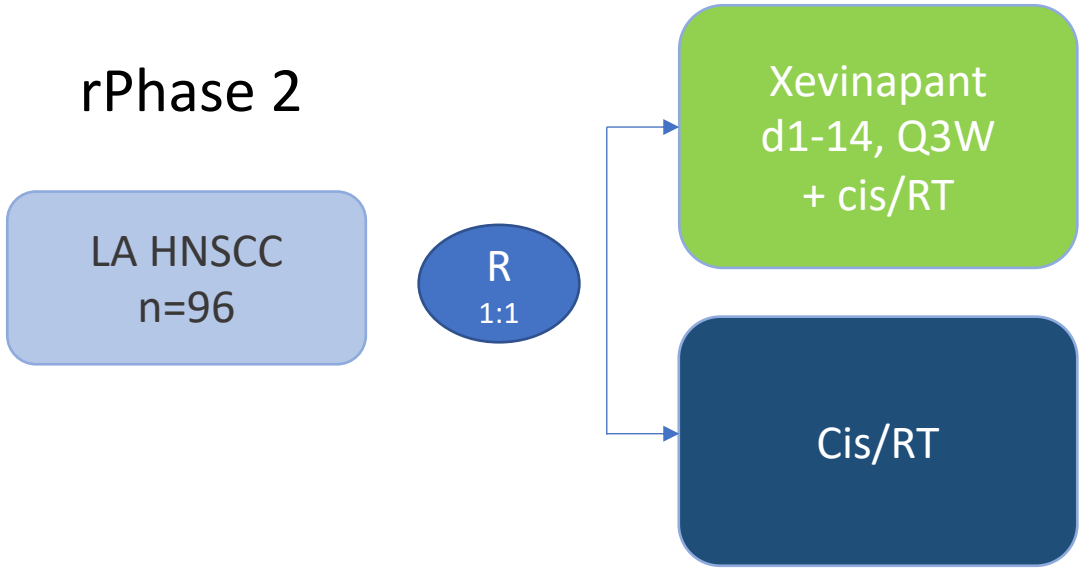
- Primary endpoints:
  - EFS
  - OS

NCT03811015

Additional Non-IO Efforts Underway in Curative Setting: *Xenivapant (Debio 1143)*

1st-in-class, orally available, inhibitor of Inhibitor of Apoptosis Proteins (IAPs), restoring sensitivity to apoptosis

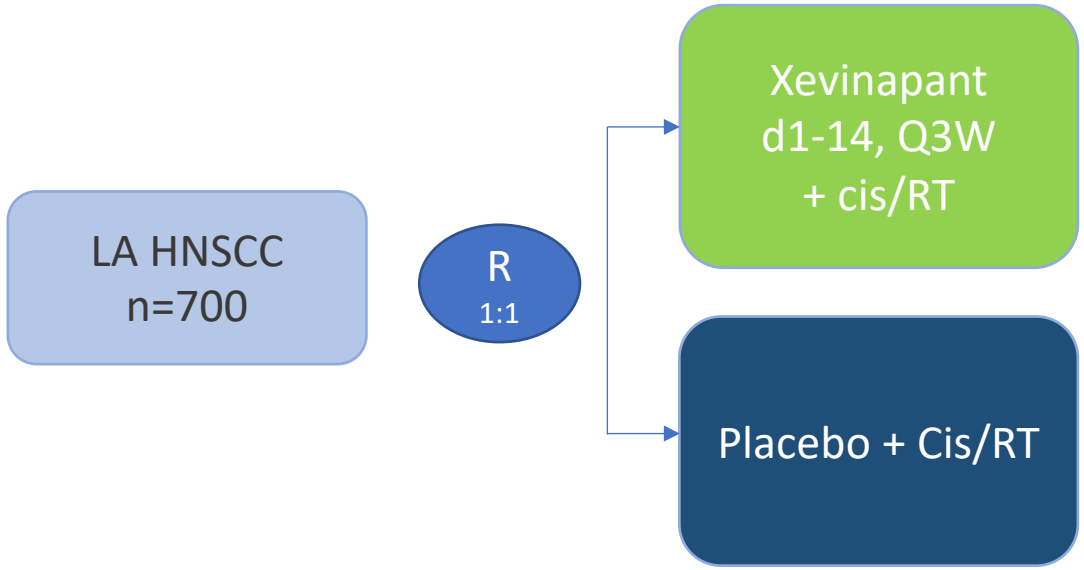




- Med 5Y OS update:
  - NR (95% CI, 40.3 mos-NE) vs 36.1 mos (95% CI, 21.8-46.7 mos)
  - adjusted HR, 0.47 [95% CI, 0.27-0.84]; *p*=0.0101

