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Olympic hotel,Tehran,IRAN

First line systemic therapy in metastatic/recurrent unresectable H&N scc

Background

- For years many single or combination regimens investigated in this setting such as:
  - Platinum + 5fu
  - Platinum + taxan
  - Cis + pmtx
  - ….

BUT : without OS benefit over cisplatin alone

TARGET THERAPY

Approved in first line…

TAEGET THERAPY

EXTREME TRIAL

442 PTs untreated M/R H/N SCC

R

- CIS or CARBO + 5FU Q 3WEEKS *6
- CIS or CARBO + 5FU **+CETUXIMAB** Q 3WEEKS*6

Maintenance cetuximab

RESULTS:

Better RR OS PFS

M os : 10.1 vs 7.2 m

PFS 5.6 vs 3.3

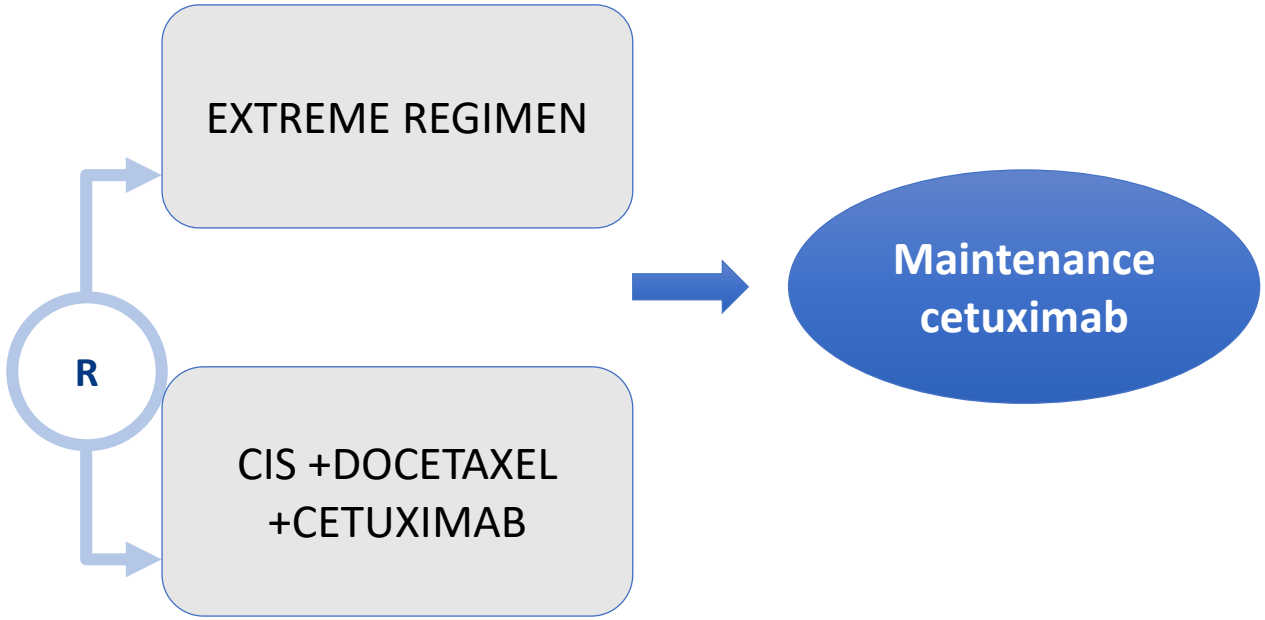
ORR 36 VS 20

Regardless of HPV

TAEGET THERAPY

TPExtreme TRIAL

541 PTs untreated M/R H/N SCC



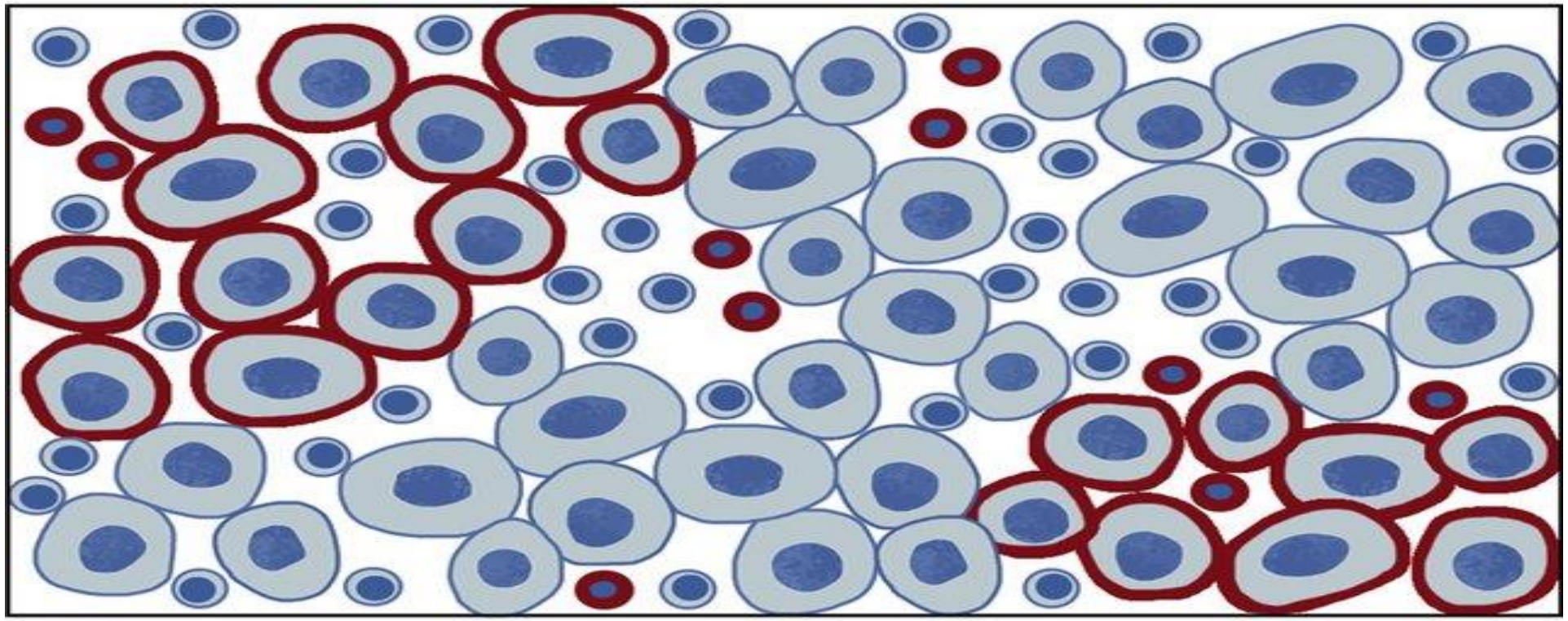
RESULTS:
SIMILLAR OS
LESS G3 TOXICITY

TARGET THERAPY

- ❑Other agents failed to show OS benefit over chemotherapy
- ❑As examples :

- Spectrum : addition of Panitumumab to cis/5fu — better PFS
- EI305 : : addition of Bevacizumab to cis/5fu — same OS

IMMUNOTHERAPY



PD-L1 negative tumor cell

PD-L1 positive tumor cell

PD-L1 negative immune cell

PD-L1 positive immune cell

$$\text{TPS} = \frac{\text{No. PD-L1 positive tumor cells}}{\text{Total No. of viable tumor cells}} \times 100$$

