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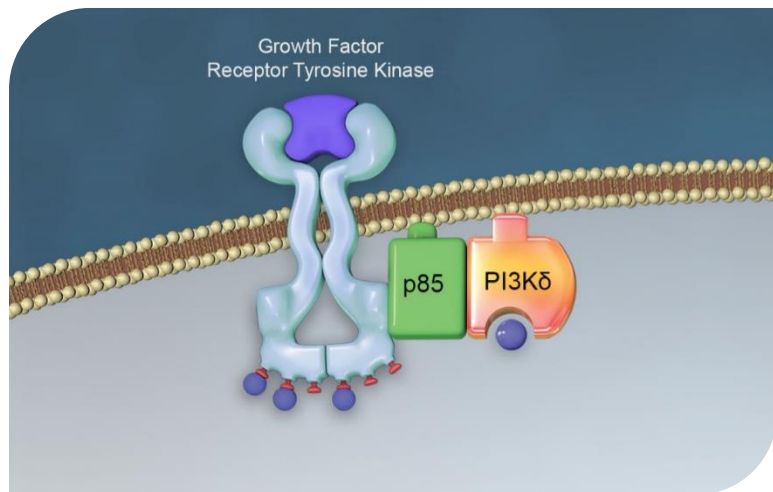
Results From a Phase 1/2 Study of INCB050465, a Potent and Highly Selective PI3K δ Inhibitor, in Patients With Relapsed or Refractory B-Cell Malignancies (CITADEL-101)

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PI3K δ in Normal Physiology

Association of PI3K δ with receptor tyrosine kinase



Class IA PI3Ks are heterodimeric lipid kinases composed of a regulatory (p85) and a catalytic subunit (p110)¹⁻³

- PI3K is activated by growth factor receptor tyrosine kinases¹⁻³

PI3K Catalytic Subunit (p110) Isoforms and Functions

α	Insulin signaling and angiogenesis ⁴
β	Platelet function ⁴
γ	White blood cell function ⁵
δ	Signaling, development, and survival of B cells⁶

1. Chalhoub N, Baker SJ. *Annu Rev Pathol.* 2009;4:127-150; 2. Fruman DA, et al. *Nat Rev Drug Discov.* 2014;13:140-156; 3. Brana I, Siu LL. *BMC Med.* 2012;10:161; 4. Liu P, et al. *Nat Rev Drug Discov.* 2009;8:627-644; 5. Hirsch E, et al. *Thromb Haemost.* 2006;95:29-35; 6. Puri KD, Gold MR. *Front Immunol.* 2012;3:256.

INCB050465 is a Potent, Highly Selective, Next-Generation PI3K δ Inhibitor

Comparative Potency and Isoform Selectivity*

	INCB050465 ¹	Copanlisib ²	Idelalisib ³	Umbralisib ⁴
PI3K δ IC ₅₀ , nM	1	0.7	2.5	22
Fold selectivity				
PI3K α	>20,000	1	>300	>10,000
PI3K β	>20,000	5	>200	>50
PI3K γ	19,000	10	>35	>48

*Biochemical assay.

INCB050465 was designed to avoid hepatotoxicity and have favorable PK exposures

1. Shin N, et al. AACR Annual Meeting. April 18–22, 2015; Philadelphia, PA, USA. Abstract 2671. 2. Liu N, et al. *Mol Cancer Ther*. 2013;12:2319–2330; 3. Phillips T, et al. 58th ASH Annual Meeting. December 3–6, 2016; San Diego, CA, USA. Abstract 4195; 4. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059–3068.
IC, inhibitory concentration; PI3K, phosphatidylinositol 3-kinases.



