Systemic Therapy in Advanced, Recurrent &Metastatic Setting HN Cancer

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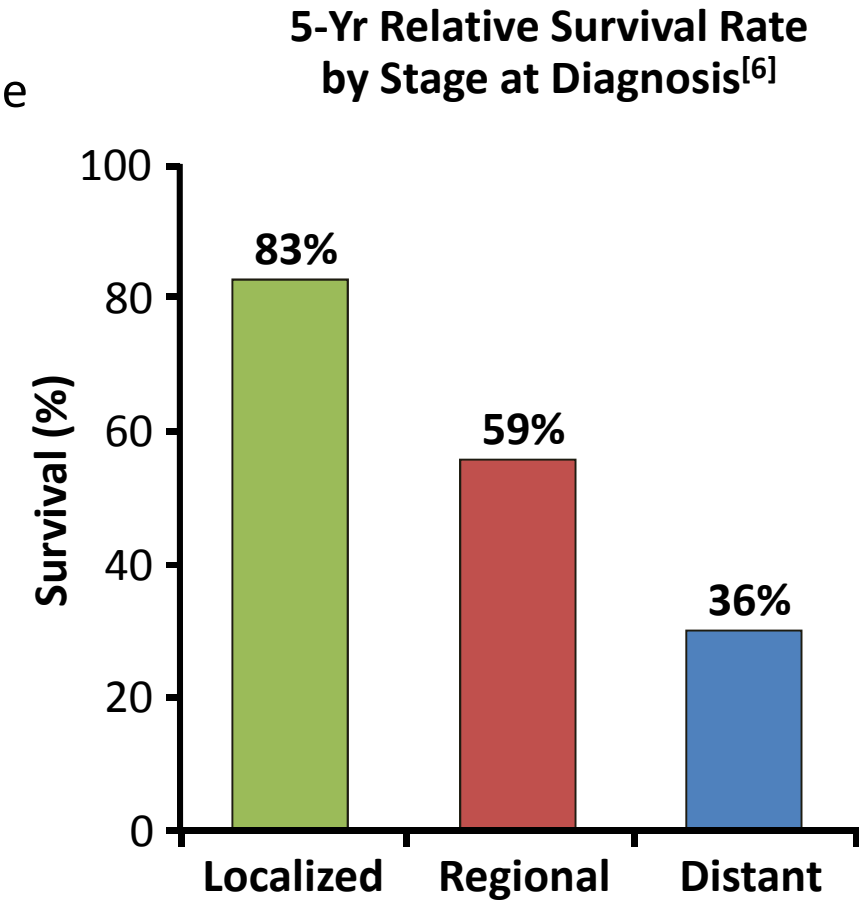
Overview

- Systemic treatment options for HNSCC
  - Cytotoxic chemotherapy for HNSCC
  - Current EGFR therapies
  - Emerging EGFR therapies
- Other emerging targets for HNSCC
- Metronomic therapy

HNSCC: Survival Rates by Stage of Disease

- High cures rates are achieved for localized and loco-regional disease using:
  - Surgery
  - Radiation
  - Chemoradiation
  - ± Induction chemotherapy
- Survival rates for recurrent/ metastatic disease remain very poor
- Better treatment options are necessary



6. SEER. Stat fact sheets: oral cavity and pharynx cancer. 2003-2009.

Treatment Options for Recurrent/Metastatic HNSCC

Recurrent/Metastatic HNSCC: Cytotoxic Agents

- Active cytotoxic agents
  - Cisplatin, carboplatin, 5-FU, taxanes, methotrexate, ifosfamide, gemcitabine (for NPC), bleomycin, others
  - Methotrexate is FDA approved for use with HNSCC but no longer commonly used in the US
- First-line therapy
  - For patients with good PS: historically platinum-based doublet (eg, cisplatin/5-FU or carboplatin/paclitaxel)
    - ORR: 30% to 40%; median OS: 6-9 mos regardless of specific drugs
    - Cetuximab commonly added to current treatment regimens
  - For patients with poor PS: use single agent or cetuximab
- Second-line therapy: taxanes, methotrexate, cetuximab

32. NCCN. Clinical practice guidelines in oncology: head and neck cancers. v.2.2013.

Anti-EGFR Therapy: Cetuximab

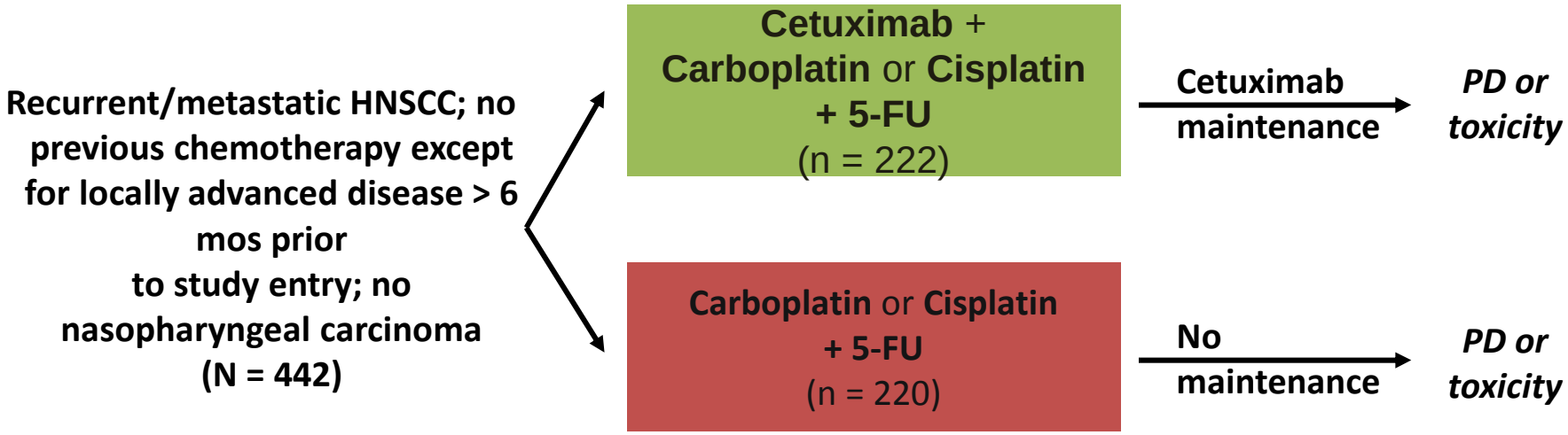
- Cetuximab is a chimeric IgG1 anti-EGFR antibody
  - May also stimulate immune system via ADCC
- Approved for HNSCC as a single agent, with chemotherapy (EXTREME study), with radiation (Bonner study)
- Efficacy data
  - Despite high EGFR expression levels in HNSCC, single-agent response rate is “only” 13% with SD rate of 33%
  - There is currently NO predictive biomarker available.

