Poziotinib for HER2 exon 20 insertion mutation-positive non-small cell lung cancer (NSCLC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

FDA Introductory Comments

September 22, 2022

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Applicant's proposed indication

Poziotinib is a **kinase inhibitor** indicated for the treatment of patients with **previously treated** locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring **HER2 exon 20 insertion mutations**.

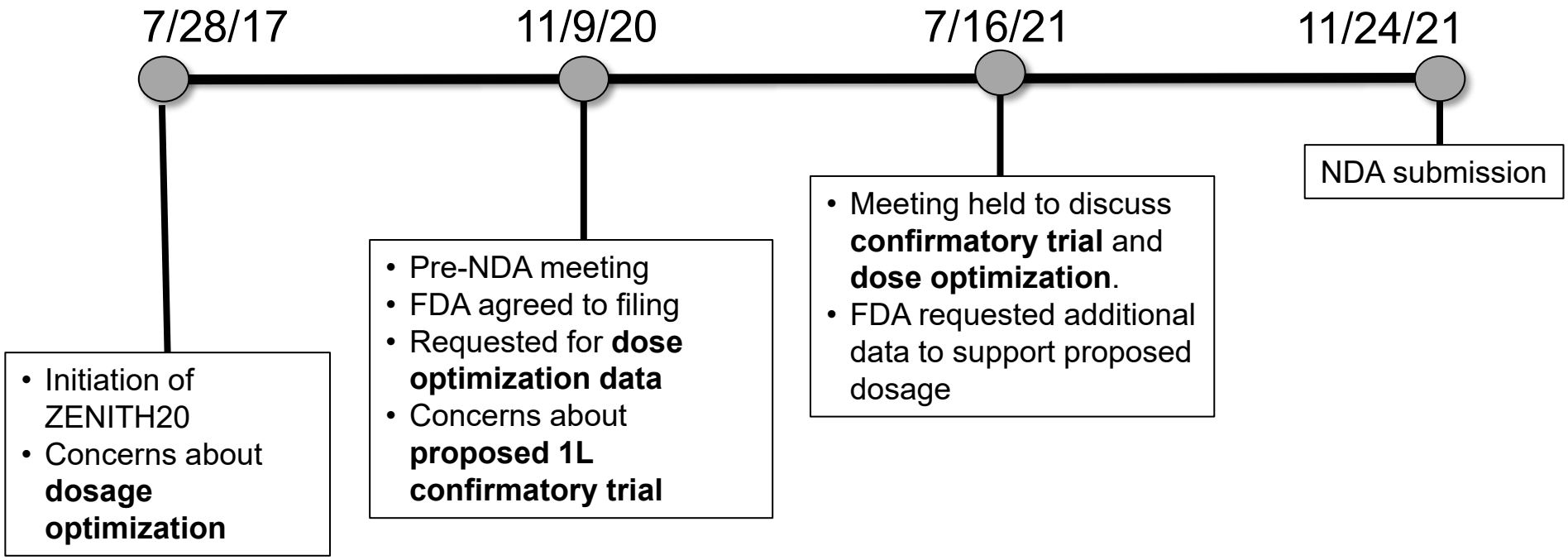
Proposed pathway: accelerated approval

Proposed dosage: 16 mg once daily (QD)

Outline

- Regulatory history & provisions of accelerated approval
- ZENITH20 study design
- Risk:benefit considerations:
  1. Efficacy results not improved over current therapy
  2. High rate of toxicity
  3. Inadequate dosage optimization
  4. Delayed confirmation of benefit
- Discussion topics and voting question for ODAC

2017: Applicant aware of FDA's concerns 2020-2021: Multiple discussions about development issues



Accelerated approval

21 CFR 314 Subpart H: Accelerated approval may be granted if the drug

- Has an effect on an intermediate/surrogate endpoint **reasonably likely to predict clinical benefit**
- Provides **meaningful therapeutic benefit** over existing treatments
- **Further investigation of the drug is required**

FDA guidance has interpreted the CFR to consider an improvement in efficacy and/or safety to be a meaningful therapeutic benefit **in the context of available therapies (e.g., those with regular approval or considered SOC)**

CFR: Code of Federal Regulations; SOC: standard of care

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ZENITH20

Completed

Cohort 2
Previously treated HER2 exon 20 insertions
N=90

Study Design

- **Multicenter, multicohort**
- **Non-randomized**
- **Locally advanced or metastatic NSCLC**
- **Range of different doses**
- **Primary endpoint: ORR by ICR**
- **Secondary endpoint: DOR**

Enrolling

Cohort 5
Previously treated or 1L EGFR or HER2 exon 20 insertions
N=85*

*Patients with HER2 exon 20 insertion mutations only

ORR: overall response rate; ICR: independent central review; DOR: duration of response; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2

Outline

Risk:benefit considerations:

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Current therapies

Agent(s)	ORR (%) (95% CI)	mDOR (mos., range)
Chemotherapy (single agent or combination)		
Docetaxel[1] Docetaxel + ramucirumab[2]	6-14 23 (20, 26)	5.6-6.2 NR
Immunotherapy		
Pembrolizumab/nivolumab[3,4]	14-19	16.3-17.2
Single agent antibody-drug conjugate (under accelerated approval)		
Trastuzumab deruxtecan[5]	58 (43, 71)	8.7 (7.1, NE)

1: TAXOTERE (docetaxel) USPI; 2: CYRAMZA (ramucirumab) USPI; 3: KEYTRUDA (pembrolizumab) USPI; OPDIVO (nivolumab) USPI; ENHERTU (fam-trastuzumab deruxtecan-nxki) USPI

mDOR: median duration of response; mos.: months; NR: not reported; NE: not estimable

ZENITH20 efficacy results

	Poziotinib 16 mg QD At least 1 prior therapy N=90	Poziotinib 16 mg QD Post-platinum and IO N=59
ORR by BICR, % (95% CI)	28 (19, 38)	25 (15, 38)
mDOR, mos. (95% CI)	5.1 (4.2, 5.5)	5.1 (3.1, 6.6)
% responders w/DOR ≥ 6 mos.	24%	20%

Data cutoff date: 3/5/2021

32% of patients received prior chemotherapy without IO

66% of patients received prior chemotherapy and IO

BICR: blinded independent central review; CI: confidence interval; IO: immune-oncology

Outline

Risk:benefit considerations:

1. Efficacy results not improved over current therapy
2. **High rate of toxicity**
3. Inadequate dosage optimization
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Summary of safety:
High rate of toxicity at 16 mg QD

- High rates of treatment interruption and dose reduction
- Very high rates of most common toxicity categories (diarrhea, mucositis, rash)
- Fatal events of pneumonitis
- Unclear whether toxicity would be improved at alternative dosages

Outline

Risk:benefit considerations:

1. Efficacy results not improved over current therapy
2. High rate of toxicity
3. **Inadequate dosage optimization**
4. Delayed confirmation of benefit

Similar ORRs across tested doses

	Cohort 2 Primary	Cohort 5 Exploratory				
Efficacy parameter	**16mg QD N=90**	**16mg QD N=10**	**8mg BID N=40**	**12mg QD N=16**	**6mg BID N=15**	**10mg QD N=14**
ORR, n (%)	25 (28%)	4 (40%)	9 (23%)	4 (25%)	2 (13%)	1 (7%)
95% CI	(19, 38)	(12, 74)	(11, 39)	(7, 52)	(2, 40)	(2, 34)

BID: twice daily

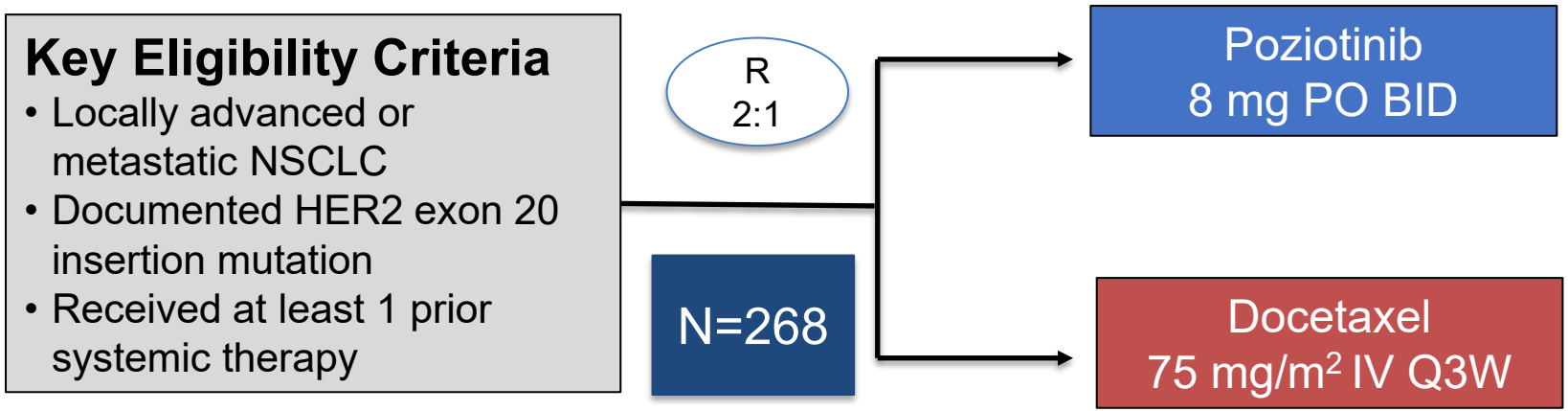
Outline

Risk:benefit considerations:

1. Efficacy results not improved over current therapy
2. High rate of toxicity
3. Inadequate dosage optimization
4. **Delayed confirmation of benefit**

Confirmatory trial:

Targeted PFS benefit of 2.5 months
8 mg BID dosage chosen over 16 mg QD dosage



Primary endpoints: PFS by ICR
Secondary endpoints: OS, ORR

PFS: progression-free survival; R: randomized; IV: intravenous; Q3W: every 3 weeks

FDA risk:benefit assessment

Risks	Potential benefits
Limited response rate with poor durability	Therapy for rare population with limited treatment options
High rate of toxicity at 16 mg QD	Oral route of administration?
Inadequate dosage optimization	
Delayed confirmation of benefit	

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Discussion topics

Discuss the overall risk:benefit of poziotinib 16 mg QD given the following:

1. Efficacy results not improved over available therapy
2. High rate of toxicity
3. Inadequate dosage optimization
4. Delayed confirmation of benefit

Voting question

Do the current benefits of poziotinib outweigh its risks for the treatment of patients with NSCLC with HER2 exon 20 insertion mutations?


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ADMINISTRATION

Poziotinib for HER2 exon 20 insertion mutation-positive non-small cell lung cancer (NSCLC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

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	Kelie Reece, Nonclinical Reviewer

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Proposed pathway: accelerated approval

Proposed dosage: 16 mg once daily (QD)

Major review issues

Overall risk:benefit of poziotinib 16 mg QD:

1. Efficacy not improved over current therapies
2. High rate of toxicity
3. Inadequate dosage optimization
4. Delayed confirmation of benefit

Outline

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Current therapies

Agent(s)	ORR (%) (95% CI)	mDOR (mos., range)
Chemotherapy (single agent or combination)		
Docetaxel[1] Docetaxel + ramucirumab[2]	6-14 23 (20, 26)	5.6-6.2 NR
Immunotherapy		
Pembrolizumab/nivolumab[3,4]	14-19	16.3-17.2
Single agent antibody-drug conjugate (under accelerated approval)		
Trastuzumab deruxtecan[5] (T-DXd)	58 (43, 71)	8.7 (7.1, NE)

1: TAXOTERE (docetaxel) USPI; 2: CYRAMZA (ramucirumab) USPI; 3: KEYTRUDA (pembrolizumab) USPI; OPDIVO (nivolumab) USPI; 4: ENHERTU (fam-trastuzumab deruxtecan-nxki) USPI

ORR: objective response rate; CI: confidence interval; mDOR: median duration of response; mos.: months; NR: not reported; NE: not estimable

Key demographic information

	Poziotinib 16 mg QD N=90
Prior therapy (%) **Chemotherapy without IO** **Chemotherapy + IO**	 **32%** **66%**
Age (years) (median, range)	60 (25, 86)
Female (%)	64
Race (%) White Asian Black/African American	 78 13 4
Never smoker (%)	66

IO: immunotherapy

Efficacy results

	Poziotinib 16 mg QD (N=90)	Post-platinum and IO (N=59)
ORR by BICR, % (95% CI)	28 (19, 38)	25 (15, 38)
mDOR, mos. (95% CI)	5.1 (4.2, 5.5)	5.1 (3.1, 6.6)
% responders with DOR ≥6 months	24	20

Data cutoff date 03/05/2021

Similar ORR and DOR relative to current therapies

Current therapies

Agent(s)	ORR (%) (95% CI)	mDOR (mos., range)
Single agent antibody-drug conjugate (under accelerated approval)		
Trastuzumab deruxtecan	*58 (43, 71)*	*8.7 (7.1, NE)*
Chemotherapy (single agent or combination)		
Docetaxel **Docetaxel + ramucirumab**	6-14 **23 (20, 26)**	5.6-6.2 NR
Immunotherapy		
Pembrolizumab/nivolumab	14-19	**16.3-17.2**
Targeted therapy		
Poziotinib	**28 (19, 38)**	**5.1 (4.2, 5.5)**

Outline

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Safety profile suggests poziotinib is highly toxic at 16 mg QD

Safety parameter	Poziotinib 16 mg QD N=368, %
Grade 3-4 AEs Grade 5 AEs	79 7
Serious AEs	42
Drug interruption	**83**
Dose reduction	**57**
Treatment discontinuation	18

AEs: adverse events

Serious adverse events in ≥ 2% of patients

Serious Adverse Event	16 mg QD N=368, %	Cohort 2 N=90, %
Dyspnea	5	7
Pneumonia	5	6
Diarrhea	3.0	2.2
Pneumonitis	**2.2**	**0**
Acute Kidney Injury	2.2	3.3