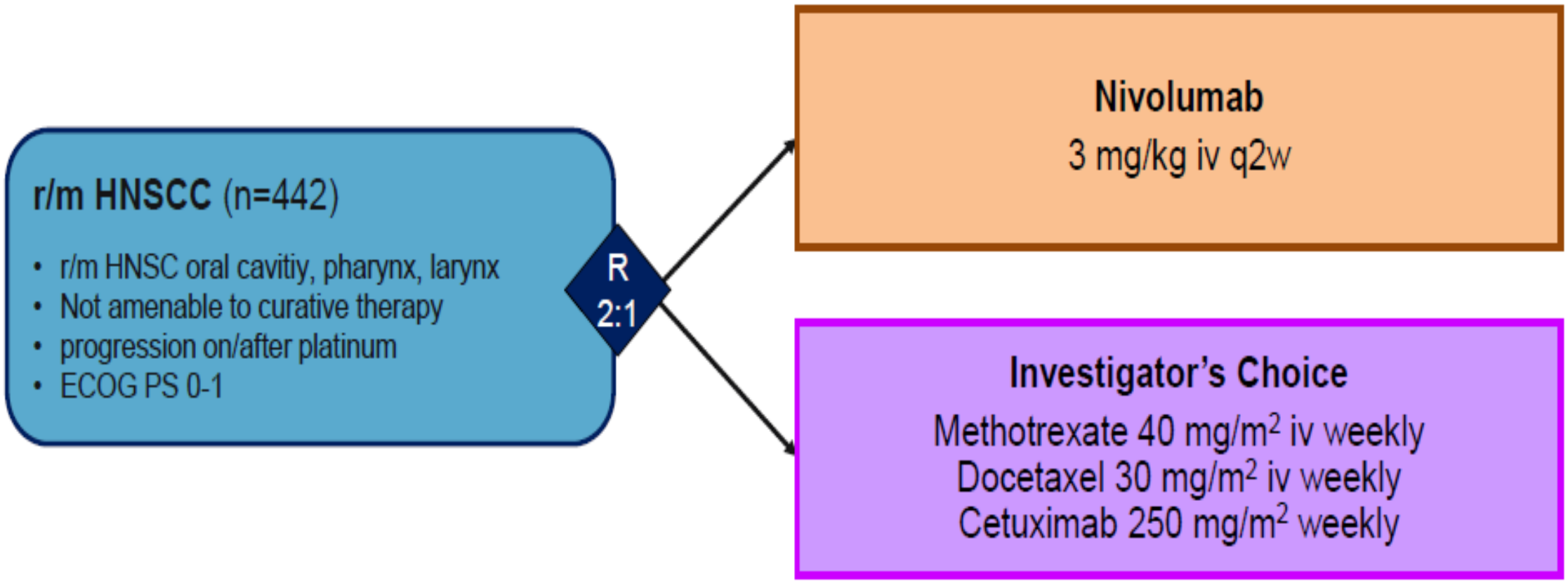
$$\text{CPS} = \frac{\text{No. PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

IMMUNOTHERAPY in 2nd line

r/m HNSCC – 2nd-Line Checkpoint Inhibitors

Trial	EAGLE (Durvalumab)	EAGLE (Durvalumab + Tremelimumab)	CheckMate-141 (Nivolumab)	Keynote-040 (Pembrolizumab
Overall Survival	7.6 vs. 8.3 months	6.5 vs. 8.3 months	7.5 vs. 5.1 months	8.4 vs. 6.9 months
HR	0.88 (0.72-1.08)	1.04 (0.85-1.26)	0.70 (0.51-0.96)	0.8 (0.65-0.98)
p-value	0.20	0.76	0.01	0.0161
ORR	17.9% vs. 17.3%	18.2% vs. 17.3%	13.3% vs. 5.8%	14.6% vs. 10.1%

