A Multicenter Phase Ⅱ Trial of Docetaxel, Cisplatin and Cetuximab (TPE) Followed by Cetuximab with Concurrent Radiotherapy in Patients with Local Advanced Squamous Cell Carcinoma of the Head and Neck (ECRIPS study)

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Background

Current Clinical Questions

- Induction chemotherapy followed by chemo-radiotherapy is a promising treatment option for locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN).

- Docetaxel, Cisplatin, and 5-FU (TPF) is the standard regimen as an induction chemotherapy

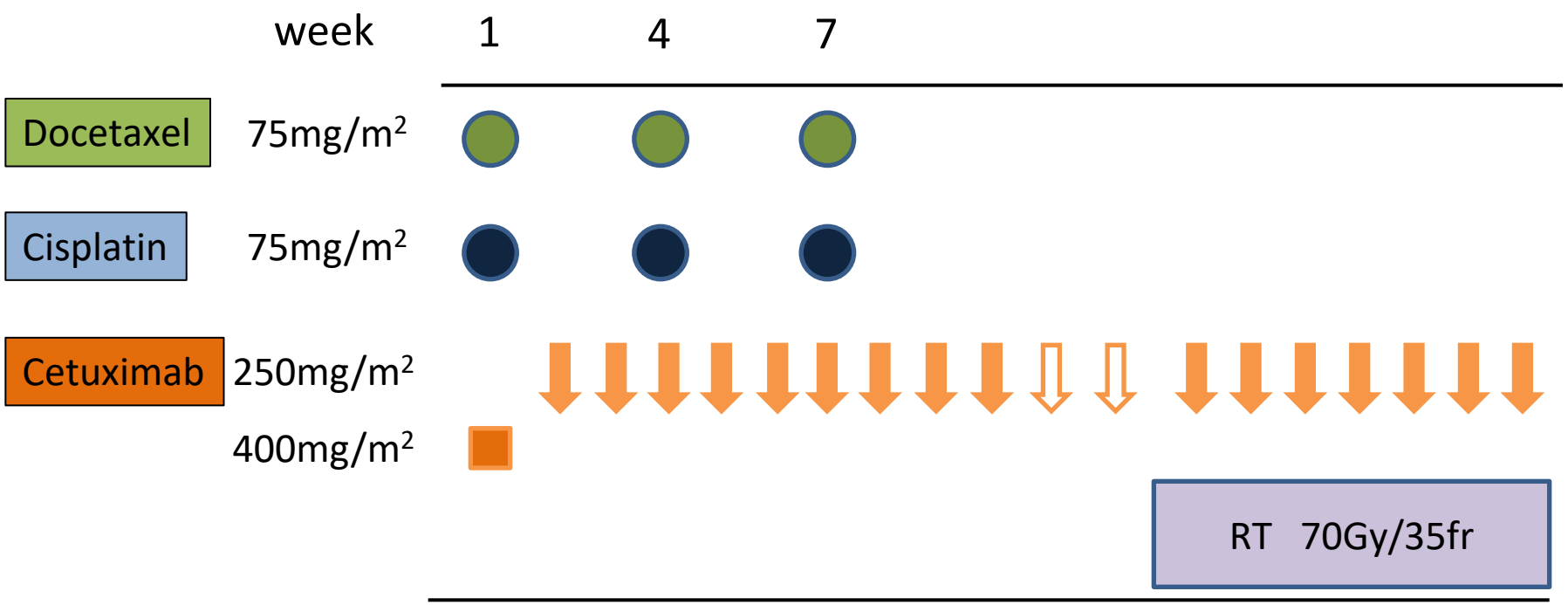
- On the other hand, TPF followed by high-dose Cisplatin with radiotherapy is currently not recommended due to toxicity concerns.

- Since TPF is toxic, adding cetuximab to TP might be a better alternative as an induction chemotherapy and cetuximab concurrent with radiotherapy might be a better partner after strong induction chemotherapy.

The aim of this Phase II Study

To assess the feasibility of docetaxel, cisplatin, and cetuximab (TPE) followed by cetuximab concurrent with radiotherapy for LA-SCCHN.