Fatal adverse events in ≥ 1 % of patients

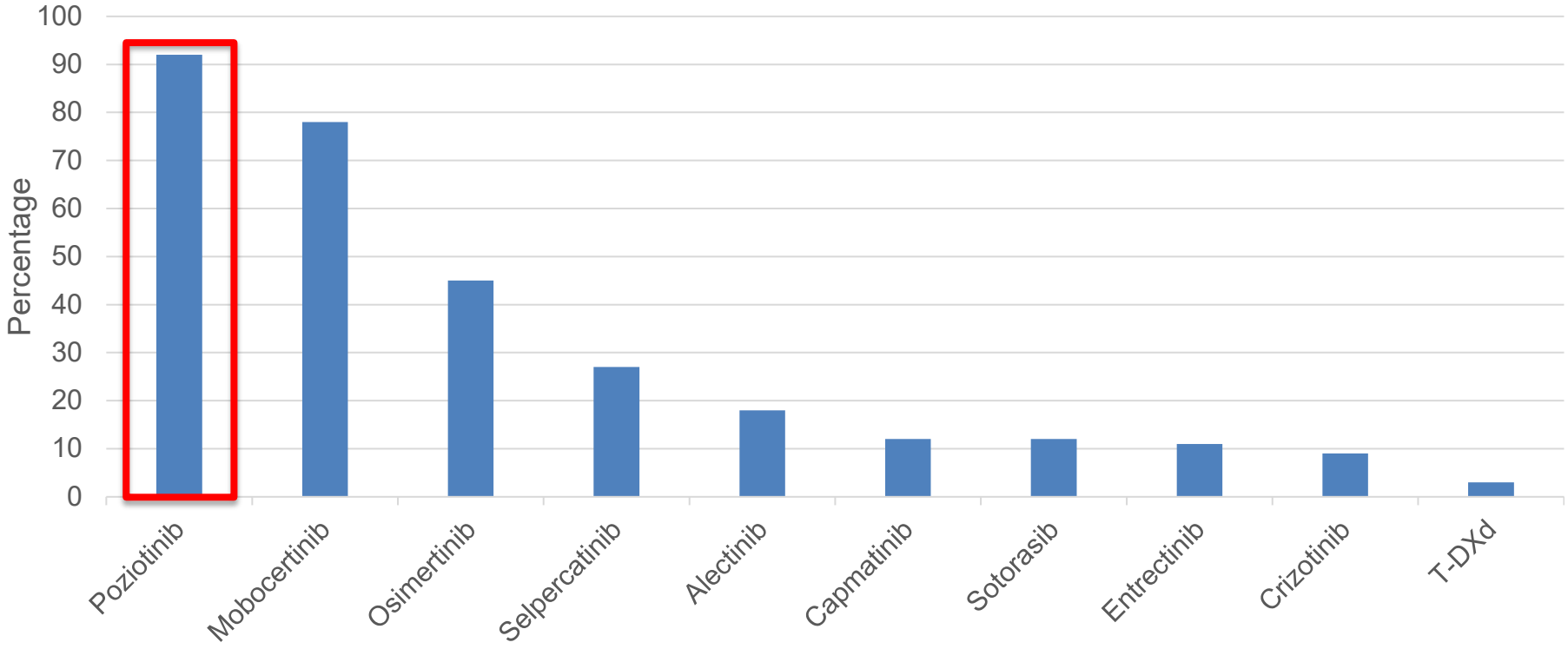
Fatal adverse event	16 mg QD N=368, %	Cohort 2 N=90, %
All Fatal AEs	**7**	**10**
Pneumonitis	**0.8**	**0**
Respiratory Failure*	1.1	3.3
Pneumonia	1.1	2.2

*Includes respiratory failure due to cardiopulmonary arrest, sepsis, heart failure, pleural effusion and stroke