Primary Objective

- To assess the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of INCB050465 in patients with relapsed or refractory B-cell malignancies (NCT02018861)



Methods

- Patients

- Age ≥ 18 years with relapsed or refractory lymphoid malignancies of B-cell origin
- Received ≥ 1 prior treatment regimen
- Had not responded or were not a candidate for SCT or other potentially curative therapy

- Assessments

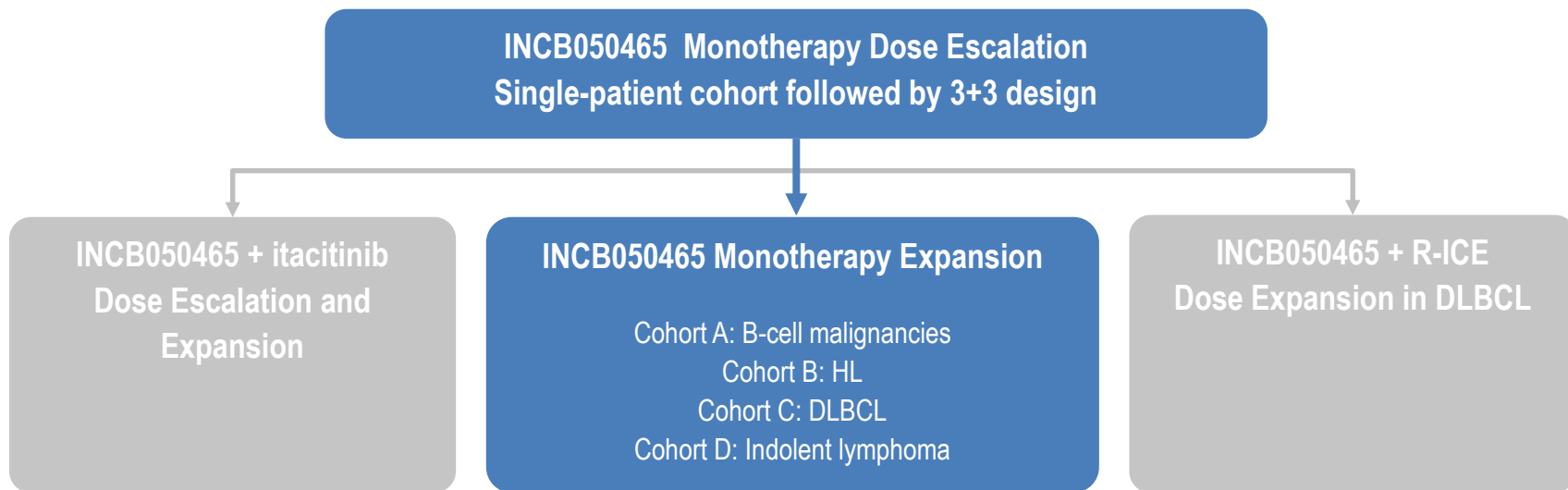
- AEs assessed using CTCAE v4.03
- Efficacy evaluated every 9 weeks using the Lugano criteria for HL and NHL¹

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059–3068.

ECOG PS, Eastern Cooperative Group performance status; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; SCT, stem-cell transplant; AE, adverse event.



Study Design



DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; R-ICE, rituximab in combination with ifosfamide, carboplatin, and etoposide.



Baseline Patient Characteristics

Characteristics	INCB050465 Monotherapy (N=72)
Age, median (range), years	66 (30–89)
>65 years, n (%)	37 (51)
Men, n (%)	41 (57)
Disease type, n (%)	
NHL subtypes of interest	55 (76)
DLBCL	23 (32)
FL	14 (19)
MZL	9 (13)
MCL	9 (13)
WM	1 (1)
CLL	6 (8)
HL	10 (14)
Patients with ≥3 prior systemic therapy regimens, n (%)	43 (60)
Prior HSCT, n (%)	21 (29)



Dose Escalation and Cohort Expansion

				Expansion doses		
Dose	5 mg	10 mg	15 mg	20 mg	30 mg	45 mg
n	1	3	3	34	27	4

- No DLTs identified within the 21-day observation window
- MTD not reached

DLT, dose-limiting toxicity; MTD, maximum tolerated dose.