Treatment schedule



Eligibility Criteria

- Pathologically Proven SCC of oropharynx, hypopharynx and larynx
- Stage III-IV (TNM 7th edition)
- Locally advanced resectable disease, including N0-N2b
- Age: 20-75 years old
- PS 0-1
- Adequate organ function
- Written informed consent

Endpoints and Statistical analysis

Primary Endpoint: Treatment Compliance

Expected and threshold values for exact binomial test were 65% and 40% and a total of 50+5 was needed with a power of 90% and one-sided significance level of 2.5%

Definition of completion of treatment

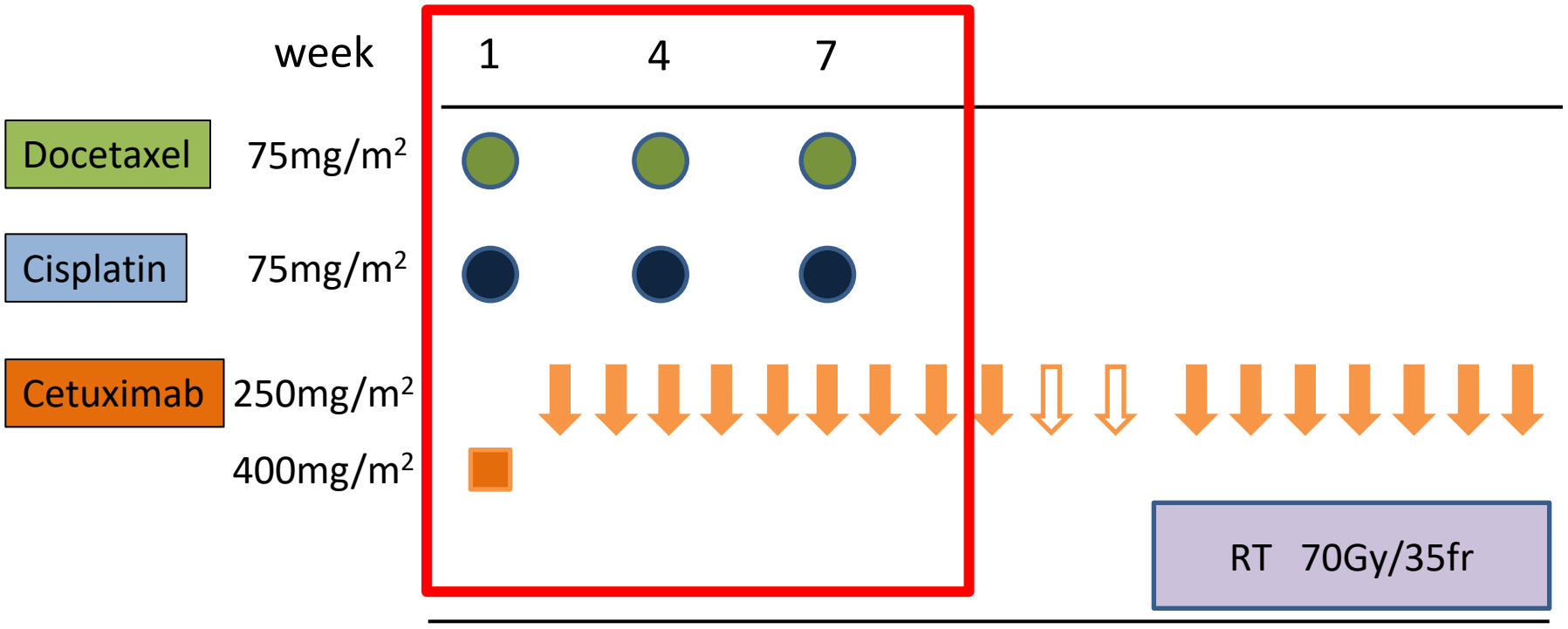
1. Induction chemotherapy (≥ 2 course)
2. The interval between last ICT and start of RT(<6weeks)
3. Full dose irradiation within 70days
4. Cetuximab administration (≥ 12 times)