Summary of common AEs: Highly toxic

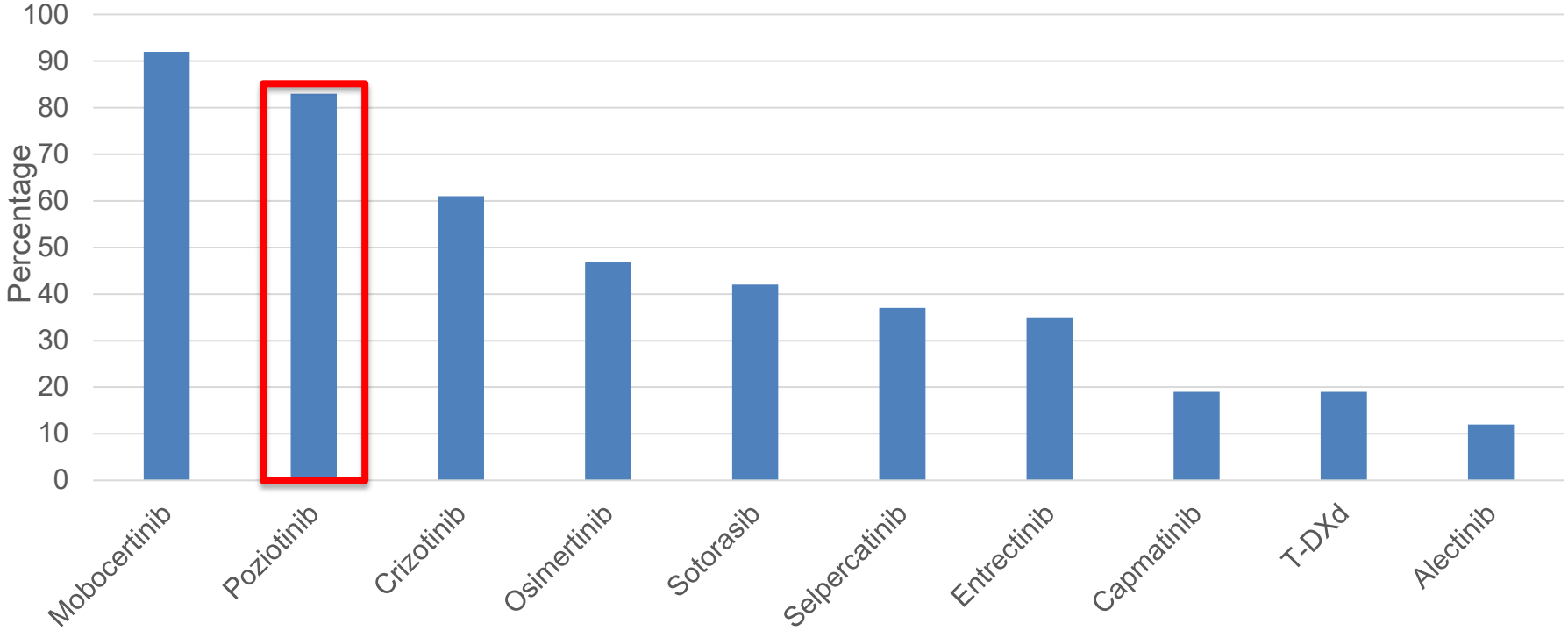
Safety parameter	Rash, %	Diarrhea, %	Mucositis, %
Any Grade AE	92	83	74
Grade 3-4 AE	**47**	**24**	19
Drug interruptions	**48**	**30**	18
Dose reductions	**30**	**18**	10

Targeted therapies for NSCLC: Higher incidence of rash with poziotinib



EXKIVITY (mobocertinib) USPI; TAGRISSO (osimertinib) USPI; RETEVMO (selpercatinib); ALECENSA (alectinib) USPI; TABRECTA (capmatinib) USPI; LUMAKRAS (sotorasib) USPI; ROZLYTREK (entrectinib) USPI; XALKORI (crizotinib) USPI; ENHERTU (fam-trastuzumab deruxtecan-nxki) USPI

Targeted therapies for NSCLC: Higher incidence of diarrhea with poziotinib



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NCI-CTCAE: Diarrhea

One of the symptoms most highly related with QOL

Grade 1	Grade 2	Grade 3	Grade 4
Increase of < 4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events, v4.03

QOL: Quality of life

Impact of diarrhea in ZENITH20

	Poziotinib 16 mg QD N=368
Incidence (all), % Grades 1-2 Grades 3-4	83 82 24
Treatment interruption, %	30
Dose reduction, %	18
Treatment discontinuation, %	2.2
% anti-diarrheal use	56

Bossi P et al. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. Annals of Oncology 2018

Patient-reported outcomes

- Measured using the EORTC QLQ-C30 and QLQ-LC13 for exploratory endpoints.
- Assessment frequency: Day 1 of Cycles 1, 2, 3, 5, 7 and EOS.
- Limitations of PRO data:
  - Insufficient measurement of patient-reported side effects at frequent, relevant timepoints.
  - Due to attrition, less than half of patients provided PRO responses at Cycle 5.
  - There was no prespecified PRO hypothesis.
- No meaningful efficacy conclusions can be derived from the PRO data.

The Applicant did not rigorously assess patient-reported symptoms and side effects, and therefore inadequately assessed tolerability of poziotinib

EORTC: European Organization for Research and Treatment of Cancer; EOS: end of study; PRO: patient-reported outcome