33. Vermorken JB, et al. J Clin Oncol. 2007;25:2171-2177. 34. Vermorken JB, et al. N Engl J Med. 2008;359:1116-1127. 35. Bonner JA, et al. N Engl J Med. 2006;354:567-578.

EXTREME:

Platinum/5-FU With or Without Cetuximab in Recurrent/Metastatic HNSCC

Randomized phase III trial

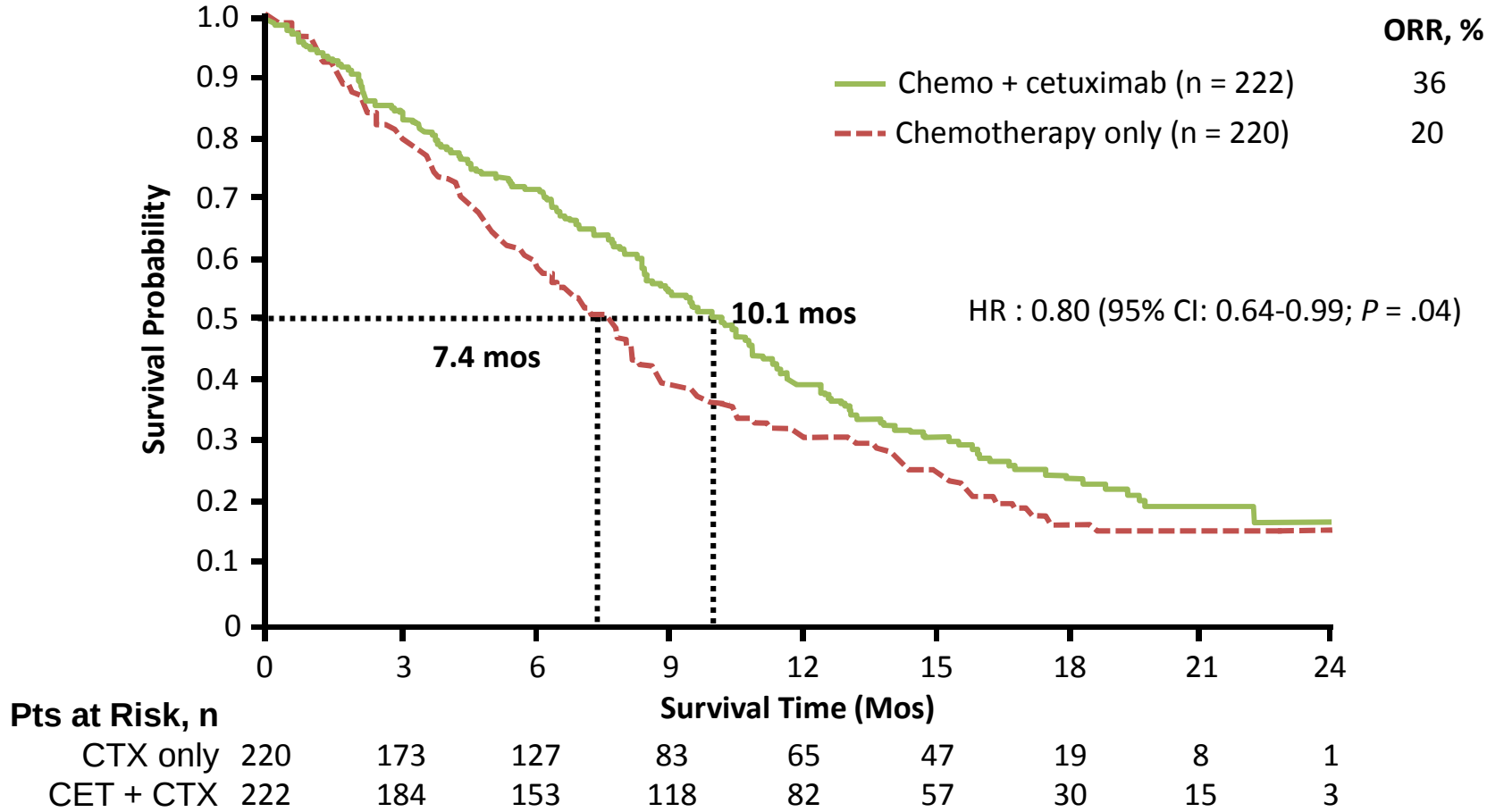


- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DCR, TTF, DoR, QoL, safety

Up to 6 cycles: cetuximab 400 mg/m^2, then 250 mg/m^2/wk until PD or unacceptable toxicity; carboplatin AUC 5 or cisplatin 100 mg/m^2 on Day 1; 5-FU 1000 mg/m^2 on Days 1-4 every 3 wks.

36. Vermorken JB, et al. N Engl J Med. 2008;350:1116-1127.

Cetuximab ± First-line Platinum in Recurrent or Metastatic HNSCC: OS



37. Vermorken JB, et al. N Engl J Med. 2008;350:1116-1127.

Cetuximab ± First-line Platinum in Recurrent or Metastatic HNSCC: Safety

Grade 3/4 AEs in ≥ 5% of Pts, n (%)	Cetuximab + Chemotherapy (n = 219)		Chemotherapy Alone (n = 215)		*P* Value*
	Grade 3/4	Grade 4	Grade 3/4	Grade 4	
Any event	179 (82)	67 (31)	164 (76)	66 (31)	.19
Neutropenia	49 (22)	9 (4)	50 (23)	18 (8)	.91
Anemia	29 (13)	2 (1)	41 (19)	2 (1)	.12
Thrombocytopenia	24 (11)	0	24 (11)	3 (1)	1.00
Leukopenia	19 (9)	4 (2)	19 (9)	5 (2)	1.00
Skin reactions	20 (9)	0	1 (< 1)	0	< .001
Hypokalemia	16 (7)	2 (1)	10 (5)	1 (< 1)	.31
Cardiac events	16 (7)	11 (5)	9 (4)	7 (3)	.22
Vomiting	12 (5)	0	6 (3)	0	.23
Asthenia	11 (5)	1 (< 1)	12 (6)	1 (< 1)	.83
Anorexia	11 (5)	2 (1)	3 (1)	1 (< 1)	.05
Hypomagnesemia	11 (5)	8 (4)	3 (1)	1 (< 1)	.05
Febrile neutropenia	10 (5)	2 (1)	10 (5)	4 (2)	1.00