CheckMate 141 Trial



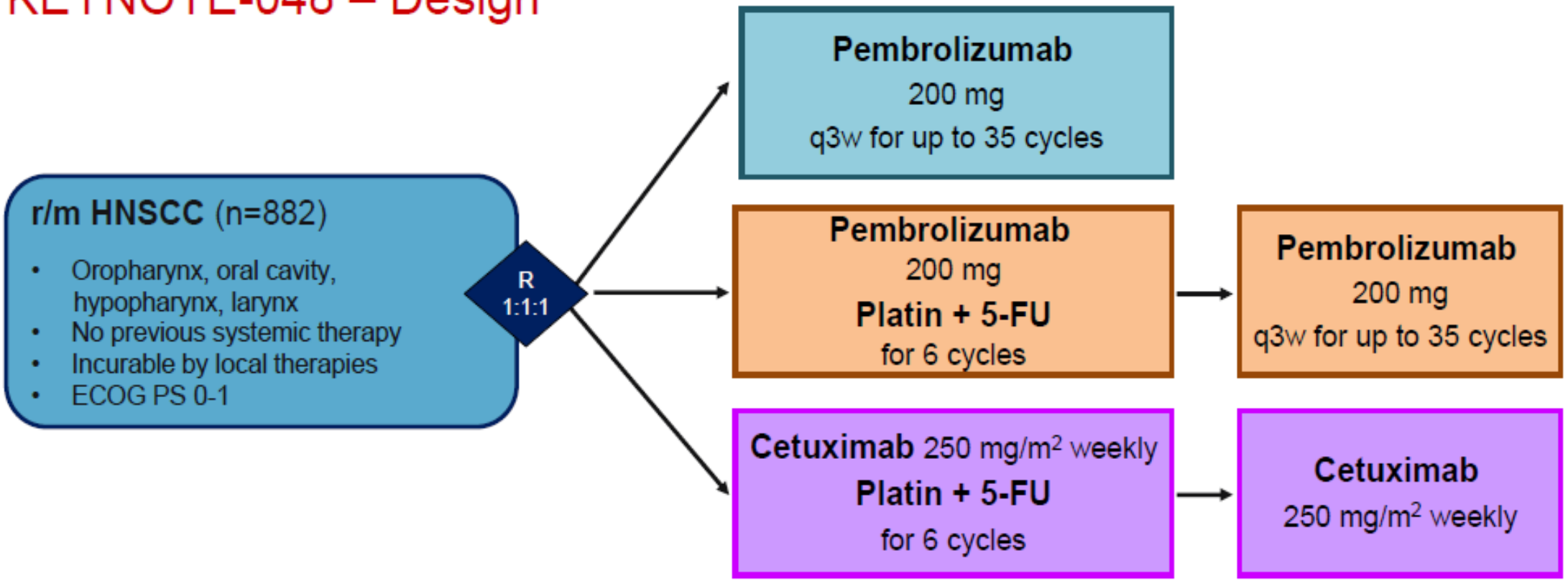
CHECKMATE 141 RESULTS

outcome	NIVO	CONTROL
mOS	**7.7 m**	5.1
1 Y OS	**%34**	19.7
ORR	**%13.3**	5.8

BIOMARKER	HR
PDL1 +	0.55
PDL -	0.89
P 16 +	0.56
P 16 -	0.73
Prior cetuximab	0.52
No prior cetuximab	0.84

IMMUNOTHERAPY in 1st line

KEYNOTE-048 – Design



Primary endpoint: OS, PFS (CPS ≥20%, CPS ≥1%, and total populations)

Secondary endpoints: PFS at 6 and 12 months, ORR, QoL, safety

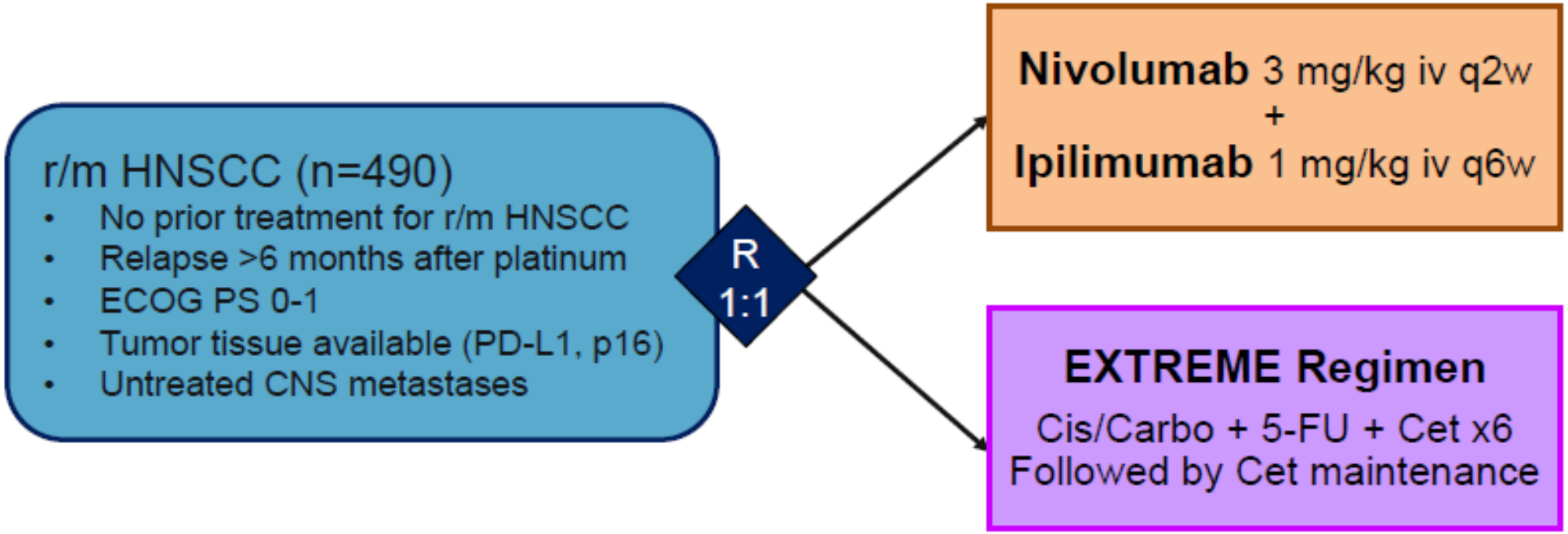
KEYNOTE 048 , median f/u 45 m
PEMBRO + CHEMO VS EXTREME