Outline

- Risk:benefit considerations:
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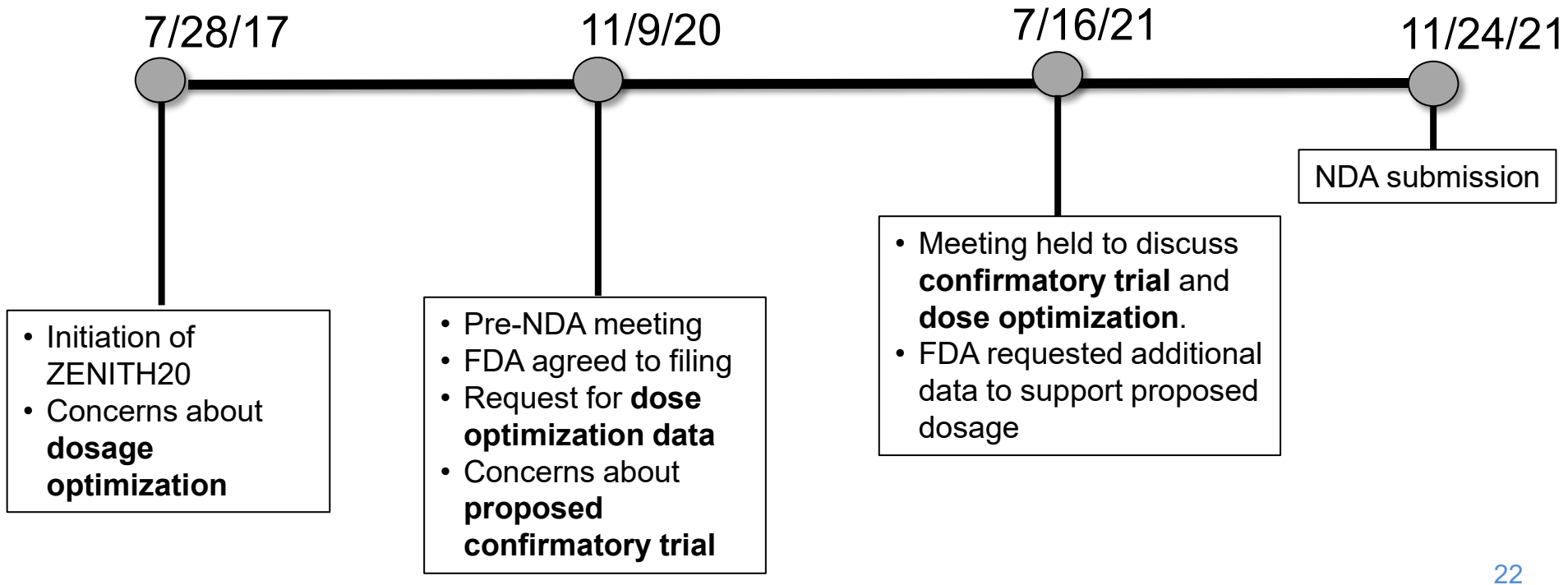
- FDA risk:benefit assessment

- Discussion topics and voting question for ODAC

2017-2021: Multiple discussions about dosage selection



Lack of adequate dosage justification

- Poor tolerability observed at proposed recommended dosage

- Uncertain if alternative dosages can improve tolerability and provide acceptable effectiveness

Determination of Applicant recommended dosage is based on limited data

Dose Finding Study: HM-PHI-102

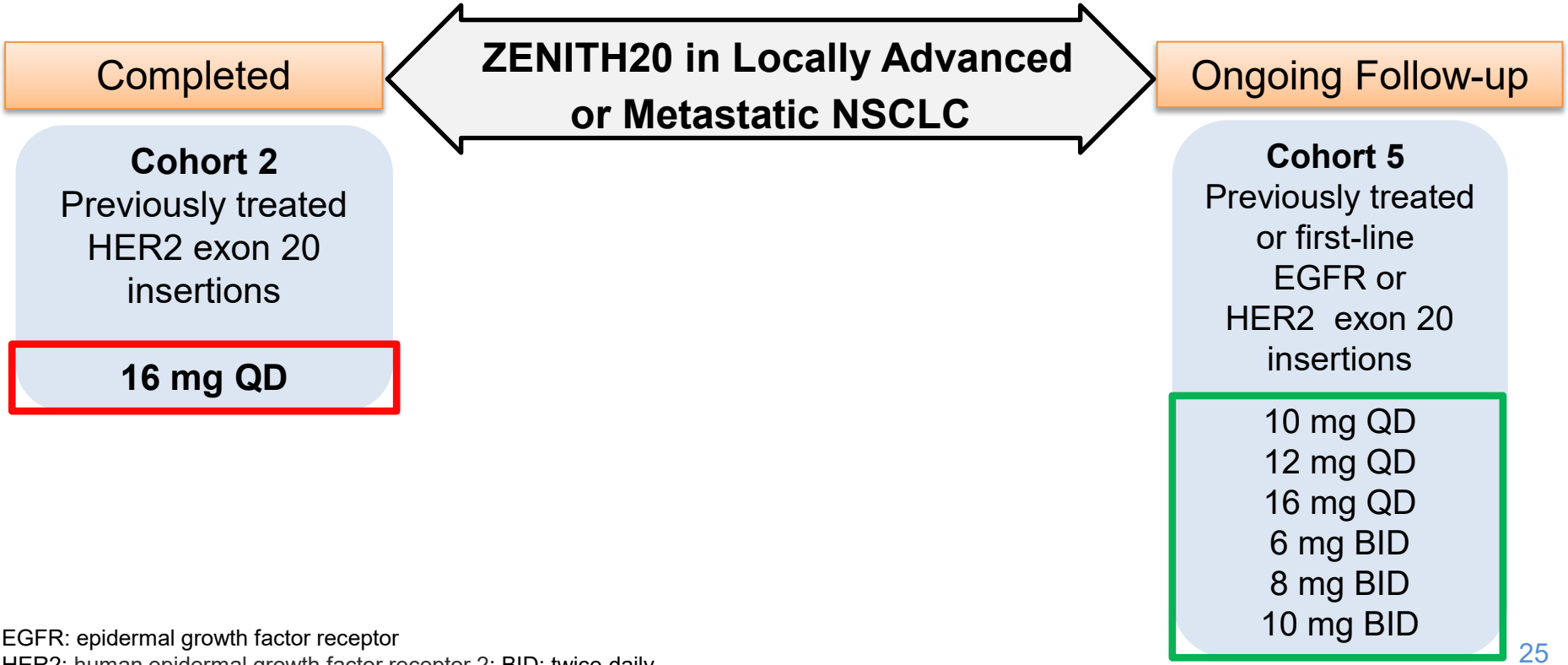
Maximum tolerated dose (MTD): 18 mg QD
Applicant Proposed Dosage: 16 mg QD