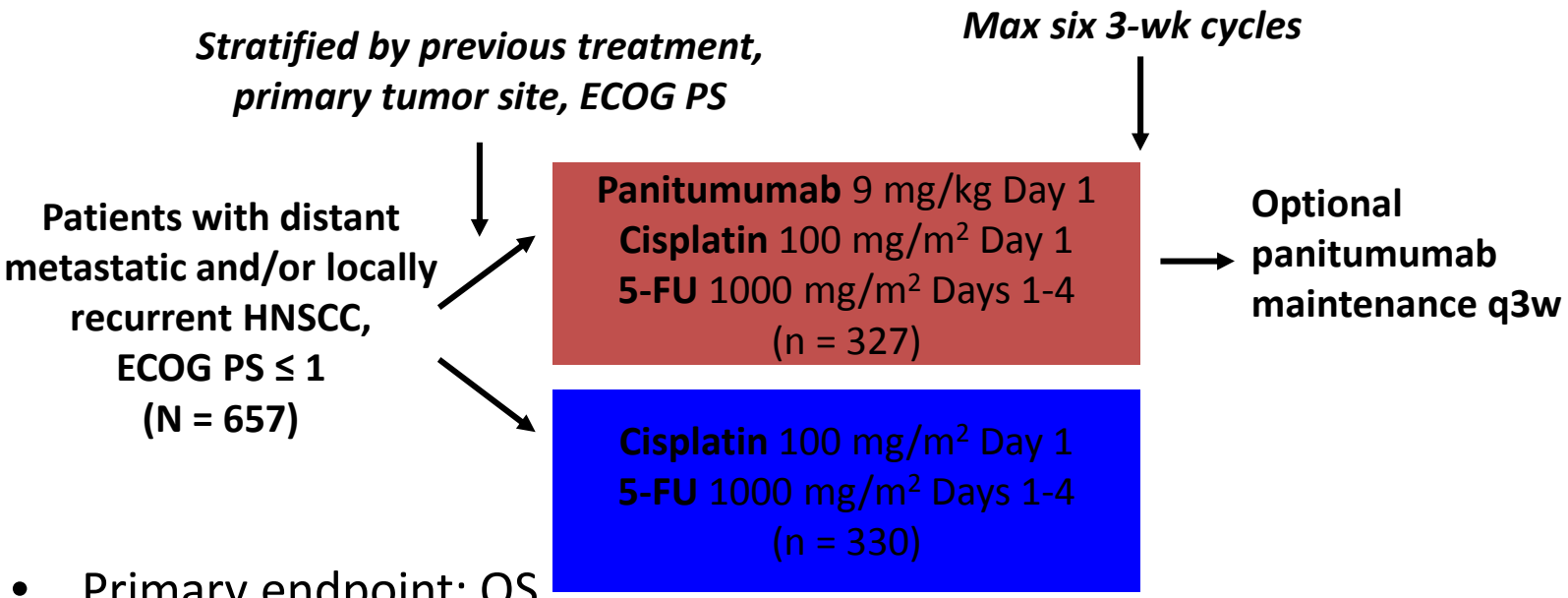
*Comparing Grade 3 and 4 combined.

38. Vermorken JB, et al. N Engl J Med. 2008;350:1116-1127.

SPECTRUM:

Cisplatin + 5-FU ± Panitumumab in Recurrent/Met HNSCC

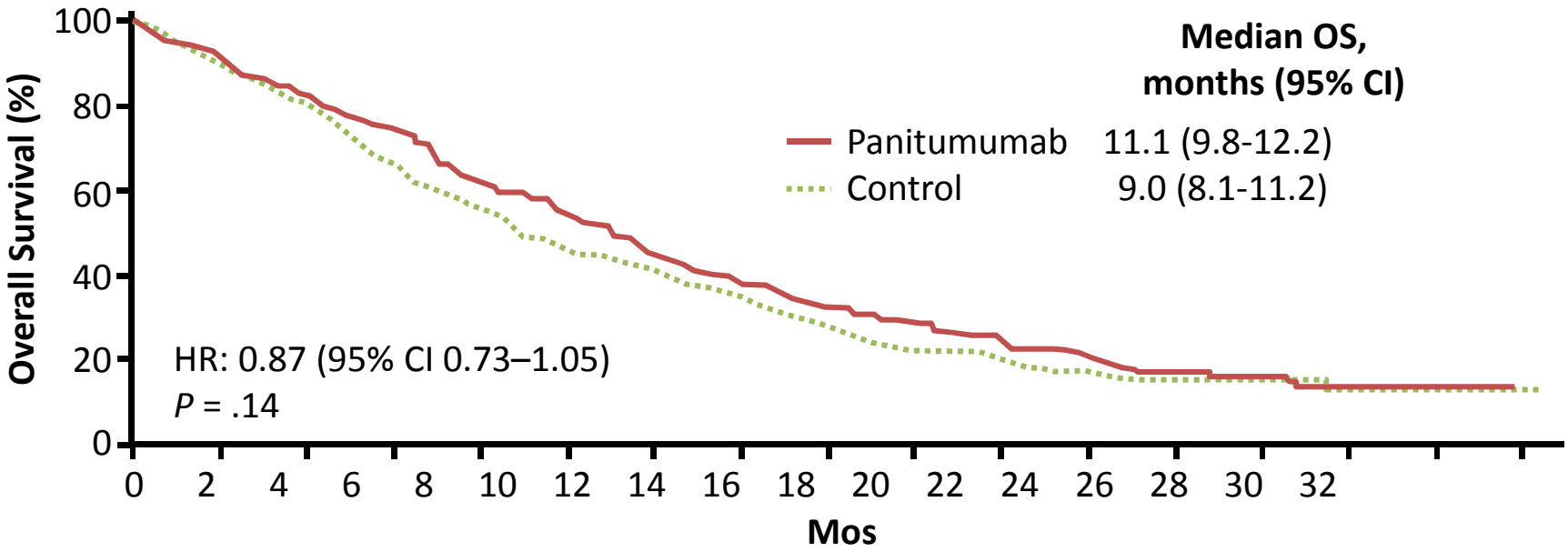
- Open-label, randomized phase III trial