outcome	Total	20≤CPS	1≤CPS<20	CPS<1
mOS	**SUPERIOR** 13 vs 11 m	**SUPERIOR** 15 vs 11 m	**SUPERIOR** 13 vs 10	SIMILLAR
PFS	SIMILLAR	SIMILLAR	SIMILLAR	SIMILLAR
ORR	SIMILLAR	SIMILLAR	SIMILLAR	SIMILLAR
DOR	**SUPERIOR**			
G3≤TOX	SIMILLAR			

KEYNOTE 048 , median f/u 45 m
PEMBRO VS EXTREME

outcome	Total	20≤CPS	1≤CPS<20	CPS<1
OS	**SUPERIOR** 12 vs 11 m	**SUPERIOR** 15 vs 11 m	SIMILLAR 11 VS 10	Lower not significant 8 VS 11 m
PFS	lower	SIMILLAR	SIMILLAR	lower
ORR	lower	lower	lower	lower
DOR	**SUPERIOR**			
G3≤TOX	**lower**			

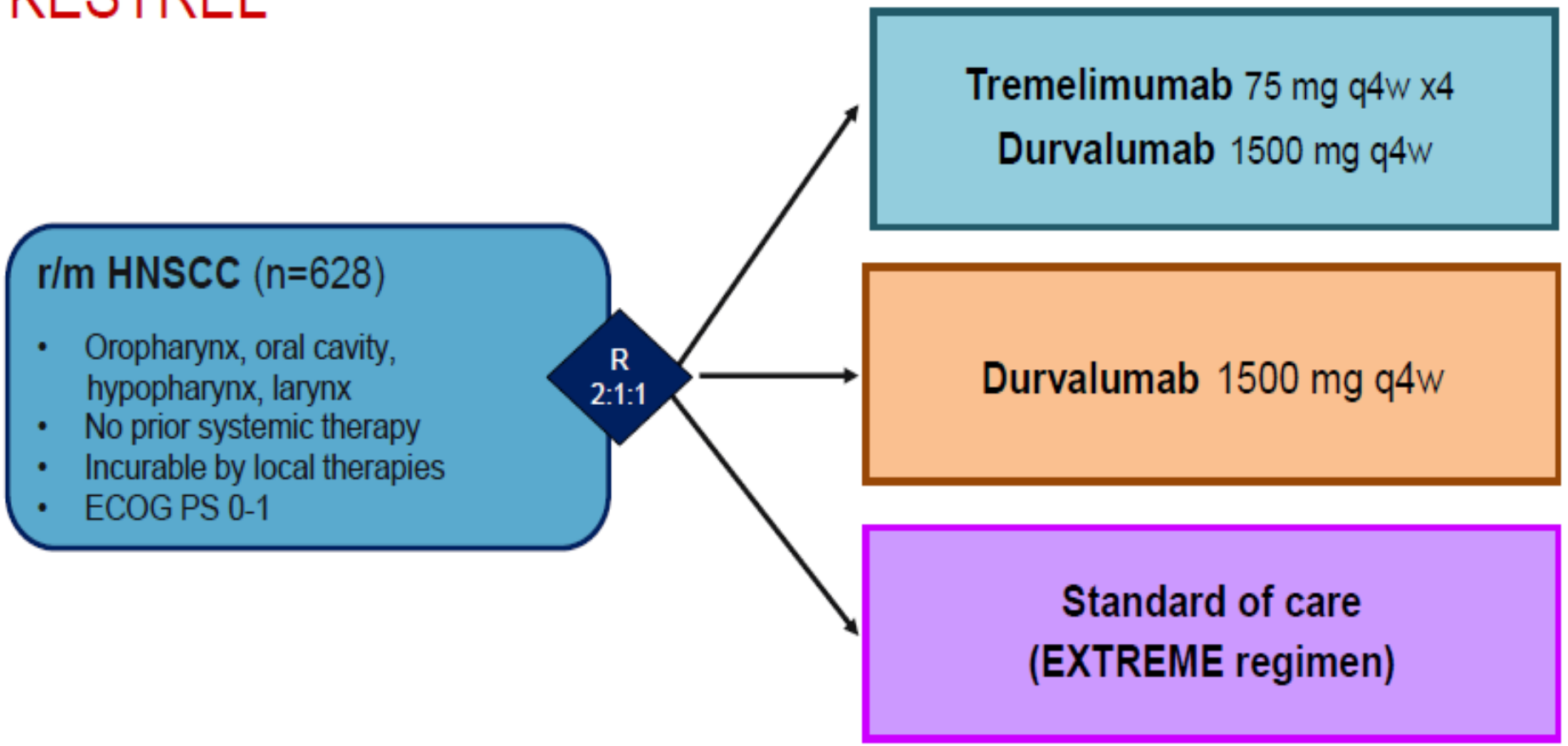
CheckMate 651



Co-Primary endpoints: PFS / OS

Secondary endpoints: ORR, time to symptom deterioration (FHNSI-10)

KESTREL



Primary endpoint: OS, PFS (Durva + Treme vs. SoC)

Secondary endpoints: ORR (Durva + Treme vs. SoC); Durva vs. SoC, Durva + Treme vs. Durva (PD-L1 TPS < 25%)

IMMUNOTHERAPY in 1st line

- Both trials did not met endpoints at first analysis :
- Similar OS (non significant improvement in CPS >)
- Although final results is pending

- **Big question** : negative effect of CTLA 4 INHIBITORS ??
- CHECKMATE 714 will answer :