Long-term Tolerability

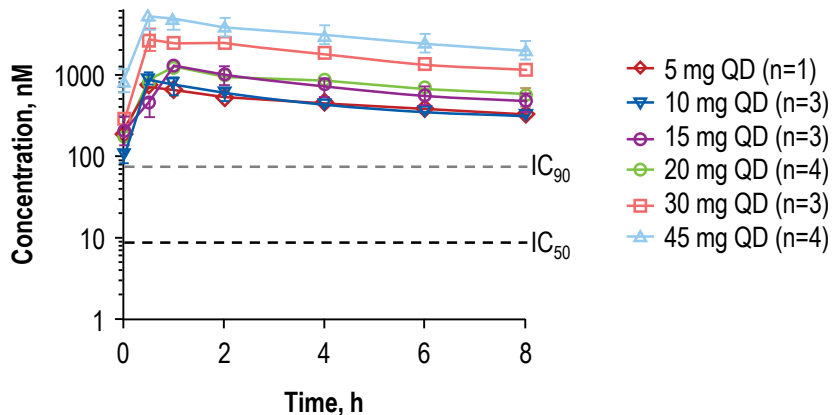
- As of September 2016, 9 of 31 patients (29%) with NHL discontinued due to AEs, most commonly ($n \geq 2$):
 - Diarrhea/colitis ($n=3$, 10%)
 - Rash ($n=2$, 6%)
 - No patient came off study for treatment-related AEs during the first 9 weeks
- In November 2016, an intermittent dosing schedule was implemented
 - New patients received 20 mg QD for 9 weeks, followed by 20 mg QW
 - Existing patients on treatment for ≥ 9 weeks were switched to QW

AE, adverse event; NHL, non-Hodgkin lymphoma; QD, once daily; QW, once weekly.



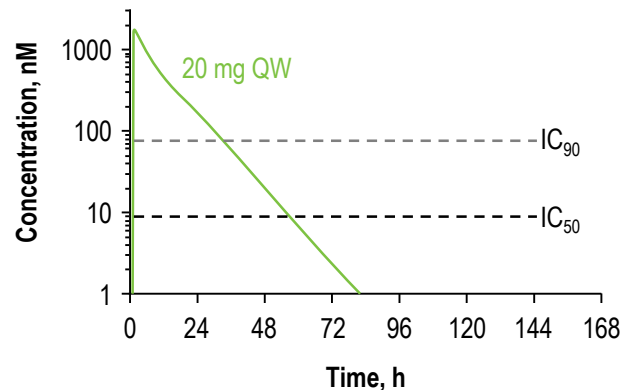
PK of INCB050465

QD Dosing at Steady State



- Approximately linear PK was observed with all INCB050465 doses
- All doses tested remained above the IC_{90} for target inhibition throughout the dosing interval

Modeling of QW Dosing



- Based on PK simulation, serum INCB050465 levels resulting from 20 mg QW dosing are predicted to exceed the IC_{90} for target inhibition for ~36 hours

IC, inhibitory concentration; QD, once daily; QW, once weekly.



TEAEs and Dose Modifications

Nonhematologic TEAEs Occurring in $\geq 20\%$ of Patients

Total (N=72)	Any Grade, n (%)	Grade 3 or 4, n (%)
Any TEAE	68 (94)	41 (57)
Diarrhea/Colitis*	26 (36)	7 (10)
Nausea	26 (36)	0
Fatigue	22 (31)	0
Rash*	22 (31)	4 (6)
Cough	17 (24)	0
Vomiting	17 (24)	0

*Includes multiple terms.

TEAE, treatment-emergent adverse event.

New or Worsening Hematologic TEAEs

Total (N=72)	Any Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neutropenia	32 (44)	10 (14)	4 (6)
Thrombocytopenia	24 (33)	3 (4)	4 (6)
Anemia	20 (28)	5 (7)	0 (0)

Dose Modifications Due to Any Grade TEAE

Event, n (%)	Total (N=72)
Interruption	30 (42)
Reduction	4 (6)
Discontinuation	14 (19)



Serious TEAEs and TEAEs of Interest

Serious TEAEs in >2 Patients

Total (N=72)	Any Grade, n (%)	Grade 3 or 4, n (%)
Any TEAE	29 (40)	25 (35)
Diarrhea/Colitis*	8 (11)	6 (8)
Pyrexia	4 (6)	1 (1)
Hypotension	3 (4)	2 (3)
Sepsis	3 (4)	3 (4)

*Includes multiple terms.