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DOR, TTR, safety

39. Vermorken JB, et al. Lancet Oncol. 2013;14:697-710.

Cisplatin + 5-FU ± Panitumumab in Recurrent/Met HNSCC: OS



- Subgroup analysis in p16-negative patients significant: 11.7 vs 8.6 mos (*P* = .01)
  - Despite questions about p16 IHC cutoff values, hypothesized that EGFR inhibitors may be ineffective in HPV+ tumors
  - Supported by lack of EGFR overexpression/amplification in HPV+ tumors

40. Vermorken JB, et al. Lancet Oncol. 2013;14:697-710.

Additional Anti-EGFR TKIs in HNSCC

- Previously small molecule anti-EGFR TKI have been less effective for HNSCC

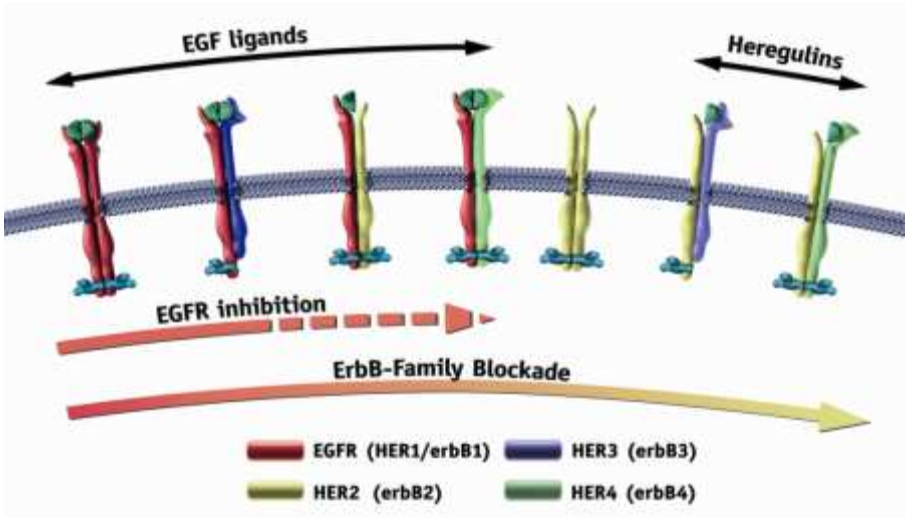
	Cohen 2003[42]	Cohen 2005[43]	Kirby 2006[44]	Soulieres 2004[45]
Agent	Gefitinib 500 mg	Gefitinib 250 mg	Gefitinib 500 mg	Erlotinib 150 mg
Median PFS or TTP, mos	3.4	1.8	2.6	2.2
Median OS, mos	8.1	5.5	4.3	6.0
1-yr OS, %	29.2	19	0	20
ORR, %	10.6	1.4	8	4.3

- Afatinib: an irreversible EGFR/erbB2/erbB4 blocker (pan-HER blockade)
  - Evaluated for HNSCC vs cetuximab

42. Cohen EE, et al. J Clin Oncol. 2003;21:1980-1987. 43. Cohen EE, et al. Clin Cancer Res. 2005;11:8418-8424. 44. Kirby AM, et al. Br J Cancer. 2006;94:631-636. 45. Soulieres D, et al. J Clin Oncol. 2004;22:77-85.

Afatinib: An ErbB Family Blocker

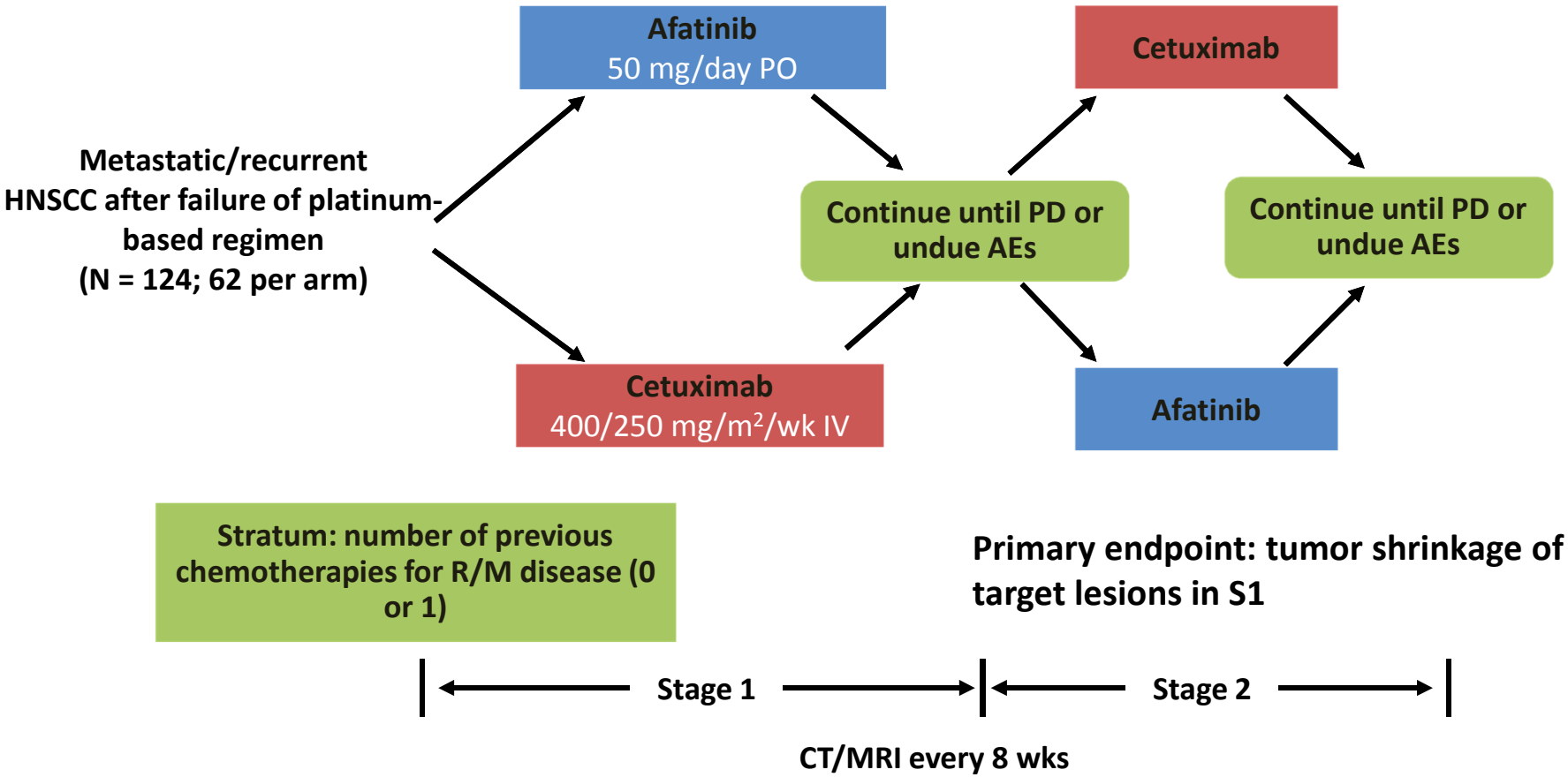
- Has demonstrated preclinical activity on ErbB1 (EGFR/HER1), ErbB2 (HER2), and ErbB4 (HER4)
- Has shown clinical activity in solid tumors (eg, in lung and breast cancer)