- Nivo + ipilimumab vs nivo in first and 2th line

Table 1. Trials of approved checkpoint inhibitors for R/M HNSCC

Authors	Study	Setting	Study arm	Control arm	Median OS		Approval
Ferris et al. [5]	CheckMate-141	Platinum-resistant	Nivo	SoC	Nivo: 7.5 months		FDA
					SoC: 5.1 months		EMA
Cohen et al. [4]	KEYNOTE-040	Platinum-resistant	Pembro	SoC	Pembro: 8.4 months		FDA
					SoC: 6.9 months		EMA (TPS ≥ 50%)
Burtness et al. [11]	KEYNOTE-048*	First-line	Pembro	EXTREME	*PD-L1* CPS ≥ 20	*PD-L1* CPS ≥ 1	FDA
					Pembro: 14.9 months	Pembro: 12.3 months	EMA
					EXTREME: 10.8 months	EXTREME: 10.4 months	
			Pembro + CT	EXTREME	*PD-L1* CPS ≥ 20	*PD-L1* CPS ≥ 1	
					Pembro + CT: 14.7 months	Pembro + CT: 13.6 months	
					EXTREME: 11.1 months	EXTREME: 10.6 months	

Treatment approach first line

Progressive/recurrent disease within 6 Ms of platinum based chemo → **Pembrolizumab nivolumab**

NO previous systemic therapy or Progressive/recurrent after 6 Ms

- CPS<1 → **Pembro+chemo (PF OR PT)**
  Extreme regimen
  TPEX regimen
- 1≤CPS<20 → **Pembrolizumab**
  Pembro + chemo
- 20≤CPS → **Pembrolizumab**