Time to Onset of Grade ≥2 TEAEs of Interest

Grade ≥2 TEAE	Median (range) time to onset, months
Diarrhea/Colitis*	4.4 (0.4–14.9)
Rash*	2.9 (1.5–9.3)

*Includes multiple terms.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

- On-treatment AST and ALT elevations: 26% and 25% (all Grade 1)
- Hypertension: 7% (all Grade 1/2)
- Hyperglycemia: 10% (1 Grade 3)

AEs during QW dosing

- No discontinuations due to TEAEs (105 patient-months)
- No Grade 4 non-hematologic TEAEs
 - Grade 3 diarrhea, n=1 (4%)
 - Grade 3 rash, n=1 (4%)
 - Both occurred shortly after the switch
- No Grade 4 neutropenia



Objective Response Rate

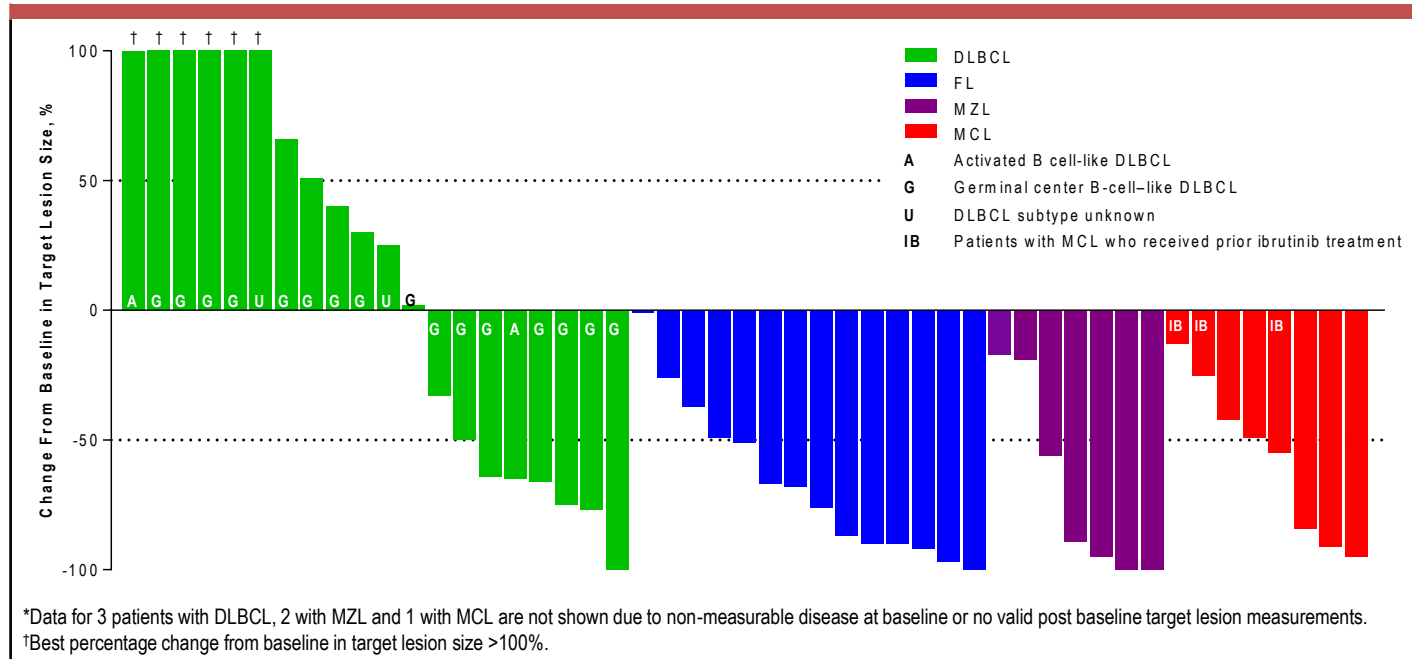
Patients	N	ORR, n (%)	CR/CMR, n
DLBCL*	23	7 (30)	4
GCB	19	6 (32)	4
ABC	2	1 (50)	0
FL	14	10 (71)	3
MZL	9	7 (78)	3
MCL	9	6 (67)	4

*Two patients had unknown DLBCL subtype.