In Vitro Molecular Potency	nM
ErbB1	0.5
ErbB2	14
ErbB4	1

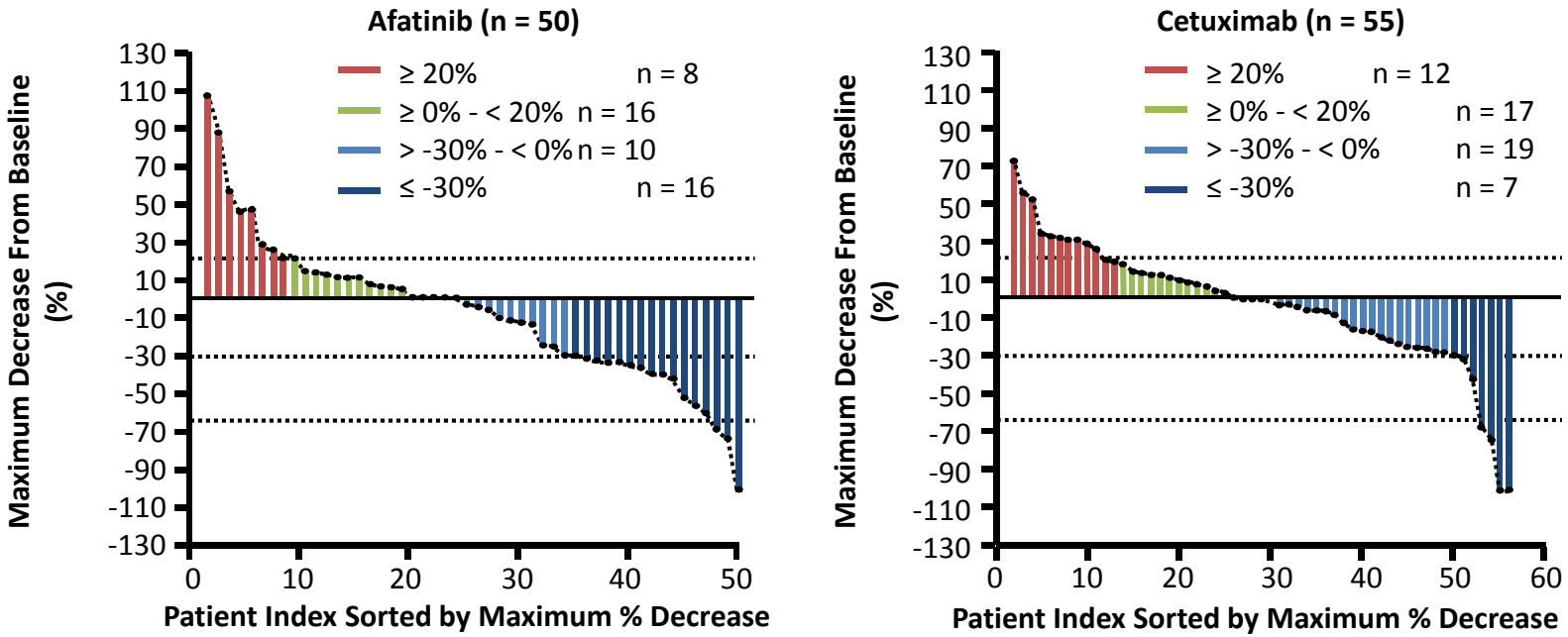
Li D, et al. Oncogene. 2008;27:4702-4711. Stopfer P, et al. Cancer Chemother Pharmacol. 2011;[Epub ahead of print]. Yap TA, et al. J Clin Oncol. 2010;28:3965-3972.