Patient Characteristics(n=54)

Age (Range)		58（35-72）
Gender	Male / Female	49 / 5
PS	0 / 1	42 / 12
Primary site	Oropharynx	19
	(P16+)	14 (73.7%)
	Hypopharynx	28
	Larynx	7

One case was excluded from full analysis set
because it was found out not to meet eligibility criteria after registration

Induction phase



Induction phase

Treatment Compliance		Relative Dose Intensity	
3 courses	44 (81.5%)	Docetaxel	0.90 (0.86-0.94)
Full dose	23 (42.6%)	CDDP	0.84 (0.80-0.88)
2 courses	6 (10.2%)		
1 courses	4 (7.4%)		

The reasons of treatment discontinuation

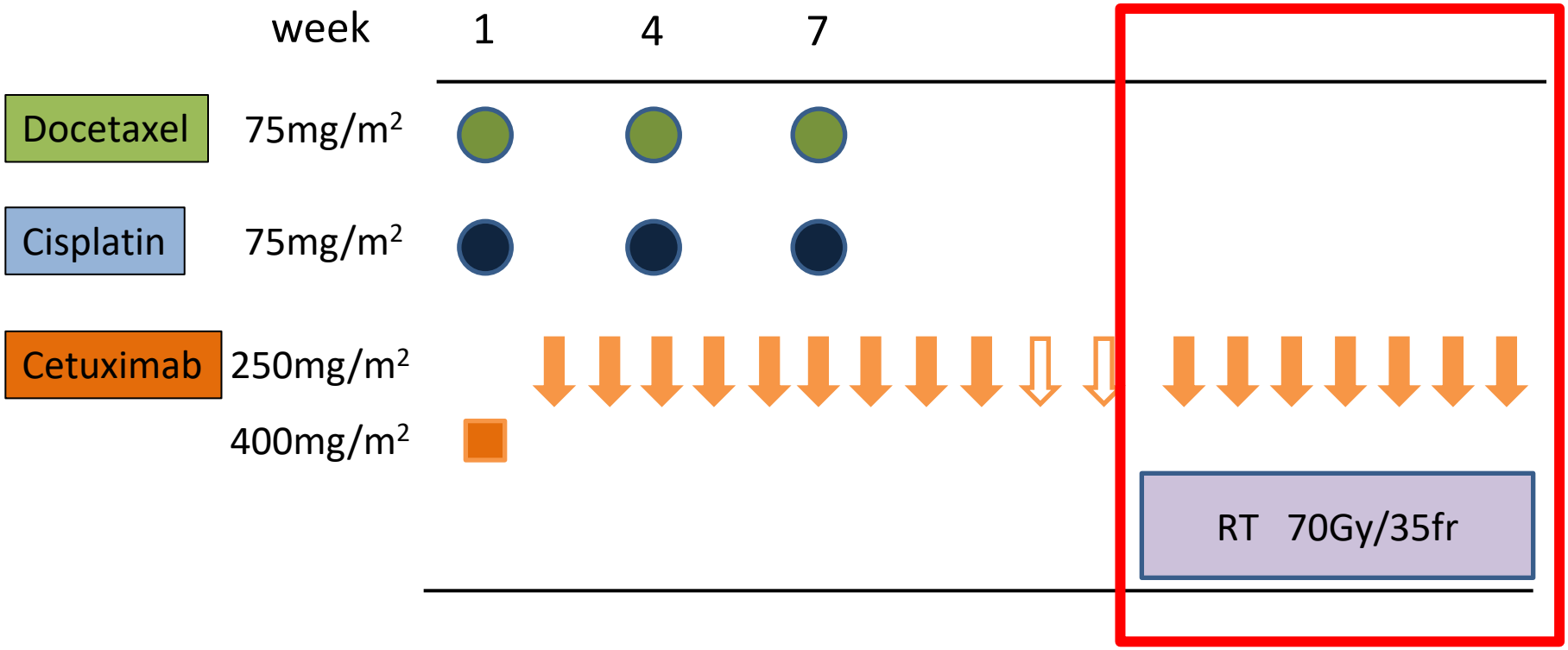
Toxicities 7 (allergy 4, infusion reaction 2, sepsis 1), disease progression 2, other reasons 1 (duodenal ulcer 1)