ABC, activated B cell-like; CMR, complete metabolic response; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell-like; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, objective response rate.



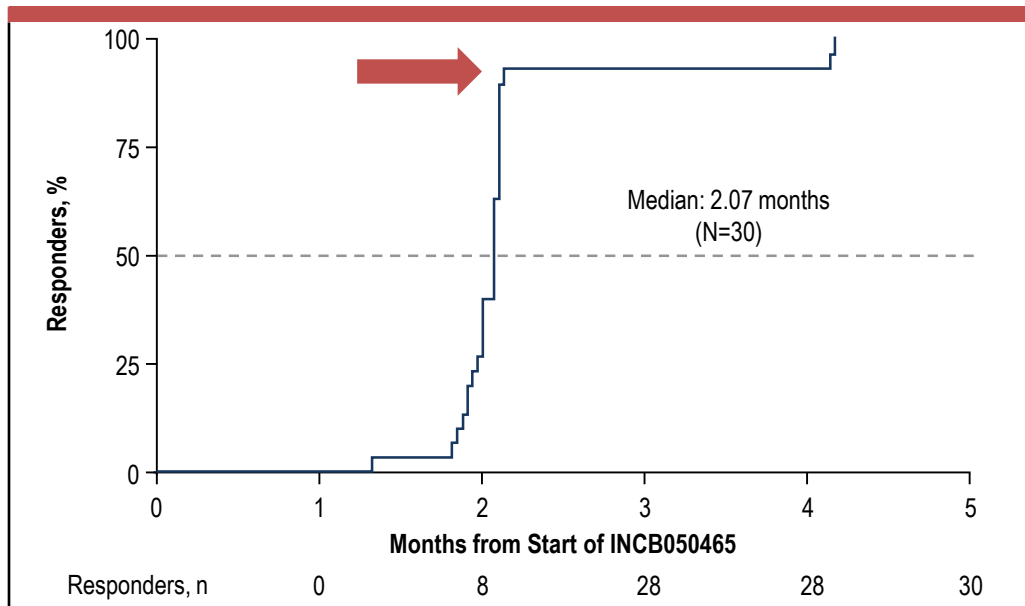
Best Percent Change From Baseline in Target Lesion Size*



DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.



Time to Response (DLBCL, FL, MCL, MZL)



- 93% of responses occurred at first assessment (~9 weeks)
- Supports switch to QW dosing after first assessment to manage long-term tolerability

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QW, once weekly.