Phase II Study: Afatinib vs Cetuximab in Recurrent/Metastatic HNSCC



48. Seiwert T, et al. Multidisciplinary Head and Neck Cancer Symposium 2012. Abstract LBPV10.

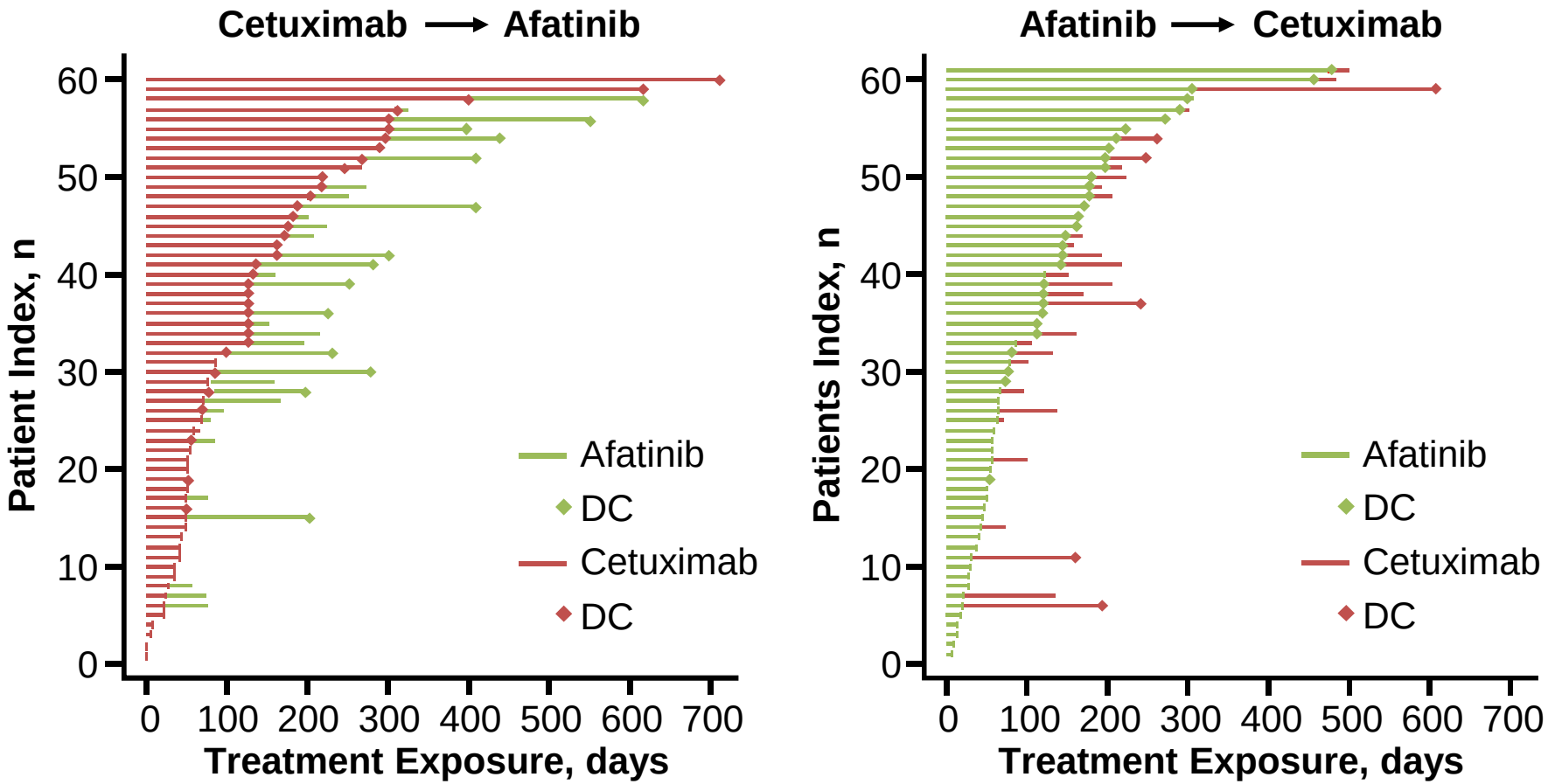
Maximum Tumour Shrinkage in Target Lesions



	Investigator Review		Independent Central Review	
	Afatinib	Cetuximab	Afatinib	Cetuximab
Total randomized, n	62	62	62	62
ORR (CR, PR), n (%)	10 (16.1)	4 (6.5)	5 (8.1)	6 (9.7)
95% CI	8.0-27.7	1.8-15.7	2.7-17.8	3.6-19.9
P value	.09		--	

49. Seiwert T, et al. Multidisciplinary Head and Neck Cancer Symposium 2012. Abstract LBPV10.

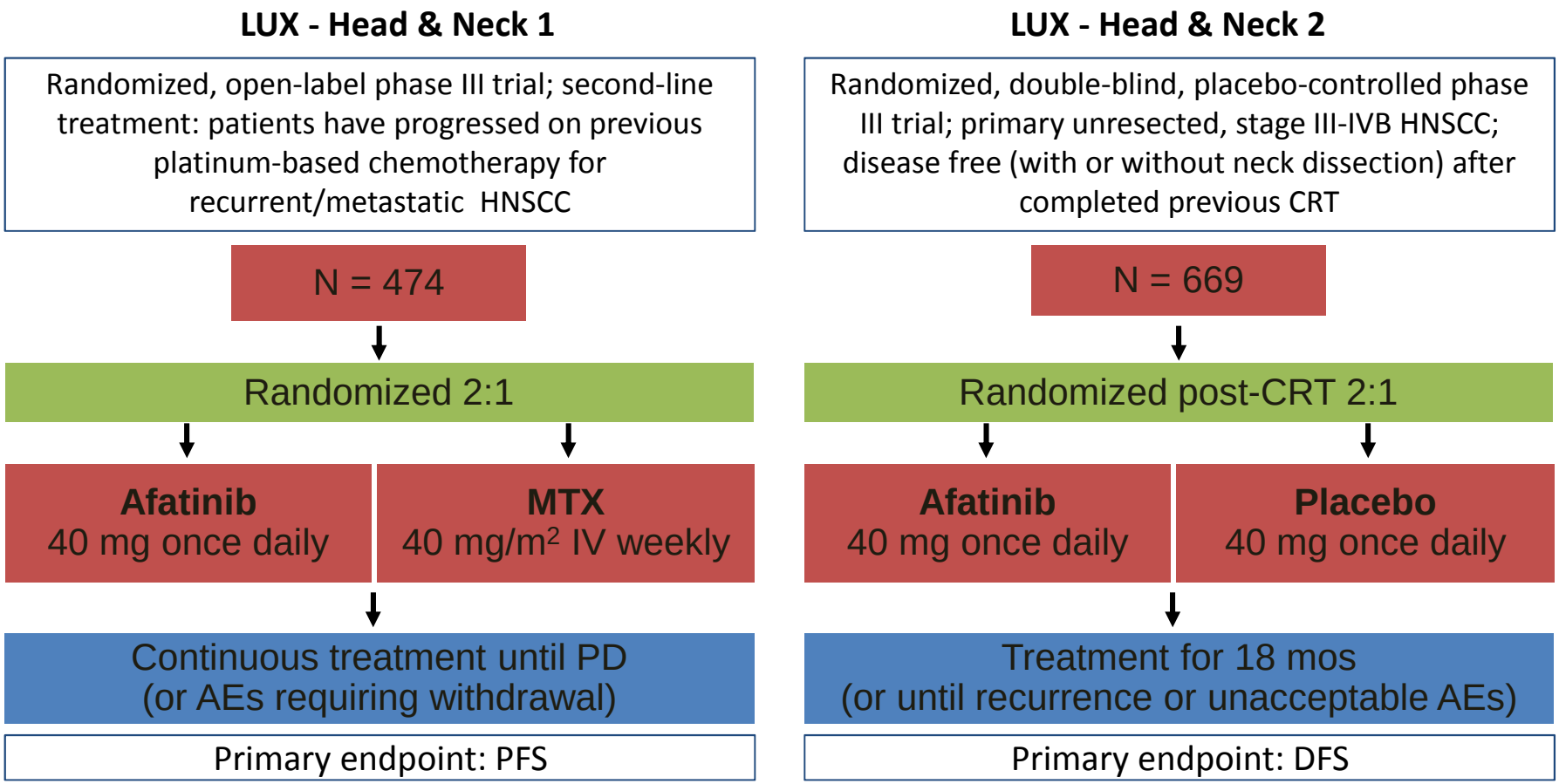
Afatinib vs Cetuximab: Treatment Duration