Bourhis J, et al. LBA33, *ESMO*, 2022

Pivotal Phase 3 TrinlynX Study Ongoing



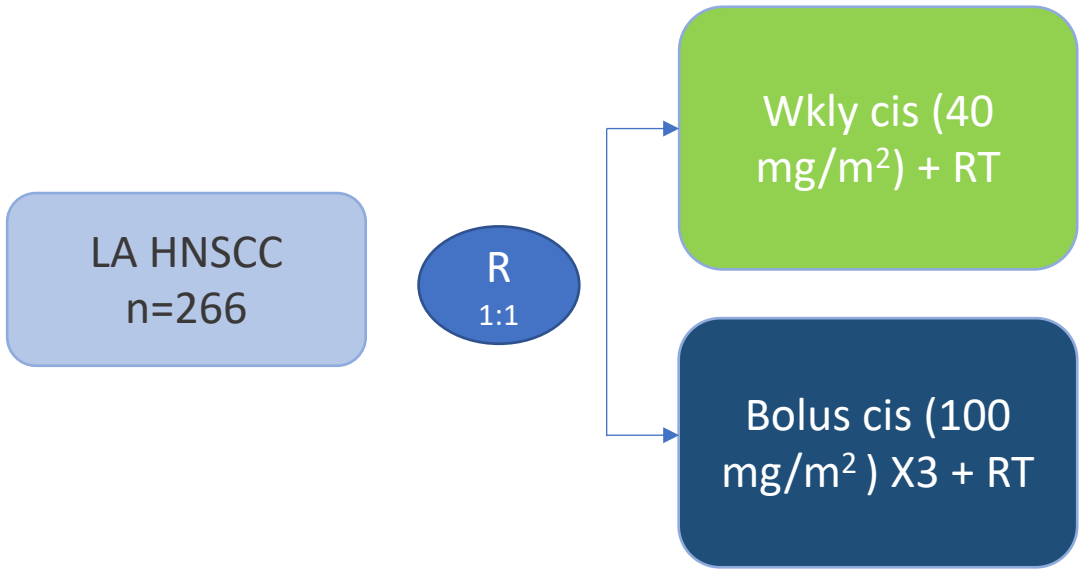
- Primary endpoint: EFS
- Powered to detect improvement in EFS by 6 mos

NCT04459715

Additional Curative Setting Updates

- Concurrent chemoRT with weekly cisplatin @ 40 mg/m^2 should be considered SoC

- JCOG1008: Weekly vs bolus cisplatin with post-op RT
  - rPhase II/III: Wkly cis non-inferior OS
  - Neutropenia, infection, renal, & ototoxicity reduced
- ConCERT: Concurrent Chemotherapy and External Beam Radiation Therapy, a non-inferiority study



- Primary endpoint:
  - 2Y locoregional control
  - 53% vs 47%, HR 0.84 (95% CI, 0.58-1.20)
- Less gr 3/4 mucositis, renal toxicity, vomiting, hospitalizations in wkly arm & fewer treatment interruptions