For rapidly progressive dis : **Pembro + chemo**

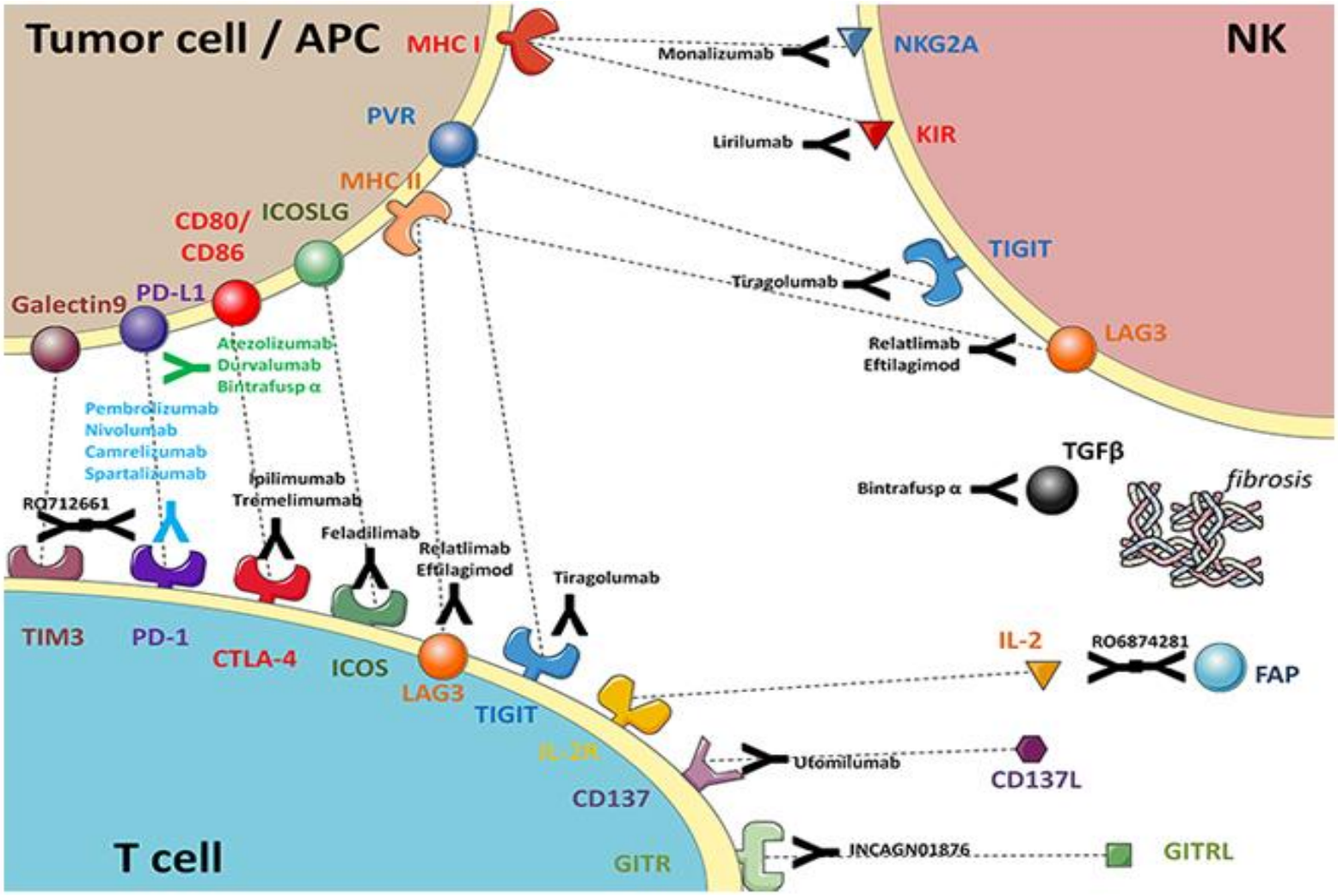
FOR PATIENTS NOT GOOD PS OR INELIGILBL FOR COMBINATION THERAPY : SINGLE AGENT IS PREFFERD OPTION

INVESTIGATIONAL APPROACH and future's potential drugs

I mentioned only some …

TARGET	DRUG	DESIGN	KEY FINDINGS	ONGOING TRIALS
EGFR	**pembro+ cetuximab**	Ph 2, 2th line , platinum res No prior ICI or Cetuximab	mOS 18 m ORR 45 %	
EGFR	**Nivolumab +cetuximab**	Ph 2 , 1st and 2th line Majority received prior ICI or cetuximab	mOS 20 , 11.4 m ORR 36 , 23 % Better RR in HPV – Better OS/RR in CPS +	
EGFR	**Afatinib+ pembro**	Ph 2, 2th line , platinum res	mOS 9 m ORR 41 % RR : regardless of cps	
VEGFR	**Lenvatinib +pembro**	Ph 1 Ph 1 2th line , ICI res	ORR 46 ORR 28	**1st line** : ph 3 RT is ongoing :pembro with or without lenvatinib in cps>1

TARGET	DRUG	DESIGN	KEY FINDINGS	ONGOING TRIALS
VEGFR	**Cabozantinib + pembro**	Ph 2 , **1st line** in CPS >1	1Y OS 68% ORR 45 %	
HRAS	**Tipifarnib**	Ph 2, 2th line	mOS 15 m ORR 55 % **FDA:breakthrogh therapy for HRAS mutant**	**Ph 3 is ongoing** ph 2 with alpelisib
pi3k	**Bupralisib+ paclitaxel**	Ph 2 RT vs placebo in 2th line	OS 10.4 VS 6.5 m	**Ph 3 is ongoing** **Several trials with PI3K inhibitors with immunotherapy is ongoing**
ADCs	**Tisotumab vedotin**	Ph 2 , 2th line after chemo or ICI (approved for cervical cancer in 2th line)	mOS 9.4 m ORR 16 %	