- Data suggest that afatinib may overcome cetuximab resistance in a fraction of patients; potential lack of cross-resistance

50. Seiwert T, et al. ASCO 2013. Abstract 6001

Afatinib: Ongoing Phase III Studies



51. ClinicalTrials.gov. NCT01345682. 52. ClinicalTrials.gov. NCT01345669.

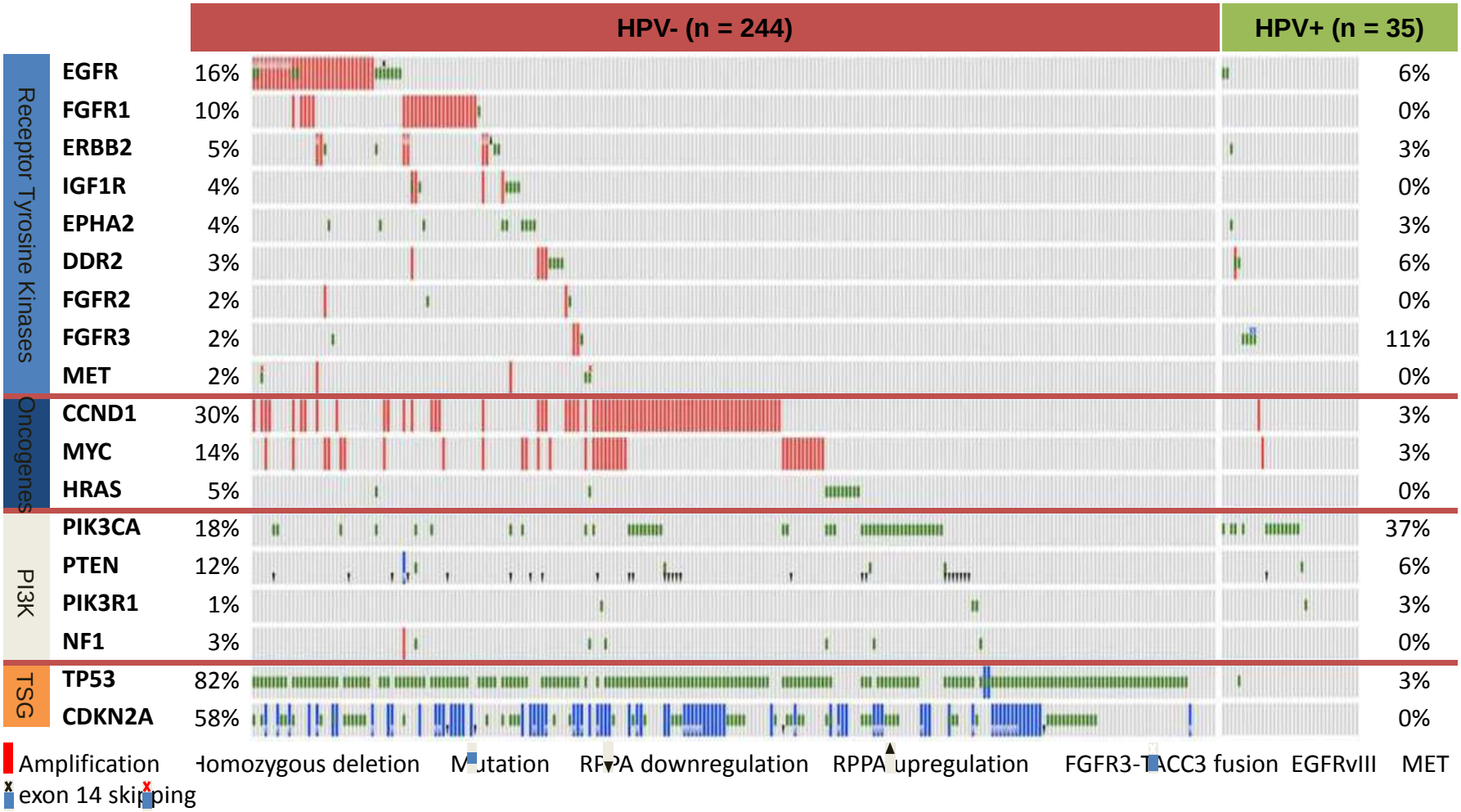
Other EGFR-Targeted Agents in Development

- Dacomitinib: EGFR/erbB2/erB4 irreversible TKI
  - Activity in HNSCC in single phase II trial
- MEHD7945A: EGFR/HER3 antibody
  - Currently in phase II testing for HNSCC vs cetuximab
  - Phase I data: MEHD7945A may overcome cetuximab resistance; heregulin identified as candidate predictive biomarker
- Sym004: polyclonal anti-EGFR antibody mix
  - Activity in HNSCC, potentially effective after cetuximab failure
- ABT-414: EGFR antibody–drug conjugate
  - Phase II testing

53. Abdul Razak AR, et al. Ann Oncol. 2013;24:761-769. 54. ClinicalTrials.gov. NCT01577173.
55. Cervantes-Ruiperez A, et al. ASCO 2012. Abstract 2568. 56. Machiels JP, et al. ASCO 2013. Abstract 6002. 57. ClinicalTrials.gov. NCT01741727.