Toxicities at induction phase (N=54)

	Grade（CTCAE ver.4.0)				
	1	2	3	4	3-4（%）
Neutropenia	0	2	15	35	93
Platelet	25	4	0	0	0
Anemia	36	11	4	1	9
Nausea	5	1	0	0	0
Anorexia	17	18	4	0	7
Mucositis	15	11	3	0	6
Skin Rush	24	21	2	0	4
Infusion reaction	0	4	2	1	6
Allergy	0	2	4	1	9
Febrile neutropenia*	0	0	20	1	39

*ABx and G-CSF were allowed after protocol amendment, due to high rate of FN.

Radiotherapy phase



Radiotherapy phase

Patients No. of start irradiation	**44 (44/54 81.5%)**
The rate of full dose irradiation	41/44 (93.2%)
Median RT dose (range)	70 (66-70) Gy
Median RT duration (range)	51 (45-60) days

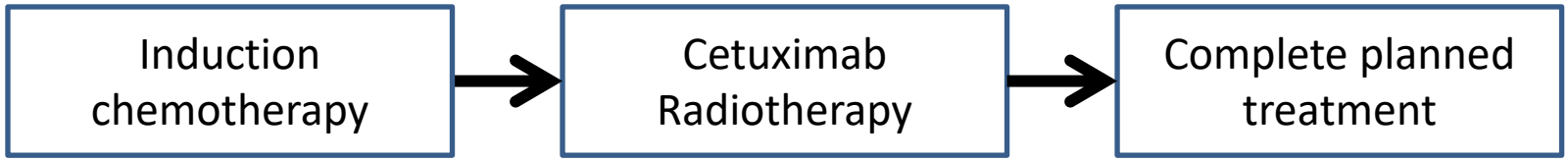
The reasons of treatment discontinuation

protocol deviation 1, local infection 1, sepsis 1

Toxicities at radiotherapy phase (N=44)

	Grade（CTCAE ver.4.0)				
	1	2	3	4	3-4（%）
Neutropenia	7	2	0	0	0
Platelet	10	0	0	0	0
Anemia	36	11	3	0	0
Nausea	5	1	0	0	0
Anorexia	15	11	6	0	14
Mucositis	2	22	20	0	45
Skin Rush	22	16	2	0	5
Infusion reaction	0	0	0	0	0
Allergy	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0

Treatment compliance (Primary Endpoint)