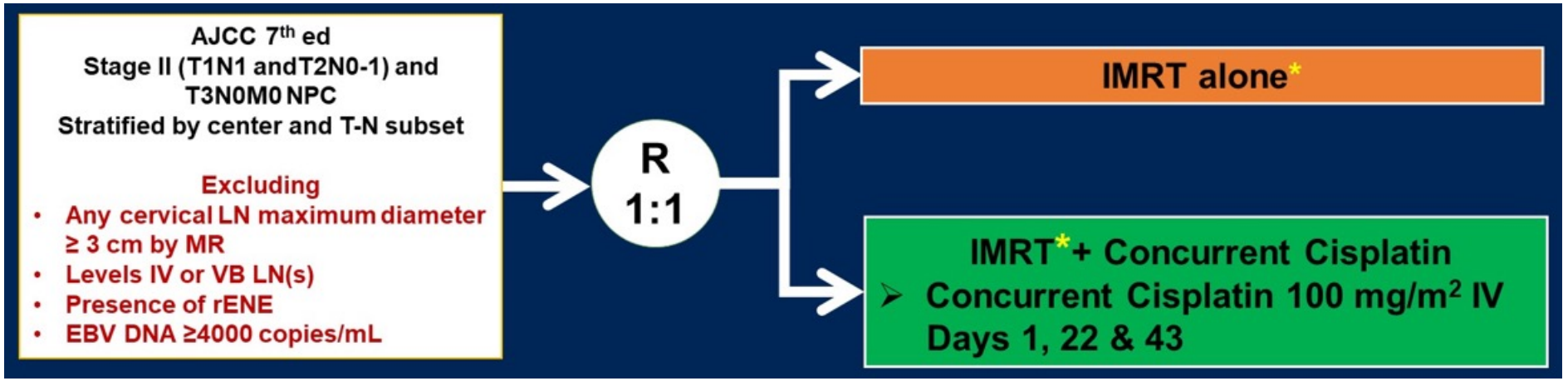
Kiyota N, et al. *J Clin Oncol*, 2022; Sharma A, et al. Abstract 6004, *ASCO*, 2022

Nasopharyngeal Carcinoma (NPC)

- Finally, a de-escalation success!

- RT alone vs chemoRT in intermediate-risk NPC; non-inferiority study
- Rationale: Concurrent cisplatin may increase acute & chronic treatment-related toxicity, and increase risk of treatment-related death

n=341



- Primary endpoint:
  - Failure-free survival @ 3Y
  - 91% vs 92%, HR 1.35 (95% CI, 0.69-2.64), *p*=0.86
- Less neutropenia, N/V, mucositis, wt loss

Ma J, et al. Abstract 6000, *ASCO*, 2022

Other Small Steps Forward

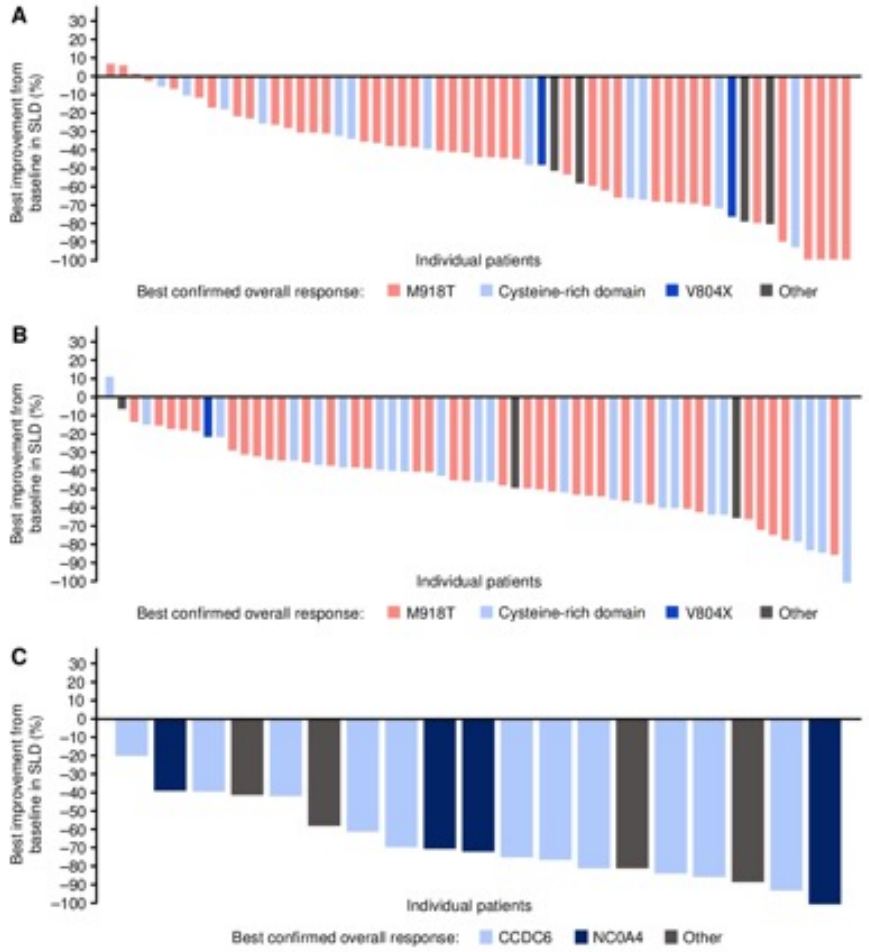
- Phase 3 docetaxel + RT vs RT alone in cisplatin ineligible LA HNSCC
  - n=356, docetaxel 15 mg/m^2 weekly X7
  - 2Y OS was 50.8% vs 41.7% (HR 0.75; 95% CI 0.57-0.98; *P*=0.035)
  - Gr 3 and above mucositis, odynophagia and dysphagia more common with docetaxel
- Phase 4 KEYNOTE-B10: pembro + carbo/paclitaxel in 1st-line R/M HNSCC
  - n=92, carbo (AUC 5)/paclitaxel 175 mg/m^2 + pembro 200 mg Q3W
  - cORR=43% (95% CI, 32-54), cORR in CPS≥1 = 38% (95% CI, 27-51)
  - Med OS = 12.1 mo (95% CI, 10-NR)
  - Pembro + carbo/paclitaxel may be considered an off-label option in pts ineligible to receive platinum/5FU backbone (cardiac contraindication, DPD deficiency, other)