→ **Not adequately justified**

%	12 mg N=3	16 mg N=7 to 8	18 mg N=6	24 mg N=3
ORR	33	14.3	17	33
TEAEs	100	100	100	100
Grade 3	100	62	33	33
Grade 4	0	0	17	0

TEAEs: treatment emergent adverse events

Alternative dosages in Cohort 5 undergoing follow-up for safety and effectiveness



EGFR: epidermal growth factor receptor
HER2: human epidermal growth factor receptor 2; BID: twice daily

Not known if alternative dosages provide similar effectiveness compared to 16 mg QD

	Cohort 2 Pivotal	Cohort 5 Exploratory				
	16 mg QD N=90	16 mg QD N=10	8 mg BID N=40	12 mg QD N=16	6 mg BID N=15	10 mg QD N=14
ORR (95% CI)	28% (19, 38)	40% (12, 74)	23% (11, 39)	25% (7, 52)	13% (2, 40)	7% (2, 34)

- ORR at alternative dosages appear similar across dosages
- Relatively small sample sizes for the alternative dosages

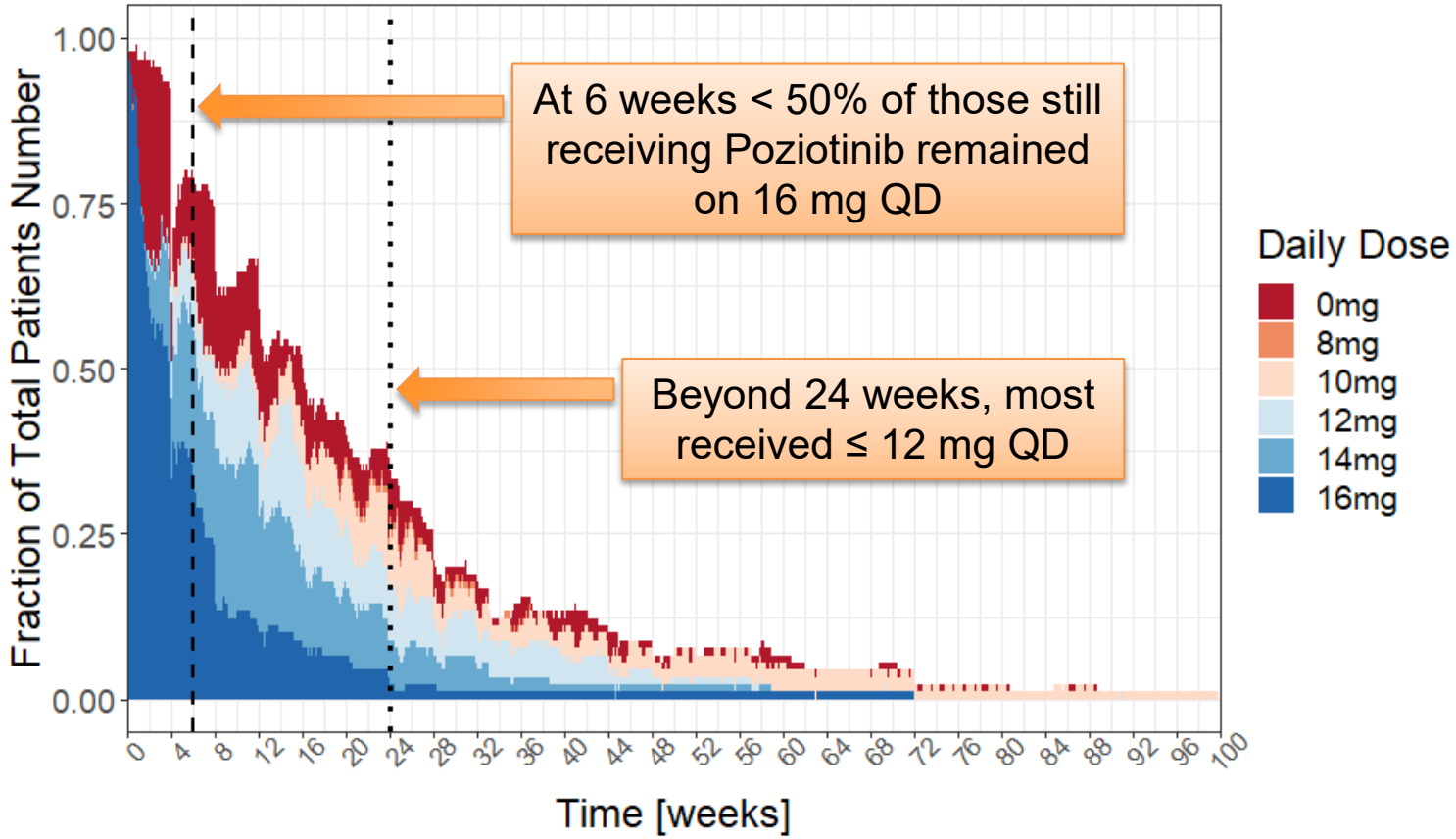
Preliminary Exposure-Response analyses do not support 16 mg QD over alternative dosages