1. Induction chemotherapy (≥ 2 course)

   92.6 %

2. The interval between last ICT and start of RT(<6weeks)

   81.5%

3. Full dose irradiation within 70days

   75.9%

4. Cetuximab administration (≥ 12 times)

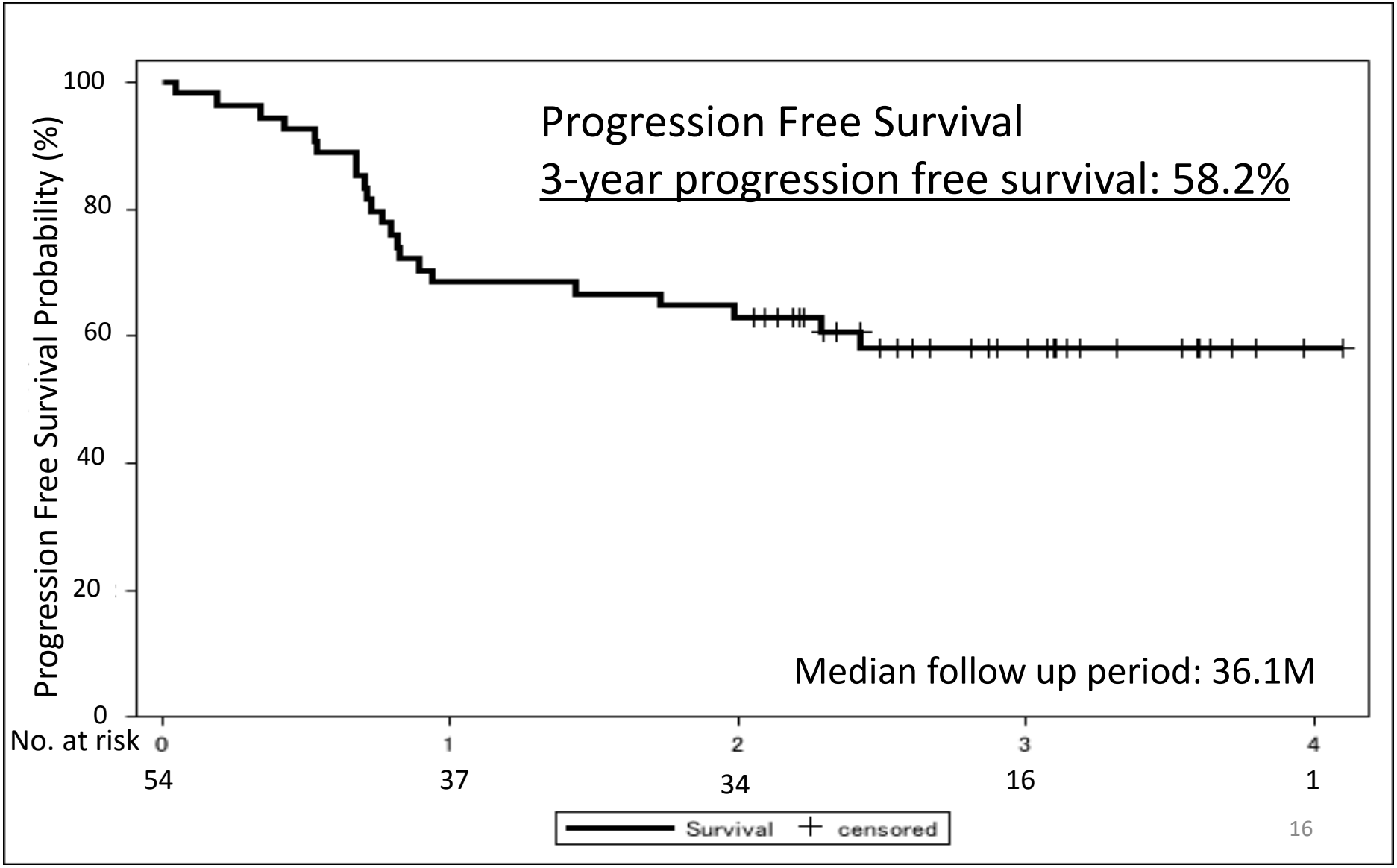
   80.0 %

Total treatment Compliance(all satisfied): 75.9% (95%CI: 62.4-86.5%)