Patil VW, et al. LBA 6003, *ASCO*, 2022; Dziensis M, et al. Abstract 6519, *ESMO*, 2022

Thyroid: ARROW Updated

- Pralsetinib in *RET*-altered thyroid cancers

	ORR	Med DoR	Med PFS
MTC, prior van &/or cabo	51%	25.8 mos	24.9 mos
MTC, treatment-naïve	72%	NR	NR
RET fusion+ FDTC	86%	17.5	19.4 mos



- Most freq TRAEs:
  - ↑ AST (39%)
  - Anemia (35%)
  - HTN (33%)
  - ↓WBCs (30%)
- Most freq serious TRAE
  - Pneumonitis (2%)
  - 1 death d/t PJP pneumonia

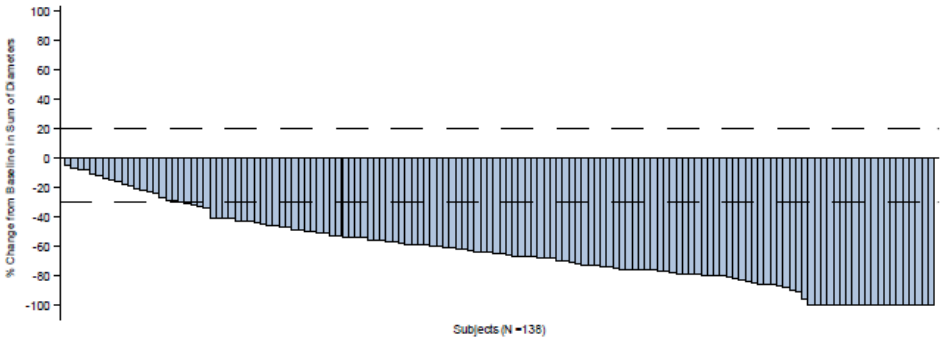
Mansfield AS, et al. Abstract 6080, *ASCO*, 2022