	Association	Conclusion
Efficacy	Inconclusive → limited data at alternative dosages	Additional data for alternative dosages needed
Safety	↑ Avg concentration associated with ↑ risk for TEAEs: • ↑ risk Grade 3+ diarrhea • ↑ risk Grade 3+ stomatitis • ↑ risk TEAEs leading to dose reduction • ↑ risk TEAEs leading to treatment discontinuation	Better safety with lower total daily dose

High rate of dosage modifications

	Cohort 2 N=90
Dose Reduction	74%
Dose Interruption	89%
Relative Dose Intensity	~12 mg QD
Time to First Dose Interruption	29 days
Duration of First Drug Interruption	8.4 days

Most received reduced dose within one month after starting 16 mg QD



Lack of dose justification

- To date there are inadequate clinical data over the relevant dose range
- Uncertain if alternative dosages will improve the risk-benefit profile
- Poor risk-benefit profile at Applicant's proposed dosage of 16 mg QD

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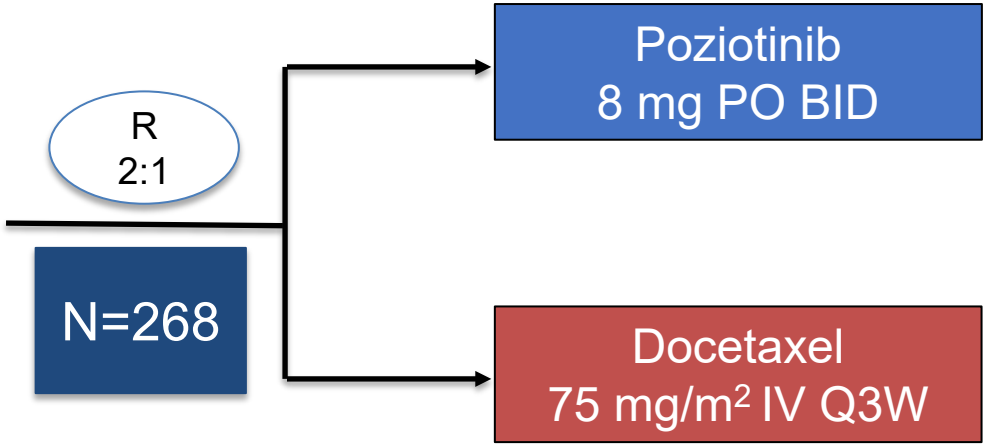
Confirmatory trial:

Targeted PFS benefit of 2.5 months
8 mg BID dosage chosen over 16 mg QD dosage

Key Eligibility Criteria
- Locally advanced or metastatic NSCLC
- Documented HER2 exon 20 insertion mutation
- Received at least 1 prior systemic therapy



Primary endpoints: PFS by IRC
Secondary endpoints: OS, ORR

PFS: progression-free survival; R: randomization; PO: by mouth; IV: intravenous; Q3W: every 3 weeks; IRC: independent review committee; OS: overall survival

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FDA risk:benefit assessment

Risks	Potential benefits
Limited response rate with poor durability	Therapy for rare population with limited treatment options
High rate of toxicity at the proposed dosage (poziotinib 16 mg QD)	Oral route of administration
Inadequate dosage optimization	
Delayed confirmatory trial	

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