Rapid Response in MCL



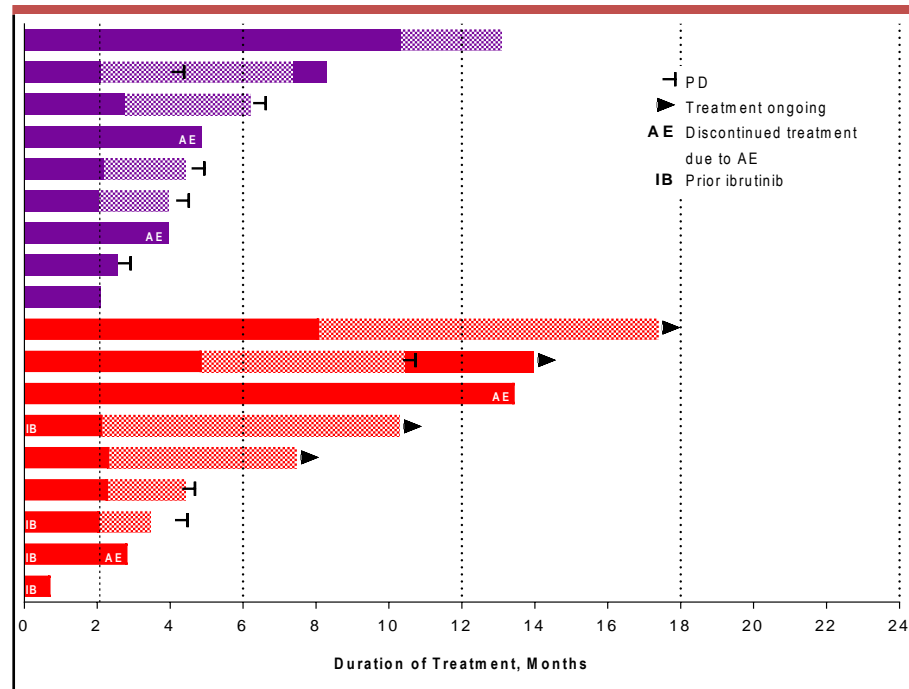
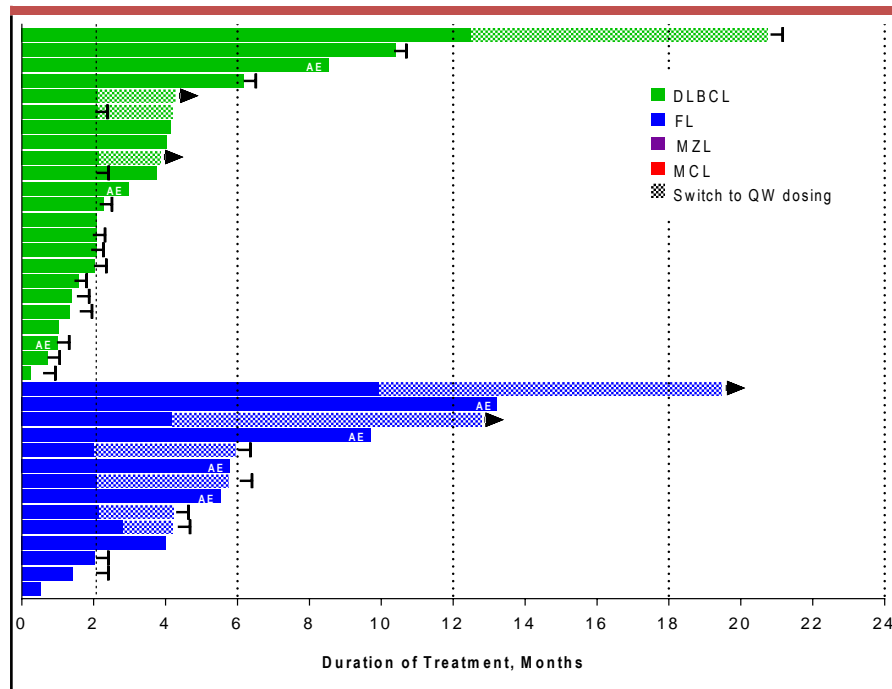
Patient treated with 20 mg QD

Image presented at the **American Association for Cancer Research Annual Meeting 2016**, New Orleans, LA, USA • April 16–20, 2016.
MCL, mantle cell lymphoma; QD, once daily.



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Duration of Treatment



Patients have remained on QW schedule for >8 months across several NHL subtypes



Summary

- INCB050465 is a potent, highly selective, next-generation PI3K δ inhibitor demonstrating dose-proportional PK
- INCB050465 monotherapy effected a high rate of rapid, deep, and durable objective responses
- INCB050465 was not associated with significant transaminase elevations or with any new or unexpected serious AEs
- Rapid response supports short-term QD dosing followed by switch to QW dosing to manage long-term tolerability
- Long-term safety and durable responses on QW schedule warrant further investigation in the ongoing phase 2 clinical studies



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