Tumor cell / APC
MHC I
PVR
MHC II
CD80/
CD86
ICOSLG
Galectin9
PD-L1
Atezolizumab
Durvalumab
Bintrafusp α
Pembrolizumab
Nivolumab
Camrelizumab
Spartalizumab
RO712661
Ipilimumab
Tremelimumab
Feladilimab
Relatlimab
Eftilagimod
Tiragolumab
TIM3
PD-1
CTLA-4
ICOS
LAG3
TIGIT
IL-2R
CD137
T cell
GITR
NK
NKG2A
Monalizumab
KIR
Lirilumab
TIGIT
Tiragolumab
LAG3
Relatlimab
Eftilagimod
TGFβ
Bintrafusp α
fibrosis
IL-2
RO6874281
FAP
Utomilumab
CD137L
JNCAGN01876
GITRL

TARGET	DRUG	DESIGN	KEY FINDINGS	ONGOING TRIALS
NKG2A	**Monalizumab+ Cetuximab**	ph 2 in 2th line with or without prior ICI	1Y OS 44% ORR 36% ORR 17 % (prior ICI)	Ph 3 is ongoing vs single cetuximab
LAG3	**Eftilagimod+ pembro**	ph 2 in 2th line	ORR 39 % OS PFS : pending	Ph 3 is ongoing Vs single pembro
TIGIT	**Tiraglumab + atezolizumab**	ph 2 in 2th line	ORR 33 % OS PFS : pending	Ph 3 is ongoing Vs single atezo in 1st line
Vaccines e6 e7	With ICI	Several ph 2 trials	ORR 22-33 Low RR as single agent	Several trials with ICIs is ongoing

Nasopharyngeal carcinoma

Table 2

First-Line Clinical Trials of Anti–PD-1 mAbs in Patients With RM-NPC.

Study	Year	Phase	Treatment	N	ORR, %	Median DoR, months	Median PFS, months (95% CI)		Median OS, months (95% CI)	
JUPITER-02[25,26] (NCT03581786)[a]	2021/2022	3	Toripalimab + GC → Toripalimab	146	79	18.0	21.4 (11.7-NR)	HR, 0.52 (0.37–0.73)	NR (NR-NR)	HR, 0.59[c] (0.37–0.94)
			Placebo + GC → Placebo	143	67	6.0	8.2 (7.0–9.8)		NR (NR-NR)	
CAPTAIN-1st[27] (NCT03707509)	2021	3	Camrelizumab + GC → Camrelizumab	134	87	8.5	10.8 (8.5–13.6)	HR, 0.51 (0.37–0.69)	NR	HR, 0.67[c] (0.41–1.11)
			Placebo + GC → Placebo	129	81	5.6	6.9 (5.9–7.9)		22.6 (19.2-NR)	
RATIONALE 309[28,29] (NCT03924986)[b]	2021/2022	3	Tislelizumab + GC → Tislelizumab	131	70	8.5	9.6 (7.6–11.7)	HR, 0.50 (0.37–0.68)	NR (23.7-NR)	0.60[c] (0.35–1.01)
			Placebo + GC → Placebo	132	55	6.1	7.4 (5.7–7.6)		23.0 (19.8-NR)	

Recurrent, Unresectable, Oligometastatic, or Metastatic Disease (with no surgery or RT option)

Preferred Regimens

First-Line[d]

- Cisplatin/gemcitabine (category 1)[16,17]

Other Recommended Regimens

First-Line[d]

- Combination Therapy
  - Cisplatin/5-FU[18,19]
  - Cisplatin or carboplatin/docetaxel[20] or paclitaxel[18]
  - Carboplatin/cetuximab[21]
  - Gemcitabine/carboplatin[1]
  - Cisplatin/gemcitabine + PD-1 inhibitor (eg, pembrolizumab or nivolumab)[22,23]
- Single Agents
  - Cisplatin[24,25]
  - Carboplatin[26]
  - Paclitaxel[27]
  - Docetaxel[28,29]
  - 5-FU[25]
  - Methotrexate[21,30]
  - Gemcitabine[31]
  - Capecitabine[32]

Subsequent-Line

- Immunotherapy
  - Nivolumab if previously treated, recurrent or metastatic non-keratinizing disease (category 2B)[33,34]
  - Pembrolizumab if previously treated, PD-L1–positive, recurrent or metastatic disease (category 2B)[35]