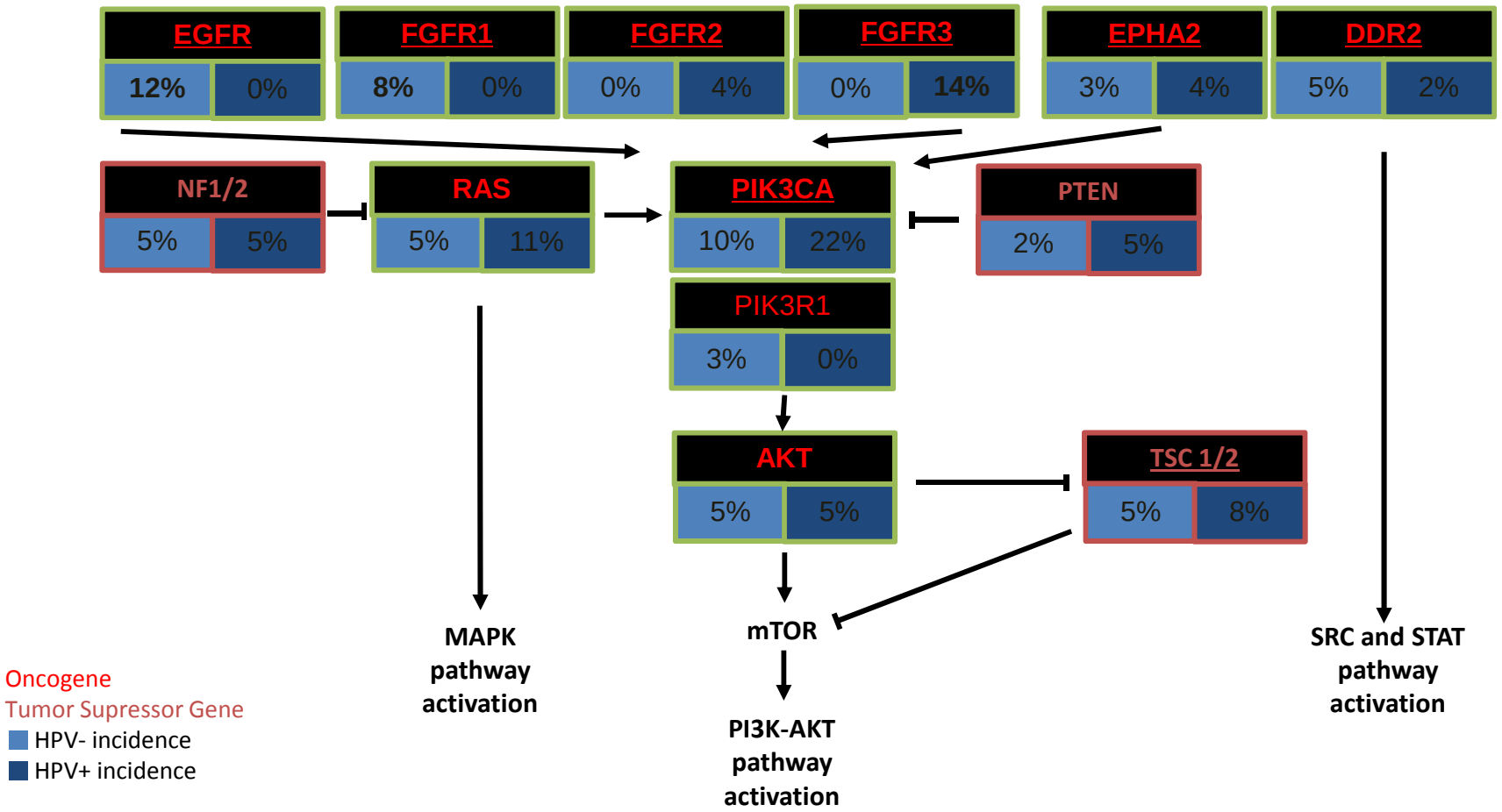
Emerging Novel Targets for HNSCC

The Cancer Genome Atlas (TCGA): Candidate Therapeutic Targets



58. Hayes DN, et al. ASCO 2013 Clinical Science Symposium. Abstract 6009.

Targetable Genetic Changes in HNSCC



60. Keck MK, et al. ASCO 2013. Abstract 6010.

Drugs in Development for HNSCC

- PI3K pathway
  - BKM120 + cetuximab (phase II)
  - BYL719 + cetuximab (phase II)
  - Temsirolimus + cetuximab (phase II)
  - Rigosertib + cetuximab (phase II)
  - GDC-0980 (phase I HNSCC expansion cohort)
- MET pathway
  - Tivantinib + cetuximab (phase II)
  - Ficlatuzumab + cetuximab (phase II)
- EGFR/HER3 pathway
  - Afatinib + cetuximab ± paclitaxel (phase II)
  - LJM716 (phase I)
- PD-1/PD-L1 immune checkpoints
  - MK3475 (phase I/II)
  - Expansion cohort of other PD-1/ PD-L1 agents
- FGFR pathway
  - BGJ398 (phase II)
- CDK4/6–cell cycle pathway
  - Palbociclib (phase I)
  - LEE011 (phase I)

METRONOMIC CHEMOTHERAPY

- Frequent administration
- Low doses ($1/10^{th}$–$1/3^{rd}$ of the maximum tolerated dose [MTD]) of drugs
- Shorter intervals without interruption.

METRONOMIC CHEMOTHERAPY

- MC exerts its anti-cancer activity-

- Inhibiting tumor angiogenesis,
- Stimulating anticancer immune response and
- Stimulating tumor dormancy
- Immunomodulatory effects

Metronomic chemotherapy clinical trials in HNSCC patients

Author	Year	Study design	Patients (n)	Protocol (n patients)	Results
Patil et al.	2015	phase II	110	celecoxib + methotrexate (57); cisplatinum (53)	OS 101 vs 66 days; PFS 249 vs 152 days
Pai et al.	2013	retrospective	64	celecoxib + methotrexate (32); no MC (32)	2-year DFS 94.6 % vs 75.4 %
Penel et al.	2010	randomised	88	cyclophosphamide (44); megestrol acetate (44)	2-month PFS 20.5 % vs 9 %; median OS 195 vs 144 days

Conclusions

- HNSCC is the 6th most common malignancy worldwide, and treatment options remain an unmet needs for patients with this disease.
- EGFR has been shown to be effect target for treatment; additional EGFR targeted agents in development.
- Evolving understanding of genetic profiling in patients with HNSCC may allow for development of additional targeted therapy.
  - ***Promising new targets include***: PI3K, FGFR, CCND1, PD1/PD-L1
  - MC is a practical option

THANKS