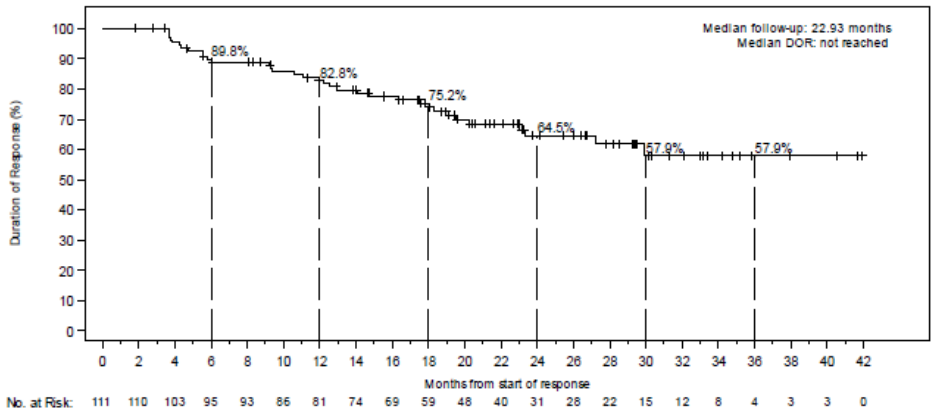
Thyroid: LIBRETTO-001 Updated

- Selpercatinib in *RET*-altered MTC

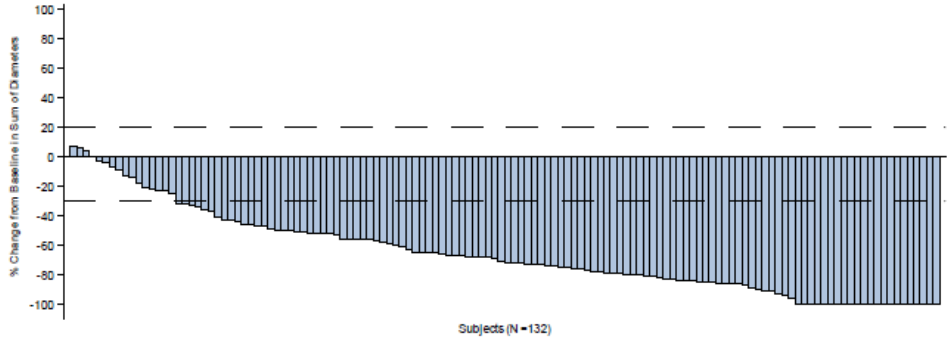
	ORR	Med DoR	Med PFS
MTC, prior van &/or cabo	81%	NR	NR
MTC, van/cabo naïve	84%	NR	34 mos (95% CI, 26 – NE)

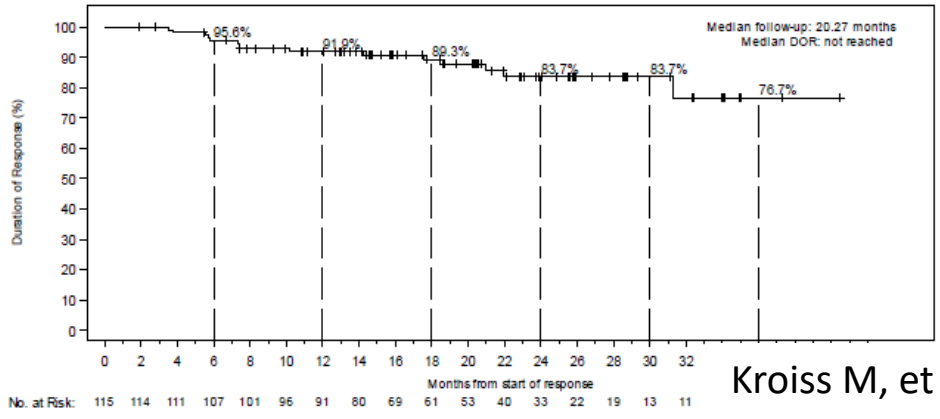
PRIOR CAB AND/OR VAN





CAB/VAN NAÏVE





Most freq TRAEs:

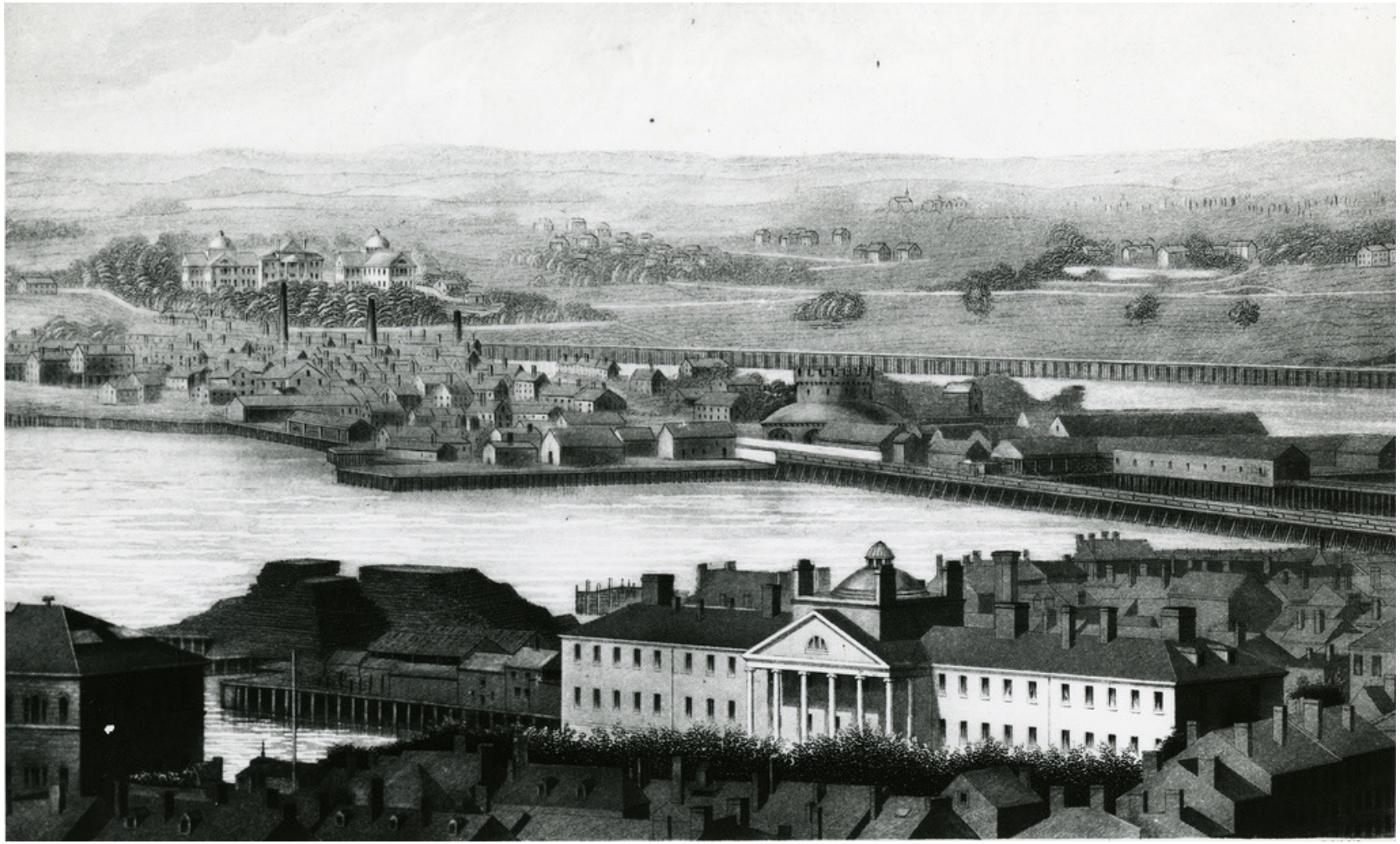
- Xerostomia (36%)
- Fatigue (35%)
- Edema (34%)
- HTN (32%)

Kroiss M, et al. Abstract 1656, *ESMO*, 2022

Future Directions

- Still need to incorporate IO into curative therapy
  - Neo/adjuvant rather than concurrent?
  - In NPC?
- Better biomarker-driven patient selection needed
- Search for more effective IO/IO combination still underway
- Gene-specific therapy in thyroid cancer
  - Acquired resistance has begun to emerge

Thank you



Massachusetts General Hospital