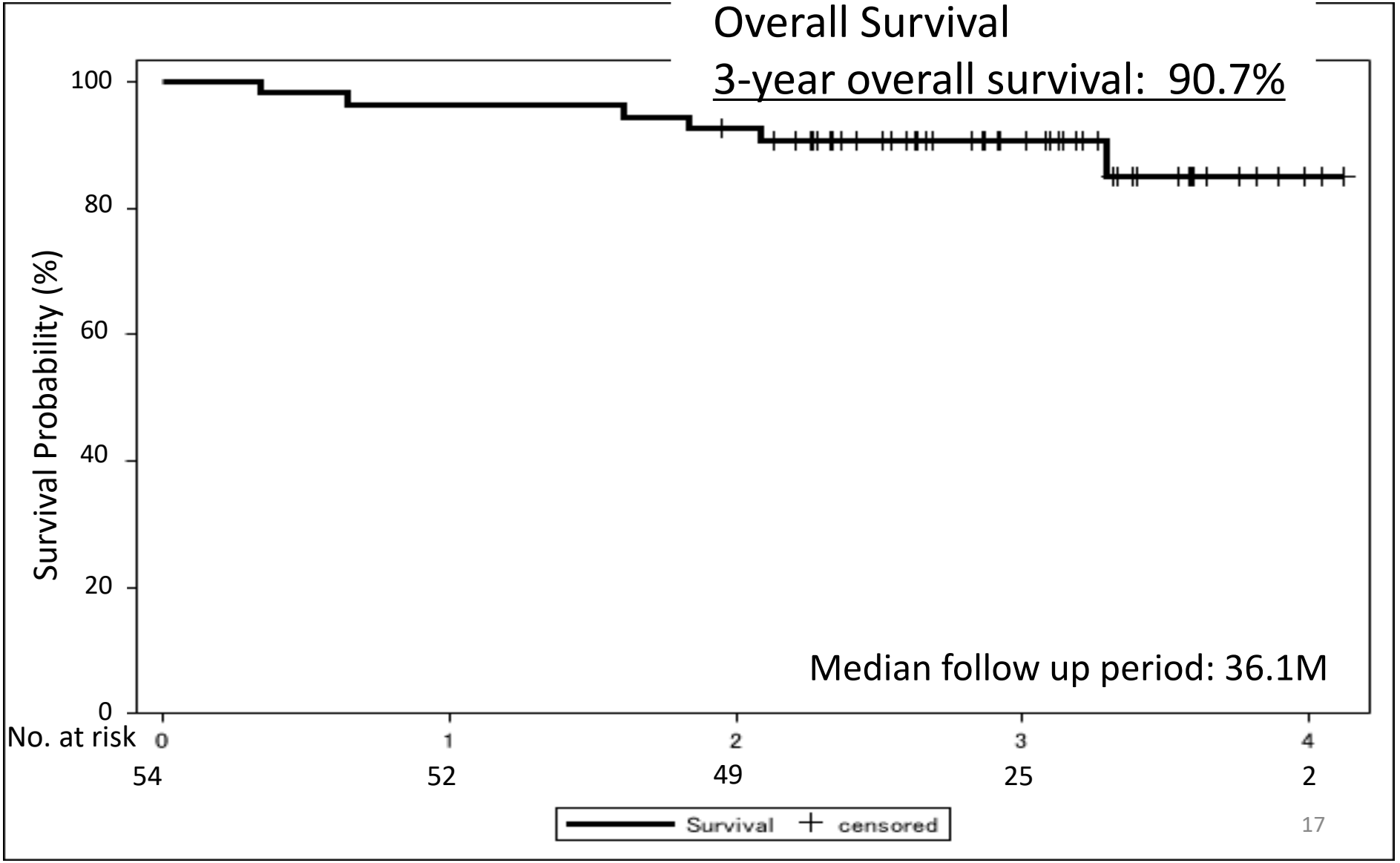
Response rate (RR)

	Induction phase		Radiotherapy phase	
CR	9	16.7%	26	48.1%
PR	30	55.6%	15	27.8%
SD	5	9.3%	0	0%
PD	1	1.9%	1	1.9%
NE	9	16.7%	12	22.2%
RR		72.3%		75.9%

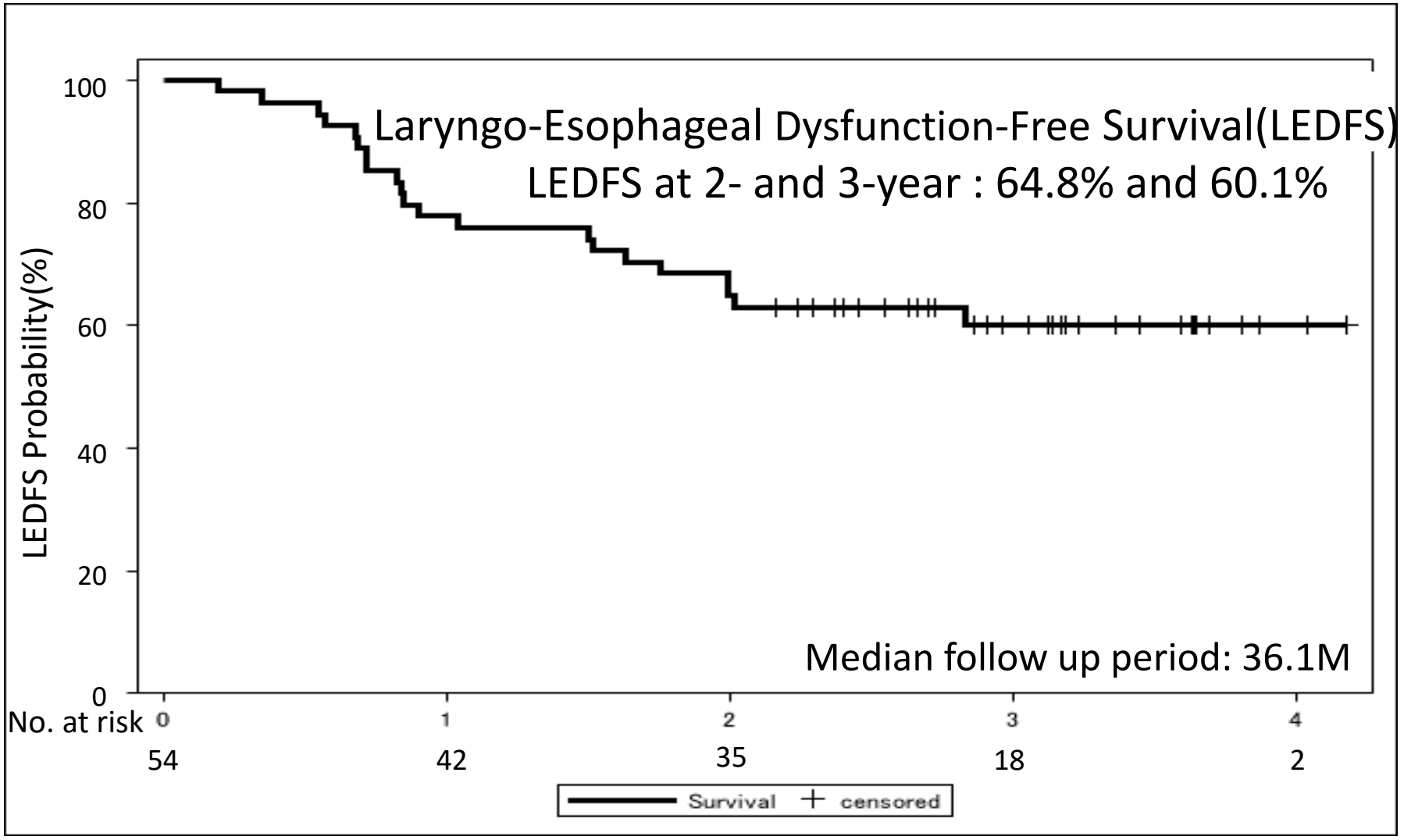
PFS


Progression Free Survival
3-year progression free survival: 58.2%
Median follow up period: 36.1M
Progression Free Survival Probability (%)
100
80
60
40
20
0
No. at risk
0
1
2
3
4
54
37
34
16
1
Survival
censored

OS


Overall Survival
3-year overall survival: 90.7%
Median follow up period: 36.1M
Survival Probability (%)
100
80
60
40
20
0
No. at risk
0
1
2
3
4
54
52
49
25
2
Survival
censored

LEDFS


Laryngo-Esophageal Dysfunction-Free Survival(LEDFS)
LEDFS at 2- and 3-year : 64.8% and 60.1%
Median follow up period: 36.1M
LEDFS Probability(%)
100
80
60
40
20
0
No. at risk
0
1
2
3
4
54
42
35
18
2
Survival
censored

Summary and Conclusions

- ✓ Induction TPE followed by cetuximab concurrent with radiotherapy was feasible with a promising efficacy.

- ✓ A phase III study to evaluate this treatment strategy is warranted.

TPE regimen was manageable at least with careful supportive treatment because of it's adverse events.
All physicians are asked to do the following.

We should---

- Focus on prevention and handling against febrile neutropenia.

- Use cetuximab and docetaxel under careful observation prepare for its incidence of allergy and infusion reaction.

- Manage this regimen by multi-disciplinary team approach.

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